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European Position Paper on Endoscopic Management of Tumours of the Nose, Paranasal Sinuses and Skull Base

**Valerie Lund, Heinz Stammberger, Piero Nicolai, Paolo Castelnuovo on behalf
of the European Rhinologic Society Advisory Board on Endoscopic Techniques
in the Management of Nose, Paranasal Sinus and Skull Base Tumours**

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European Position Paper on Endoscopic Management of Tumours of the Nose, Paranasal Sinuses and Skull Base

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NB. The authors are aware that certain rare histologies have been omitted. As this is an evidence based review, there is insufficient information in the literature thus far on all individual types of tumour managed endoscopically to warrant a separate section in every case.

Summary

Valerie Lund*, Heinz Stammberger, Piero Nicolai, Paolo Castelnovo on behalf of the European Rhinologic Society Advisory Board on Endoscopic Techniques in the Management of Nose, Paranasal Sinus and Skull Base Tumours.

Tumours affecting the nose, paranasal sinuses and adjacent skull base are fortunately rare. However, they pose significant problems of management due their late presentation and juxtaposition to important anatomical structures such eye and brain. The increasing application of endonasal endoscopic techniques to their excision offers potentially similar scales of resection but with reduced morbidity. The present document is intended to be a state-of-the art review for any specialist with an interest in this area

- to update their knowledge of neoplasia affecting the nose, paranasal sinuses and adjacent skull base;
- to provide an evidence-based review of the diagnostic methods;

- to provide an evidence-based review of endoscopic techniques in the context of other available treatments;
- to propose algorithms for the management of the disease;
- to propose guidance for outcome measurements for research and encourage prospective collection of data.

The importance of a multidisciplinary approach, adherence to oncologic principles with intent to cure and need for long-term follow-up is emphasized.

Key words: sinonasal, nasal cavity, pituitary, benign, malignant, tumours, endonasal, endoscopic, nose, paranasal sinuses, skull base

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1. Introduction

1-1 Aims and Objectives

As part of an initiative by the European Rhinologic Society, a group of internationally recognised experts from many disciplines have been invited to contribute to an Advisory Board, which has considered the present knowledge and published evidence concerning endoscopic techniques in the management of tumours, both benign and malignant, affecting the nose, paranasal sinuses and adjacent skull base. The aims have been to consider endoscopic techniques in the context of existing techniques, to highlight areas where further high quality evidence is required and to consider ways in which this may be achieved. In undertaking this evidence based review, the authors have concentrated on those tumours subjected to endoscopic resection, which have most frequently been reported in the literature and as a consequence certain less common histologies have been omitted. Nonetheless similar principles may be applied in the endoscopic management of these rarer tumours.

1-2 Methodology

A similar methodology has been used as for the European Position Paper on Rhinosinusitis and Nasal Polyps (EP3OS)⁽¹⁾. However, the participants recognise that when considering a surgical technique, the ability to provide placebo-controlled randomised trials, ie levels I & II is compromised by ethical considerations. Furthermore, the rarity of these tumours makes the acquisition of large cohorts difficult. Nonetheless, the group are cognisant of the necessity to critically examine what has been published in the light of evidence based recommendations and recognise that most series can only be considered as providing evidence at level III & IV and recommendations at levels C & D.

1-3 Search strategy

A Medline review of the literature was performed to identify relevant contributions from 1966 onwards. More detail is given in the specific sections.

Table 1-1. Category of evidence⁽²⁾.

Ia	Evidence from meta-analysis of randomised controlled trials
Ib	Evidence from at least one randomised controlled trial
IIa	Evidence from at least one controlled study without randomisation
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Table 1-2. Strength of recommendation.

A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated recommendation from category I evidence
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

2. Surgical anatomy

It goes without saying, that there is no “new” anatomy in the sinus and skull base region since the advent of endoscopic approaches – no new anatomic terminology, no new topographical relations. What has changed however, is the way one looks at anatomical structures with the endoscope⁽³⁻⁹³⁾. Unlike traditional or microscope-based open approaches where the surgical field usually narrows from a wide external exposure to the structures in question, endoscopes allow for an “inverted funnel” approach with the nostrils being the narrowest segment of access. From here, the surgical field widens depending on the specifications of the endoscopes used. Classical anatomical dissection techniques either follow structures like vessels, nerves, muscles or are displayed in different CT- or MRI-sections. The latter technique results in excellent comparability of anatomical slices and images in various planes, enabling the surgeon to identify and follow structures both on consecutive scans as well as anatomical dissection planes. Endoscopic endonasal surgery initially relied on coronal scans in CT, as this was the plane in which anatomical structures would present to surgeons on their way through the sinuses and along the anterior skull base. Nonetheless the challenge remained for surgeons to fuse the serial sections into a three-dimensional, spatial model of reality in their minds.

The transnasal endoscopic techniques take advantage of an optical possibility not available to the unaided eye, nor a microscope: to view “around the corner”. Rigid endoscopes with deflecting lenses require an initially linear straight corridor for the anatomical approach; at the end of this straight cor-

ridor however, they allow a view onto structures well beyond the right angle, which today can be reached with special instruments also passed through the same corridors.

Anatomical descriptions must therefore take into consideration these “new” ways and possibilities of visualisation. Anatomical structures for instance in a lateral recess of the sphenoid sinus look different when viewed from medially, i.e. the sphenoid sinus proper, via a 30° or 45° lens, compared to a view from “anteriorly” with 0° lenses or the microscope. This applies even more to the structures in the sella and parasellar region, the clivus and intracranial compartments such as the third and the lateral ventricles, the optic chiasm or vascular structures like the circle of Willis.

This supplement therefore does not aim to provide a detailed description of well known topographical features, but to give some examples of surgical endoscopic approaches and their relating anatomical structures. This is best seen in Section 5: “Endonasal Endoscopic Surgical Approaches”, but in many of the other chapters as well. Detailed anatomical descriptions and relevant studies are listed in the references of this section. The feasibility of endoscopic approaches to a significant degree depends on critical anatomical structures in the corridors and their immediate topographical vicinity. The risk and complication potential is not so much related to the size of a lesion but rather to the endoscopic corridor(s) of approach.

3. Incidence and epidemiology

3-1 Benign tumours

Benign tumours of the sinonasal tract are a histologically diverse group of neoplasms, which can be divided into several groups: fibro-osseous (osteoma, chondroma, ossifying fibroma, and fibrous dysplasia), neural-related (schwannoma, neurofibroma, and meningioma), hamartomatous (respiratory epithelial adenomatoid hamartoma), odontogenic (ameloblastoma, and calcifying epithelial tumour of Pindborg), vascular (haemangioma, haemangiopericytoma, juvenile nasopharyngeal angiofibroma, and pyogenic granuloma), and inverted papilloma⁽⁹⁴⁾.

Osteoma is the most common benign sinonasal tumour, and it has been reported to be seen on 1% of routine sinus radiographs, most commonly localized to the frontal sinus⁽⁹⁵⁾. The overall incidence of paranasal sinus osteomas in patients with coronal sinonasal CT scans due to sinonasal symptoms was 3%⁽⁹⁶⁾. Osteomas usually presents between the second and sixth decades, with a predilection of fifth and sixth decades^(96,97). Male to female ratio is 1.3-2:1. The frontal sinus was the most frequently involved site (57%)(of these lesions 37% were in the immediate vicinity of the frontonasal duct and 21% above and lateral to the ostium), followed by the maxillary, ethmoid and the sphenoid sinuses. Maxillary sinuses are affected in about 20% of cases^(96,98). Involvement of the sphenoid sinus region is extremely rare^(99,100). Osteomas can occur in conjunction with Gardner's syndrome, which is an autosomal-dominant condition consisting of osteomas (usually multiple), soft tissue tumours (such as epidermal inclusion cysts or subcutaneous fibrous tumours), and polyposis of the colon. This triad of symptoms should prompt gastroenterology referral if this is suspected, as malignant degeneration of these colonic polyps will occur in 40% of patients^(101,102).

Fibro-osseous lesions are a heterogeneous group and the commonest fibro-osseous lesions of the sinonasal tract are ossifying fibroma and fibrous dysplasia. Other lesions include giant cell granuloma, fibromyxoma, osteoblastoma. Both fibrous dysplasia and ossifying fibroma are more common in females than in males^(103,104). Usually fibrous dysplasia presents in the first two decades⁽¹⁰⁵⁾. There are two forms: polyostotic (15%–30%), involving more than one bone, and monostotic (70%–85%), involving only one bone⁽¹⁰⁶⁾. McCune-Albright syndrome (the polyostotic form fibrous dysplasia, precocious puberty, café-au-lait spots) is the most rare and preferentially involves young girls⁽¹⁰⁷⁾. Twenty-five percent of monostotic cases arise in the facial skeleton⁽¹⁰⁸⁾. The maxilla and mandible are the most common sites in the head and neck, although it has been reported throughout the maxillofacial skeleton,

including the sphenoid intersinus septum⁽¹⁰⁶⁾. Asymptomatic fibrous dysplasia is often an incidental finding on X-ray obtained for other reasons (trauma or evaluation of hearing loss). The sphenoid bone and central skull base are frequently involved in such cases. Growth is variable, and usually slows after puberty but this is not invariable⁽¹⁰⁹⁾. Fibrous dysplasia has a low rate of malignant transformation^(106,108,110). Transformation occurs in 0.5% of polyostotic forms and in 4% of lesions in patients with McCune-Albright syndrome^(106,111). Ossifying fibroma is usually diagnosed in the third to fourth decade and mainly affects bones. It is more commonly found in the mandible (75%) or maxilla (10–20%) and lesions in the nasoethmoidal region are rare⁽¹⁰³⁾. A more aggressive variant called 'juvenile ossifying fibroma' occurs in the young. Juvenile ossifying fibromata was defined by Reed and Hagy⁽¹¹²⁾ as 'a localised actively growing destructive lesion occurring predominantly in children. It predominantly affects male subjects.

Less than 5% of aneurysmal bone cysts occur in the craniofacial bones⁽¹⁰³⁾. The mandible is involved in 66% of the cases while maxilla only in 33% of cases. Aneurysmal bone cysts in the orbitoethmoid complex is very rare^(113,114). Aneurysmal bone cyst is slightly more frequent in females and develops in about 90% of patients during the first two decades of life^(115,116). Giant cell tumours of the craniofacial bones are rare. The most common sites involved are the sphenoid and ethmoid bones. Osteoblastoma is a benign bone tumour. Clinical presentation can be similar to other fibro-osseous lesions^(103,117).

Inverted papilloma (IP) accounts for 0.5 percent to 4 percent^(118,119) of the surgically removed nasal tumours with an incidence ranging from 0.6 to 1.5 cases per 100,000 inhabitants per year^(120,121). The age at onset ranged from 15 to 96 years old, with the highest incidence was seen in the 5th and 6th decades of life⁽¹²²⁾. The male to female ratio was reported as 2 to 5:1^(123,124). There were no significant racial differences⁽¹²⁵⁾. The duration of symptoms varied from 5 months to 20 years with mean duration of 3.9 years⁽¹²²⁾. The frequency of inverted papilloma in apparently normal bilateral polyps varies between 0.00% and 0.92%. The incidence of inverted papilloma in unremarkable recurrent cases of nasal polyps is rare. This rate is similar to the one observed in patients undergoing first surgery. Age, gender, and number of recurrences did not influence the frequency of this diagnosis⁽¹²⁶⁾. Since multiple sites within the nasal cavities and paranasal sinuses were involved, it is not always easy to determine the location of the origin of inverted papillomas. However, the ethmoid region, the lateral wall of nasal fossa and the maxillary sinus are the most fre-

quent sites of origin of inverted papilloma. The frontal sinus is exceedingly rare (the ethmoid region in 48%, the maxillary sinus in 28%, the sphenoid sinus in 7.5%, the frontal sinus in 2.5%, the inferior turbinate in 2.5%, and the septum in 2.5%)⁽¹²⁵⁾. Inverted papilloma is generally unilateral, bilateral involvement of the sinonasal tract is very rare, reported in less than 1%⁽¹²⁴⁾ to 9%⁽¹²⁷⁾ of patients. The numerous publications on inverted papilloma differ widely in their reported incidence of associated carcinoma, which ranges from 0 to 53 per cent^(128,129). The true population base for these figures is uncertain, given that many series were reported from tertiary centers, where recurrent and problematic cases are likely to be over-represented⁽¹³⁰⁾. Mirza et al.⁽¹³⁰⁾ found that the rates of synchronous and metachronous carcinomatous transformation of inverted papilloma are 7.1 and 3.6 per cent, respectively and 11 per cent malignant transformation in recurrent inverted papillomas after carefully reviewing the literature. The mean time taken to develop a metachronous carcinoma was 52 months (range six to 180 months). Some reports suggest that the development of squamous cell carcinoma in IP is heralded by a reduced cellular apoptosis, which is triggered by human papilloma virus infection⁽¹³¹⁾.

Juvenile angiofibroma (JA) is a rare benign vascular tumour that accounts for 0.5% of all head and neck tumours and its general incidence is approximately 1:150,000^(132,133). In a national retrospective cohort study to estimate the incidence rate of JA in the Danish population, an overall incidence rate of 0.4 cases per million inhabitants per year was found. The median age at diagnosis was 15 years (range 10-24 years), the incidence rate of the population at risk reached 3.7 cases per million⁽¹³⁴⁾. Carrillo et al.⁽¹³⁵⁾ reported that the median age at diagnosis was 18.5 years (range 18-35 years) and all of their patients were males. Only male adolescents were identified. Altogether only 30 female patients have been reported in the literature. It is questionable whether all the previously presented female cases in the literature are in fact JA⁽¹³⁴⁾. In many of the papers, the female cases cannot be further analyzed and could not be decided whether the tumours were angiofibroma or variants of angiofibroma. However, a larger series of 299 JA cases from 6 studies included no female patients⁽¹³⁶⁻¹⁴¹⁾. In spite of the reports of hormonal disorders in patients with JA and the presence of androgen and/or estrogen receptors in tumour tissues, apparently no alterations of hormonal serum levels were observed, and the hormonal influence on JA is still controversial^(142,143). The findings of the partial or complete losses of the Y chromosome and gains of the androgen receptor gene due to gains of chromosome X in the recent genetic analysis of JA indicates an androgen related pathophysiological process in JA⁽¹⁴³⁾.

Schwannomas can occur in all parts of the body but are relatively more frequent in the head and neck region (25-45% of all cases)⁽¹⁴⁴⁾. Approximately 4% of these lesions of the head

and neck involve the nasal and paranasal cavities⁽¹⁴⁵⁾. In the paranasal sinuses they are reported mainly in the nasoethmoid compartment, less frequently in maxillary sinus, septum, sphenoid and frontal sinuses⁽¹⁴⁶⁾. Most cases occur between the second and fifth decade of life; there is no specific association with sex or race⁽¹⁴⁷⁾. There is, by contrast, a very low risk of malignancy for schwannomas; however, in literature there are reports of malignant degeneration in long standing benign schwannomas⁽¹⁴⁸⁾. The risk of malignant transformation rises to 10%-15% in Von Recklinghausen's disease⁽¹⁴⁹⁾.

Lobular capillary hemangioma (pyogenic granuloma) mainly affects the female population, with a peak incidence in the third decade (range 11-65 years)^(150,151). Sinonasal localisation ranges from 7% to 29%, the anterior portion of the nasal septum and the turbinates being the most frequently involved areas^(152,153). Nasal trauma and hormonal imbalances have been postulated as possible etiologic factors⁽¹⁵⁴⁾.

Pleomorphic adenoma is the third most common benign tumour of the sinonasal tract after osteoma and inverted papilloma⁽¹⁵⁵⁾. It usually affects patients in the fifth decade of life, with a slight female predominance. The nasal septum is the most frequently affected site followed by maxillary sinus^(156,157). There are many other benign tumours such as leiomyoma, paraganglioma, hemangioma, myoepithelioma, oncocytoma, etc. Since they occur sporadically in the sinonasal area, the information in the literature to draw conclusions is scarce. However, they share the same epidemiologic profile with other benign tumours. They will not be mentioned separately.

3.2 Malignant Tumours

Sinonasal neoplasms are uncommon neoplasms, they account only for 1% of all malignancies^(158,159) and for 3% of all upper respiratory tract malignancies and accounting for only 3% to 5% of all head and neck malignancies^(160,161). Annual incidence is 0.5-1 new cases /100,000 inhabitants in Italy⁽¹⁶²⁾, whereas relatively high rates for sinonasal malignancies (SNM) were found in Asian and African populations, the highest age-adjusted rates, between 2.5 and 2.6 per 100,000 per annum, occurring in Japanese males⁽¹⁶³⁾. Aytunde reports sinonasal malignancies (SNM) account for 1.57% of all rhinologic diseases in his series. Sinonasal malignancies are more common in males. The male to female ratio is reported between 1.2-2.7/1^(164,165). In the antrum the male:female ratio is 2:1, and in the ethmoid sinus the male:female ratio is 1.4:1. Overall 75% of all malignant tumours occur in persons older than 50 years⁽¹⁶⁶⁾.

The most common sinonasal malignancies are the primary epithelial tumours followed by the non epithelial malignant tumours. In the group of epithelial SNMs the squamous cell carcinoma dominated, and in the nonepithelial SNMs, the most common group was malignant lymphoma. The prevalence of

the different malignant tumours in the literature is extremely variable. The incidence of epithelial SNMs ranges between 52.9% to 91%^(166,167). In a series of 115 patients, Svane-Knudsen (168) reported that 64% had well-differentiated squamous cell carcinomas (SCC), adenocarcinomas, and adenocystic carcinomas. Non-Hodgkin's lymphomas (NHL) and undifferentiated carcinomas represented 9% and 2.6%, respectively. Zbaren et al.⁽¹⁶⁹⁾, in a German series of 216 cases, found 56% to be epidermoid carcinomas and 14% to be adenocarcinomas. Similarly, Haraguchi et al.⁽¹⁷⁰⁾, in 60 Japanese patients, found a predominance of well-differentiated SCCs (25%) followed by melanomas and NHLs (23%) and a small number of undifferentiated carcinomas (5%). On the other hand, in areas where there is a high incidence of nasal-paranasal neoplasms, the histopathological spectrum is different from the one described in low-risk areas. Undifferentiated carcinomas in Chinese high-risk areas (ie, Hong Kong) constitute more than 80% of all nasal-paranasal malignancies⁽¹⁷¹⁾. Incidence, site and histological type can vary in different geographical areas which may be due to occupational, social and genetic factors⁽¹⁷²⁾. For all nose and sinus tumours, the nose is the primary site in 25% and the sinuses 75%, and of all sinus neoplasms 60% to 80% originate from maxillary sinus⁽¹⁶⁶⁾. However, it is not easy to determine the exact site of origin with large tumours. As a result, the tumour distributions in the literature are variable⁽¹⁶⁶⁾.

Squamous cell carcinoma is the most common tumour of the sinonasal malignancies. Approximately 60% to 73% of squamous cell carcinomas originate in the maxillary sinus, 20% to 30% in the nasal cavity, 10% to 15% in the ethmoid sinus, and 1% in the sphenoid and frontal sinuses^(155,165,166). Among the carcinomas of the nose and paranasal sinuses, sinonasal gland carcinomas represent the second most frequent type of malignant epithelial tumour and the paranasal sinuses are the most common site of minor salivary gland involvement⁽¹⁷³⁻¹⁷⁶⁾. Adenoid cystic carcinoma (ACC) accounts for fewer than 1% of all head and neck malignancies and 10% of all salivary gland neoplasms^(176,177). Lupinetti et al.⁽¹⁷⁸⁾ reported that most patients were Caucasians (72.4%), non-smokers (48.4%), and non-drinkers (74.4%) in their ACC series. Sinonasal ACC accounts for 10% to 25% of all head and neck ACC⁽¹⁷⁶⁾. The maxillary sinus (47%) and the nasal cavity (30%) were the most common primary tumour sites. ACC has a propensity for perineural spread and bony invasion, which can lead to significant skull base involvement and intracranial extension⁽¹⁷⁸⁾.

Adenocarcinoma is the third most common mucosal epithelial malignancy found in this area, after squamous cell carcinoma and adenoid cystic carcinoma⁽¹⁷⁹⁾, and represents approximately 8% to 15% of all sinonasal cancers^(180,181). The incidence is less than 1 case per 100,000 inhabitants per year⁽¹⁸²⁾, occurring predominately among men with a mean age of presentation of 60 to 65 years⁽¹⁸³⁾. However, in the northern part of Spain, the incidence is 0.19 cases/100,000 inhabitants per year⁽¹⁸⁴⁾. The

median age of onset lies between 50 and 60 years⁽¹⁸³⁾ and in wood dust related tumours even earlier⁽¹⁸⁵⁾. Men develop adenocarcinoma four times more frequently than women, reflecting the occupational hazard implicated⁽¹⁸⁶⁾. It is located most frequently (85%) in the ethmoid sinus and the upper part of the nasal cavity. One study using endoscopic endonasal surgery showed that woodworkers' adenocarcinomas constantly originated in the olfactory cleft, appearing as polyp-like neoplasms with well-defined bodies⁽¹⁸⁷⁾. Nasal adenocarcinoma on sinus CT scans showing a unilateral expanding opacity of the olfactory cavity should raise the suspicion of nasal adenocarcinoma⁽³⁴⁾. It only exceptionally arises in other sites of the nasal cavity (maxillary sinus in 10%) and these cases are usually not related to wood dust exposure⁽¹⁸⁸⁾.

The association between wood dust exposure and adenocarcinoma of the sinuses is also well established. It is estimated that woodworkers have 500 times elevated risk compared to the male population and up to 900 times compared to the population in general⁽¹⁸⁵⁾. It has been shown that the true risk factor is the actual exposure to wood dust particles, and not the possible exposure to chemical products used in the industry, such as polish, varnish or protectors⁽¹⁸⁵⁾. Hard wood types as ebony, oak and beech confer the highest risk of developing sinonasal adenocarcinomas⁽¹⁸⁹⁾, increased further by inhalation of formaldehyde or substances normally used in this type of industry⁽¹⁹⁰⁾. The strong relation of adenocarcinoma to exposure to wood dust makes it a disease almost exclusive to carpenters and furniture makers. Therefore, in many countries (Australia, Germany, Great Britain, Belgium, France, etc.), it is considered an industrial disease^(189,191-194). The furniture makers who are likely to be exposed to the fine wood dusts of threshold $>5\text{mg}/\text{m}^3/\text{day}$ are at greater risk^(167,195,196). Many findings indicate a dose-response relationship^(190,197,198), with a higher incidence of tumours occurring among workers exposed for longer periods. Recent studies have shown that even short periods of exposure (< 5 years) can lead to an increased risk of carcinoma. In general, the normally long latency period is estimated at 40 years⁽¹⁹⁹⁾, although it can range between 20 and 70 years⁽¹⁹⁵⁾. Despite this clear etiology, it is still unknown by what molecular mechanism sinonasal adenocarcinomas develop. Because wood dust does not have mutagenic properties, it is hypothesized that prolonged exposure to and irritation by wood dust particles stimulate cellular turn-over by inflammatory pathways^(186,200).

Sinonasal mucoepidermoid carcinoma accounts for 0.6% of all salivary tumours and 4.8% of all mucoepidermoid carcinomas. The most common site is maxillary antrum followed by nasal cavity, nasopharynx and ethmoid sinuses in order of decreasing frequency^(163,201). Thorium dioxide, when used as an imaging agent, may cause antral squamous and mucoepidermoid carcinomas⁽¹⁶⁶⁾. Although no other definitive risk factors for mucoepidermoid carcinoma have been identified, minor trau-

ma and chronic irritation have been implicated in the etiology of sinonasal tract cancers in general⁽²⁰²⁾. Acinic cell carcinomas account for approximately 1% of salivary gland tumours and 10% to 15% of all sialocarcinomas⁽²⁰³⁻²⁰⁶⁾. Acinic cell carcinomas are found predominantly in the parotid gland and are somewhat unusual in other locations⁽²⁰³⁻²⁰⁶⁾. In the sinonasal tract, acinic cell carcinomas are extremely rare⁽²⁰⁷⁻²¹⁰⁾. To date, only 11 cases of sinonasal acinic cell carcinoma have been described in the English-language literature⁽²¹¹⁾. Acinic cell carcinomas are most common in the fifth and sixth decades of life but are seen in patients of all ages, including children⁽²⁰³⁻²⁰⁶⁾. In the sinonasal tract, the ages in reported cases range from 42 to 76 years (median, 59 years). There is a discrepancy in the literature about whether acinic cell carcinomas occur more often in men or women in general; however, there is no sex related difference in the occurrence of sinonasal acinic cell carcinomas^(203,205).

Relative risk rates for sinonasal epithelial malignancies have been determined for several chemical agents (chromates, nickel compounds, isopropyl alcohol, and mustard gas) and for several occupations (i.e. nuclear refinery work, leather work in boot and shoe manufacturing, chrome pigment work, metal-worker, textile worker, construction worker, bakers, flour milling and farmer) even in the apparent absence of causal agents⁽²¹²⁾. Reported increased risks to different industries were reported as follows: the metal industry (relative risk ranging from 3.1 to 5.9), the textile industry (ranging from 2.9 to 17.0), the mining and construction industry (ranging from 2.3 to 5.3), and the agricultural industry (ranging from 1.9 to 3.3)⁽²¹²⁾. Among women, exposure to textile dust was associated with an elevated risk of squamous cell carcinoma and adenocarcinoma. For squamous cell carcinomas, the risk increased with the duration and the level of exposure. The risks associated with the different types of textile fibers (cotton, wool, and synthetic fibers) were similar and the results did not permit to incriminate a particular type of textile⁽²¹³⁾. Thorium dioxide, when used as an imaging agent, causes antral squamous and mucoepidermoid carcinomas⁽¹⁶⁶⁾.

Smoking is associated with an elevated risk of nasal cancer, especially squamous cell carcinoma of the maxillary antrum^(165,166,214). However, some reports did not find any increased risk for sinonasal tract malignancies associated with tobacco and alcohol⁽²¹⁵⁾. Since no persuasive evidence was found that smoking is an etiologic factor in sinonasal carcinoma, further research is needed.

Since the early 1980s, when evidence was provided on the possible involvement of human papilloma virus (HPV) in the aetiology of both benign respiratory papillomas and squamous cell carcinomas, a substantial number of studies have explored this issue and its deoxyribonucleic acid has been found in both the inverted papilloma and the cells of neighbouring, apparently

normal mucosa⁽²¹⁶⁾. The current evidence linking HPV to at least a proportion of benign sinonasal papillomas is convincing. Syrjaenen⁽²¹⁷⁾ based on the analysis of over 1,000 such lesions, reported that HPV-6 and HPV-11 is present in one third (33.3%) of inverted papillomas and this detection rate is higher than most other reported extragenital papillomas, except those of the larynx and bronchus. Tang et al.⁽²¹⁸⁾ detected human papilloma virus in up to 86% of inverted papilloma cases. The 2005 International Agency for Research on Cancer evaluation on the carcinogenicity of HPV in humans⁽²¹⁹⁾ concluded that there is sufficient evidence for the carcinogenicity of HPV in the oral cavity and oropharynx, limited evidence in the larynx, and inadequate evidence in sinonasal cavities⁽²²⁰⁾. However, some previous reports have suggested a possible implication of HPV in the development of several carcinomas of the sinonasal region^(217,221,222). In 1993, Kashima et al.⁽²²³⁾ found human papillomavirus (HPV) positive in 4% of squamous cell carcinomas. Alos et al.⁽²²⁰⁾ detected HPV DNA in tumour tissue of 20% of sinonasal squamous cell carcinoma patients. The tumours affected predominantly men by a proportion of approximately 3:1; no significant differences in sex and age were found between HPV-positive and-negative groups. There were no significant differences in tumour stage at presentation. Despite the similar clinical characteristics and staging at presentation, patients with HPV-positive tumours had a significantly better prognosis than those with HPV-negative neoplasms⁽²²⁰⁾. Syrjaenen⁽²¹⁷⁾ showed that 21.7% of sinonasal carcinomas analysed were positive for HPV. Low risk HPV types 6 and 11 are usually confined to benign lesions, whereas the reverse is true for the oncogenic HPV types 16 and 18; and the presence of squamo-columnar junctions and squamous cell metaplasia in the sinonasal system⁽²¹⁷⁾. The discrepancies reported by several studies might result in part from technical reasons, but it is also possible that sinonasal lesions have a heterogeneous aetiology (HPV related and non-related) and/or that some novel (yet unidentified) HPV types exist in these lesions, which are detected by some studies but not by others.

Primary sinonasal tract mucosal malignant melanomas are rare, accounting for between 0.3% and 2% of all malignant melanomas and about 4% of head and neck melanomas⁽²²⁴⁻²²⁸⁾. The head and neck represents the most common site of mucosal malignant melanoma with a suggested incidence of about 0.018/105 to 0.051/105 per year^(225,229,230). Sinonasal tract mucosal malignant melanomas represents up to 4% of all sinonasal tract neoplasms^(226,229,231). In the National Cancer Data Base report by the American College of Surgeons Commission on Cancer and the American Cancer Society of more than 84,000 melanomas seen from 1985 to 1994⁽²²⁴⁾, only 1.3% were melanomas that arose from mucosal surfaces, of which 55% were of the head and neck. Sinonasal tract mucosal malignant melanomas were found to be equally common in men and women. A higher proportion of melanoma was identified in black patients (10.4%)⁽²³²⁾. In general, the mean age

for sinonasal tract mucosal malignant melanomas (64.3 years) is later in life than cutaneous malignant melanomas. Sinonasal tract mucosal malignant melanomas is a more lethal disease in patients older than 60 years, a finding similar to cutaneous melanoma⁽²³²⁾. Tumours originating in the sinuses are less common than those arising in the nasal cavity, but sinus tumours may grow asymptotically until late in the disease course^(231,233). A third of patients had neck metastases, which often preceded distant metastasis, and distant metastasis always were rapidly fatal⁽²³⁴⁾.

The incidence of olfactory neuroblastoma was found 0.4 cases/million inhabitants per year⁽²³⁵⁾. The incidence of olfactory neuroblastoma is difficult to establish, but the tumour is not as rare as is commonly reported and probably represents more than 5% of all nasal malignant tumours⁽²³⁵⁻²³⁷⁾. Olfactory neuroblastoma occurs over a wide age range (3–90 y), with a bimodal peak in the second and sixth decades of life⁽²³⁸⁻²⁴⁰⁾. Occasional cases have also been reported in children younger than 10 years^(168,237). Olfactory neuroblastoma affects male and female patients with similar frequency and can be found in all age groups^(237,241). No known cause exists for this tumour⁽²⁴²⁾, although diethylnitrosamine injections can induce tumours in hamsters at the site of the olfactory epithelium⁽²⁴³⁾. No hereditary patterns have been described for this neoplasm, and there is no apparent racial predilection⁽²³⁸⁾.

Extrapulmonary neuroendocrine carcinomas (SNEC) only account for 4% of all SNECs⁽²⁴⁴⁾, and very few cases of SNECs of head and neck have been reported previously⁽²⁴⁵⁾. Less than 250 cases of head and neck SNEC have been published so far, including 48 cases of SNEC in the nasal and paranasal cavities^(246,247). The majority of patients with SNEC of the head and neck are male. Although there seems to be an association with cigarette smoking, the association is not as strong as that with pulmonary SNEC^(248,249). Although the neoplasm has been described at any age between 16 and 77 years, the prevalent distribution is in the fifth and sixth decade^(250,251). No particular risk factors for this tumour appears to have been identified^(247,252,253).

Although tumours of this type occur in a variety of organs and sites, small cell undifferentiated carcinoma (ScCC) of the sinonasal tract is a rare malignancy, with the reported series all having fewer than 10 patients⁽²⁴⁸⁾. In the M.D. Anderson series of neuroendocrine tumours, there were only 7 cases of small cell carcinoma⁽²⁵⁴⁾. The paucity of well-documented cases precludes generalization about the clinical features. Within this limitation, the mean age at presentation is approximately 50 years (range 26–77 years), and there is no sex predilection. Anatomic sites include the nasal cavity, ethmoid sinuses, and maxillary sinus⁽²⁵⁵⁾.

Sinonasal undifferentiated carcinoma (SNUC) is a rare tumour, with fewer than 100 reported cases in the world literature⁽²⁵⁶⁾. There is a male predominance (2–3:1). The age range is broad, usually ranging from the third to ninth decades; the median age at presentation is in the sixth decade⁽²⁵⁷⁻²⁵⁹⁾. There are no known etiologic agents. SNUCs are typically negative for Epstein–Barr virus (EBV)⁽²⁵⁸⁻²⁶⁰⁾. Some cases have been reported to develop following radiation therapy for nasopharyngeal carcinoma⁽²⁵⁸⁾.

The annual incidence of the Ewing's Sarcoma Family of Tumours (ESFT) in the United States is 2.1 cases per million children, and they account for approximately 2% of all cancers in children and young adults⁽²⁶¹⁾. ESFT is more common in male than in female patients and has a greater incidence in white and Hispanic children than in black or Asian children^(262,263). ESFT is not felt to be inherited and is not associated with any cancer syndromes. In 95% of cases, at (11;22)(q24;q12) translocation is detected⁽²⁶⁴⁾. Sinonasal tract involvement is extremely rare, with about 50 cases reported in the English literature. Most of them were observed in the maxillary sinus, whereas less than 10 cases each involved the ethmoid and nasal fossa [also known as PNET- primitive neuroectodermal tumour].

Hemangiopericytomas are unusual vascular tumours, which accounts for only 1% of all vascular neoplasms and for 3%–5% of sarcomas⁽¹⁷⁹⁾. They rarely occur in the paranasal sinuses and nasal cavity. The rate of head and neck involvement ranges between 15% and 25%, with sinonasal tract localisation present in 5% of patients⁽¹⁷⁹⁾. Ethmoid, nasal cavity and sphenoid sinus are the preferential sites of origin⁽²⁶⁵⁾. Although the tumour affects all ages, they occur most commonly in adults in the sixth and seventh decades of life^(266,267). No gender predominance is reported^(267,268). Trauma, steroid therapy, and altered hormone secretions are proposed as predisposing factors^(269,270).

Sarcomas of the head and neck are rare tumours, accounting for 4–10% of all sarcomas⁽²⁷¹⁻²⁷⁴⁾ and fewer than 1% of all malignancies of the head and neck region^(275,276). Sarcomas of the sinonasal tract make up for about 15% of sinonasal tumours⁽²⁷⁷⁾. Oral and maxillofacial sarcomas present at any age from 5 months to 77 years (mean 42) and male to female ratio of 3:1 with predilection for the mandible.1,2. The mean age and male: female ratio in Africa is lower than in Western series⁽²⁷⁸⁾.

Osteosarcoma is a rare bone tumour that occurs primarily in long bones. Overall incidence is 1:100,000 inhabitants per year, and 6–13% of cases occur in the head and neck region⁽²⁷⁹⁾. Osteosarcoma had peak prevalence in the third decade with equal gender distribution. The occurrence in the paediatric age is very rare⁽²⁸⁰⁾. In the maxillofacial region, it tends to occur a decade later than in long bones. Osteosarcoma accounts for 0.5%–1% of all sinonasal tract tumours⁽²⁸¹⁾. In children with

osteosarcoma, about 3% carry a germ line mutation in p53, with the majority of these having a family history suggesting Li-Fraumeni syndrome⁽²⁸²⁾. The incidence of osteosarcoma has been increasing by about 1.4% per year for the past 25 years⁽²⁸³⁾. The etiology of osteosarcomas remains unknown. Bone abnormalities and diseases as Paget's disease of bone, fibrous dysplasia, myositis ossificans, other hereditary pathologies like retinoblastoma, Li-Fraumeni syndrome, and previous chemotherapy and irradiation for other malignancies have been suggested as specific risk factors^(284,285).

Rhabdomyosarcoma is the most frequent soft tissue sarcoma in the paediatric age, accounting for up to 75% of all child sarcomas and 6% of all paediatric cancers. The embryonal subtype is the most common. Mesenchymal rhabdomyosarcoma is rare and the head and neck region is the most commonly involved site (37%)⁽²⁸⁶⁾. Occurrence of head and neck rhabdomyosarcoma in adults is rare. Only 10% of all soft tissue tumours and 1% of all neoplasms in the sinonasal tract are rhabdomyosarcomas⁽²⁸⁷⁾. Sinonasal tract localisation is present in about 8% of all adult age rhabdomyosarcomas⁽²⁸⁸⁾.

Chondrosarcoma make up only 10–20% of malignant primary bone tumours, with 5–10% located in the head and neck. Maxillary sinus is the most frequently involved site^(289,290). In the skull base, chondrosarcomas typically occur at the petroclival synchondrosis. The lesion is commonly diagnosed in the sixth decade. The paediatric population is rarely affected. There is no gender predominance⁽²⁸⁸⁾. However, in some reports it is more frequently seen in males^(278,291). The etiology of chondrosarcomas remains unknown. Meanwhile, associated conditions include multiple hereditary exostosis, Ollier's disease, Maffucci's syndrome, previous intravenous thorium dioxide contrast use, Paget's disease of bone, chondromyxoid fibroma, and previous irradiation⁽²⁹²⁾.

Leiomyosarcoma is rare in the oro-facial region⁽²⁷²⁾ and accounts for approximately 7% of all soft tissue sarcomas. It comprised the fourth most common sarcoma, mainly in the maxilla, and with a 5:1 male:female ratio⁽²⁷⁸⁾. Sinonasal tract localisation is rare with about 40 cases reported in the literature⁽²⁹³⁾.

Fibrosarcoma with mandibular predominance and equal sex distribution was the fifth most common sarcoma. Liposarcoma, fibromyxosarcoma, neurofibrosarcoma, ameloblastic sarcoma and synovial sarcoma are rare^(272,278).

Sinonasal lymphomas, either primary or secondary are mostly non-Hodgkin lymphomas and are the second most common malignant tumours following carcinomas occurring in the sinonasal tract. Non-Hodgkin lymphomas are classified into B and T-NK subtypes according to lymphocytic phenotype^(155,294). There is a difference in incidence, epidemiology, and

cell type between Western and Asian countries. In Western countries, lymphomas are infrequent and sinonasal tract involvement varies between 0.2%–2% of all non-Hodgkin lymphomas⁽²⁹⁵⁾. They constitute 5.8 to 8% of the extranodal lymphomas arising in the head and neck area^(294,296). B-cell lymphomas are predominant and tend to affect paranasal sinuses in the elderly^(155,294). In Asian and South American countries, the incidence of non-Hodgkin lymphomas of the nasal region is much higher than in the United States and they account for 2.6 to 6.7% of all lymphomas and are the second most frequent group of extranodal lymphomas after gastrointestinal lymphomas. T or NK cell lymphomas are predominant and the nasal cavity is mainly involved in younger people^(297,298). Epstein-Barr virus is considered important in the etiopathogenesis of lymphomas, especially for specific lymphomas such as Burkitt lymphoma and nasal NK-T lymphoma. In Asian countries, the prevalence of EBV-positive T-cell lymphomas is similar to the prevalence of EBV virus infection and differ from the findings of the more common EBV-negative B-cell nasal lymphomas in the United States. These findings suggest that EBV plays a role in the development of nasal T-cell lymphomas and that the incidence of EBV infection may explain the reported “East-West” difference in the incidence of nasal T-cell lymphomas^(155,294,297).

Most of the malignant tumours of the sinonasal regions are primary in origin. Metastasis of malignant tumours to the sinonasal area occurs infrequently and usually presents at the late stage of primary disease. More than 50% of sinonasal metastases take origin from a renal carcinoma⁽²⁹⁹⁾. Other most common primary sources in decreasing order after the kidney, are lung (12%), urogenital ridge (12%), breast (9%), and gastrointestinal tract (GI tract) (6%)⁽³⁰⁰⁾. The most common metastatic sites are the maxillary sinus (50%), followed by the ethmoid sinus (18%) and nasal cavity (15%)⁽²⁹⁹⁻³⁰²⁾. However, some reports from East Asia are very different when compared with European and North American reports. Different incidences of malignant neoplasms in the primary site may explain the result of different incidences of sinonasal metastatic tumour⁽³⁰³⁾. Although the mean age of patients with sinonasal metastases varies in different primary origins, the highest incidence is in the sixth decade in men and the seventh decade in women⁽³⁰⁴⁾.

It is more appropriate to consider chordomas as low-grade malignancies with the potential for metastasis. Chordomas are slow-growing, locally aggressive tumours. Approximately 25% of chordomas arise in the clivus and constitute about 0.15% of all primary intracranial neoplasms⁽³⁰⁵⁾. The ages of the patients ranged from 4 to 76 years, with a predominance for the third and fourth decades in intracranial localizations⁽³⁰⁶⁾. The male-to-female ratio is reported 2:1 by Weber et al.⁽³⁰⁷⁾ and 2:3 by Stippler et al.⁽³⁰⁶⁾. No associations with irradiation or any other environmental factors has been observed. A small percentage of cases have a familial pattern of inheritance⁽³⁰⁸⁾.

4. Diagnosis

4-1 Clinical

Tumours affecting the sinonasal region and skull base usually present late as their presenting symptoms are often banal and therefore, overlooked by patients and their clinicians, particularly in primary care where these conditions are rarely encountered. The recent onset of unilateral nasal symptoms, which do not improve with a short course of medical therapy should prompt referral for specialist assessment. Orbital and neurological symptoms should generally be referred *ab initio*.

4-2 Imaging

Imaging studies play a key role in pretreatment assessment and preoperative planning of benign and malignant lesions involving the sinonasal tract, nasopharynx, and adjacent skull base. Computed tomography (CT) and magnetic resonance imaging (MRI) are used in a complementary fashion when characterizing tumours in this region to accurately assess their loco-

regional extent including any bone and neurovascular extension or nodal involvement. They are also of paramount importance in intraoperative guidance and post-operative surveillance. These anatomic areas are very complex and understanding the radiological features typical of the different pathologies requires a thorough knowledge of anatomy. For the sake of clarity, the present review will separately analyze pre-treatment assessment, intra-operative evaluation, and post-operative surveillance.

4-2-1 Pre-treatment evaluation

The aims of imaging are to distinguish tumour from inflammatory reactions and secretions, elucidate the nature of the tumour (benign vs. malignant), and map its extent⁽³⁰⁹⁾. These goals are best achieved by MR. However, CT is the first investigation commonly obtained in a patient with symptoms suggesting a disease involving the sinonasal tract and/or the adjacent skull base. Apart from patients with fibro-osseous lesions, where CT can properly define the nature of the lesion and its

Table 4-1. Clinical features by site of origin.

Primary Site	Symptoms
<i>Nasal cavity:</i>	
- inferiorly into palate	nasal blockage, bleeding, discharge, hyposmia
- posteriorly into nasopharynx and eustachian orifice, compression of eustachian tube	mass, ulceration, fistula middle ear effusion/deafness
- antero-superiorly into the nasal bone	glabellar mass
- externally into skin	mass/ulceration
- superiorly into anterior cranial fossa	minimal, personality change?, headache, neurological deficit cerebrospinal fluid leak / meningitis (rarely)
<i>Maxillary sinus</i>	
- medially into nasal cavity	<i>as above</i>
- anteriorly into cheek directly or via infraorbital canal	mass, ulceration of skin, paraesthesia
- posteriorly into pterygoid region and infratemporal fossae	trismus and pain
- inferiorly into the palate or alveolar ridge	mass, loosening of the teeth, malignant oro-antral fistula
- superiorly into orbit	proptosis, diplopia
<i>Ethmoid sinuses</i>	
- medially into nasal cavity	<i>as above</i> , can cross to contralateral side
- inferolaterally into maxilla	mucus retention
- medially into orbit	proptosis, chemosis, diplopia, visual loss, epiphora
- superiorly into the anterior cranial fossa	minimal, personality change?, neurological deficit, cerebrospinal fluid leak/meningitis (rarely)
<i>Frontal sinus</i>	
- anteriorly	mass on forehead or glabella
- posteriorly into anterior cranial fossa	<i>as above</i>
- inferiorly into nasal cavity, orbit	<i>as above</i>
- medially to contralateral side	nil of note till breaches confines of sinus

borders, the other lesions require an MR with gadolinium enhancement. This should include high-resolution (3 mm) T1-weighted and T2-weighted images of the sino-nasal tract, orbit, skull base, and the adjacent intracranial compartment, acquired in the axial, coronal, and sagittal planes. Fat-saturated T1-weighted techniques are usually included to identify the presence of disease beyond the paranasal sinuses (i.e., perineural spread or intracranial extension)⁽³¹⁰⁾. Additional sequences, to be used in selected conditions, include the following: 1) MR cisternography with heavily T2-weighted (3DFT-CISS, DRIVE) thin sections (0.6 mm or less), a technique, which has been advocated⁽³¹¹⁾ to determine the relationships of tumour with cisternal cranial nerve segments; 2) high resolution GE sequences with sub-millimetric isotropic slices (FIESTA; VIBE) to image the intraforaminal segment of cranial nerves⁽³¹²⁾; 3) FLAIR (fluid-attenuated inversion recovery), which helps in differentiating CSF from the cystic/fluid content of tumours or secondary mucocoeles abutting the skull base; 4) MR angiography, which enables a detailed visualisation of the entire course (or segments) of internal carotid artery (ICA).

Sinonasal tract and anterior skull base

Benign tumours of the sinonasal tract and anterior skull base are rare. Osteomas are the most frequent but many are diagnosed by chance and do not require surgery. Papillomas (inverted, oncocytic, fungiform) are the most common indication for surgery. CT commonly shows a space-occupying lesion with low/moderate bone resorption involving the ethmoid-nasal complex and/or the maxillary sinus. While the possibility of characterizing the lesion based on CT imaging is quite low, the endoscopic appearance may be highly suggestive. MR has the well known advantage over CT to differentiate inflammatory changes from the lesion and to identify the so-called “cerebriform” or “columnar” pattern, which is evident on T2 and contrast-enhanced T1 sequences and reflects the histological architecture of the lesion. The loss of the cerebriform pattern may be a sign of a concomitant carcinoma, which is usually associated with a more extensive bone erosion. The finding on CT of focal hyperostosis or osteitic changes^(313,314) as indicators of the area of origin of the lesion, can also be appreciated on MR⁽³¹⁵⁾.

Juvenile angiofibroma (JA) originates from the pterygo-palatine fossa but at an early stage tends to involve the adjacent sino-nasal cavities. Submucosal growth and invasion of the cancellous bone of the basisphenoid are distinct features that are easily identified by enhanced CT or MR⁽³¹⁶⁾. “Finger-like projections” with sharp and lobulated margins are the hallmark of JA growth in the soft tissues and along canals and foramina of the skull base. Intradiploic spread of the lesion can be better differentiated from normal medullary content on MR by combining a plain T1 with a post-contrast T1 without or with fat-saturation⁽³¹²⁾. Furthermore, the presence of several signal voids within the lesion on both T1 and T2 sequences, indicat-

ing major intra-lesional vessels, corroborates a diagnosis of JA.

In intermediate/large-size JA pre-operative assessment includes angiography, which provides a detailed map of the lesion’s vascular supply, showing connections with the external and occasionally internal carotid artery and the vertebral arteries and branches of the contralateral carotid system. This examination is commonly performed concomitantly to embolisation, which has the intent of decreasing intraoperative bleeding. While the currently available methods of embolisation provide excellent devascularization of feeders coming from the internal maxillary artery and its branches as well as from the ascending pharyngeal artery, control of major vascularization from the internal carotid artery is demanding. Devascularization by direct tumour puncture and embolisation is associated with an unacceptable risk of major neurologic complications⁽³¹⁷⁾ and has been therefore abandoned. In case of encasement of the internal artery, which is indeed a very rare event, the balloon occlusion test and sacrifice of the ICA or, as a less invasive procedure, stenting of the intratemporal carotid artery may be considered.

Olfactory groove meningioma typically presents as an extra-axial, durally based lesion involving the anterior skull base. Characteristic MRI features are isointensity to slight hypointensity on T1-weighted images; the appearance on T2-weighted images is variable. Homogenous enhancement is invariably obtained after contrast agent administration, even when the lesion is densely calcified. Specific information required for planning surgery includes defining the relationship of the lesion with neurovascular structures, especially the anterior cerebral arteries and their branches, and the presence of subpial invasion, suggested by an increased signal on flair MR sequences⁽³¹⁸⁾.

The key issues in imaging patients with a malignant tumour of the sinonasal tract are mapping of anterior skull base and orbit involvement, and assessment of perineural spread. All these goals are better achieved by MR than with CT. One crucial point when assessing anterior skull base involvement is analysis of the signal intensity at the interface between the ethmoid and brain: the cribriform plate with its double periosteal layer; the dura mater and the subarachnoid space. On enhanced T1 or fat saturated T1 (VIBE), the three layers compose a “sandwich” of different signals. When a neoplasm abuts against the cribriform plate without interrupting the hypointense signal, the lesion should be considered extracranial. Effacement of the hypointense signal lower layer by tumour implies bone-periosteum penetration. In this case, if an uninterrupted thickened and enhancing dura is visible, the neoplasm may be defined as intracranial-extradural. Conversely, focal or more extensive replacement of enhanced thickened dura by tumour signal indicates intracranial-intradural extension. Brain invasion is suggested by the presence of edema⁽³¹²⁾.

Displacement and distortion of orbital walls are frequently observed in both ethmoid and maxillary cancers. The presence of these findings does not necessarily imply that the patient requires a clearance of the orbit, which is a mutilating operation indicated only when tumour breaches through the periorbita. Though definitive assessment of the integrity of this structure is obtained in most cases intraoperatively, information provided by MR may be relevant for surgical planning and informed consent discussion⁽³¹²⁾. When a thin and regular hypointensity is still visible on T2 images between tumour and orbital fat, the periorbita should be considered intact⁽³¹⁹⁾.

Perineural spread is typically observed in adenoid cystic carcinoma and more rarely in squamous cell carcinoma, lymphoma, and melanoma. MR can correctly predict the presence of perineural spread with 95% sensitivity but can only map the entire extent of spread in around 60% of cases⁽³²⁰⁾. Apart from nerve enhancement and nerve enlargement, which are signs more predictive of perineural spread⁽³¹²⁾, there are other suggestive features: enlargement or, less frequently, destruction of skull base foramina, obliteration of fat planes around a nerve or within a foramen, replacement of the normal CSF signal within Meckel's cave, and convexity of the lateral cavernous sinus wall. The use of high-spatial resolution post-contrast fat saturation VIBE permits a detailed evaluation of skull base foramina without artifacts with special reference to the discrimination between the nerve and surrounding vascular plexus⁽³¹²⁾.

Although all malignancies of the sinonasal tract share similar imaging features, there are some specific findings that can help in characterizing the lesion. For instance, olfactory neuroblastoma, which more commonly has the epicenter in the upper nasal cavity and/or adjacent ethmoid cells, may present a marginal cyst in the intracranial component or hyperostosis of adjacent bones. MR features of chondrosarcoma reflect the presence of chondroid avascular matrix surrounded by a more vascularized peripheral growing tissue. On T2 sequences, the chondroid matrix is hyperintense because of high water content, while ossified or cartilaginous areas appear hypointense. Gadolinium administration results in enhancement of the vascularized peripheral rim, which contrasts with the non-enhancing chondroid matrix. Other than perineural spread, there are two other patterns of spread that can suggest a diagnosis of adenoid cystic carcinoma: subperiosteal bone invasion and extent into fat spaces⁽¹⁵⁵⁾.

Planum, tuberculum, and sella

A series of different lesions can be observed in these areas: meningiomas, craniopharyngiomas, and pituitary adenomas. Understanding the relationship of the lesion with the pituitary stalk, optic chiasm, ICA, cavernous sinus, middle and anterior cerebral arteries is crucial for establishing the feasibility of an endoscopic approach. This information is best obtained by MR.

The most typical MR finding for craniopharyngioma is a heterogeneous suprasellar-sellar signal mass containing a cystic component, well defined, with internal uniform signal, hyperintense on both T1 and T2 sequences. However, a variety of different MR patterns may be present, including solid, calcified, CSF-like, hematin-like, and protein-like signals. A solid component is also invariably present, often partially calcified⁽³²¹⁾.

Regardless of their size, pituitary adenomas share some common MR findings. T1 sequences are the most appropriate to identify these lesions, which are generally hypointense and to discriminate them from the adjacent normal parenchyma, which, unless completely compressed, is more hypointense. On T2 sequences, hyperintensity is more commonly observed in macroadenomas⁽³²¹⁾. According to Iuchi et al.⁽³²²⁾, high T2 signal suggests a soft tumour and, therefore, better predicts respectability.

Clivus

Chordomas and chondrosarcomas are the most frequently encountered clival lesion. The MR appearance of chordoma varies in relation to the histologic pattern of the lesion. In a rather high percentage of cases, MR shows heterogeneous hyperintensity on T2, with possible dark areas reflecting the presence of mucoid or old hemorrhagic areas, respectively. Soft tissue components show iso to hypointensity on T1, and variable degrees of contrast enhancement. Sagittal plain T1 sequences are particularly useful, as the hypointense tumour tissue replacing the hyperintensity of the clival bone marrow can be clearly seen. Some of the typical features of chondrosarcoma have been previously reported. It is noteworthy that calcifications largely vary, ranging from small and scattered to large, dense, and diffuse.

Petrous apex

Lesions in this area include chordomas, chondrosarcomas, and extensions of petroclival meningiomas and nasopharyngeal carcinomas. Among benign lesions the most frequently encountered is cholesterol granuloma, which appears hyperintense in both T1 and T2 sequences and does not enhance after contrast medium administration. A peripheral hypointense rim on both T2 and T1-weighted images, due to expanded cortical bone and hemosiderin deposits, can be observed⁽³²³⁾. Assessment of the relationship with ICA is critical to select the proper corridor of endoscopic access.

4-2-2 Intraoperative evaluation

The development of image-guided systems (optical and electromagnetic) has enabled sinus/skull base surgeons to monitor the position of surgical instruments, based on a pre-operative CT scan, and to navigate the skull base and the sino-nasal cavities with more precision. Recent updates include the integration of CT angiography and CT and MR fusion techniques into

image-guided systems⁽³²⁴⁾. However, these systems do not provide a real-time update of intraoperative findings. This limitation may lead the surgeon to underestimate the risk of injuring vital structures, as in the case of tumour lesions of the sphenoid massively eroding bone and laterally displacing internal carotid arteries (ICA) or optic nerves (ON). In such instances, removal of the lesion starts along the midline and invariably results in medialization of the ICA and ON, which is obviously not recorded by the system and may be misleading for the surgeon. These problems have been overcome with the advent of intraoperative imaging. Imaging data are acquired during surgical procedures and subsequently uploaded in the navigation system. The ideal requirements for intraoperative imaging include portability, rapid image acquisition, compatibility with commercially available image-guided surgery systems, and patient safety. Although both CT and MR may be used for intraoperative imaging, CT is more commonly accepted⁽³²⁵⁾.

Cone beam CT (CBCT), which has been extensively used in the dental and oral surgery fields for in-office examination, is gaining popularity even in otorhinolaryngology for both office

and intraoperative diagnosis. In comparison to standard CT, CBCT permits the structure of interest to be imaged within a single rotation with a subsequent decrease in time and radiation exposure. One limitation of CBCT is some loss of quality in soft tissue imaging, which can hinder the differentiation between fluid in the dissected cavities and polyps, inflamed mucosa, or retained secretions⁽³²⁵⁾. Endoscopic findings may obviously help the surgeon to overcome this limitation.

Apart from the cost of a high-field MR, which is the major drawback in comparison to CT, interventional MRI still requires dedicated operating rooms and instrumentation compatible with the magnetic field generated by the coils. Introduction of portable MR will undoubtedly contribute to its more common use.

4-2-3 Postoperative surveillance

Postoperative surveillance, mainly based on MR studies, is aimed at detecting residual/ recurrent lesions and possible complications (i.e., mucocoele). Understanding the radiologic features of the healing process in a large surgical cavity created

Table 4.2. Malignant sinonasal tumours. Pre-treatment imaging.

Tasks	CT	Standard MR	Study planes	Additional MR sequences
To distinguish tumour from retained mucus	Adequate, though less sensitive than MR. (3 mm slice thickness better than 1 mm)	TSE T2 weighted sequences are indicated. (slice thickness 3 mm)	Axial and coronal planes	FLAIR sequence to differentiate CSF from the cystic/fluid content of tumours or mucocoeles
To assess periorbital invasion	Bone erosion precisely shown by CT. The periorbital is not usually distinguished from tumour signal. (slice thickness 1 to 2 mm)	SE T1 and TSE T2-weighted sequences are indicated. Periorbital can be more easily separated from tumour signal. (slice thickness not > 3mm)	Axial and coronal planes	STIR (orbital fat signal suppressed) may be used to increase detection of orbital fat infiltration.
To assess dura mater invasion	Though skull base erosion is precisely shown by CT, only large dura breakage is detected. Contrast enhancement is required. (slice thickness 1 to 2 mm)	TSE T2 and post-contrast SE T1-weighted sequences are indicated. (slice thickness not > 3mm)	Axial, coronal and sagittal planes	
To assess perineural spread	Limited to indirect signs (fat effacement or enlargement of foramina, muscular atrophy)	Direct demonstration of the abnormal nerve by enhanced fat saturated SE T1 weighted sequences (slice thickness not > 3mm)	Axial and coronal planes	GE sequences with sub-millimetric isotropic slices (FIESTA; VIBE) to image the intraforaminal segment of cranial nerves
To assess relationships of tumour with cisternal cranial nerve segments	Not indicated	TSE T2 weighted sequence (slice thickness < 3 mm)	Axial, coronal (and sagittal planes)	MR cisternography with sub-millimetric isotropic slices (3DFT-CISS; DRIVE)
To analyse the intracranial/upper neck internal carotid artery course	CT angiography (requires contrast agent injection, high spatial resolution acquisition). MIP reconstructions		Axial, coronal (and sagittal planes)	MR angiography (requires contrast agent injection). MIP reconstructions

SE: Spin Echo sequence; TSE: Turbo Spin Echo sequence; STIR: Short Tau Inversion Recovery sequence; GE: Gradient Echo sequence; FIESTA: Fast Imaging Employing Steady State sequence; VIBE: Volume Interpolated Breath-Hold Examination sequence; 3DFT-CISS: three-dimensional constructive interference in a steady state sequence; DRIVE: driven equilibrium radio frequency reset pulse sequence; MIP: Maximum Intensity Projection

Table 4.3 Benign sinonasal tumours: juvenile angiofibroma- pre-treatment imaging and tasks.

Tasks	CT	Standard MR	Study planes	Additional MR sequences
To distinguish the lesion from retained mucus	Adequate, though less sensitive than MR. (3 mm slice thickness better than 1 mm)	TSE T2 weighted sequences are indicated. (slice thickness 3 mm)	Axial and coronal planes	
To assess the intra-diploic and intracranial extent	Adequate, though less sensitive than MR. Early acquisition post contrast enhancement is required. (2-3 mm slice thickness)	TSE T2 weighted sequence and pre and post-contrast SE T1-weighted sequences are indicated. (slice thickness < 3 mm)	Axial, coronal (and sagittal planes)	GE sequences with sub-millimetric isotropic slices (FIESTA; VIBE)
Tasks	Angiography			
To devascularize lesions	Unilateral/bilateral embolisation of major arterial feeders arising from external carotid artery (IMA, ascending pharyngeal artery). PVA particles are generally used (diameter from 250 to 500 microns)			

MA: Maxillary Artery, PVA: Polyvinyl alcohol; TSE: Turbo Spin Echo sequence; FIESTA: Fast Imaging Emploting Steady State sequence; VIBE: Volume Interpolated Breath-Hold Examination sequence

at the interface between the sinonasal tract and the adjacent skull base is of paramount importance for correct interpretation of the MR images obtained during follow-up. Furthermore, pre-operative examination should be available for comparison and the radiologist should obtain information about the exact extent of the resection, the residual presence of microscopic or macroscopic disease, possible interposition of flaps, results of pathologic analysis of the specimen, and the postoperative use of adjuvant treatment. Since many vascular flaps have been recently introduced to close large dural defects with the intent of preventing CSF leak and to promote faster and more complete healing, understanding their appearance with as few variables at MR can allow the radiologist to avoid mistakes in differential diagnosis between findings related to a regular or impaired (flap displacement or necrosis) healing process and presence of a persistent/recurrent lesion⁽³²⁶⁾.

Another key issue in post-treatment MR follow-up is distinguishing between the lesion and inflammatory tissues, such as granulation tissue, which may still escape detection even by expert clinicians and radiologists⁽³¹⁰⁾. In such cases, PET/CT examination may give additional information. Up to now, however, most of the experience acquired with PET/CT has relied on fluoro-deoxy-glucose (FDG) uptake. Unfortunately, FDG accumulates in both cancer and inflammatory cells due to an increased glycolytic activity, making uncertain whether an area of increased FDG uptake necessarily represents tumour. The introduction of new agents, such fluoro-deoxy-thymidine, which accumulate only in actively replicating cells, might help in differentiating tumour and inflammatory lesions.

Post-operative imaging is mandatory in all malignancies involving the sinonasal tract and the skull base as well as in some benign lesions such as osteoma, juvenile angiofibroma, pituitary adenomas, epidermoid cysts, craniopharyngiomas, and meningiomas, which due to their deep location or submucosal pattern of growth, are not easily picked up by endoscopic evaluation. In IP, MR is indicated only when a sinus that was originally involved by the lesion is not accessible for exploration due to scar closure, the patient is symptomatic, or a

residual/recurrent lesion has been histologically documented. Recurrent malignant lesions, if diagnosed at an early stage, may be still amenable to salvage treatment. Therefore, it is necessary that patients are followed with periodic MR. A commonly accepted schedule includes examination at 4-month intervals for the first 1-2 years after treatment and subsequently every 6 months^(309,327). In tumours that are prone to develop late recurrences such as chondrosarcoma, adenoid cystic carcinoma, and olfactory neuroblastoma, imaging surveillance should be extended beyond the usual 5-year date from treatment.

4-3 Histopathology

The sinonasal region and skull base is a region with the greatest histological diversity in the body and this is reflected in the following extensive list from the WHO classification⁽³²⁸⁾, which has been used in this document. Where available ICD codes have been appended. In this document, we have concentrated on those tumours where reasonable cohorts have been published in the literature. This includes neoplasms affecting the nasal cavity, paranasal sinuses, pituitary and skull base but not the nasopharynx as this was felt to currently be beyond our remit. The exception to this is juvenile angiofibroma for the reasons given below.

Table 4.4. Histopathology and ICD-O codes* according to WHO classifications of tumours. (* whenever available)

NASAL CAVITY AND PARANASAL SINUSES

- 1) Malignant epithelial tumours
- 2) Neuroendocrine tumours
- 3) Benign epithelial tumours
- 4) Soft tissue tumours
- 5) Tumours of bone and cartilage
- 6) Haematolymphoid tumours
- 7) Neuroectodermal tumours
- 8) Germ cell tumours
- 9) Secondary tumours

1) Malignant epithelial tumours

Lymphoepithelial carcinoma ICD-O 8082/3

Sinonasal undifferentiated carcinoma ICD-O 8020/3

Neuroendocrine tumours

Squamous cell carcinoma

Keratinizing squamous cell carcinoma ICD-O 8070/3

Non-keratinizing (cylindrical cell, transitional) carcinoma currently no separate ICD-O

Verrucous carcinoma ICD-O 8051/3

Papillary squamous cell carcinoma ICD-O 8052/3

Basaloid squamous cell carcinoma ICD-O 8083/3

Spindle cell carcinoma ICD-O 8074/3

Adenosquamous carcinoma ICD-O 8560/3

Acantholytic squamous cell carcinoma ICD-O 8075/3

Adenocarcinoma

Intestinal-type adenocarcinomas ICD-O 8144/3

(Subclassification according to Barnes 1986)

Papillary - type

Colonic - type

Solid - type

Mucinous - type

Mixed

Sinonasal non-intestinal-type adenocarcinomas

ICD-O 8140/3

Low-grade adenocarcinoma

High-grade adenocarcinoma

Salivary gland-type carcinoma

Adenoid cystic carcinoma ICD-O 8200/3

Acinic cell carcinoma ICD-O 8550/3

Mucoepidermoid carcinoma ICD-O 8430/3

Epithelial-myoepithelial carcinoma ICD-O 8562/3

Clear cell carcinoma ICD-O 8310/3

2) Neuroendocrine tumours

Typical carcinoid ICD-O 8240/3

Atypical carcinoid ICD-O 8249/3

Small cell carcinoma, neuroendocrine type ICD-O 8041/3

3) Benign epithelial tumours

Sinonasal (Schneiderian) papillomas

Inverted papilloma (Schneiderian papilloma, inverted type) ICD-O 8121/1

Oncocytic papilloma (Schneiderian papilloma, oncocytic type) ICD-O 8121/1

Exophytic papilloma (Schneiderian papilloma, exophytic type, everted type) ICD-O 8121/1

Respiratory epithelial adenomatoid hamartoma; no ICD-O

Salivary gland-type adenomas (Main types)

Pleomorphic adenoma ICD-O 8940/0

Myoepithelioma ICD-O 8982/0

Oncocytoma ICD-O 8290/0

4) Malignant soft tissue tumours

Fibrosarcoma ICD-O 8810/3

Undifferentiated high grade pleomorphic Sarcoma („MFH“) ICD-O 8830/3

Leiomyosarcoma ICD-O 8890/3

Embryonal rhabdomyosarcoma ICD-O 8910/3

Alveolar rhabdomyosarcoma ICD-O 8920/3

Angiosarcoma ICD-O 9120/3

Malignant peripheral nerve sheath tumour ICD-O 9540/3

5) Borderline and low malignant potential tumours of soft tissue

Desmoid-type fibromatosis ICD-O 8821/1

Inflammatory myofibroblastic tumour ICD-O 8825/1

Glomangiopericytoma (Sinonasal-type haemangiopericytoma) ICD-O 9150/1

Extrapleural solitary fibrous tumour ICD-O 8815/1

6) Benign soft tissue tumours

Myxoma ICD-O 8840/0

Leiomyoma ICD-O 8890/0

Haemangioma ICD-O 9120/0

Schwannoma ICD-O 9560/0

Neurofibroma ICD-O 9540/0

Meningioma ICD-O 9530/0

7) Malignant tumours of bone and cartilage

Chondrosarcoma ICD-O 9220/3

Mesenchymal chondrosarcoma ICD-O 9240/3

Osteosarcoma ICD-O 9180/3

Chordoma ICD-O 9370/3

8) Benign tumours of bone and cartilage

Fibrous dysplasia; no ICD-O Code

Osteoma ICD-O 9180

Osteoid osteoma ICD-O 9191/0

Osteoblastoma ICD-O 9200/0

Osteochondroma (exostosis) ICD-O 9210/0
 Chondroma ICD-O 9220/0
 Chondroblastoma ICD-O 9230/0
 Chondromyxoid fibroma ICD-O 9241/0
 Giant cell lesion ICD-O None
 Giant cell tumour of bone ICD-O 9250/1
 Ameloblastoma ICD-O 9310/0
 Nasal chondromesenchymal hamartoma; no ICD-O Code

9) Haematolymphoid tumours

Extranodal NK/T cell lymphoma ICD-O 9719/3
 Diffuse large B-cell lymphoma ICD-O 9680/3
 Extramedullary plasmacytoma ICD-O 9734/3
 Extramedullary myeloid sarcoma ICD-O 9930/3
 Histiocytic sarcoma ICD-O 9755/3
 Langerhans cell histiocytosis ICD-O 9751/1
 Juvenile xanthogranuloma; no ICD-O Code
 Rosai – Dorfman disease (Sinus histiocytosis with massive lymphadenopathy); no ICD-O Code

10) Neuroectodermal tumours

Ewing sarcoma ICD-O 9260/3
 Primitive neuroectodermal tumour (PNET) ICD-O 9364/3
 Olfactory neuroblastoma (esthesioneuroblastoma) ICD-O 9522/3
 Grading (Grade 1 – 4) according to Hyams 1988 based on:
 Architecture
 Pleomorphism
 Neurofibrillary matrix
 Rosettes
 Mitosis
 Necrosis
 Glands
 Calcification
 Melanotic neuroectodermal tumour of infancy ICD-O 9363/0
 Mucosal malignant melanoma ICD-O 8720/3
 Heterotopic central nervous system tissue(nasal glioma) ICD-O None

11) Germ cell tumours

Immature teratoma ICD-O 9080/3
 Teratoma with malignant transformation ICD-O 9084/3
 Sinonasal yolk sac tumour (endodermal sinus tumour) ICD-O 9071/3
 Sinonasal teratocarcinoma ICD-O None
 Mature teratoma ICD-O 9080/0
 Dermoid cyst ICD-O 9084/0

12) Secondary tumours (Mainly metastases from primary tumours of...)

Kidney
 Lung
 Breast
 Thyroid
 Prostate
 Others

NASOPHARYNX

- 1) Malignant epithelial tumours
- 2) Benign epithelial tumours
- 3) Soft tissue neoplasms

Nasopharyngeal angiofibroma* ICD-O 9160/0
 *Although juvenile angiofibroma is known to arise from the posterior nasal cavity and not the nasopharynx, the WHO classification includes this lesion here

- 4) Haematolymphoid tumours
- 5) Tumours of bone and cartilage
- 6) Secondary tumours

TUMOURS OF THE SELLA REGION

- 1) Tumours of the pituitary gland proper
- 2) Craniopharyngioma
- 3) Chordoma
- 4) Meningioma
- 5) Secondary tumours

1) Tumours of the pituitary gland proper

Pituitary adenoma

Typical adenoma ICD-O 8272/0
 Atypical adenoma ICD-O 8272/1
 Growth hormone producing adenoma ICD-O 8272
 Prolactin producing adenoma ICD-O 8271/0
 TSH producing adenoma ICD-O 8272/0
 ACTH producing adenoma ICD-O 8272/0
 Gonadotropin producing adenoma ICD-O 8272/0
 Null cell adenoma ICD-O 8272
 Plurihormonal adenoma ICD-O 8272/0
 Pituitary carcinoma ICD-O 8272/3
 Gangliocytoma ICD-O 9492/0
 Granular cell tumour ICD-O 9580/0

Pituitary carcinoma
 Gangliocytoma
 Granular cell tumour

2) Craniopharyngioma

3) Chordoma

4) Meningioma

- 5) Secondary tumours (Metastases from primary tumours from...)
 Breast
 Lung
 Gastrointestinal tract

5. Endonasal endoscopic surgical approaches

5-1 Introduction

During the past two decades, endoscopic endonasal surgery to the skull base has become a feasible and increasingly popular option for the treatment of lesions in this area. Detailed anatomical studies have improved the understanding of the skull base anatomy from the endoscopic perspective. This development, coupled with the use of intra-operative image guidance and customized instruments, has enabled skull base surgeons to approach deeply seated lesions using minimal access techniques. The feasibility and the safety of such extended approaches have been well established and reproduced in numerous studies^(59,329-338). As a result, current expanded endonasal approaches (EEA) can provide access to the anterior, middle and posterior cranial fossa^(46,50). Surgical expertise acquired by leading centers from around the world has led to the establishment of endoscopic endonasal approaches as a critical tool in the armamentarium of sinonasal and skull base surgeons.

Surgical advantages of EEA in comparison with traditional transcranial approaches include access to deeply seated lesions, a more direct midline exposure, decreased brain parenchyma injury, lack of neurovascular structure manipulation, prompt decompression of the visual apparatus when indicated and early tumour devascularization^(332-334,339). Similar oncological results to those obtained with traditional open approaches have been documented for sinonasal, sellar and skull base lesions^(329,333,336,337,339-341). Piecemeal resection of malignant tumours does not seem to compromise oncologic results as long as clear margins are confirmed with frozen section⁽³⁴²⁾. From the patient's perspective, decreased surgery time, decreased length of stay, increased patient comfort and lack of external incision are significant advantages of the EEA⁽³³⁸⁾.

To date, EEAs have not yet reached their limits. Tumour type, size, shape, fibrosity, vascularity, extradural locoregional extension, vessel encasement, dural invasion and intradural extension are not contraindications to endoscopic endonasal approaches. Two critical factors guide the choice of favoring an EEA over traditional approaches⁽⁵⁰⁾. First, one must consider the relationship of the lesion to critical neurovascular structures. EEA are ideal for lesions in which the neurovascular structures are located on perimeter of the tumour, allowing access to the lesion with minimal manipulation of normal neurovascular structures. Second, the experience of the surgical team must be considered. The ability to maintain good visualisation, achieve hemostasis⁽³⁴³⁾, deal with vascular complications and perform appropriate reconstructions⁽³⁴⁴⁻³⁴⁶⁾ is essential for optimal surgical results.

5-2 General principles

5-2-1 Bilateral exposure

Endoneurosurgery requires a binarial approach to allow for a two-surgeon, three or four-hand technique. Bimanual dissection is facilitated by bilateral nasal access as it provides the necessary space for instrument manipulation, allows for dynamic movement of the scope, and improves the angle for dissection. Out-fracturing of the inferior turbinates and out-fracturing or removal of one or both middle turbinates widens the nasal corridor. These steps provide a wider access to the posterior and superior nasal cavity and skull base.

A wide nasal corridor enables exposure of key anatomical landmarks, prevents crowding of instruments, minimizes soiling of the lens and helps maintain an unobstructed view of the surgical field. Wide bilateral sphenoidotomies are extended laterally to the level of the pterygoid plates and lateral wall of the sphenoid sinus, superiorly to the planum sphenoidale and inferiorly to the floor of the sphenoid sinus. Partial or complete removal of the posterior nasal septum facilitates bilateral instrumentation without deviation of the septum and increases lateral angulation.

5-2-2 Resection

Endoscopic tumour resection uses the same techniques as when using the microscope for visualisation. Internal debulking, capsular mobilization, extracapsular dissection of neurovascular structures, coagulation and removal of the capsule are sequentially performed with a bimanual technique, enabling tactile depth perception throughout the resection. Depending on the consistency of the tumour, various debulking techniques may be employed including bimanual suction, ultrasonic aspirator and piece meal removal with true-cut forceps.

5-2 Modular approaches

Endoscopic endonasal approaches have been organized in modules based on anatomical corridors (Table 5.1)^(46,47,50,342). The sphenoid sinus is the epicenter at the crossroads of the sagittal and coronal planes and is the starting point for many of the surgical modules.

5.3.1 Transsellar approach⁽⁴⁶⁾

The transsellar approach is primarily used for pituitary pathology such as pituitary adenomas and Rathke's cleft cysts. It provides access to the medial cavernous sinus for pituitary adenomas that extend laterally behind the cavernous ICA.

Table 5.1. Classification of endonasal approaches to the ventral skull base.

SAGITTAL PLANE	
-	Transfrontal
-	Transcribriform
-	Transtuberculum/Transplanum
-	Transsellar
-	Transclival
-	Superior third
-	Transsellar(intradural)
-	Subsellar (extradural)
-	Middle third
-	Panclival
-	Transodontoid and foramen magnum/craniovertebral approach
CORONAL PLANE	
-	Anterior coronal plane
-	Supraorbital
-	Transorbital
-	Middle coronal plane
-	Medial petrous apex
-	Petroclival approaches
-	Inferior cavernous sinus/Quadrangular space
-	Superior cavernous sinus
-	Infratemporal approach
-	Posterior coronal plane
-	Infrapetrous
-	Transcondylar
-	Transhyoglossal
-	Parapharyngeal space
-	Medial (jugular foramen)
-	Lateral

Exposure

The sphenoidotomies are widened to expose the sphenoid lateral recesses, the planum-tuberculum junction and optic-carotid recesses (OCR). If needed, the posterior ethmoidal cells are exenterated to expose the medial orbital wall. The floor of the sphenoid is drilled back to reach the most inferior aspect of the floor or, if necessary, to reach the level of the clivus. This enhances the rostro-caudal trajectory into the suprasellar and retrosellar space. Intrasphenoidal septations are drilled down to provide unimpeded instrumentation and to avoid the “ice-cream cone” effect where the instruments are displaced medially (the apex of the cone). Removal of these septations is completed using a careful technique since they may lead directly towards the vertical canal of the ICA. The mucosa over the sella is removed. In select cases the rest of the sphenoid sinus mucosa may be removed to facilitate the identification of surgical landmarks, the sellar prominence in the center, the bone strut covering the superior intercavernous sinus (SIS) above, the clival recess below, the carotid prominences lateral to the sella and more superiorly the optic nerves, and the medial and lateral OCRs. Bone removal over the sellar face extends laterally beyond the medial aspect of the cavernous sinuses (CS) and superiorly and inferiorly to expose both the SIS and IIS. The mOCR does not need to be opened

unless the tumour extends to the suprasellar and lateral optico-carotid cisterns.

Intrasellar dissection

Dura mater is opened in an X pattern and the inferior flap is reflected caudally. The superior flap is left intact, preventing the suprasellar tumour from herniating and obscuring the vision. Internal debulking is completed using two suctions, which enables controlled removal of tumour with less trauma to the normal pituitary, stalk and cavernous sinus and its contents. Once the posterolateral tumour dissection is complete (from CS to CS laterally and posteriorly toward the clivus-dorsum junction), the superior part of the dura is opened to complete the superolateral dissection. Three areas deserve special attention to avoid persistent tumour, namely the area posterior to the carotid genu in the cavernous sinus, the medial OCR (from within the sella), and the anterior lip of the dura at the level of SIS beneath sellar-tuberculum junction. Residual gland is often found plastered to the undersurface of the diaphragm. If the diaphragm does not descend concentrically, residual tumour in the suprasellar space should be suspected and explored. If suprasellar dissection is necessary, the bone overlying the medial OCR must be removed to allow the identification of the optic nerves and internal carotid arteries.

Cavernous sinus extension

In the event of cavernous sinus extension, the medial cavernous wall can be examined from within the sella. Since the carotid siphon is usually displaced anteriorly, the space between the posterior clinoid and the siphon offers an ideal corridor to enter the cavernous sinus. Tumour can also be followed inside the CS.

5-4 Expanded endonasal approaches – sagittal plane

The sagittal plane modules extend from the frontal sinus to the second cervical vertebra, enabling access through the crista galli, planum, tuberculum, dorsum sella, and clivus (Table 5.1).

5-4-1 Transtuberculum/Transplanum approach⁽⁴⁶⁾

Extrasellar pituitary adenomas with suprasellar extension, meningiomas and select craniopharyngiomas require a combined transsellar/ transplanum approach with removal of the tuberculum. This allows one stage removal of the entire tumour with direct visualisation.

Exposure

Bony exposure of the trans-sellar approach is extended rostrally completing bilateral posterior ethmoidectomies. Ethmoid sinus septations are removed flush with the anterior cranial base and the lamina papyracea bilaterally. To prevent injury to the olfactory neuroepithelium, the exposure should not extend anterior to the posterior ethmoidal arteries (PEA) and the most rostral margin of the nasal septum should be left attached

to the skull base. The planum sphenoidale is drilled eggshell-thin from a rostral-to-caudal direction. After opening the most rostral aspect of the sella and removing the bony strut over the SIS, this venous structure is exposed, cauterized and mobilized or divided. This enables direct access to the tumour's suprasellar extensions to the prechiasmatic cisterns. If the optic-carotid recesses must be accessed intradurally, the optic strut (LOCR) and the medial clinoids are removed to prevent the need for traction on the tumour and risk of avulsing a perforator vessel. The paraclinoid carotid canals can also be opened using the Kerrison rongeur. Arterial feeders arising from the distal portion of the paraclinoid CA at the level of the medial OCR as well as from the PEAs may be identified and coagulated.

Intradural dissection

For extracranial tumours, extracapsular dissection is performed through the parachiasmatic cisterns. Identification of the paraclinoid carotid artery, as it emerges intradurally at the level of the medial OCR, is essential. This requires prior removal of the bony canal covering this segment of the ICA. Following the ICA leads to the optic nerve, which is located slightly superior. To perform an extracapsular dissection, the capsule should be thinned sufficiently and be pliable enough, to allow sharp dissection of the arachnoid bands in the parachiasmatic cisterns. Utmost attention should be applied when working along the superior surface of the lesion, as the AcoA and recurrent artery of Heubner may be draped over the tumour. Coagulation of the base of the tumour at the tuberculum/sellar junction should only proceed after identification of the stalk since it is most often adherent to the posterior margin of the capsule and can easily be damaged during this step. Efforts should be taken to preserve the subchiasmatic perforating vessels during the subchiasmatic extracapsular dissection.

5-4-2 Transcribiform⁽⁴⁶⁾

Common indications for the transcribiform approach include the repair of CSF leaks, encephaloceles/ meningoceles, access to benign intracranial tumours such as olfactory groove meningiomas and the resection of sinonasal malignancies with skull base invasion such as olfactory neuroblastomas.

Exposure

The transcribiform approach encompasses the area of the cribriform plates. Its anterior limits are the crista galli and the frontal sinuses (i.e. transfrontal approach), while the posterior limit is the planum sphenoidale. Laterally, it is bounded by the roof of the ethmoid sinus (fovea ethmoidalis) and medial orbital wall (lamina papyracea). This approach can be performed unilaterally or bilaterally.

This module extends the rostral limit of the previous approach to the level of the crista galli or even the frontal sinus if required. The attachment of the anterior nasal septum to the skull base is resected. Complete ethmoidectomies are per-

formed with exposure of the medial orbital walls. The lamina papyracea can be removed to gain lateral exposure or as oncological margins, although the periorbital fascia should not be disrupted. The ethmoidal arteries (AEA and PEA) are identified, coagulated and transected medial to the lamina papyracea, contributing to tumour devascularization.

A frontal sinusotomy is required but its extent and laterality varies according to the extent of disease and the exposure required. A Draf III or endoscopic Lothrop, which includes the bilateral removal of the sinus floors and inter-sinus septum, is most often required. However, in select cases a Draf IIA that involves the removal of the ipsilateral frontal sinus floor lateral to the middle turbinate, or a Draf II B that involves the removal of the entire ipsilateral frontal sinus floor lateral to the nasal septum, will suffice.

The skull base is drilled rostro-caudally starting at the frontoethmoidal recess. Prior to drilling the cribriform plate, the soft tissue lining including olfactory filaments and branches of ethmoidal arteries must be coagulated. This step further contributes to tumour devascularization. After bilateral removal of the cribriform plate, the crista galli is drilled until eggshell thin and fractured. Olfaction is sacrificed during this approach although in many patients is likely to be already compromised

Intradural dissection

The exposed dura is coagulated and incised individually on both sides of the falx. Tumour is debulked sequentially from each side, exposing the free edge of the falx bilaterally. After coagulation of the falx and any feeding vessels arising from the falcine arteries, it is incised, creating a single intradural working cavity. Tumour debulking is continued at the median area. Dura anterior to tumour/brain junction is not opened, to prevent parenchymal herniation. Extra-capsular dissection is pursued using gentle counter-traction and sharp dissection. Sub-pial invasion may be encountered and requires gentle sub-pial dissection. Dissection over the superior pole of the tumour proceeds along the interhemispheric fissure, paying attention to the A2 and frontopolar arteries that will be draped over the tumour surface. Extra-capsular dissection may also proceed towards the parasellar cistern (inferior pole), enabling identification of the optic nerves and the AcoA. This provides proximal control of both A2 during dissection along the interhemispheric fissure.

5-4-3 Transclival⁽⁴⁷⁾

The clivus can be divided in three portions along the rostral-caudal direction. The upper third includes the dorsum sella and posterior clinoids down to the level of Dorello's canal. The middle third extends from Dorello's canal down to the jugular foramen. The lower third extends from jugular foramen through the cervicomedullary junction and foramen magnum. Common indications include the surgical treatment of menin-

giomas, chordomas, and chondrosarcomas, which are the most common tumours in the clival region. A transclival approach has been used for the treatment of highly selected vertebrobasilar aneurysms that are not amenable to endovascular treatment.

Superior third of the clivus

The rostral extension of the superior portion of the clivus is bounded by the dorsum sellae in the midline and the posterior clinoids in the paramedian region. These bony structures may be removed either intradurally via a transsellar approach or extra-durally via a sub-sellar approach, elevating the contents of the pituitary fossa en bloc and allowing for posterior access.

Transsellar exposure (intradural)

A transtuberulum/transplanum approach is first performed. Rostral exposure only needs to reach the tuberculum/platum junction. Bone covering the sellar face is removed to expose the SIS, ISS and the sella-clivus junction. Dura is incised in a cruciform manner over the parasellar cistern, the lower triangle running along the SIS. The dura over the pituitary is opened using a similar technique, taking care not to transgress the pituitary capsule. The SIS is ligated and transected, communicating the suprasellar and sellar dural openings. If present, the ISS must also be transected. The diaphragma sellae is cut in the midline to expose the stalk. The diaphragma sellae is then cut in a paramedian direction to release the stalk circumferentially. The ligaments connecting the pituitary capsule to the lateral sellar dura or medial cavernous sinus wall are systematically transected along the lateral contour of the gland. The gland may be mobilized superiorly, enabling exposure and coagulation of the dura above the posterior clinoids. These bony structures are then drilled until eggshell thin and carefully removed, avoiding injury to the ICA and abducent nerve located laterally and posteriorly. The dorsum sellae as well as the upper part of the clivus are also drilled, giving a direct view of the retrosellar space.

If more bone needs to be removed at the median area, a pituitary gland transposition is required. Once the gland is freed from its pituitary ligaments and the stalk from the diaphragm, it can be elevated towards the suprasellar space and prechiasmatic cistern and coated with a thin layer of fibrin glue to prevent dessication⁽³⁴⁷⁾. Transposition of the pituitary gland enables an unobstructed visualisation of the posterior wall of the sella.

Sub-sellar exposure (extradural)

The posterior clinoids and dorsum sellae may be removed through an extradural route, especially for median retrosellar lesions that extend caudally. A transplanum approach is required only if access to a rostral tumour extension is needed. The sellar face, the bone over the SIS and ISS as well as the portion of the middle third of the clivus between the vertical

carotid canals directly below the sella is removed. The sellar dura is not opened, enabling en bloc elevation of the pituitary fossa. This gives access to drill the posterior clinoids and dorsum sellae.

Once the exposure to the superior clivus is complete, the dura is opened and initial efforts should aim at identifying neurovascular structures within the interpeduncular and basilar cisterns including the PcoA and the III CN. If the membrane of Lilliequist is not violated, efforts should be made to avoid its transgression as it prevents spread of blood beyond the suprachiasmatic cisterns.

Middle third of the clivus

Isolated removal of this part of the clivus is rarely needed. Its removal is usually undertaken as part of a panclival exposure.

Panclival approaches

Modifications of the initial bilateral sphenoid exposure are needed to gain caudal access. Wide sphenoidotomies must be performed as they provide deeper positioning of the scope and direct caudal view. The basopharyngeal fascia is stripped from the floor of the sphenoid sinus and clival face. The sphenoid sinus floor is drilled flush with the clivus. Before drilling the clivus, it is important to identify the vidian nerve and artery, as they travel in their canal to join the anterior genu of the ICA⁽⁷¹⁾. Clivus bone above the level of the vidian canal can only be removed in the median region, between the carotid canals. If drilling of the petrous bone inferior and lateral to the anterior genu of the ICA is required, the vidian canal should be used as the superior limit⁽³⁴⁸⁾.

After meticulous coagulation of the underlying dura and basilar venous plexus, the dura is opened by midline. The dural incision is extended laterally under the horizontal petrous ICA to the fossa of Rosenmuller just as the Eustachian tubes disappear obliquely into the skull base. Opening of the dura at the level of the ICA genu should be performed under direct visualisation as the abducent nerves travel in this space, entering Dorello's canal just medial, superior, and dorsal to the anterior CA genu. Care should be taken to identify neurovascular structures namely the vertebral arteries, vertebro-basilar junction, basilar artery, pons, and cranial nerves V to X.

5-4-4 Transodontoid and foramen magnum/craniovertebral approach^(47,68,349)

Exposure of the foramen magnum and odontoid requires additional soft tissue removal following the panclival module. The nasopharyngeal mucosa is removed from the sphenoclivus junction to the level of the soft palate. Laterally, care should be taken to stay medial to the Eustachian tubes as the parapharyngeal carotid is directly posterolateral to the Eustachian tube. Ectatic parapharyngeal ICAs may limit exposure lateral to the fossa of Rosenmuller. The paraspinous muscles and the

atlantooccipital membrane are exposed and partially resected to expose the anterior arch of C1. Bone removal is guided by the pathology and concerns for cranio-cervical stability⁽³⁵⁰⁾. For exposure of the foramen magnum, only the superior aspect of C1 ring needs to be drilled exposing the tip of the odontoid. The medial aspects of the occipital condyles are removed without entering the joint capsule. For transodontoid exposure, the anterior arch of C1 is resected and the odontoid process of C2 is exposed. The anterior cortex of the dens and the trabecular bone are drilled and the posterior cortical shell is removed preferentially piecemeal after sharp dissection. After removal of the dens, the normal dura (or underlying pannus) covering the brainstem is exposed. The rostrocaudal trajectory offered by the endoscope enables visualisation of the cervical spinal cord down to the level C1-C2. Caudal exposure is limited by the inability to move the instruments beyond the nasal bones anteriorly and superiorly and the hard palate posteriorly and inferiorly. The line connecting these two points is defined as the nasopalatine line (NPL). The NPL accurately predicts the most inferior extent of an endoscopic endonasal approach. However, flexion of the neck as well as angled instruments and lenses can enhance the inferior extent of the approach.

5-5 Expanded endonasal approaches – Coronal plane

EEA approaches in the coronal plane are divided into anterior, middle, posterior coronal planes, corresponding to the cranial fossae.

5-5-1 Anterior coronal plane: Supraorbital and transorbital approaches

In the supraorbital approach, the medial wall of the orbit is removed and the orbital soft tissues are displaced to visualize the orbital roof. The transorbital approach is used for intracanal lesions that are inferior and medial to the optic nerve. Access is gained between the inferior and medial rectus muscle with preservation of extraocular muscle function.

5-5-2 Middle coronal plane⁽⁵⁰⁾

The approaches used to access the mid-coronal plane are grouped on the basis of their relationship to the petrous carotid artery. Infrapetrous approaches give access to the medial petrous apex and the petroclival junction. The suprapetrous approaches give access to the inferior and superior cavernous sinus as well as the infratemporal/middle fossa.

Medial petrous apex approach

The exposure begins with wide bilateral sphenoidotomies and removal of the basopharyngeal fascia from the sphenoid face down to the clivus. The sphenoid floor is drilled flush with the clival recess and the clivus itself may also be partially removed if needed. A wide middle meatal antrostomy is performed, providing access to the back wall of the antrum. The sphenopalatine and posterior nasal arteries are identified and ligated at the

level of the sphenopalatine foramen. The back wall of the maxillary sinus is removed, gaining access to the pterygopalatine. Detailed anatomical studies of the pterygopalatine fossa using an endonasal endoscopic approach have been described^(19,76). The soft tissues of the pterygopalatine fossa are elevated in a medial to lateral direction to expose the medial aspect and the base of the pterygoid plates. The vidian canal (pterygoid canal) should be identified early since it represents, along with the middle pterygoid plates, critical surgical landmarks for endoscopic approaches to the petrous apex^(71,348). The vidian canal leads directly to the anterior genu of the ICA as its petrous portion turns up to form the vertical paraclival ICA. The medial pterygoid plate (MPP) is drilled medial and inferior to the vidian canal while following it posteriorly, towards the foramen lacerum. After identifying the anterior genu of the ICA, the lateral and superior part of the MPP can be removed. To access the petrous apex, drilling of the bone covering the paraclival carotid may be required if the ICA needs to be mobilized laterally⁽³⁵¹⁾. Greater access can also be provided by drilling a portion of the lateral clivus at its junction with the petrous apex.

Petroclival approaches

This approach begins as a medial petrous apex exposure. As drilling of the MPP proceeds, the vidian canal can usually be found just lateral to the junction of the sphenoid floor with the MPP. The vidian canal is drilled circumferentially, following it back to the anterior genu of the ICA^(71,348). The anterior genu of the ICA represents the lateral margin of this approach and is the most important landmark. The bone overlying the genu, horizontal petrous and the vertical paraclival segments of the ICA can be removed to uncover the carotid and enable its lateral displacement. The medial portion of the clivus is safely drilled after identification of the anterior genu of the ICA. The lateral portion of the clivus at the petroclival junction is drilled up to the clival recess of the sphenoid. The cavernous sinus represents the superior boundary of this exposure and the middle fossa, the lateral boundary. Opening of the dura deep to the clivus will give access to the prepontine cistern.

Inferior cavernous sinus/Quadrangular space approach

This exposure builds on to the petroclival approach. Removal of the posterior wall of the maxillary antrum is extended laterally until the maxillary branch (V2) of the trigeminal nerve is identified travelling superiorly towards the foramen rotundum. The MPP is drilled inferior and medially to the vidian canal. Next, the bone between the vidian canal and V2 is drilled away, knowing that this bony corridor narrows progressively as it deepens. Removal of this bone gives access to the quadrangular space, which is delimited by the parasellar ICA medially, the V2 and dura of middle fossa laterally, horizontal petrous ICA inferiorly, and the VIth cranial nerve superiorly. Bone covering the horizontal petrous ICA, the anterior genu and parasellar ICA may need to be removed if mobilization of the carotid is required. Access to the inferior cavernous sinus is

gained by opening the dura from the genu of the ICA (medial) toward the V2 (lateral).

Superior cavernous sinus approach

This module requires similar bone removal and ICA exposure as performed for the inferior cavernous sinus module. Prior to dural incision, it is advised to identify the medial margin of the ICA in the sella so that it can be protected during dural opening. The dura incision is initiated directly over the superior lateral portion of the cavernous sinus and performed in a medial-to-lateral direction. Often, the cavernous sinus has thrombosed and little venous bleeding occurs during initial opening. However, bleeding is encountered once tumour is removed. This approach has served for tumours refractory to medical treatment or radiosurgery and for patients with established cranial nerve deficits⁽⁴⁴⁾.

Infratemporal approach

Tumours approached through this route often create a corridor through the maxillary sinus, extending rostrally in the middle

fossa and laterally in the infratemporal fossa. The infratemporal module begins once the MPP is isolated, the vidian canal is identified and the maxillary antrostomy is completed. The MPP is identified and removed flush with the middle cranial fossa and foramen rotundum. Tumour debulking is begun only after the anterior genu of the ICA and horizontal petrous segment of the ICA are identified. The internal maxillary artery and its branches must be isolated and ligated. The dissection is extended laterally until the lateral pterygoid plate (LPP) is identified. The LPP is drilled rostrally until flush with the middle fossa and foramen ovale. Venous bleeding from the pterygopalatine venous complex may be profuse enough to require packing and staged resection, allowing the venous complex to thrombose. Since the bony landmarks are often eroded, image guidance is required for these interventions.

5-5-3 Posterior coronal plane

The posterior coronal plane extends from the foramen magnum across the occipital condyle and hypoglossal canal to the jugular foramen.

Infrapetrous approach⁽⁵⁰⁾

This module builds on the infratemporal approach. After identifying the V2, the vidian canal and the anterior genu of the ICA, the MPP is drilled flush with the middle fossa and foramen rotundum. As the LPP is resected, V3 is identified along its posterior edge and guides drilling flush with the middle fossa and the foramen ovale. The cartilaginous segment of the Eustachian tube is resected for about 1cm. The inferior surface of the petrous apex is reached by drilling the bone between the horizontal petrous segment of the ICA and the Eustachian tube, medial to V3. The horizontal petrous and vertical paraclival segment of ICA are identified and skeletonized. Finally, drilling and tumour dissection proceeds inferior to the petrous ICA into the petrous apex.

Others

Other endoscopic approaches along the posterior coronal plane, such as the transcondylar, transhypoglossal and parapharyngeal space approaches, have been described to address other skull base lesions. Although they are part of the armamentarium of skull base surgeons, they are not used for sinonasal pathologies and will not be reviewed here.

5-6 Conclusion

- Endoscopic endonasal surgery has evolved significantly over the past two decades. Presently, the entire ventral skull base can be accessed endonasally in the sagittal and coronal planes using entirely endoscopic techniques.
- The choice of a specific surgical route should be guided by the tumour characteristics, patient co-morbidities and skill and experience of the operating team. Each patient should be evaluated with a 360° approach, considering the least

Table 5.2. Training programme for endonasal cranial base surgery

Level	Procedures
Level I	Endoscopic sinonasal surgery Endoscopic sphenoidectomy Sphenopalatine artery ligation Endoscopic frontal sinusotomy
Level II	Advanced sinus surgery Cerebrospinal fluid leaks Lateral recess sphenoid Sella/pituitary (intrasellar)
Level III (Extradural)	Medial orbital decompression Optic nerve decompression Sella/Pituitary (extrasellar) Petrous apex (medial expansion) Transclival approaches (extradural) Transodontoid approach (extradural)
Level IV (Intradural)	A. Presence of a cortical cuff <ul style="list-style-type: none"> - Transplanum approach - Transcribriform approach - Pre-infundibular lesions B. Absence of cortical cuff (direct vascular contact) <ul style="list-style-type: none"> - Transplanum approach - Transcribriform approach - Infundibular lesions - Retro-infundibular lesions - Transclival approach - Foramen magnum approach C. ICA dissection
Level V	A. Middle coronal plane (paramedian) <ul style="list-style-type: none"> - Suprapetrous carotid approaches - Infrapetrous carotid approaches - Transpterygoid approach - Infratemporal approach B. Posterior coronal plane (paramedian) C. Vascular surgery

Table 5.3 Intra-operative complications after expanded endonasal surgeries in 800 patients.

Category	Consequence	Type of lesion and/or deficit
Vascular (0.9%)	Death (0%)	• ∅
	Transient deficit (0.1%)	• P1 perforator
	Permanent deficit (0.4%)	• Pontine bleed (quadriplegic)
		• Imax laceration (hemiplegic)
No deficit (0.4%)	• Frontopolar avulsion (R lower limb paresis)	
Neural Injury (2.0%)	Permanent deficit (0.5%)	• 1 Ophthalmic (already blind)
		• 2 ICA lacerations
	Transient deficit (1.5%)	• IX, X, XII (1 case)
		• IX, X (1 case)
		• VI (2 cases)
Transient deficit (1.5%)	• III nerve (2 cases)	
	• V3 motor (1 case)	
	• VI nerve (4 cases)	
	• IX, X (1 case)	
		• Hemiparesis (4 cases)

R = right; L = left; ICA = internal carotid artery; Imax = internal maxillary artery

destructive route with the least complications to achieve the most complete lesion resection. Modular approaches should be combined as mandated by the lesion and its location^(46,47,50). However, when a lesion cannot be completely removed through an EEA approach, an open route may be considered or a combination of endonasal and open approaches^(329,333,334).

- A training format that is incremental and modular, has been proposed for all endonasal surgeons, irrespective of their specialty (Table 5.2)⁽³⁴²⁾. A level must be fully mastered prior to proceeding to the next since a higher level translates into increased anatomical complexity, technical difficulty and potential risk of neurovascular injury. As for all surgical procedures, a learning curve exists for each module⁽³³⁹⁾, the one for the EEA paramedian approaches may be the steepest. To assess the complications related to a large series of EEA, 800 cases of expanded endoscopic procedures performed by our team were reviewed. Intra-operative (Table 5.3) and post-operative (Table 5.4) complications have been compiled and categorized. These results demonstrate that expanded endoscopic procedures are safe when performed by experienced surgeons. However, serious complications may still occur and must be minimized as much as possible. The familiarity with endoscopic ventral skull base anatomy, proper instrumentation, an experienced surgical team, and adherence to endoscopic surgical principles are essential ingredients for safe endoscopic surgery and complication avoidance at each level.

Table 5.4 Post-operative complications after expanded endonasal surgeries in 800 patients.

Category	Consequence	Type of complication
Infection (1.4%)	Death (0.1%)	• Meningitis + Status epilepticus (1 case)
	Successfully treated (1.1%)	• Intradural abscess (1 case)
		• Extradural abscess (1 case)
Deficit (0.1%)	Death (0.7%)	• Meningitis (7 cases)
		• Intradural abscess - incapacitated (1 case)
Systemic (2.8%)	Successfully treated (2.1%)	• PE < 30 d (2 case)
		• PE > 30 d (2 cases)
		• Pneumonia + MI < 30 d (1 case)
	Permanent deficit (0.6%)	• Multiorgan failure > 30 d (1 case)
		• Acute renal failure transfusion (1 case)
Delayed deficit* (1.9%)	Transient deficit (1.3%)	• Respiratory failure (7 cases)
		• PE < 30 d (5 case)
	Permanent deficit (0.6%)	• MI (3 cases)
		• Immediate postop asystole (1 case)
Delayed deficit* (1.9%)	Transient deficit (1.3%)	• Visual deficit (perfusion) 2 cases
		• Visual deficit (late hypotension) 1 case
	Permanent deficit (0.6%)	• Visual deficit (hematoma) 1 case
		• Hemiplegia (post-op apoplexy) 1 case
		• Visual deficit (encephalocele) 1 case
Transient deficit (1.3%)	• Visual deficit (hematoma) 4 cases	
	• Visual deficit (nasal balloon) 2 case	
	• III nerve (hematoma) 1 case	
	• Proptosis (retrobulbar hematoma) 1 case	
		• Ataxia (OGtube passed clivectomy) 1 case

PE = pulmonary embolism; MI = myocardium infarct; d = days.

* There were 5 patients who presented seizures during the postoperative period with no sequelae.

- Endonasal endoscopic surgery is still in rapid evolution and its limits have not yet been reached. Outcome data for sinonasal pathologies and other skull base lesions is promising with oncologic outcomes comparable to open surgical approaches but with less morbidity^(329,333,336,337,339-341). The collective experience will need to be assessed in the future to describe long-term tumour control.

6 Benign sinonasal tumours

6-1 Epithelial

6-1-1 Inverted papilloma

Search strategy

A Medline and Pubmed review of the literature was performed to identify case series of inverted papillomas that were published from 1966 onwards. In those instances where a single centre had generated more than one case series from overlapping periods, data from the most recent series was used.

Case series were included in this series if there was a clear description of the pathology, surgery and follow-up. Some texts mixed external and endoscopic procedures and the patients who had these mixed procedures were usually excluded as they often lacked detail. In some series, a Caldwell Luc procedure was done to access the floor and anterior wall of the maxillary sinus before endoscopic medial maxillectomy became the procedure of choice^(352,353). Patients who had a combined endoscopic and Caldwell Luc approach are not detailed in this review as there have been few patients who have had this approach and it is not possible to discern their follow-up period. However, Woodworth et al. describe 24 patients who had undergone a combined endoscopic and Caldwell Luc approach with one recurrence (mean follow-up of 40 months for their whole series of 114 patients)⁽³⁵⁴⁾.

Introduction

Inverted papilloma are relatively uncommon benign epithelial tumours of the nasal cavity that generate considerable interest because they are locally aggressive, have a tendency to recur, and are associated with malignancy. Patients with inverted papilloma should have thorough surgery to remove all mucosal disease and all of the specimen should be examined for evidence of atypia or synchronous malignancy. Recurrent disease and metachronous carcinoma can develop up to a few years after surgery. Long-term follow-up is recommended to detect recurrence, as disease can become extensive before it becomes symptomatic.

Incidence and aetiology

The incidence of inverted papilloma has not been reported in epidemiological studies of normal population groups. On the basis of one series when only the patients in the local population were considered and the tertiary referral cases were excluded the incidence was 4.3 cases per million per year⁽¹³⁰⁾. Inverted papilloma accounts for 0.5 percent to 4 percent of the surgically removed nasal tumours^(118,119) with an incidence ranging from 0.6 to 1.5 cases per 100,000 inhabitants per year^(120,121). The age at onset ranged from 15 to 96 years old, with

the highest incidence was seen in the 5th and 6th decades of life⁽¹²²⁾. The male to female ratio was reported 2 - 5:1^(123,124).

There were no significant racial differences⁽¹²⁵⁾. The duration of symptoms varied from 5 months to 20 years with mean duration of 3.9 years⁽¹²²⁾. The frequency of inverted papilloma in apparently normal bilateral polyps varies between 0.00% and 0.92%. The incidence of inverted papilloma in unremarkable recurrent cases of nasal polyps is rare. Age, gender, and number of recurrences did not influence the frequency of this diagnosis⁽¹²⁶⁾. Since multiple sites within the nasal cavities and paranasal sinuses are involved, it is not always easy to determine the location of the origin of inverted papillomas. However, the ethmoid region, the lateral wall of nasal fossa and the maxillary sinus are the most frequent sites of origin of inverted papilloma. The frontal sinus is exceedingly rare (the ethmoid region in 48%, the maxillary sinus in 28%, the sphenoid sinus in 7.5%, the frontal sinus in 2.5%, the inferior turbinate in 2.5%, and the septum in 2.5%)⁽¹²⁵⁾. Inverted papilloma is generally unilateral, and bilateral involvement of the sinonasal tract is very rare, reported in less than 1%⁽¹²⁴⁾ to 9% of patients⁽¹²⁷⁾.

Human papilloma virus has been implicated in causing inverted papilloma and its DNA has been found in both the inverted papilloma and the cells of neighbouring normal appearing mucosa⁽²¹⁶⁾. Removing the neighbouring normal-appearing predisposed mucosa may be required to reduce the rate of recurrence⁽³⁵⁵⁾. Once inverted papilloma has recurred, the risk of subsequent recurrence increases to up to 58%⁽³⁵⁶⁾.

Clinical presentation

Inverted papilloma can present with nasal obstruction, epistaxis, and epiphora if it impinges on the drainage of the nasolacrimal system. Occasionally it can cause a mucocoele or expand enough to produce proptosis. The diagnosis of inverted papilloma is suspected in anyone with a unilateral nasal polyp but histology is the cornerstone in making a diagnosis⁽³⁵⁷⁾.

Diagnosis and imaging

Inverted papilloma usually present as a unilateral nasal polyp that is white as opposed to translucent or oedematous, and they are firm. This is not always the case as polyps that look idiopathic or inflammatory can be inverted papilloma. It transpires that approximately 1% of all nasal polyps have a significantly different pathology after histological examination than was predicted preoperatively or preoperatively⁽³⁵⁷⁾ so it is important to send polyps for histological examination. In inverted papilloma, it is important to send off as much tissue for analysis as possible to confirm or exclude malignancy.

CT is the primary mode of imaging prior to surgery. This can discern if there is any erosion of bone that would alert the surgeon to the possibility that there might be some malignancy. There is often some hyperostosis or sclerosis in the area adjacent to inverted papilloma or flecks of calcification within the papilloma⁽³⁵⁸⁾. MRI can contribute by clearly delineating whether opacification within the sinuses on CT is due to mucus or papilloma⁽³⁵⁹⁾. This is very helpful when deciding the best surgical approach for disease within the frontal sinus. Inverted papilloma within the frontal sinuses is uncommon but when it occurs it poses a surgical challenge. Often a median drainage procedure is required to allow angled endoscopes and instruments to be used from the contralateral side to remove diseased mucosa lying laterally within the sinus. This is worth knowing preoperatively to plan the surgery.

Staging

Inverted papilloma are sometimes based on a narrow pedicle so some workers recommended that staging of this tumour depends on the site of tumour attachment, not on their volume^(360,361).

Histology

Inverted papilloma most commonly arise from the lateral wall of the nasal cavity with local extension to the paranasal sinuses. Occasionally disease may extend to the nasopharynx, and more rarely traverse the cribriform plate or orbit particularly if they are associated with malignancy. They rarely arise from the nasal septum⁽³⁶⁷⁾, and the histology of septal lesions warrant a critical analysis as to whether they are truly inverted or not. The term “inverted papilloma” describes the histological

Table 6.1 Staging systems for inverted papilloma.

Author	Staging System
Krouse ⁽³⁶²⁾	<p>Type 1: Tumour totally confined to the nasal cavity. The tumour can be localized to one wall or region of the nasal cavity, or can be bulky and extensive within the nasal cavity, but must not extend into the sinuses or into any extranasal compartment. There must be no concurrent malignancy.</p> <p>Type 2: Tumour involving the ostiomeatal complex, and ethmoid sinuses, and / or the medial portion of the maxillary sinus, with or without involvement of the nasal cavity. There must be no concurrent malignancy.</p> <p>Type 3: Tumour involving the lateral, inferior, superior, anterior, or posterior walls of the maxillary sinus, the sphenoid sinus, and / or the frontal sinus, with or without involvement of the medial portion of the maxillary sinus, the ethmoid sinuses, or the nasal cavity. There must be no concurrent malignancy.</p> <p>Type 4: All Tumours with any extranasal / extrasinus extension to involve adjacent, contiguous structures such as the orbit, the intracranial compartment, or the pterygomaxillary space. All tumours associated with malignancy.</p>
Han et al. ⁽³⁶³⁾	<p>Group 1: Tumour involvement limited to the nasal cavity, lateral nasal wall, medial maxillary sinus, ethmoid sinus, and sphenoid sinus.</p> <p>Group 2: Same as group 1 except that tumour extends lateral to the medial maxillary wall.</p> <p>Group 3: Tumour extends to involve the frontal sinus.</p> <p>Group 4: Tumour extends outside the sinonasal cavities (i.e., orbital or intracranial extension).</p>
Kamel et al. ⁽³⁶⁴⁾	<p>Type 1: Tumour originating from the nasal septum or lateral nasal wall.</p> <p>Type 2: Tumour originating from the maxillary sinus.</p> <p><i>[This classification focuses on origin and not size / extent of tumour-does not analyze frontal sinus separately]</i></p>
Oikawa et al. ⁽³⁶⁵⁾	<p>T1: Tumour limited to nasal cavity.</p> <p>T2: Tumour limited to ethmoid sinus and / or medial and superior portions of maxillary sinus.</p> <p>T3: Tumour involves lateral, inferior, anterior, or posterior walls of maxillary sinus, sphenoid sinus, or frontal sinus.</p> <p>T3-A: without extension to frontal sinus or supraorbital recess.</p> <p>T3-B: involving frontal sinus or supraorbital recess.</p> <p>T4: Tumour extends outside sinonasal cavities (orbital or intracranial extension) or associated with malignancy.</p>
Cannady et al. ⁽³⁶⁶⁾	<p>Group A: Inverted papilloma confined to the nasal cavity, ethmoid sinuses, or medial maxillary wall.</p> <p>Group B: Inverted papilloma with involvement of any maxillary wall (other than the medial wall), or frontal sinus, or sphenoid sinus.</p> <p>Group C: Inverted papilloma with extension beyond the paranasal sinuses</p>

appearance of the epithelium inverting into the stroma with a distinct and intact basement membrane that separates and defines the epithelial component from the underlying connective tissue stroma. Histologically the tumour may be associated with atypia, dysplasia, carcinoma in situ, as well as frank squamous cell carcinoma. An inverted papilloma with synchronous carcinoma occurs when there is no history of previous surgery. The carcinoma may arise from the papilloma itself or it may be found as a separate lesion⁽³⁶⁸⁾. An inverted papilloma with metachronous carcinoma develops at the site of a previously benign inverted papilloma. The numerous publications on inverted papilloma differ widely in the observed incidence of associated carcinoma, ranging from 0%⁽¹²⁹⁾ to 53%⁽¹²⁸⁾. One report reviewed the incidence of malignancy in inverted papilloma in 63 case series of 3058 patients where adequate data has been described⁽¹³⁰⁾ (see Table 6.1). Eleven series found atypia in a total of 88 cases out of 958 patients (1.1%). Nine series noted dysplasia in 56 cases out of 454 patients (1.9%). Nine series found carcinoma in situ in 14 cases out of 414 patients. There were 163 (7.1%) cases of synchronous carcinoma out of 2297 cases. The vast majority were squamous cell carcinomas. There were also cases of transitional cell carcinoma, adenocarcinoma, mucoepidermoid carcinoma and verrucous carcinoma. Metachronous carcinomas were reported in 74 cases out of 2047 cases representing a transformation rate of 3.6%. However, the true population base for these figures is uncertain given that many series are reported from tertiary centres that are likely to be over representative of recurrent and problematic cases. No significant association between atypia or dysplasia and recurrence or malignant transformation was found. The mean time interval to developing a metachronous carcinoma was 52 months (range 6-180 months). The estimated malignant potential for recurrent disease is up to 11%.

Table 6.2. Incidence of pathological changes in inverted papilloma (based on all the reviews listed after this table up to diagnosis and imaging)^(120,123,124,127-130,216,353,355,356,367,369-417).

Pathology	Incidence/case series	Percentage
Atypia/Number in case series	88/958	1.1%
Dysplasia/ Number in case series	9/454	1.9%
Carcinoma in situ/ Number in case series	14/414	3.4%
Synchronous carcinoma/ Number in case series	163/2297	7.1%
Metachronous carcinoma/ Number in case series (mean follow-up 52 months)	74/2047	3.6%

Treatment

Most surgeons agree that recurrence is either the result of incomplete removal of the original tumour or a field change in mucosa, which nonetheless looks normal at the time of surgery. Recurrence occurs more often with limited resection⁽²¹⁶⁾. To rule out a synchronous malignancy and to reduce the recurrence rate and the need for repeated surgical procedures, as

well as reducing the possibility of progression to metachronous malignancy, complete resection of the involved mucosa and mucoperiosteum is advocated. The choice of surgical technique has leaned heavily towards the need for the complete removal of diseased mucosa given the pathology of inverted papilloma. Secondary to this is the desire to reduce surgical morbidity.

Recurrence rates of up to 78% have been reported for conservative surgery comprising polypectomy or local excision⁽¹²³⁾. Historically, the gold standard is an external approach with a medial maxillectomy via a lateral rhinotomy or midfacial degloving^(216,369). Vrabec⁽²¹⁶⁾ reported a recurrence rate of only 2% using a lateral rhinotomy with a modified Weber-Ferguson incision with a mean follow-up of 8.9 years. Of late, however, endoscopic resection has been given increasing consideration because it obviates the morbidity of an external approach⁽³⁷⁰⁾. Endoscopes have made complete endonasal tumour resection possible even in unfavourable sites such as the anterior wall and floor of the maxillary sinus⁽³⁵²⁾. The main objective is to remove all the diseased mucosa and mucoperiosteum.

Surgical approaches:

- Headlight intranasal polypectomy
- Caldwell Luc procedure
- Medial maxillectomy
- Lateral rhinotomy
- External procedures of the frontal sinus
- Endoscopic intranasal polypectomy
- Endoscopic maxillary antrostomy/ethmoidectomy
- Sphenoidotomy
- Endoscopic medial maxillectomy
- Median drainage procedure to gain access to the frontal sinus

Results

Historically, the external procedure is the method against which others are judged⁽³⁶⁷⁾. External approaches include a lateral rhinotomy, Caldwell-Luc, midfacial degloving or various techniques that allow access to the frontal sinus.

The introduction of the endoscope has meant that inverted papilloma can be removed with less surgical morbidity but the anterior wall and floor of the maxillary sinus have been difficult to access. In these patients, a Caldwell Luc procedure was done to remove diseased mucosa in these areas. However, more recently the endoscopic medial maxillectomy technique has meant that the whole lining of the maxillary sinus can be removed endoscopically and this has superseded the Caldwell Luc approach in the vast majority of cases^(371,372). Similarly, it has been difficult to remove all diseased mucosa in the frontal sinus by endoscopic means before the median drainage approach was popularised⁽³⁷³⁾. Angled endoscopes now make it possible, with the right curettes and forceps, to access most areas of the paranasal sinuses.

Reported recurrence rates of inverted papilloma vary widely, ranging from 0% to 78%⁽³⁷⁰⁾. Recurrence of inverted papilloma may depend on several factors including tumour location, extent, histology, multicentricity, method of removal and length of follow-up. The main factor in tumour recurrence is the thoroughness of removal⁽³⁶⁷⁾. Most recurrences are thought to develop because of an inadequate resection at the site of origin⁽³⁷⁴⁾. Bielamowicz et al.⁽¹²³⁾ found a statistically significant difference between the recurrence rates in patients treated with a medial maxillectomy (20%) versus those treated with a conservative resection (47%). This is borne out in a review of the literature, with limited transnasal procedures having a higher recurrence rate. Recurrence rates are higher in revision cases⁽³⁵⁴⁾ and this is probably due to the pathology or problems accessing the site of disease in this subgroup.

Mirza et al. found that recurrence rates in 63 case series was 12.8% for endoscopic procedures (n = 484), 17.0% for lateral rhinotomy with medial maxillectomy (n = 1025) and 34.2% for limited resections such as nasal polypectomy (n = 600)⁽¹³⁰⁾.

An updated review of the literature shows that it is possible to remove diseased mucosa as thoroughly using endoscopes as it is by external approaches (see Table 6.2). When comparing the results of external and endoscopic techniques it should be noted that the postoperative follow-up period was shorter in the endoscopic group. Most recurrent disease occurs in the first nine months⁽³⁵³⁾ and therefore the recurrence rates for the endoscopic group (14.5%) compare with the external group (16.7%) as the follow-up rates were 3 years 1 month and 5 years 2 months, respectively.

The advantage of the endoscopic technique is the absence of a facial incision, negligible facial swelling, a shorter inpatient time, and a reduction in postoperative pain and dysaesthesia. In addition, the endoscope offers improved visualisation with enhanced discrimination of tumour from normal tissue. With modern camera systems the magnification gives better visibility and the lens systems allow visualisation around corners.

The main area where disease has been difficult to completely remove endoscopically has been the anterior wall and floor of the maxillary sinus and within the frontal sinus. With the use of 45 and 70 degree endoscopes and the technique of endoscopic medial maxillectomy and the median drainage proce-

Table 6.3. Recurrence rates of inverted papilloma^(120,123-125,127-130,216,352-356,367,369,370,372,375-431).

Surgical approach	Recurrence/ case series	Percentage	Mean Follow-up
Endoscopic resection	173/1190	14.5%	3 yrs 1 month (documented in ⁸¹²)
Lateral rhinotomy with medial maxillectomy	207/1239	16.7%	5yrs 2 months (documented in ⁸⁹⁹)
Limited resection such as nasal polypectomy	208/606	34.4%	Inadequate data

ure it may be that future studies will show a reduction in recurrence rates using the endoscopic technique.

A review of the literature supports endoscopic resection as a method of treating most inverted papilloma^(125,352-354,413-420,423,425,431) (Table 6.3).

This is the same conclusion that Busquets and Hwang arrived at in their meta-analysis (Table 6.4)⁽⁴³²⁾. The exceptions include where there is scarring of the frontal recess, distortion from previous surgery, very advanced disease and associated malignancy⁽¹²⁵⁾.

Table 6.4. Summary of recurrence rates of inverted papilloma reported by Busquets et al.⁽⁴³²⁾.

Surgical approach	Recurrence/ case series	Percentage
Endoscopic resection	86/714	12%
Non endoscopic resection	138/692	20%
Historical non endoscopic	131/692	19%

Discussion

A review of the literature shows that endoscopic removal of inverted papilloma gives as good, if not better, results when compared to external approaches. Whichever technique is used there is good evidence that the outcome relates to how thoroughly the diseased mucosa is removed. The morbidity with the endoscopic technique is less with no facial incision, less facial swelling, a shorter inpatient time, a reduction in postoperative pain and dysaesthesia. It is very important that all of the specimen is examined histologically to look for atypia or malignancy as this would alter management. Recurrence rates are significant and have been reported several years after surgery although most occur in the first year. The relative contraindications for the endoscopic technique are where disease involves the frontal sinus and there is scarring or new bone formation in the frontal recess and if there is associated malignancy. The median drainage procedure and endoscopic medial maxillectomy technique along with angled endoscopes and a range of curved instruments mean that almost all areas of the paranasal sinuses can be accessed endoscopically and diseased mucosa removed.

Conclusions

- There is good evidence that the outcome relates to how thoroughly the diseased mucosa is removed.
- A review of the literature shows that endoscopic removal of inverted papilloma gives as good, if not better, results when compared to external approaches.
- It is very important that all the specimen is examined histologically to look for atypia or malignancy.
- The advantage of the endoscopic technique is the absence of a facial incision, negligible facial swelling, a shorter inpatient time, and a reduction in postoperative pain and dysaesthesia.

- The main area where disease has been difficult to completely remove endoscopically has been the anterior wall and floor of the maxillary sinus and within the frontal sinus but these areas can now be accessed endoscopically in most patients.

6-2 Bony and Fibro-osseous tumours

Introduction

Fibro-osseous lesions belong to a broad spectrum of benign bony abnormalities that can affect all regions of the paranasal sinuses^(104,433,434). Fibrous dysplasia, ossifying fibroma and osteoma are the three classic entities of this group of bony tumours^(104,433-436). Fibrous dysplasia was first described by Lichtenstein in 1938 and later by Lichtenstein and Jaffe as a monostotic or polyostotic tumour-like lesion, which is composed of fibrous stroma and an osseous tissue^(433,437,438). Ossifying fibroma was first described by Montgomery in 1927⁽⁴³⁹⁾ and has its origin mostly in the mandibular bone^(440,441). Vieira is credited as the first physician, who reported of a sinus osteoma case, which could successfully be removed by him in 1506^(442,443). Vallisneri described in 1733 the true bony origin of sinonasal osteomas^(104,434,444). The most important characteristics of the fibro-osseous lesions are given in Table 6.5.

6-2-1 Fibrous dysplasia

Definition

Three forms of fibrous dysplasia can be distinguished⁽⁴⁴⁵⁾: monostotic fibrous dysplasia (MFD), polyostotic fibrous dysplasia (PFD) and Albright's syndrome^(446,447). MFD is the most common form (80%) and 20% of these cases are localized in the head and neck region. PFD accounts for about 20% of cases and various areas of the skeleton can be involved. Albright's syndrome is rare and comprised of polyostotic FD, sexual precocity and cutaneous pigmentation. The incidence of FD involving the sinonasal system is not known⁽⁴⁴⁷⁾. Most commonly affected sites are the maxillary and mandible in the head and neck though ethmoid and sphenoid sinuses can be affected⁽⁴⁴⁸⁾.

Aetiology

The aetiology of FD remains obscure. Pensler et al. investigated cultures derived from the involved bone in two children with MFD and in one child with Albright's syndrome and showed a two- to threefold increased level of estrogen and progesterone receptors by radioimmunoassay and immunocytochemical assay. From their results, they concluded that estrogen may play a major role in the bony metabolism of FD⁽⁴⁴⁹⁾. The actual cause of fibrous dysplasia and related disorders, including McCune-Albright syndrome, has been recently defined as a set of mutations in the GNAS1 gene, located on chromosome 20q13.2, that normally codes for the alpha subunit of the G-protein⁽⁴⁵⁰⁻⁴⁵²⁾.

Histology

Histology shows slow replacement of medullary bone by abnormal fibrous tissue with different stages of bone metaplasia^(433,447).

Clinical presentation

Mostly FD develops during the first two decades of life^(433,447,453) and tends to stabilize after puberty^(447,454). The female to male ratio is almost 1:1⁽⁴⁵⁴⁾. Facial asymmetry is the most common clinical sign of FD in the head and neck^(108,448,453,455), followed by pain, ocular symptoms and neurological changes^(447,454,456,457). For the diagnosis of FD, the "groundglass" bone appearance on CT scans⁽⁴⁵⁸⁾ with bone window is the most useful radiographic sign⁽⁴⁵⁹⁾. Patients with MFD are usually asymptomatic and they can simply be observed.

Treatment

Medical therapy for FD is restricted to symptomatic relief. Bisphosphonates have been shown to decrease the incidence of fractures and bony pain⁽⁴⁶⁰⁻⁴⁶²⁾. The endocrinologic effects of McCune-Albright syndrome can also be treated medically: octreotide can decrease growth hormone secretion; radioactive iodine, methimazole, and propylthiouracil can be applied for hyperthyroidism; spironolactone and ketoconazole can be used as antiandrogens⁽⁴⁵⁸⁾. The surgical treatment of choice depends on the patient's symptoms, extent of the disease and age. Since FD is a rare condition, no general recommendation or larger series exist in the literature. Most authors recommend in severe cases local controlled surgical resection based on the location and the severity of the symptoms^(445,447,454,456,463). Some authors have reported endonasal endoscopic treatment of FD, especially for the relief of ocular symptoms (optic nerve decompression) or chronic rhinosinusitis^(110,453,456,463-468).

6-2-2 Ossifying fibroma

Definition

Ossifying fibroma (OF), also known as cemento-ossifying fibroma, psammomatoid OF, is a benign tumour composed of bone, fibrous tissue, calcification and cementum^(433,440,469,470). OF is most commonly located in the facial skeleton and usually invades the mandible, but can rarely occur in other areas as the maxilla, ethmoid sinus and nasal cavity⁽⁴⁴⁰⁾ with a more aggressive behavior.

Aetiology

The aetiology of OF has so far not been clarified. Trauma has been reported to play a major role in the development of OF, especially of the cemento-ossifying fibroma⁽⁴⁷¹⁾.

Histology

OF shows demarcated margins consisting of fibrous tissue with varying amounts of mineralized or calcified psammomatoid bodies⁽⁴⁷²⁾.

Clinical presentation

Patients with OF usually present between the second and fourth decades of life, and female incidence is more frequent than male incidence⁽⁴⁴¹⁾ with a male to female ratio of 1:5⁽⁴⁷³⁾. Ossifying fibroma of the mandible is usually asymptomatic. Depending on its extent, it can lead to facial pain, swelling, nasal obstruction, rhinosinusitis and ocular symptoms^(440,471,474,475). An aggressive variant of OF is termed “juvenile OF”, which has an onset at an earlier age. It is clinically more aggressive with extension of the tumour to the paranasal sinuses and orbit⁽⁴⁷⁶⁾. CT images show a characteristic sharp-demarcated expansile mass covered by a thick shell of bone with a multiloculated internal appearance and a content of varying density^(440,477).

Treatment

The treatment of choice is dependent on the site of tumour location. Asymptomatic mandible lesions can be observed but tumours invading the midfacial portion and the sinonasal tract show a more aggressive behavior and need surgical resection. Since there is a high chance for recurrence, most authors recommend when possible a total removal of the tumour^(447,454,456,473,478). Since OF is very rare, larger series on pure endonasal resection are not reported. In case reports, some authors have achieved tumour resection via an endoscopic approach^(440,471,479). Draf et al.⁽⁴⁸⁰⁾ reported on endonasal micro-endoscopic resection of four OF without any complications. In two cases, the surgery was done for optic nerve decompression. In OF with a large extension, most authors recommend a combined approach including craniofacial resection^(473,478,481).

6-2-3 Osteoma

Incidence

Osteoma is the most common bone tumour of the facial region⁽⁹⁷⁾. It is a benign, slowly growing neoplasm and arises mostly from the frontal sinus (57%) followed by the ethmoid, maxillary sinus and sphenoid sinus^(96,104,464,482-485). The incidence of osteoma ranges from 0.43%⁽⁴⁸⁶⁾ (skull X-rays study) to 3% in an analysis of CT scans (96). The male to female ratio ranges from 1.5:1 to 3.1:1 with a male predominance in most series^(101,104,442,482,487). Osteomas may be diagnosed at any age but mostly between the third and fourth decades of life^(101,104,488).

The growth rate of osteomas ranges from 0.44 to 6.0 mm/year⁽⁴⁸⁹⁾. Malignant transformation of osteomas has never been described⁽⁴⁹⁰⁾.

Aetiology

The aetiology of osteomas is controversial and still unresolved. There are three classically discussed theories: developmental, traumatic and infectious. In the developmental theory, previously silent embryonic stem cells become activated later in life and lead to uncontrolled bone formation. In the traumatic and

infectious theories, an inflammatory process is regarded as the inciting factor for bony tumour formation^(487,491,492).

Histology

Histologically three different types of osteoma can be distinguished. The eburnated type is composed of dense cortical bone and is also known as the ivory or compact osteoma. The mature type, also called osteoma spongiosum contains cancellous bone. The mixed form contains elements of both ivory and mature types^(101,104,442,492-494).

Clinical presentation

The most common clinical symptom of osteoma is frontal headache or facial pain. As many as 60% of patients with frontal sinus osteoma complain of headaches^(97,101,104,464,482,494,495). In expanding tumours, this is probably due to an obstruction of the natural drainage of the sinuses, which leads to chronic rhinosinusitis^(104,490). However, many patients with an osteoma are asymptomatic and the diagnosis is made incidentally on radiologic imaging obtained for other reasons⁽¹⁰²⁾. Expanding osteomas may lead to orbital and/or intracranial complications. Several authors have reported osteomas causing orbital symptoms such as diplopia, epiphora, facial distortion and even blindness^(468,482,492,493,496-501). Intracranial complications occur when osteomas impinge on the dura. This may lead to intracranial mucocele, CSF leak, meningitis, brain abscess, or pneumatocele as a first symptom^(442,483,502-522).

Imaging

On CT scans osteoma appears as homogenous, very dense and well-circumscribed lesions. In cases where there is suspicion of intracranial involvement, MRI is recommended^(97,484).

Treatment

Concerning the surgical resection most authors agree that small, asymptomatic lesions do not need surgery and a “wait and scan” policy can be chosen^(104,482,490). Rapid growth of the tumour and symptomatic patients with chronic rhinosinusitis due to tumour obstruction, massive headaches or facial deformity should be operated^(101,104,482,502). Smith and Calcaterra⁽¹⁰²⁾ recommended surgery if the tumour occupies more than 50% of the frontal sinus.

In general, the surgical approaches can be classified as endonasal, external or combined procedures. Several authors have reported on external or combined procedures in large osteomas. Largely to achieve a better aesthetic result, a coronal incision with the development of an osteoplastic flap is recommended^(97,482,523). During the development of functional endoscopic surgery, some authors have reported cases of endonasal resection of osteomas^(464,494,524). Larger series on endonasal removal of paranasal sinus osteomas are rare. Table 6.6 gives an overview of the series (n > 8), where osteomas have been treated by an exclusively endonasal approach.

Conclusions

- Osteoma is the most common bone tumour of the facial region.
- Osteomas may be asymptomatic but can be associated with headache due to secondary obstruction of a paranasal sinus or produce orbital symptoms such as diplopia, epiphora, facial distortion and even blindness. Occasionally, they may present with an intracranial mucocele, CSF leak, meningitis, brain abscess, or pneumatocele as a first symptom.
- Osteomas are frequent incidental findings and on CT scans appear as homogenous, very dense and well-circumscribed lesions.

Table 6.5. Main characteristics of fibro-osseous lesions of the nose and paranasal sinuses.

	Fibrous Dysplasia	Ossifying fibroma	Osteoma
Incidence	Not known	Not known	0.43% to 3%
Most frequent site of origin	Mandible and maxilla	Mandible	Frontal sinus
Histology	Replacement of bone by fibrous of tissue	Fibrous tissue, calcification	Ivory, mature and mixed type
Age of presentation	First to second decade	Second to fourth decade	Third to fourth decade
Male to female ratio	1:1	1:5	1.5 – 3.1 :1
Radiology	'Ground glass' appearance on CT	Expansile mass with sharp demarcation	Homogenous, dense well-circumscribed
Symptoms	Facial asymmetry	Painless swelling, nasal obstruction	Frontal headache
Malignant transformation	0.5% in polycystic form	Not known	No reports
Treatment	Observation; surgery only in symptomatic cases	Observation; if possible complete surgical resection in extended cases	Observation in asymptomatic cases; Surgery in symptomatic patients and complications

Table 6.6. Reports (n > 8) on endonasal resection of paranasal sinus osteomas.

Author	Nr. of patients	Most common location	Follow-up (months)	Recurrence
Bignami et al. ⁽⁵²⁵⁾	11	FS	40	0
Brodish et al. ⁽⁴⁶⁴⁾	9	Eth	1-17	0
Castelnuovo et al. ⁽⁵²⁶⁾	22	Eth	53	0
Schick et al. ⁽⁴⁸²⁾	23	FS	11	3 Residuals
Seiberling et al. ⁽⁵²⁷⁾	23	FS	36	0

(FS: Frontal Sinus; Eth: Ethmoid cells)

- Larger series on endonasal removal of paranasal sinus osteomas are rare but this approach can be undertaken depending on the size and position of the lesion.

6-3 Benign Vascular

6-3-1 Juvenile angiofibroma

Search strategy

The literature review was focused on outcomes following endoscopic removal of small (stages I and II) and large (stages III and IV) juvenile angiofibroma. The data presented in this review were derived from a PubMed search using the keywords "juvenile angiofibroma", "endoscopic sinus surgery", and "endoscopic anterior skull base". The search was not limited to only English-language articles. Studies reporting outcomes following endoscopic resection juvenile angiofibromas of at least five cases were automatically eligible for inclusion. In those instances where a single centre had generated more than one case series from overlapping periods, data from the most recent series was used (mentioning it in the corresponding table). Otherwise, studies were selected on the basis of full-text availability, relevance to the review question and if data presented added to the general discussion of the review. The bibliography of selected articles was manually searched for other relevant studies.

Some texts mixed external and endoscopic procedures being the patients who had these mixed procedures were excluded. Tables containing mixed procedures or surgeries on other than juvenile angiofibromas were considered when the data of the angiofibroma was available.

Introduction and Incidence

Juvenile angiofibroma (JA) is a benign tumour associated to young males between 9 and 19 years of age. It makes about 0.05% of head and neck tumours, with an incidence between 1:5,000-1:60,000 (528) and 1:6,000-1:16,000 in the USA (529,530) being among the most frequent of the adolescence. In the Middle East and in India, the incidence seems to be much higher than in Europe ⁽⁶⁵⁾.

Aetiology

Recent studies show genetic changes to be involved in the origin; others believe JA to be a vascular malformation ⁽⁵³¹⁾ in the sense of non-resorption of a primitive artery of the first brachial arch with the presence of non-chromaphinic paraganglionic cells ⁽⁵³²⁾. The theory on the genetic origin is sustained by findings of chromosome 17 deletions, including regions of the suppressor gen p53 and the oncogen Her-2/neu ⁽⁵³³⁾. Additionally, the inherited Gardner syndrome could be associated in six cases of angiofibroma together with chromosome aberrations ⁽⁵³⁴⁾.

Clinical presentation

JAs are locally aggressive and destructive, spreading from the nasal cavity to the nasopharynx, paranasal sinuses, and orbit skull base with intracranial extension. JA display a slow and locally expansive growth starting at the basisphenoid and the sphenopalatine foramen. Dumbbell shape extension into the pterigopalatine fossa and then the infratemporal fossa, the cavernous sinus or intracranial may occur⁽⁵³⁵⁾. The vascular supply is provided mainly from the internal maxillary artery. There are rather innocuous presenting symptoms such as progressive unilateral nasal obstruction (80-90%) with rhinorrhea and recurrent unilateral epistaxis (45-60%). Headaches (25%) may appear secondarily to the blockage of the paranasal sinuses and compression of the Eustachian tube produces a secretory otitis media with conductive hearing loss. With the tumour extension into the paranasal sinuses a chronic rhinosinusitis and swelling of the face / cheek (10-18%) may appear. Involvement of the orbit and or the endocranium display neurologic deficits⁽⁶⁵⁾. Other symptoms: alterations in olfaction, rhinolalia clausa, otalgia, and reduced vision.

Diagnosis & Imaging (Table 4.3)

This fibrovascular tumour is characterised by typical radiological findings and by predictable growth patterns. Tumour extension and blood supply can be accurately determined by CT, MR imaging, angio-MRI, and angiography to select the least traumatic approach with secure haemostatic control and maximum preservation of the anatomy responsible for facial growth. Pre-operative biopsy is unnecessary and not recommended due to the risk of severe bleeding.

CT basically provides the bony landmarks for the surgery, whereas MRI, displaying a homogeneous contrast enhancement, helps in differentiating tumour from chronic rhinosinusitis secondary to the blockage of affected paranasal sinuses. Moreover, it easily delineates potential intracranial extension and offers an ideal method for follow-up without irradiation⁽⁵³⁶⁾.

Additional angio-MRI provides a picture of the vascular supply avoiding a diagnostic angiography.

Angiography and embolisation

Depending on the material employed for the angiography, embolisation can be performed 24-48 hours before surgery. The vascular supply comes mainly from the internal maxillary artery, the ascending pharyngeal artery⁽⁵³⁷⁾ and the vidian artery.

When using resorbable materials, the interval between embolisation and surgery should not exceed 48 hours as the supply artery can quickly be recanalized⁽⁵³⁸⁾. Onyx is a recent material which displays some technical advantages such as deep penetration into the lesion, thus producing extensive tumour infarction, the ability to embolize extensive portions of the tumour

through fewer arterial catheterisations, and the safety of catheter withdrawal despite often substantial reflux along the embolic catheter⁽⁵³⁹⁾.

Branches originating as “neovascularization” from the internal carotid artery are rare in extracranial tumours, but can be observed when the cavernous sinus is involved (medially or laterally). These new vessels can be embolized; however the risk of a complication is higher. Alternatively, direct intratumoural embolisation under general anaesthesia has been proposed for such cases. A slow injection of the tumour is performed with either a mixture of cyanoacrylate, lipiodol, and tungsten powder through an intranasal or lateral percutaneous route under radiographic control⁽⁵⁴⁰⁾.

Embolisation provides a 60-70% reduction of the intraoperative bleeding and the need for blood transfusions⁽¹³⁴⁾. Direct intraoperative identification and ligation or coagulation of the major supplying vessels, with the help of a hypotensive general anaesthesia, can be an alternative to the embolisation in both smaller⁽⁵⁴¹⁾ and higher staged tumours⁽⁵⁴²⁾. When both external carotid artery systems are involved in the vascular supply, both internal maxillary arteries should be embolized⁽⁵⁴³⁾ to prevent the formation of an alternative vascular supply.

Embolisation, pre-operative autologous donation and the cell saver system for immediate re-transfusion of the collected blood after filtration are important tools for dealing with blood loss in angiofibroma surgery as they minimize blood transfusions.

Staging

Different staging systems have been proposed based on the tumour extension. Sessions et al.⁽⁵⁴⁴⁾ classification from 1981 was modified 1996 by Radkowski et al.⁽⁵⁴⁵⁾. Fisch proposed another in 1983⁽⁵⁴⁶⁾, revised in 1989 by Andrews et al.⁽⁵⁴⁷⁾. In 1984, Chandler et al.⁽⁵³⁵⁾, based their classification on that for nasopharyngeal carcinomas. Bremer⁽⁵⁴⁸⁾, in 1986 and Antonelli in 1987⁽¹³²⁾ presented another staging system. Recently, Önerci⁽⁵⁴⁹⁾, Carrillo et al.⁽¹³⁵⁾, and Snyderman et al.⁽⁵⁵⁰⁾ have made proposals for new classifications. Table 6.7 summarizes all classifications.

Treatment

The surgical approach has undergone a change of paradigms in the last two decades. Four aspects may have influenced this change:

- 1) With increased endoscopic surgical skills, together with a better understanding of the complex anatomy of the paranasal sinuses and surrounding vital structures, many rhinologists have increasingly applied their expertise in endoscopic sinus surgery to the resection of nasal and sinus tumours, including endoscopic approaches beyond the paranasal sinuses.

- 2) Advances in radiological imaging (high resolution CAT scan, MRI, angio-MRI) have contributed to improved surgical planning and tumour resection.
- 3) Improvements of adjuvant techniques, such as embolisation, better surgical instruments, navigational systems, or even intraoperative imaging systems. Improved embolisation techniques plus the use of radiofrequency devices have produced a shift in the endoscopic removal of angiofibromas from the classical “en-bloc” removal to “piece-meal” resections. The reduction in the tumour volume enables better and more comfortable access to anatomically difficult areas. Additionally, navigational systems may provide information to access areas beyond the paranasal sinuses.
- 4) Another reason for abandoning external approaches is to avoid their well-known morbidity.

The first reports about minimally invasive endoscopic resections were published during the nineties for low staged angiofibromas (stages I and II) showing, firstly, the feasibility and secondly, proving a similar recurrence rate compared to external approaches, but with reduced risks and morbidity^(14,551-560).

With increasing experience, a progressive shift from stages I and II has been observed towards Radkowski / Andrews stages IIC and IIIA respectively⁽⁵⁶¹⁻⁵⁶⁹⁾.

It is not the aim of this paper to detail the surgical steps of the endoscopic approach. What seems to be important to prevent recurrences is the subperiosteal dissection of the tumour attachment at the basisphenoid with drilling of the denuded bone to remove residual disease, which may not be immediately evident^(316,562).

For larger tumour extensions with infratemporal involvement, Khalifa and Ragab⁽⁵⁷⁰⁾ have proposed an endoscopic assisted antral window approach. This enables the dissection of the tumour from the masticator muscles and the fat of the cheek. Hackmann et al.⁽⁵⁴³⁾ also presented endoscopic-assisted approaches, classified as any approach in which a surgical incision was combined with endoscopy, which they used in six cases. Direct endoscopic approaches to the pterigopalatine fossa and the infratemporal space have been proposed, showing the potential range of purely endoscopic tumour access⁽⁵⁷¹⁾. Additionally, experience has shown that tumour fragmentation (“piece-meal resection”) helps to completely assess the extension⁽⁵⁶²⁾, but is not associated secondarily with increased recurrence rates.

Other non-surgical treatment options have been proposed. External-beam therapy is advocated to address recurrent and extensive (intracranial) lesions^(133,572,573). Recent radiotherapy series report tumour control in 85% after applying 30-35 Gy in advanced stages. In both series, the recurrent tumour was salvaged with either further surgery, further radiotherapy, or in

1 case, both. One patient developed a basal cell carcinoma of the skin within the radiation field 14 years after radiotherapy, 3 developed cataracts 5–10 years after radiotherapy, and 1 had a delayed, transient central nervous system syndrome^(574,575).

Intensity-modulated radiotherapy to deliver 3,400–4,500 cGy⁽⁵⁷⁶⁾ to 3 patients with extensive disease involving the cavernous sinus and skull base gamma-knife (20-Gy dose) to treat 2 cases (Chandler stage III and IV) following incomplete surgical excision⁽⁵⁷⁷⁾ has been used.

Radiotherapy can produce long-term sequelae in adolescents, such as growth impairment⁽⁵⁷³⁾. Also, the central nervous system syndrome⁽⁵⁷⁸⁾ can result from radiation damage to the brain displaying early with encephalopathy, or late, months or years after radiation therapy, with dementia, or possibly radiation-induced tumours. Although malignant transformation of JA after radiotherapy has been observed^(579,580), it has been recommended as an adjuvant therapy for unresectable tumours, failure of complete tumour removal, or for extensive intracranial extension^(133,545,581).

Chemotherapy with doxorubicine and dacarbazine has been proposed for recurrences, although the experience is limited and its use proposed for selected cases with locally aggressive growth^(582,583).

Hormonal therapy has not been formerly evaluated yet, despite promising studies⁽⁵⁸⁴⁾. A recent study does not show any positive effect⁽⁵⁸⁵⁾. The number of cases studied in both was too few to allow conclusions.

Results

An overview of the literature has been summarized in Table 6.8.

The rate of recurrent tumours is rather low for smaller staged lesions, increasing in the higher staged tumours. Comparison with external approaches is biased because larger tumours have tended to be resected using these open operations. It should also be noted that there are publications referring to “residual” disease, meaning focal enhancement on imaging (mainly MRI) but without symptoms and stable in size during follow-up.

Discussion

The endoscopic approach of JA is a minimally invasive procedure with a low morbidity that has enabled the radical removal of JAs up to an Andrews-Fisch stage IIIA. Endoscopic surgery can be undertaken for recurrent JAs after previous endoscopic⁽⁵⁶²⁾ or after external approaches⁽⁵⁸⁶⁾.

Complications of the endoscopic approach can be rated as similar to a total sphenoidectomy. Recently, a loss of tear-

ing causing a dry eye has been specifically related to endonasal removal of angiofibromas in four of seven cases^(587,588), most probably due to damage to branches of the sphenopalatine ganglion or the ganglion itself. Other complications, such as hypaesthesia V2/V3, trismus, sinusitis, or the need of blood transfusions⁽⁵⁴³⁾ are not directly linked to the endoscopic procedure, but to the extent of surgery.

Blood loss during endoscopic removal is variable. Table 6.9 summarises the blood loss measured in some studies. For Nicolai et al.⁽⁵⁶⁴⁾ the amount of blood loss is intimately linked to the quality of the embolisation and to the tumour volume / extension, this latter point being confirmed by Önerci⁽⁵⁶⁵⁾. For Snyderman et al.⁽⁵⁵⁰⁾, there is a significant correlation of the blood loss to a new staging systems based on residual vascularity. Indeed, the embolisation procedure has been shown to decrease the intraoperative blood loss statistically, to 650 ml in the embolized group as compared to an average of 1,200 ml in the non-embolized group ($p < 0.05$). Similarly, the need for peroperative blood transfusion was reduced ($p < 0.005$)⁽¹³⁴⁾.

In those series comparing the blood loss between endoscopic and open JA removal, the mean blood loss seemed to be lower in the endoscopic approaches^(541,589), and in lower staged tumours⁽⁵⁴¹⁾ although, generally, a bias has to be considered: larger tumours were more frequently addressed by an open approach, while staged I and II were mainly operated on endoscopically.

Some authors have introduced the KTP laser, the ultrasonic scalpel, or the diode laser to reduce the bleeding intraoperatively^(563,571,590-592).

Subperiosteal dissection and drilling of the basisphenoid and other bony parts where the JA had been attached seem to be the key to avoid recurrences⁽³¹⁶⁾. Furthermore, on the basis of a review of preoperative CT and MRI on 72 patients, Lloyd et al.⁽⁵⁹³⁾ found that in 60%, JAs expanded posteriorly along the pterygoid canal with invasion of the cancellous bone of the pterygoid base and greater wing of the sphenoid and they determined that 93% of recurrences occurred in patients with imaging evidence of invasion of the sphenoid diploe through the pterygoid canal.

The duration of the surgical procedure might be a relative disadvantage for the endonasal procedures⁽⁵⁶²⁾, although here a “learning curve” has to be considered. Notwithstanding this, if it avoids the morbidity of external approaches, both surgeons and patients are probably happy to accept a longer procedure. Hospital stays appear to be shorter after endoscopic JA removal compared to external surgery^(589,594), but again a bias has been introduced comparing mainly low staged versus high staged tumours.

In pre-endoscopic times, initial tumour control rates achieved figures around 97%, but with a (symptomatic) recurrence rate of about 50%, but being lower after primary surgery at 34%⁽⁵⁹⁵⁾. Also, preoperative embolisation is considered a risk factor showing a higher recurrence rate and earlier recurrences^(595,596), with a statistically significant difference⁽⁵⁹⁷⁾. However, the recurrence rate seems to be more related to the involvement of specific sites, such as the basisphenoid⁽³¹⁶⁾ anterior skull base^(598,599), the infratemporal fossa and the cavernous sinus^(532,553), the pterygoids and pterygopalatine fossa⁽⁵³²⁾ indicating that the higher staged, and therefore more extensive tumours tend to develop a higher rate of recurrence^(134,531,589). Also, specific infiltration of certain areas, e.g. the basisphenoid via the Vidian canal⁽³¹⁶⁾ is important, as well as residual vascularity after embolisation⁽⁵⁵⁰⁾.

Conclusions

- Pre-operative biopsy is unnecessary and not recommended due to the risk of severe bleeding.
- Embolisation, pre-operative autologous donation and the cell saver system for immediate re-transfusion of the collected blood after filtration are important tools for dealing with blood loss in angiofibroma surgery as they minimize homologous blood transfusion.
- En bloc resection is not necessary to achieve surgical cure. On the contrary, piece-meal resections seem to facilitate the approach to difficult anatomic locations, particularly when considering that the surgery is usually performed in immature noses. Therefore, the size of the tumour should no longer be a principle criterion for the surgical planning.
- The use of an endoscopic approach to excise small juvenile angiofibromas (stages I and IIA, B) is supported by excellent results from a number of operative series published in recent years. Recurrence rates are comparable to classical external approaches. However, with the exception of one prospective study⁽⁵⁹⁵⁾ in which the patients were consecutively included and data prospectively collected, all other papers are based on retrospective data, thus being experienced-based and evidence level III, with strength of recommendation C⁽²⁾.
- Extended juvenile nasopharyngeal angiofibromas (Radkowski / Andrews-Fisch stages IIC, IIIA/B) are still a surgical challenge; however, there is increased experienced-based evidence (evidence level III, strength of recommendation C) that endoscopic resection of large or an extended tumour is feasible in expert hands.
- Prior staging systems did not account for the route of intracranial extension and the vascularity of the tumour. New staging systems seem to better predict of immediate morbidity (blood loss; need for multiple operations) and tumour recurrence.

Table 6.7. Staging proposals for juvenile angiofibromas.

Author / stage	Sessions ⁽⁵⁴⁾	Fisch ⁽⁵⁶⁾	Chandler ⁽⁵³⁾	Bremer ^(54b)	Antonelli ⁽⁵²⁾	Andrews ⁽⁵⁷⁾	Radkowski ^(54b)	Önerd ⁽⁵⁹⁾	Carrillo ⁽⁶⁰⁾	Snydermann ⁽⁵⁵⁾
I	1981 (n=23) IA limited to posterior nasal cavity and / or choanal border	1983 (n=41) I limited to the nasopharynx and nasal cavity without bone destruction	1984 (n=13) I confined to nasopharynx	1986 (n=30) IA limited to posterior nares or nasopharynx vault	1987 (n=23) I limited to nasopharynx and / or nasal fossa	1989 (n=15) I limited to the nasopharynx and nasal cavity. Bone destruction negligible or limited to the sphenopalatine foramen	1996 (n=23) IA = Sessions	2006 (n=36) I extension to the nose, nasopharyngeal vault, and sphenoid sinus	2008 (n=54) (A) medial, with tumour limited to nasopharynx, nasal fossae, maxillary antrum and anterior ethmoid cells	2010 (n=35) I no significant extension beyond the site of origin and remaining medial to the midpoint of the pterygopalatine space
II	IIA minimal lateral extension to pterigopalatine fossa	II invading the PMF and the maxillary, ethmoid, and sphenoid sinus with bone destruction	II extending into nasal cavity and/or sphenoid sinus	IIA minimal lateral extension through the sphenopalatine foramen into medial PMF	II extending into sphenoid sinus and / or PMF	II invading the PMF or the maxillary, ethmoid, or sphenoid or sinus with bone destruction	IIA = Sessions	II extension to the maxillary sinus or the anterior cranial fossa, full occupation of the PMF, limited extension to the ITF, or the pterygoid plates posteriorly	(B) invasion to pterygomaxillary fissure or anterior infratemporal fossa with tumour < 6 cm in diameter	II extension to the paranasal sinuses and lateral to the midpoint of the pterygopalatine space
III	IIIB full occupation of pterigopalatine fossa with or without orbital bone erosion	III extending into one or more of the following: antrum, ethmoid sinus, pterygomaxillary lateral to the cavernous sinus	III extending into one or more of the following: antrum, ethmoid sinus, pterygomaxillary and infratemporal fossae, orbit, and/or cheek	III full occupation of PMF displacing posterior wall of antrum forward. Superior extension eroding orbital bone	III beyond stage II, limits extending to one or more of the following structure: maxillary sinus, ethmoid, orbit, infratemporal fossa, cheek, palate	III involving the infratemporal fossa or orbital region without intracranial involvement	IIIB = Sessions	III deep extension into the cancellous bone at the base of the pterygoid or the body and the greater wing of the sphenoid, significant extension to the ITF or pterygoid plates posteriorly or orbital region, and obliteration of cavernous sinus	(C) extension to pterygomaxillary fissure or anterior infratemporal fossa with tumour ≥ 6 cm in diameter	III locally advanced with skull base erosion or extension to additional extracranial spaces, including orbit and infratemporal fossa, no residual vascularity following embolisation
IV	IV massive invasion of cavernous sinus, the optic chiasmal region, or pituitary fossa	IV extending into cranial cavity	IV intracranial extension	IV intracranial extension through the sphenopalatine foramen	IV intracranial extension	IV intracranial extension	IIIC = Sessions or posterior to pterigoid plates	IV intracranial extension between the pituitary gland and internal carotid artery, tumour extension posterolateral to the internal carotid artery, and extensive intracranial extension	(D) extension to posterior infratemporal fossa or roof of skull base	IV Skull base erosion, orbit, infratemporal fossa Residual vascularity
V	IVB extensive intracranial extension w / wo invasion of the cavernous sinus	IVB invading the infratemporal fossa or orbit with intracranial extradural (parasellar) involvement	IVB erosion of skull base – extensive intracranial w / wo cavernous sinus	IVB full occupation of PMF displacing posterior wall of antrum forward. Superior extension eroding orbital bone	IVB full occupation of PMF displacing posterior wall of antrum forward. Superior extension eroding orbital bone	IVB full occupation of PMF displacing posterior wall of antrum forward. Superior extension eroding orbital bone	IIIC = Sessions or posterior to pterigoid plates	(E) extensive skull base and intracranial invasion.		

V Intracranial extension, residual vascularity
M: medial extension
L: lateral extension

Table 6.8. Results after endoscopic removal of juvenile angiofibromas.

Author* (year of publication)	Total n	Classification	n + stage	Mean follow-up in months (range)	Recurrence / residual
Schick (1999) ⁽⁶⁰¹⁾	5	Fisch	5 type II	(5-39)	No (0%)
Jorissen (2000) ⁽⁵⁵³⁾	13	Radkowski / Andrews * / Sessions	2 stage IA 2 stage IB 2 stage IIA 2 stage IIB 4 stage IIC 1 stage IIIA	35.3 (12-72) (f-u available for 11 patients)	1 recurrence after 6 mo of a stage IIC (cured by ESS) 1 recurrence of a stage IIIA after 4 mo. Regression after embolisation of ICA.
Roger (2002) ⁽⁵⁵⁷⁾	20	Radkowski	4 stage I 7 stage II 9 stage IIIA (Including 7 recurrences after open surgery).	22	2 residual of stage IIIA were asymptomatic 30 and 36 mo after surgery
Önerci (2003) ⁽⁵⁶⁵⁾	12	Radkowski	8 stage IIC 4 stage IIIA	Min. 6 mo	No recurrence in stage IIC 2 residual asymptomatic in stage IIIA with no progression after 24 mo f-u
Nicolai (2003) ⁽⁵⁶⁴⁾	15	Andrews	2 type I 9 type II 3 type IIIA 1 type IIIB	50 mo (24-93) [SD +/- 19.9]	1 residual (24 mo postop)
Naragi (2003) ⁽⁶⁰²⁾	12	Bremer	2 stage IA 2 stage IB 3 stage IIA 5 stage IIB	15	2 (endosc.-C-L). Recurrence rate 18%
Wormald (2003) ⁽⁵⁶⁹⁾	7	Radkowski	1 stage I 2 stage IIA 3 stage 1 stage IIC	45 (SD 1.9 years)	No
Munoz del Castillo (2004) ⁽⁶⁰³⁾	11	Andrews	8 type II		36.3% recurrence
Mann (2004) ⁽⁶⁰⁴⁾	15	Fisch	Stages I-III (number of cases not specified)	(12-240) (referred to a total of 30 patients with JA)	1 (stage not mentioned)
Pryor (2005) ⁽⁵⁶⁷⁾	6	-	-	14	no recurrences 1 patient underwent endoscopic removal secondarily after prior treatment elsewhere
Hofmann (2005) ⁽⁵⁶²⁾	21	Andrews	1 type I 15 type II 5 type IIIA	51.7 (5-120)	3 (14.3%) recurrences (2 underwent endoscopic resection, one gamma- knife) + 3 asymptomatic***
Sciaretta et al. (2006) ⁽⁵⁶⁸⁾ Includes Pasquini (2004) ⁽⁵⁶⁶⁾	9	Radkowski / Andrews **	1 stage IA 4 stage IIA 1 stage IIB 2 stage IIC 1 stage IIIA	18.1 (6-75)	1 recurrence of a stage IIB 20 mo postop, now staged IIA: reoperated by ESS, 25 mo disease-free.
Tosun (2006) ⁽⁵⁸⁶⁾	9	Radkowski	2 stage IA 2 stage IB 3 stage IIA 2 stage IIIA	20.6 (12-55)	No recurrence 2 endoscopically assessed were recurrent tumours.
Borghai (2006) ⁽⁵⁴¹⁾	23	Radkowski	5 stage IA 9 stage IB 4 stage IIA 5 stage IIB	33.1 (14-57)	1 recurrence (4.3%) of a stage IIB 19 mo postop. Endoscopic re-operation, now 28 mo disease-free
Eloy (2007) ⁽⁵⁹⁴⁾	6	Radkowski	1 stage I 1 stage IB 4 stage IIB	67	1 recurrence cured by ESS. 1 residual non-symptomatic nodule regressing on MRI 4 years postop)
Andrade (2007) ⁽⁶⁰⁵⁾	12	Andrews	8 stage I 4 stage II	5-42 ¹ 24 (12-60) ²	No
Yiotakis (2008) ⁽⁶⁰⁶⁾		Radkowski	Stages between I-IIB	10.5 (6-36)	1 recurrence ³

Table 6.8. Results after endoscopic removal of juvenile angiofibromas.

Author* (year of publication)	Total n	Classification	n + stage	Mean follow-up in months (range)	Recurrence / residual
Gupta (2008) ⁽⁵⁹⁵⁾	28	Radkowski	6 stage I 14 stage IIA 6 stage IIB 2 stage IIC	Min.12 mo (12-65)	No recurrence. 1 residual (prior recurrence of stage IIC) 7 had prior external approaches, the recurrences being approached now endoscopically.
Hackmann (2009) ⁽⁵⁴³⁾ Includes Carrau (2001) ⁽¹⁴⁾	15	-	4 had prior surgery	48 (12-120) (incl. 16 cases w mcombined / open surgery)	1 (not specified)
Bleier (2009) ⁽⁵⁸⁹⁾	10	Andrews	1 stage I 8 stage II 1 stage IIA	24.4 (3.6-88.4) (incl. 8 cases w open surgery)	No
Ardehali (2009) ⁽⁵⁸⁷⁾	47****	Radkowski	21 stages IA to IIB 22 stage IIC 3 stage IIIA 1 stage IIIB	33.1 (8-74)	6 / 31 recurrences of primary treated patients; 1 stage IA, 1 stage I B 2 stage IIA; 1 stage IIIA and 1 stage IIC). 3/ 16 recurrences in secondarily treated (1 stage IIIA, 2 stage IIC Five patients embolized before surgery. 4 patients combined approach

SD = standard deviation; mo = months; ICA = internal carotid artery; 1 = in the abstract; 2 = in the text; *only first author mentioned, in chronologic order. ** Radkowski chosen among the staging systems used in the paper; ***MRI-enhancement without symptoms or growth during f-u of 3, 5 and 10 years, respectively; Rec.-rate: recurrence rate. 3=2 recurrences attributed to transpalatal approach in the text, but one found for endoscopic approach in table 2; ****31 (66%) cases were primarily treated, the remaining 16 (34%) cases were treated secondarily being previously operated by conventional or endoscopic methods; 43 cases were approached endoscopically and 4 cases by combined approaches.

Table 6.9. Amount of blood loss for surgery of juvenile angiofibromas.

Author*	Endoscopic approach: mean blood loss (in ml)
Glad ⁽¹³⁴⁾	650 after embolisation 1200 without embolisation
Borghei ⁽⁵⁴¹⁾	666 in stage IA 680 in stage IB (0.2 packs blood transfusion) 1068 in stage IIA (0.75 packs blood transfusion) 1319 in stage IIB (1.8 packs blood transfusion)
Roger ⁽⁵⁵⁷⁾	350 (median, 300)
Nicolai ⁽⁵⁶⁴⁾	372 (range 80 – 600)
Önerci ⁽⁵⁶⁵⁾	1000 in stages IIC 1500 in stages IIIA
Pryor ⁽⁵⁶⁷⁾	225
Hofmann ⁽⁵⁶²⁾	50-2000
Eloy ⁽⁵⁹⁴⁾	575
Gupta ⁽⁵⁹⁵⁾	168 ± 24 with embolisation 360 ± 35 without embolisation
Ardehali ⁽⁵⁸⁷⁾	770 with embolisation 1403 without embolisation
Giavroglu ⁽⁶⁰⁷⁾	506
Nakamura ⁽⁵⁹⁰⁾	560
Ochi ⁽⁵⁹¹⁾	228

*Only first author listed

7. Malignant

7-1 Epithelial

7-1-1 Squamous cell carcinoma (SCC)

Review search strategy

The literature review was focused on outcomes following endoscopic resection of sinonasal SCC. The data presented in this review were derived from a PubMed search using the MeSH keywords carcinoma, paranasal sinuses, squamous cell, endoscopy and surgery. The search was limited to English-language articles, published in the past 20 years. Studies reporting outcomes following endoscopic resection of SCC were automatically eligible for inclusion. Otherwise, studies were selected on the basis of full-text availability, relevance to the review question and if data presented added to the general discussion of the review. The bibliography of selected articles was manually searched for other relevant studies. In those instances where a single centre had generated more than one case series from overlapping periods, data from the most recent series was used.

Case series were included in this review if there was a clear description of the pathology as squamous cell carcinoma (SCC). Some texts mixed external and endoscopic procedures and the patients who had these mixed procedures were excluded.

Introduction

Cancers of the nasal cavity and paranasal sinuses are uncommon, comprising less than 1% of all malignancies and only 3% of those arising in the head and neck region. Fewer than 700 cases of sinonasal malignancies are diagnosed in England, United Kingdom (Figure 7.1) each year. Sinonasal malignancies occur twice as often in males as in females, and are most often diagnosed in the fifth to seventh decade of age. The majority of these tumours are squamous cell carcinoma, although a variety of other malignancies such as sarcoma, adenoid cystic carcinoma, lymphoma, melanoma, and olfactory neuroblastoma may also occur at this site.

Sinonasal malignancies have traditionally been associated with a poor prognosis. Anatomical proximity of the nasal cavity and paranasal sinuses to the skull base, brain, orbit, and carotid artery makes complete surgical resection of sinonasal tumours a challenging and sometimes impossible task and is one of the reasons for poor outcome of these malignancies. In addition, tumours of the paranasal sinuses and nasal cavity tend to be asymptomatic at early stages, presenting more frequently at late stages once extensive local invasion has occurred. This unfortunate combination of complex surrounding anatomy with late advanced stage presentation, therefore leads to the frequent local recurrence and subsequent poor outcome.

Incidence and etiology

Squamous cell carcinoma (SCC) is the most common malignancy of the sinonasal tract. The incidence of SCC has been reported in the literature to be between 27.8%⁽⁶⁰⁸⁾ and 92%⁽¹⁶⁷⁾ of all sinonasal malignancies over a 10-year period. These tumours are twice as common in men as in women with a male-to-female ratio of 2:1. The age range is wide with a peak incidence between 60 to 70 years of age⁽⁶⁰⁹⁾. An association between SCC and nickel exposure has been shown by Pedersen et al.⁽⁶¹⁰⁾. They reported that workers at a nickel refinery in Norway developed SCC at 250 times the expected rate, with a latent period varying from 18 to 36 years.

Inverted papilloma is also associated with SCC in approximately 10% of the cases⁽⁶¹¹⁾. This may be synchronous or metachronous. Based on the literature, the malignancy rates of synchronous and metachronous carcinoma is 7.1% and 3.6%, respectively. An inverted papilloma with synchronous carcinoma can occur even when there is no previous history of surgery. The carcinoma may arise from the papilloma itself or it may be found as a separate lesion⁽³⁶⁸⁾. An inverted papilloma with metachronous carcinoma can develop at the site of a previously benign inverted papilloma. The numerous publications on inverted papilloma differ widely in the observed incidence of associated carcinoma, ranging from 0%⁽¹²⁹⁾ to 53%⁽¹²⁸⁾. One report reviewed the incidence of malignancy in inverted papilloma in 63 case series of 3058 patients where adequate data has been described⁽¹³⁰⁾ and found the incidence of malignancy to be 2.1%. There were 163 (7.1%) cases of synchronous carcinoma out of 2297 cases. The vast majority were squamous cell carcinomas. Metachronous carcinomas were reported in 74 cases out of 2047 cases representing a transformation rate of 3.6% (Table 7.1).

A systematic review of the literature on survival outcomes of SCC arising from inverted papilloma concluded that oncological outcomes were comparable to primary sinonasal SCC, although some patients presented with highly aggressive disease with haematogenous distant metastasis⁽¹³¹⁾.

Although tobacco and alcohol are major risk factors for SCC of the upper aerodigestive tract, they do not appear to be associated with sinonasal carcinogenesis⁽⁶¹²⁾. Patients with index tumours of other areas of the aerodigestive tract did not appear to have an increased risk of developing sinonasal tumours⁽⁶¹³⁾. The incidence of sinonasal SCC arising as a second primary in patients with head and neck cancer has been reported to be low (0.2%) by Wolpoe et al. but warrants inclusion of the sinonasal tract in routine head and neck surveillance⁽⁶¹⁴⁾.

Clinical presentation and site

Due to the late presentation of patients it is often difficult to distinguish the exact site of origin, which also compounds attempts at staging the tumour⁽⁶¹⁵⁾. Despite the widespread use of the TNM classification in literature, it is far from satisfactory⁽⁶¹⁶⁾. Tumours arising in different sites are grouped together in the same T stage and it is clear that a tumour in the ethmoid region that rapidly involves the skull base has a prognosis different than that for a tumour in the floor of the maxillary sinus. The histological diversity of tumours, with their range of natural histories, also invalidates the 5-year survival rate.

The maxillary sinus is the most common site of origin (Table 7.2) followed by the ethmoid. These tumours often arise within the middle meatus, and have been regarded as antroethmoidal or nasoethmoidal^(617,618). Primary SCC of the frontal and sphenoid sinuses is extremely rare. De Monte et al.⁽⁶¹⁹⁾ identified only nine cases of primary sphenoid SCC in a 21-year retrospective review at a tertiary centre.

In general, malignancies of the paranasal sinuses do not cause symptoms until they have expanded to a significant size or have extended through the bony confines of the sinus cavity. Initial symptoms of a paranasal sinus malignancy include nasal obstruction, epistaxis, pain, and episodes of sinusitis. These symptoms are often nonspecific and may even be suggestive of chronic rhino sinusitis⁽⁶²⁰⁾. As these tumours tend to present at a more advanced stage, a high degree of suspicion is required to avoid inadvertent delay in diagnosis. In a study by McKay et al., sixty-seven percent of patients with sinonasal SCC presented with advanced disease (T4a or T4b)⁽⁶⁰⁹⁾. Tumour expansion takes place circumferentially along the paths of least resistance. Expansion inferiorly towards the oral cavity may be associated with swelling of the gingiva or palate with loose teeth, while orbital invasion may lead to ocular symptoms such as proptosis, diplopia, decreased acuity, and restriction of ocular motion. Extension laterally into the pterygoid musculature may cause trismus and deeper invasion into the infratemporal fossa. Anterior extension through the anterior maxillary wall may cause visible cheek swelling and numbness from involvement of the infraorbital nerve. In rare cases, posterior and superior extension into the skull base, dura and brain may lead to headache, cerebrospinal fluid leak, and central nervous system deficits.

Nodal metastasis in paranasal SCC is associated with a poor prognosis. In a large series of 704 patients with paranasal sinus malignancies, which included 189 (26%) SCC, Cantu et al.⁽⁶²¹⁾ reported that the highest incidence of node metastasis was found in maxillary SCC, particularly those with T2 tumours. At presentation, 16 (10.3%) of the 156 patients with maxillary SCC had evidence of nodal metastasis. None of the patients with SCC in the ethmoid group (33 patients) presented with positive lymph nodes. Eleven of the 16 patients of maxillary

SCC with nodal metastasis were staged as T2, one as T3, three as T4a and one as T4b, respectively. The overall nodal recurrence rate (not specific for SCC) was estimated at 4.3% and 12.5% for ethmoid and maxillary malignancies, respectively. This compared with 3% for the ethmoid and 20.5% for the maxillary sinus in the SCC group. The incidence rate was even higher among the 77 patients with T2 stage SCC (26%). The overall survival probability at 2 years was estimated at 45.7% and 55.9% for ethmoid and maxillary SCC, respectively, and fell to 18.7% for ethmoid 45.2% for maxillary at 5 years. Nodal metastasis was associated with a poorer prognosis. Patients with nodal metastasis at presentation (not specific for SCC) had a 2-year overall survival probability of 26.7% and 48.5% for tumours arising in the ethmoid and maxillary sinuses, respectively. This fell to 0% and 16.8% for ethmoid and maxillary tumours, respectively at 5 years.

SCC of the paranasal sinuses has a high propensity for neural invasion as noted by Gil et al.⁽⁶²²⁾. In their cohort of 72 patients with SCC, over a fifth (22%) was found to have neural invasion on histopathology analysis after surgical excision of the tumour. Neural invasion was positively correlated with positive excision margins. The 5-year overall survival among patients with paranasal epithelial carcinomas was significantly higher at 66% for those without neural invasion compared to 57% for those with neural invasion ($p = 0.01$).

Imaging (Table 4.2)

A combination of computed tomography (CT) and magnetic resonance imaging (MRI) is now established as the optimum assessment of sinonasal malignancy⁽⁶²³⁾. CT and MRI are of particular value in assessing the skull base, orbit and pteryopalatine and infratemporal fossae. Although MRI offers better differentiation of tumour from surrounding tissue and fluid, coronal CT is still required for the demonstration of bone erosion particularly in the region of the cribriform plate⁽⁶²⁴⁾. Thus, the extent of local tumour spread may be determined with a degree of accuracy in excess of 98%. However, the final determinant of penetration of the dura and orbital periosteum requires per-operative frozen section assessment. Knowledge of the tissue characteristics and site of origin can be of value in distinguishing some of the commoner sinonasal malignancies such as squamous cell carcinoma, adenocarcinoma, adenoid cystic carcinoma, olfactory neuroblastoma and chondrosarcoma. Imaging, particularly MRI also plays an important role in the post-therapeutic follow-up of patients, indicating areas of residual or recurrent disease, defining suspicious areas for biopsy⁽⁶²⁵⁾. Post-operative surveillance is best achieved with three planar T1-weighted MRI, with, and without, gadolinium and axial T2-weighted sequences. The subtraction of the T1 pre- and post gadolinium T1 sequences can be of particular value in delineating recurrence.

Positron emission tomography (PET) should be considered in all patients as part of the initial evaluation for metastatic dis-

ease⁽⁶²⁶⁾. Distant metastatic disease may modify the management strategy from curative to palliative intent. In addition, preoperative PET imaging can serve as a baseline for comparison after surgical intervention, especially if unexpected areas of increased activity are noted.

CT and MRI data can be used for computer aided surgery (CAS) and preoperative planning. CAS can be used in facilitating precise endoscopic resection of sinonasal malignancy. Preoperative triplanar review of the images, assist in the understanding of the intimate relationship of the tumour to the associated critical structures, including the orbit, cribriform plate, and pterygomaxillary or infratemporal fossa. Surgical navigation allows preoperative imaging data to be directly correlated with the operative field providing a better safety profile intraoperatively. Novel software applications further enhance the capabilities of CAS technology. CT-MRI fusion technology merges the two modalities to better delineate the extent of the tumour and its involvement of the contiguous paranasal structures⁽⁶²⁷⁾. Three-dimensional CT angiography offers an effective means of assessing the relationship of skull base lesions to the internal carotid artery⁽⁶²⁸⁾.

Results following endoscopic resection of sinonasal SCC

Although relatively large series of SCC of the maxillary sinus were found in the literature review^(167,173,608,629), obtaining accurate survival figures was not straightforward. Comparison across studies was often compounded by heterogenous patient cohorts and treatment modality. The majority of cases received radiotherapy combined with some form of maxillectomy with or without orbital clearance⁽⁶²⁹⁾. In addition, the majority of tumours was T3 or T4 at presentation^(167,173) and had frequently extended posteriorly into the pterygoid region, which significantly reduces long-term survival. The overall 5-year survival of maxillary SCC was reported at 25%, although patients with T1 tumours at presentation were higher at 55%⁽⁶⁰⁸⁾.

Few studies reported oncological outcomes of SCC exclusively following endoscopic excision. Some studies reported on endoscopic assisted surgery combined with conventional open approaches, whilst others compared outcomes between surgery and radiotherapy⁽⁶⁰⁹⁾. Most published data are derived from a heterogenous patient cohort of varied histological type, where the main objective was to compare outcomes between endoscopic and craniofacial resection^(327,630-632). Where studies did report outcomes following endoscopic resection of malignant tumours, there was frequently insufficient SCC cases for exclusive analysis^(17,419,633-636).

Only one published study was identified from the literature review to have reported outcomes for endoscopic resection of sinonasal SCC⁽⁶³⁷⁾. This was a small cohort study of 11 patients with a mean age of 62.5 years. Radiation or chemotherapy was used in 8 patients. Seven patients underwent surgery using a

strictly endoscopic approach, whereas four required combined endoscopic and neurosurgical resection. Local recurrence and distant metastatic rates were 20% and 0%, respectively. Overall survival and disease-free survival were both calculated at 91%, with mean follow-up of 31.5 (range 6 – 88) months.

Eighteen studies^(17,327,419,465,478,609,631,632,634-643) were identified to be potentially relevant and had evaluated oncological results following endoscopic resection, performed as the sole procedure or in combination with craniofacial resection. These were available in full-text version and were included for analysis.

Data related to SCC was scarce. Twelve articles^(17,327,419,465,609,631,632,635-638,641) included some reports on SCC (Table 7.3).

A total of 150 patients with SCC were pooled from the data available (Table 7.3). In those instances where a single centre had generated more than one case series, from overlapping periods, data from the most recent series was used. Sixty-four patients underwent the traditional craniofacial resection (tCFR), 40 patients underwent endoscopic assisted surgery with an appropriate open approach and 39 were managed purely with endoscopic surgery (Table 7.4). Seven patients were deemed unresectable or declined surgery and were treated with radio- and chemotherapy. Only one study reported exclusively on endoscopic surgery for SCC⁽⁶³⁷⁾.

Of the 39 patients who underwent purely endoscopic surgery, data was available only for 23 patients. Individual data was collated from five studies^(419,636,637,639,641), and is summarised in the Table 7.5. Patient demographics, tumour staging, site of origin, extent of tumour invasion, recurrence and site of distant metastasis were not consistently reported in all of the five studies. Twenty-three patients, with a mean age of 59.8 (range 25 – 85) years, were analyzed. The male-to-female (12M: 6F, 5 unreported) ratio was 2:1. Contrary to previous studies, which reported a preponderance of advanced disease, 65.2% of patients had either T1 or T2 tumours at presentation. This may represent selection bias of the authors to offer endoscopic resection of the tumour. Six patients (26.8%) had local recurrence of SCC, which was higher than that reported by Nicolai et al.⁽³²⁷⁾ 12%. One of the six patients who had local recurrence also had distant metastasis (patient #5, Table 5). Another patient (Patient #16, Table 7.5), who did not have local recurrence, was found to have distant metastasis to the brain. At latest follow-up, 19 patients (82.6%) were alive with no evidence of disease. Three patients (two T1 and one T2) died of their disease, including the patient who had distant metastasis to the brain. One patient died of other causes.

Other reports of patients that were treated endoscopically lacked data documentation. These include 3 patients with SCC in a cohort of 49 patients reported by Lund et al.⁽⁶³⁵⁾. One of

these patients died at 40 months follow-up, one was alive with disease and the third was disease free. The follow-up of this cohort ranged from 6 – 126 months (mean 36 months). They report overall of survival of 88% at 5 years for the entire cohort. There was insufficient data to calculate survival outcome for the SCC patients. Eviatar et al. ⁽⁴⁶⁵⁾ report one case of a 76 year old patient treated with endoscopic approach in a cohort of six patients with malignant sinonasal tumours that were treated in a 7 year period. This patient remains disease free 4 years after the surgery. More recently, Nicolai et al. ⁽³²⁷⁾ reported their experience of 134 patients with malignant sinonasal tumours managed exclusively with endoscopic approach. This included 16 patients with SCC. They report a 5 year disease specific survival of 91.4% (standard deviation 3.9%) for the entire cohort of 134 patients treated with the endoscopic approach.

Two studies compared endoscopic outcomes with a tCFR cohort ^(632,638), whilst another two compared between endoscopic and combined approach ^(327,631). All studies were retrospective reviews of outcomes, with study cohorts ranging from 2 to 133 patients. When the studies were assessed against the Oxford Centre for Evidence Based Medicine Levels of Evidence criteria ⁽⁶⁴⁴⁾, all studies were regarded as having Level 4 evidence.

Discussion

For sinonasal SCC involving the anterior skull base (ASB), if the pre-operative imaging suggests that the tumour has extended through the dura or beyond, a formal craniofacial approach is generally favored and has been the gold standard. However, this approach has been associated with significant morbidity and perioperative mortality. In the past few years, there have been reports on the surgical outcome of endoscopic resection of ASB tumours including sinonasal SCC. However, in the selection of the endoscopic approach one would expect the results of an endoscopic approach to be at least the same, if not better, than conventional craniofacial resection. Proponents of the traditional craniofacial approach (tCFR) argue an en bloc resection possible with the tCFR is impossible with endoscopic approaches, which at best is “piecemeal resection” of the tumour. Proponents of the endoscopic approach, however, are of the opinion that in resecting tumours involving the ASB, whichever the approach, an en bloc resection is rarely possible. In fact, optimum endoscopic visualisation enables a wide-field three-dimensional resection close to an en bloc resection in most cases. Proponents of both approaches agree, the resection is aimed at achieving negative margins. Endoscopic approach offers several other advantages ⁽⁶³³⁾. The operation time is shorter, and is associated with less morbidity and shorter hospital stay ⁽⁶³²⁾. Patients do not experience the serious complications that can be associated with craniofacial resection nor are they likely to be subject to the reduction in quality of life. Nicolai et al. ⁽³²⁷⁾ reported a complication rate of 6% following endoscopic resection of malignant tumour com-

pared to 16% after craniofacial resection. The most common complication after endoscopic approach was CSF leak, followed by mucocele formation.

The decision to undertake an endoscopic approach rests on several factors. Factors related to the patients’ general health and medical co-morbidities together with their availability for long-term follow-up will also play a part in the decision-making process. Consequently, endoscopic resection may be ideal for those patients who are elderly or have significant health problems.

Conclusions

- Data on endoscopic surgery for sinonasal SCC is limited although the accrued data from the pooled patients appears promising. Comparison between the pooled data and of previously published outcomes is compounded by the heterogeneous patient population and small cohort of each tumour stage. Nonetheless, the overall disease-free-survival rate appears to be comparable with conventional approaches. The mean follow-up period is however limited to less than 4 years. The overall survival following craniofacial resection of sinonasal SCC was 67% at three years and falling to 64% at five years follow-up ⁽⁶²⁹⁾.
- Whichever surgical technique is used there is good evidence that the outcome is related to how thoroughly the tumour has been removed. A wide-field three-dimensional resection undertaken with optimum endoscopic visualisation, achieving negative margins offers resection of the tumour as close to an *en bloc* resection, which is rarely possible in practice. The overall morbidity and mortality associated with endoscopic resection of sinonasal SCC appears to be less than with traditional approaches.
- Given the low incidence of sinonasal SCC and the expertise required to manage this pathology, it would a long period for any institution to accrue sufficient numbers of cases for analysis. As such, a multi-centre study is with

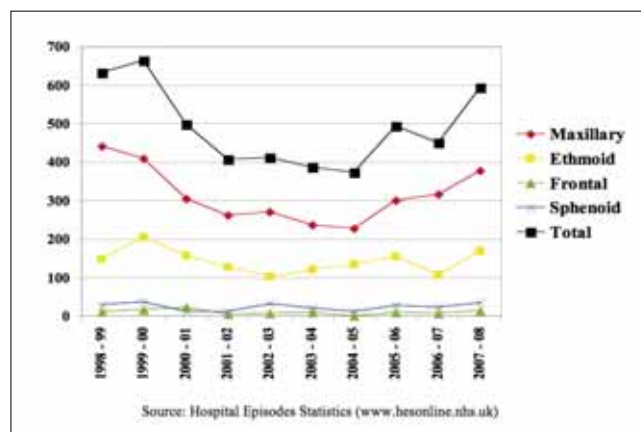


Figure 7.1. Trends in sinonasal malignancies (all histological types) diagnosed in England (United Kingdom) from 1998 to 2008, according to anatomical site.

long follow-up is required to compare oncological outcomes with open approaches such as craniofacial resection when the cribriform plate is involved.

Table 7.1. Incidence of squamous cell carcinoma in inverted papilloma (130).

Pathology	Incidence/case series	Percentage
Incidence of malignancy/ Number in case series	63/3058	2.1
Synchronous carcinoma/ Number in case series	163/2297	7.1
Metachronous carcinoma/ Number in case series (mean follow-up 52 months)	74/2047	3.6

7-2 Malignant Non-Epithelial

According to the WHO Classification of Head and Neck Tumours (328), non-epithelial malignant nasal and sinus tumours are made up of Adenocarcinomas and Salivary Gland Type Tumours. Malignant non-epithelial tumours make up 10 to 20% of all primary malignant neoplasms of the nasal cavity and sinuses (645,646). The most common sinonasal carcinoma is squamous cell carcinoma except in the regions with significant wood dust exposure where adenocarcinoma is more common.

Table 7.3. Publications selected for data related to sinonasal squamous cell carcinoma.

First author (year)	Total number of malignant sinonasal tumours	Total number of SCC in the series
1 Eviatar (2004) (465)	6	1
2 Castelnuovo (2006) (17)	13	3
3 Poetker (2005) (419)	16	5
4 Shipchandler (2005) (637)	11	11
5 Buchmann (2006) (631)	78	33
6 McKay (2007) (609)	73	30
7 Kim (2008) (632)	40	7
8 Chen (2006) (641)	7	1
9 Lund (2007) (635)	49	3
10 Podboj (2007) (636)	16	6
11 Nicolai (2008) (327)	184	25
12 Eloy (2009) (638)	66	25
Total	559	150

Table 7.2. Distribution of sinonasal squamous cell carcinoma based on anatomical site

	Lavertu et al. 1989 (617)	Spiro et al. 1989 (618)	Dulguerov et al. 2001 (173)	Cantù et al. 2008 (621)	Total (%)
Maxillary sinus	48	65	62	156	331 (73)
Ethmoid sinus	6	11	19	33	69 (15)
Sphenoid sinus	0	2	0	0	2 (0.4)
Nasal cavity	0	11	42	0	53 (11.6)
Total	54	89	123	189	455 (100)

Table 7.4. Number of sinonasal squamous cell carcinoma by different approaches.

First author (year)	SCC	tCFR: traditional craniofacial	Combined	Endoscopic	Remarks
Eviatar (2004) (465)	1			1	
Castelnuovo (2006) (17)	3		3		Endoscopic nasal and anterior craniotomy
Poetker (2005) (419)	5			5	
Shipchandler (2005) (637)	11		4	7	
Buchmann (2006) (631)	33		33		Open approaches complemented with endoscopic
McKay (2007) (609)	30	23			7 underwent RT with chemo
Kim (2008) (632)	7	7			
Chen (2006) (641)	1			1	
Lund (2007) (635)	3			3	
Podboj (2007) (636)	6			6	
Nicolai (2008) (327)	25	9		16	
Eloy (2009) (638)	25	25			
Total	150	64	40	39	7 treated with RT/Chemo

7-2-1 Adenocarcinoma

Adenocarcinoma is a glandular malignancy of the sinonasal tract. It is divided into 2 main groups: 1) intestinal-type adenocarcinoma and 2) non-intestinal-type adenocarcinoma. Non-intestinal-type adenocarcinoma is further divided into low grade and high grade subtypes⁽⁶⁴⁷⁾.

1) Intestinal-type Adenocarcinomas (ITAC)

This carcinoma resembles adenocarcinoma of the intestinal tract.

Epidemiology and Etiology

This tumour has a male predominance probably due to occupational exposure and usually presents in the 5th and 6th decades (mean age at presentation 58 years)⁽⁶⁴⁵⁾. Wood dust and leather dust have been shown to be associated with the development of this tumour in several different countries with a considerable delay between exposure and presentation of up to 40 years⁽⁶⁴⁶⁾. It is thought that the larger dust particles may

be involved as they are preferentially accumulated in the nose. The carcinogens involved are still unknown but may include alkaloids, saponins stilbenes, aldehydes, quinones, flavonoids, terpenes, fungal proteins and tannins^(212,648).

Clinical Features

These tumours present with nasal obstruction, rhinorrhoea and epistaxis often unilateral. If tumours are large, they may disrupt ocular mobility and cause proptosis. Extension into the intracranial cavity may result in neurological symptoms, especially frontal lobe symptoms. Extension may also occur into the pterygopalatine and infratemporal fossae with altered facial sensation. Lymph node involvement can be seen in less than 10% of cases^(645,648,649). The tumour is best evaluated with both CT and MRI scanning. CT gives valuable information regarding the bony boundaries of the nasal cavity and sinuses, while MRI allows differentiation between soft tissue and secretions and better delineates soft tissue extension into regions outside the sinonasal cavities⁽⁶²³⁾. The most common areas affected are

Table 7.5. Summary of data of patients who underwent endoscopic resection for sinonasal squamous cell carcinoma

Patient no.	Gender	Age	Extent*	Staging	Recurrence	Metastasis	Follow-up (months)	Status
1	M	63	E	T1	N	N	25	DFS
2	F	68	E, CP, LNW, Orbital wall	T3	N	N	54	DFS
3	F	66	Septum, M, Nasal cavity	T2	N	N	31	DFS
4	M	66	E, M, Mt	T3	N	N	30	DFS
5	M	54	Septum, LNW	T2	Y	N	15	DFS
6	M	85	E, M, S, CP, PMF, LNW	T4a	Y	N	6	DFS
7	M	54	Ant & LNW	T1	N	N	9	DFS
8	Unknown	70	M, E	T1N0	N	N	89	DFS
9	Unknown	40	St	T1N2b	Y	Y	10	DOD
10	Unknown	61	Mt	T1N0	N	N	21	DFS
11	Unknown	63	E, M	T2N0	Y	N	92	DFS
12	Unknown	65	Septum	T2N0	Y	Y	7	DOD
13	M	49	Not stated	Stage IVB	Y	N	57	DFS
14	M	69	E, NF	T2	N	N	63	DFS
15	F	47	NF	T1	N	N	62	DFS
16	F	80	NF	T1	N	Y	28	DOD
17	M	50	E	T3	N	N	34	DFS
18	M	35	E	T2	N	N	89	DFS
19	M	40	E	T4	N	N	78	DFS
20	F	71	IT, NF, Septum & torus	T4b	N	N	77	DFS
21	M	25	E, PE, St, Mt, ant wall SS	T4	N	N	58	DFS
22	F	77	E & MT	T2	N	N	19	DOC
23	M	77	NC	T1	N	N	3	DFS
Summary	12 males	59.78		T1 = 8	Yes = 6	Yes = 3	41.6	DFS = 21
	6 female	(mean)		T2 = 7			(mean)	DOD = 3
	5 unknown	25 - 85		T3 = 3	No = 17	No = 20		DOC = 1
		(range)		T4 = 4			3 - 92	AWD = 1
							(range)	

* Extent: E= ethmoids, M= maxillary sinus, S= sphenoid sinus, Mt= middle turbinate, St= superior turbinate, CP= sphenoid plate, LNW= lateral nasal wall, PMF= pterygomaxillary fossa, NF= nasal fossa, PE= posterior ethmoids, NC= nasal cavity

** Data for patient #1 - #7 is derived from Shipchandler et al. (2005)⁽⁶³⁷⁾, #8 - #12 from Poetker et al. (2005)⁽⁴¹⁹⁾, #13 from Chen (2006)⁽⁶⁴¹⁾, #14-#17 from Nicolai et al. (2007)⁽⁶³⁹⁾, #18 - #23 from Podboj and Smid (2007)⁽⁶³⁶⁾.

DFS = disease free survival, AWD = alive with disease, DOD = died of disease, DOC = died of other causes.

the ethmoid sinus (40%) followed by the nasal cavity (27%) and the maxillary sinus (20%)⁽⁶⁴⁵⁾. However in woodworkers one group has suggested that the majority of tumours originate in the olfactory cleft^(34,187).

Histology

There are 2 published classifications of these tumours, Barnes⁽⁶⁴⁵⁾ and Kleinsasser and Schroeder⁽¹⁸³⁾. The Barnes classification⁽⁶⁴⁵⁾ is preferred as it is simpler and is the classification presented in Table 7.6.

Table 7.6. Barnes Classification of adenocarcinoma⁽⁶⁴⁵⁾.

Types	Prevalence (approximate varies from author to author)	Differentiation	3 yr Cumulative Survival#
Papillary	18%	Well differentiated	82%
Colonic	40%	Moderately differentiated	54%
Solid	20%	Poorly differentiated	36%
Mucinous	14%	Mucinous	48%
Mixed	8%	Mixed differentiation	71%

= derived from Kleinsasser and Schroeder⁽¹⁸³⁾.

The Kleinsasser and Shroeder classification divides the mucinous type of tumour into alveolar and signet ring tumours⁽¹⁸³⁾. Franchi et al.⁽⁶⁴⁷⁾ showed that such a division had no prognostic significance.

ITAC are generally locally aggressive with a local recurrence rate of around 50%, local lymph node spread of about 10% and distant metastasis rate of 20%^(183,645,647,650). The cumulative disease specific five year survival rate is between 40 and 60% with most deaths occurring in the first three years. As the average presentation of these tumours is generally late, with a majority of T3 and T4 tumours, staging tumours according to the TNM staging system has little prognostic significance⁽⁶⁴⁷⁾.

2) Sinonasal non-intestinal-type adenocarcinomas

The tumours are divided into low- and high-grade subtypes with low grade presenting mostly in the ethmoid cells and the high grade in the maxillary sinus⁽⁶⁵¹⁾. These tumours may present in the nasal cavity or in any combination of the above. Low-grade has a more indolent course presenting with unilateral nasal obstruction and epistaxis while high-grade tumours may present with additional symptoms associated with extension of the tumour into the orbit (double vision, proptosis), infratemporal fossa (infra-orbital nerve sensory changes) or intra-cranial cavity (frontal lobe symptoms and headache)⁽⁶⁵¹⁾. Low grade tumours have an excellent prognosis with 5 year survival of up to 85%⁽⁶⁵²⁾ while high grade tumours have a very poor prognosis with 3 year survival of around 20%⁽⁶⁵¹⁾.

7-2-2 Salivary Gland Type Carcinomas

Salivary gland type adenocarcinomas are uncommon occurring in 5-10% of sinonasal adenocarcinomas⁽⁶⁵³⁾. They are thought to originate from the seromucinous glands of the nasal and sinus epithelium. Table 7.7 lists the types and occurrence of all sinonasal salivary tumours (both malignant and benign).

Table 7.7. Types and occurrence of all sinonasal salivary tumours^(202,651,653,654).

Tumour Type	Percentage Occurrence
High-grade Adenocarcinoma Not Otherwise Specified	30%
Adenoid Cystic Carcinoma	17%
Mucoepidermoid Carcinoma	5%
Low-grade Salivary-type adenocarcinoma (various types including mucoepidermoid & acinic cell carcinoma	21%
Pleomorphic adenoma*	23%

*benign

NB This nomenclature predates the most recent WHO classification⁽³²⁸⁾.

Adenocarcinoma Not Otherwise Specified may be considered a diagnostic entity on its own and is often poorly differentiated with a poor prognosis in keeping with other poorly differentiated adenocarcinomas^(645,651,653). Adenoid cystic carcinoma is the most common salivary gland malignant tumour originating most commonly in the maxillary sinus (60%) and nasal cavity (25%). Diagnosis is often delayed and the patient usually presents with unilateral nasal obstruction and epistaxis but often has an increased incidence of pain, paraesthesia and anaesthesia. The extent of tumour spread is often underestimated by radiology as perineural spread, which is common in this tumour often remains undetected and the long term survival is poor with 7% 10 year survival⁽⁶⁵⁵⁾ with most patients dying of local recurrence rather than distant metastasis⁽⁶⁵⁶⁾. Long-term follow-up is thus mandatory to detect late recurrences. The other salivary gland malignancies are all very rare and not individually presented.

Treatment

Most studies on the treatment of sinonasal malignancies do not separate the histological types of tumours and present series where the treatment of these tumours are lumped together^(17,419,478,481,630,631,633-636,641,643,657,658) (Table 7.8). There are only a few published studies^(200,648,652,653,659-661) where the adenocarcinomas have been separately reported. A great deal of the evidence for the treatment of non-epidermoid malignancies comes from separating these tumours from other tumours in the published studies.

Table 7.8. Numbers of adenocarcinomas reported in the literature.

First Author (Year)	Total number of Malignant sino-nasal tumours	Total number of Adenocarcinomas
Lund (1998) ⁽⁴⁷⁸⁾	167	42
Stammberger (1999) ⁽⁶⁵⁸⁾	43	7
Thaler (1999) ⁽⁶⁴³⁾	4	1
Goffart (2000) ⁽⁶³³⁾	78	40
Roh (2004) ⁽⁶³⁴⁾	47	2
Poetker (2005) ⁽⁴¹⁹⁾	16	2
Ganly (2005) ⁽⁶⁵⁷⁾	334	107
Batra (2005) ⁽⁶³⁰⁾	25	3
Buchmann (2006) ⁽⁶³¹⁾	78	2
Castelnuovo (2006) ⁽¹⁷⁾	18	10
Chen (2006) ⁽⁶⁴¹⁾	7	4
Howard (2006) ⁽⁴⁸¹⁾	259	62
Lund (2007) ⁽⁶³⁵⁾	49	15
Podboj (2007) ⁽⁶³⁶⁾	16	5
Total	1141	302

The central issue in the treatment of adenocarcinomas is to prevent loco-regional recurrence as most patients die as consequent of a local recurrence rather than because of metastasis either local or systemic^(635,653,662). Treatment is focussed on removing the tumour where possible with a clear margin and this depends upon the site of the tumour. Pedunculated or isolated tumours attaching to turbinates or the septum can be easily removed with a good margin of normal tissue either by endoscopic or open approach. The treatment controversy is around tumours that abut or transgress the skull base or orbit. The current gold standard for the treatment of these tumours remains a craniofacial resection (CFR)^(200,478,481,630,659,661), which involves a craniotomy to expose the anterior skull base from above and traditionally an open approach to the nasal and sinus cavity allowing resection of the cribriform plate, ethmoids, fovea ethmoidalis, anterior face of sphenoid and septum. Orbital involvement is determined by whether the orbital

periosteum is breached or not. If not breached, this structure is preserved. Post operative irradiation is advocated by most authors^(200,659,660,663,664). Adjuvant chemotherapy is rarely given⁽²⁰⁰⁾. The three year disease specific survival rate is around 72% and the five year survival rate for this procedure is around 60%⁽²⁰⁰⁾. However, it is well recognized that CFR resection is not a benign procedure and has a significant morbidity with 33% of patients suffering complications and a mortality of 4.5%⁽⁶⁵⁷⁾. With the increased usage of the endoscope in the 1990s, the nasal component of the CFR was more commonly performed endoscopically and this procedure was termed a combined endoscopic craniofacial resection (CECFR). Nicolai et al. compared their results for CECFR with wholly endoscopic resection and found that for adenocarcinoma the five year disease free survival was 60% compared to 80% for the wholly endoscopic approach. However, the indication for performing a combined approach was in patients that had more extensive tumour usually with dura and brain invasion so it is really not possible to compare these outcomes⁽³²⁷⁾.

In the 1990s, reports began to appear detailing wholly endoscopic resection of adenocarcinomas of the sinonasal cavity⁽⁶⁶²⁾. Again most of these publications combined adenocarcinoma with other histological groups making true outcome assessment of this new technique difficult (Table 7.9).

The initial limitations of the wholly endoscopic approach was the ability of the surgeon to access extension of the tumour onto and through the dura and into brain^(327,633). The stated principles of a wholly endoscopic resection remain the same as those for CFR in that the aim is to achieve a complete local resection to prevent local recurrence^(659,661). The wholly endoscopic approach is different from the standard CFR approach in that the tumour in the nose is debulked until the tumour attachment is clearly identified. Once this is clear, the surgical approach to resect the entire tumour including a margin of

Table 7.9. Adenocarcinoma resected by an entirely endoscopic approach.

First Author (year)	Total cases n =	AdenoCa n =	DXT n =	Recurrence rate for entirely endoscopic resection (follow-up is mean time for all patients)
Stammberger (1999) ⁽⁶⁵⁸⁾	36	7		5 clear of disease at 30 months
Shah (1999) ⁽⁶⁶²⁾	1	1		1 clear of disease at 12 months
Goffart (2000) ⁽⁶³³⁾	66	40*	87.9%	5 year disease specific survival 57.6%
Roh (2004) ⁽⁶³⁴⁾	19	2	78.9%	1 recurrence at 40 months
Poetker (2005) ⁽⁴¹⁹⁾	16	2	0%	No recurrences at 19 months
Batra (2005) ⁽⁶³⁰⁾	9	2	78%	1 recurrence at 24 months
Lund (2007) ⁽⁶³⁵⁾	47	14	76%	1 recurrence at 36 months
Podboj (2007) ⁽⁶³⁶⁾	16	5	60%	No recurrence at 84 months
Nicolai (2008) ⁽³²⁷⁾	134	44	35%	5 year disease specific survival 94.4%
Bogaerts (2008) ⁽⁶⁵⁹⁾	44	44	100%	5 year disease specific survival 83%
Jardeleza (2009) ⁽⁶⁶¹⁾	12	12	75%	91.6% disease specific survival at 30 months

*Some of these patients may have had an additional craniotomy as part of the procedure

normal tissue is planned^(327,658,661,665). New endoscopic techniques for accessing previously difficult regions such as the frontal sinus, areas of the maxillary sinus and infra-temporal fossa are now able to be overcome^(630,640,659,661). New endoscopic surgical techniques such as frontal drillout or Draf III procedure allow full access to tumour extension into the frontal sinus or onto the posterior wall of the frontal sinus⁽⁶⁶⁶⁾. Endoscopic medial maxillectomy gives access to the entire maxillary sinus and the infratemporal fossa⁽⁶⁶⁷⁾. The current major controversy is whether the wholly endoscopic resection compromises the outcome by the resection been performed in most instances in a piecemeal fashion^(640,662,667,668). The other area of debate is whether it is necessary to achieve clear margins and if it is worthwhile going to the effort to document such margins both during the endoscopic and CFR approaches. The margins of an anterior skull base resection (either including or excluding the lamina papyracea) are usually bony or cartilaginous and this can provide difficulty for the surgeon to be able to obtain a representative sample to send for frozen section⁽⁶⁵⁹⁾. In addition, the incidence of recurrence after surgery in patients with positive and negative margins is similar⁽⁶⁵⁹⁾. As most patients receive post-operative radiotherapy, the positive margins (and normal resection margins) are all included in the post-operative treatment fields. Additional advantages of an endoscopic resection are the improved visualisation of the tumour borders provided by the magnification achieved with the use of endoscopes, lack of skin incisions and lack of resection of normal tissue (maxilla, nasal bones, sinuses) to be able to visualize the extent of the tumour^(630,640,659,661,665,668). However, it is well recognized that wholly endoscopic resection of tumours abutting or breaching the normal confines of the sino-nasal cavity is technically demanding and that the learning curve for such techniques is significant and takes considerable time to achieve and that these procedures should not be adopted until such a level of expertise has been developed within the skull base team⁽⁶⁶¹⁾.

7-3 Malignant neuroectodermal tumours

7-3-1 Olfactory neuroblastoma/Esthesioneuroblastoma

Search Strategy

A Medline and Pubmed review of the literature was performed of all case series of olfactory neuroblastoma published from 1990 onwards. If a single centre had published more than one case series, data from the most recent series was used.

Introduction

Olfactory neuroblastoma is an uncommon malignant neoplasm believed to arise from the olfactory epithelium. The histological origin of olfactory neuroblastoma is uncertain and has resulted in the use of various names for this tumour, but the only two terms used in recent published literature are olfactory neuroblastoma and olfactory neuroblastoma. Since Berger and

Luc first described olfactory neuroblastoma in 1924, more than 1025 cases of this tumour have been reported in the world literature, mostly as single or small case reports. More cases of olfactory neuroblastoma have been reported in the last 20 years^(237,238). Three other factors contribute to the controversy associated with this neoplasm namely the tumour shows varying biological activity, ranging from indolent growth with patients surviving with known tumour for many years, to a highly aggressive neoplasm capable of rapid widespread metastasis with survival limited to a few months. Secondly, olfactory neuroblastoma is easily confused with other undifferentiated neoplasms of the nasal cavity. Thirdly, no universally accepted staging system is currently available⁽²⁴¹⁾.

Incidence and aetiology

The incidence of olfactory neuroblastoma is difficult to establish, but the tumour is not as rare as is commonly reported, and probably represents >5% of all nasal malignant tumours. Olfactory neuroblastoma occurs over a wide age range (from 3 to 90 years) with a bimodal peak in the second and sixth decades of life^(240,669). Sporadic cases have also been reported in children less than 10 years of age⁽²³⁸⁾.

The exact cell of origin of olfactory neuroblastoma is thought to be the basal reserve cell, the olfactory stem cell that gives rise to both the neuronal and the epithelial sustentacular cells. Proposed sources have included Jacobson's vomero-nasal organ, the sphenopalatine ganglion, the ectodermal olfactory placode, Loci's ganglion, autonomic ganglia in the nasal mucosa, and finally the olfactory epithelium⁽²³⁷⁾. Although a neuronal or neural crest origin is supported by the presence of neurofilaments in olfactory neuroblastoma, until recently⁽⁶⁷⁰⁾, little evidence has linked olfactory neuroblastoma directly to the olfactory epithelium.

The olfactory neuroepithelium is a unique neurosensory organ, because the olfactory neurones are continuously being replaced throughout adult life. Three cell types are classically recognised in the olfactory epithelium: the basal cells, located against the basement membrane; the olfactory neurosensory cells; and the sustentacular supporting cells, the processes of which extend onto the luminal surface. The spherical basal cells constitute a stem-cell compartment, which confers to this tissue its peculiar ability to regenerate not only physiologically but also when damaged by trauma or environmental insults⁽⁶⁷¹⁾.

The basal cells express neural cell adhesion molecules (NCAM) and the mammalian homologue of *Drosophila* achaete-scute (MASH) gene⁽⁶⁷²⁾. These progenitor cells differentiate into olfactory neurosensory cells, which show progressive maturation from the basement membrane to the epithelial surface. Each layer can be characterised by olfactory-specific and neuronspecific markers. Immature olfactory cells can be expressed GAP43, a 24 kDa membrane-associated protein

kinase C involved in turnover of polyphosphoinositide⁽⁶⁷³⁾. As these cells mature, they grow axons to the olfactory bulb and migrate towards the surface; they express olfactory marker protein⁽⁶⁷⁴⁾, and NCAM but not GAP43⁽⁶⁷⁵⁾. In the mid 1990's olfactory neuroblastoma tumours were found to express HASH, the human homologue of the MASH gene, but stained negative for olfactory marker protein. So far, HASH has only been shown in medullary thyroid carcinoma and certain small cell lung cancers⁽⁶⁷⁶⁾. The basal cells of the olfactory neuroepithelium are presumably the progenitor of the olfactory neuroblastoma⁽²³⁸⁾. No known cause exists for this tumour⁽²⁴²⁾, although diethylnitrosamine injections can induce tumours in hamsters at the site of the olfactory epithelium⁽²⁴³⁾. No hereditary patterns have been described for this neoplasm and there is no apparent racial predilection.

Clinical presentation

These tumours present with unilateral nasal obstruction, and epistaxis. Impairment or loss of the sense of smell is not common as a clinical symptom as might be expected, in part because olfaction is preserved on the contra lateral side in some tumours and in part because some patients fail to notice its gradual loss. Extension into the intracranial cavity rarely causes neurological symptoms as invasion of the frontal lobe only produces symptoms after massive involvement. Large tumours rarely invade the orbit and produce ocular symptoms.

Diagnosis and imaging

The stage at initial presentation is highly predictive of survival and accurate staging is essential. Appropriate evaluation includes both computed tomography (CT) and magnetic resonance imaging (MRI), to help define the likely extent of the disease both at the primary site and in the neck. However, these imaging modalities are complimentary and should be performed in all cases. Fine-cut spiral overlapping CT scan in all three dimensions is the radiological study of choice. Olfactory neuroblastoma does not have any specific radiological appearance but its site in the olfactory cleft makes it a likely diagnosis in its early stages. It is seen as a homogenous soft-tissue mass in the nasal vault, with uniform and moderate contrast enhancement and occasionally the adjacent bone can be hyperostotic. CT images are essential for correct staging and should be carefully examined for erosion of the lamina papyracea, cribriform plate, and fovea ethmoidalis. MRI enables a better estimate of tumour spread into surrounding soft tissue areas in particular it can indicate whether the tumour has involved or traversed the dura and can differentiate mucus from tumour^(677,678) but MRI has a tendency to overstage the extent of disease. A case of olfactory neuroblastoma demonstrating an increase in uptake of technetium - ^{99m} - ethylcysteinate dimer (^{99m}Tc-EDC) has shown this may help to diagnose tumours of neural crest origin⁽⁶⁷⁹⁾. MRI can but it has a tendency to overestimate the extent of the disease.

Staging

Kadish and co-workers⁽⁶⁸⁰⁾ were the first to propose a staging classification, using three categories, Group A, B and C (Table 7.10). A further system was proposed with the advent of advances in imaging⁽²⁴¹⁾, based on the TNM system (Table 7.11). Although a system of classification has been proposed, various attempts have been made to modify the Kadish system^(240,681). Other authors suggest that by using the Kadish staging system and the Hyams grading system independently they can predict patients outcome with more accuracy⁽⁶⁸²⁾. Hyams grading system is based on histology and will be referred to in the next section.

Histology

Olfactory neuroblastoma is an uncommon sinonasal tumour, and can often be confused with other neoplasms, e.g. sinonasal undifferentiated carcinoma, neuroendocrine carcinoma, melanoma, lymphoma, plasmacytoma, embryonal rhabdomyosarcoma, Ewing's sarcoma, peripheral primitive neuroectodermal tumours, vascular tumours etc.⁽⁶⁸²⁾. It was this frustrating feature that prompted Ogura and Schenek⁽⁶⁸³⁾ to describe olfactory neuroblastoma as the "great impostor". The diagnosis of olfactory neuroblastoma can be problematic and consequently, histochemical, immunochemical and ultrastructural investigations are often needed to support the diagnosis⁽⁶⁸⁴⁾. Westra and colleagues from Johns Hopkins reviewed 37 cases of diagnosed olfactory neuroblastoma and excluded 8 (21.6%) because they did not meet diagnostic inclusion criteria⁽⁶⁸⁵⁾. Hirose et al.⁽⁶⁸⁴⁾ from the Mayo Clinic Tissue Registry reviewed 30 cases of olfactory neuroblastoma and found that 4 (13.3%) were excluded because they lacked neural or neuroendocrine markers. Exhibiting only epithelial markers, they were considered examples of sinonasal undifferentiated carcinoma.

It is reported that a diagnosis of olfactory neuroblastoma by light microscopy is not difficult when the tumour is well differentiated and consists of homogenous small cells with uniform round to oval nuclei, with rosette or pseudorosette formation, and eosinophilic fibrillary intercellular background material. Hyams et al.⁽⁶⁸⁶⁾ proposed a grading system for olfactory neuroblastoma, Grades I being well differentiated to IV undifferentiated, based on several tumour histological parameters: preservation of lobular architecture, mitotic index, nuclear polymorphism, fibrillary matrix, the presence of HW (Horner Wright) or FW (Flexner-Wintersteiner) rosettes, and the presence or absence of tumour necrosis. When the tumour is undifferentiated with anaplastic hyperchromatic small cells that show many mitotic figures and scant cytoplasm, differentiating the tumour from other small-cell nasal neoplasms by light microscopy becomes difficult. To summarise, the pathologic distinction of poorly differentiated small cell neoplasms of the nasal cavity is difficult and can only be based on the results of antigen expression using a panel of antibodies by immunohis-

tochemistry and if necessary confirmed by electron microscopy. There is still a lack of consensus relating to these prognostic histological features. Support for the prognostic value of Hyams and co-workers grading⁽⁶⁸⁶⁾ has been published⁽⁶⁸⁷⁾. Histopathological staging according to Hyams has also been advocated more recently in predicting survival and prognosis^(682,688). Hirose and colleagues found that a high degree of S-100 immunopositivity and a low (< 10%) Ki-67 labelled index (a marker for proliferation) was associated with better survival. There are conflicting data on the prognostic role of p53 tumour suppressor gene mutations⁽⁶⁸⁴⁾.

Treatment and Results

The Primary Site

A combination of surgery and radiotherapy is the most frequently used approach, and the one that achieved the highest cure rates^(689,690). Despite the lack of support for single-modality treatment regimes⁽⁶⁹¹⁾, a substantial number of patients are treated by surgery or radiotherapy alone. The difference in survival between the combined treatments and radiotherapy alone is significant (Table 7.12). The 5-year disease-specific survival in the literature is reported between 52–90%⁽²⁴¹⁾. Surgery alone was associated with lower survival combined with a combination of radiotherapy and chemotherapy, or triple modality treatment (surgery, radiotherapy and chemotherapy). Although the results were 15–20% better, the differences from the best combination were not statistically significant, probably because of the limited number of patients⁽⁶⁸⁹⁾. These results were compiled from the MEDLINE database from 1990–2000, without language tags. There were 26 treatment studies that formed the basis for the above tabulations and data extracted from these studies comprised the total number of patients, the staging system used, the patients' distributions by stage and the histological grade and the treatment used. Outcome data consisted of recurrence free survival at 3 years and 5 years, overall survival at 5 and 10 years, and the results by stage, grade and treatment modality.

In five studies, olfactory neuroblastoma were histo-pathologically graded according to Hyams et al., the mean 5 year survival was 56% (SD 20) in patients with grades I or II tumours and 25% (SD20) in those with tumours of grade III or IV. This difference was significant (odds ration 6.18 {95% CI 1.30 – 29.3}). In 25 studies that used the Kadish classification, the mean 5 year survival for these three groups was Group A 72% (SD 41), Group B 59% (SD 44) and Group C 47% (SD 16), respectively. On average, 5% (SD 7) of patients presented with cervical lymph node metastases. In the studies of survival data according to N stage, only 29% of N+ patients were treated successfully, compared with 64% of N0, a significant difference (Odds ratio 5.1 {95% CI 1.6 – 17.0}).

Surgery

Most institutions favour surgery as the first treatment modality, followed by radiotherapy^(240,478,681,685,692-696).

Endocranial extension and a close relation to the ethmoid roof and cribriform plate have conventionally led to a combined transfacial and neurosurgical approach. Craniofacial resection allows for an en bloc resection of the tumour with better assessment of any intracranial extension and protection of the brain and optic nerve. The resection should include the entire cribriform plate and crista galli. It is said that the olfactory bulb and overlying dura should be removed with the specimen although there is no clear evidence to support the assertion that the whole of the bulb should be removed⁽⁶⁹⁷⁾. Open surgery has long been regarded as the gold standard, with results available for decades. A craniotomy is probably not justified for T1 tumours where there is clear radiological evidence of a normal cribriform plate and no involvement of the upper ethmoidal cells although this clinical picture is seldom seen. The evolution of surgical techniques has created another surgical option in the form of endonasal endoscopic surgery. The use of endoscopic surgery for olfactory neuroblastoma followed by the use of the stereotactic radiosurgical gamma knife therapy has recently been used^(239,698). One report of 10 cases with a mean follow-up of 38 months used endoscopic resection alone without any recurrence although only 2 had Kadish stage C⁽⁶⁹⁹⁾. In the last decade, numerous articles with small numbers have been published on the endoscopic resection of olfactory neuroblastoma. Devaiah et al. reviewed the literature with a meta-analysis and showed that an endoscopic approach gave a better survival rate⁽⁷⁰⁰⁾. The aim of this study was to compare results of open, endoscopic, endoscopic-assisted, and nonsurgical treatments since the first publication that mentioned an endoscopic removal in the literature. This analysis extracted sufficient data in 361 subjects and the statistically significant results for the full cohort are summarized in Table 7.13^(419,640,690,701-710).

Endoscopic surgery produced overall better survival rates than open surgery with no significant difference between follow-up times in the endoscopic and open surgery groups (Table 7.14). As the gold standard open procedure considerably predated endoscopic treatment, they also grouped the data according to the publication year. The endoscopic surgery group maintained better survival rates (Table 7.15). This data shows evidence for the efficacy of endoscopic surgery in olfactory neuroblastoma. There are more cases of long-term follow-up in the open surgery group than the endoscopic treatment group and most of the open surgery tumours belonged to the Kadish C and D stages, whereas the endoscopic techniques were used more commonly for Kadish A and B tumours. This reflects how endoscopic surgery has mainly been used for less extensive lesions. This might not only be a reflection of the size of the tumour but their pathology as more extensive lesions might be expected to be more invasive and less differentiated although this cannot be ascertained from the data available⁽⁷⁰⁰⁾.

The most recent publication on endoscopic endonasal resection for all Kadish groups has just been published by Folbe et al. ⁽⁷¹¹⁾. This is a retrospective, multicenter study with 23 patients operated endoscopically with postoperative radiotherapy in 16 patients. The mean follow-up was 45.2 months with one recurrence. The authors conclude that endoscopic surgery is replacing craniofacial resection and that oncologic control is not sacrificed when good endoscopic resection techniques are used.

Radiotherapy

Standard radiotherapeutic techniques include external megavoltage beam and a three-field technique; an anterior port is combined with wedge later fields to provide a homogeneous dose distribution. The doses range from 55 Gy to 65 Gy with the majority receiving above 60 Gy. Currently it is considered that radiotherapy should play a role in the management of olfactory neuroblastoma, particularly in patients who have had incomplete surgical resection or who present with residual disease ^(706,709,712). In a small retrospective series, a comparison was made between conventional radiotherapy and stereotactically guided conformal radiotherapy (SCRT). It was concluded that SCRT improved target coverage and sparing of organs at risk ⁽⁷¹³⁾.

Chemotherapy

Olfactory neuroblastoma is regarded as a chemosensitive tumour based on multiple reported responses to treatment ^(702,714-716). Neoadjuvant therapy is seldom curative on its own and it may be of no benefit in some patients. Individuals who respond to preoperative chemotherapy have a greater chance of long term disease-free survival ⁽⁷¹⁴⁾. It has been proposed that Hyams' grading is an important predictor of response to chemotherapy ⁽⁷¹⁷⁾, and it has been suggested that cisplatin-based chemotherapy is helpful in advanced, high-grade olfactory neuroblastoma and should be considered the choice in the systemic treatment of these patients.

Neoadjuvant chemotherapy has been advocated for patients with advanced disease at the University of Virginia over a 20 year period ⁽⁶⁹²⁾. In thirty four consecutive patients, two thirds showed a significant reduction of tumour burden with adjuvant therapy and patients that showed a response to neoadjuvant therapy demonstrated a significantly larger disease-free mortality rate. Preoperative chemotherapy consisted of cyclophosphamide (650 mg/m²) and vincristine (1.5 mg/m²; maximal dose, 2 mg) there were administered every 3 weeks for 6 cycles. Adriamycin was used in combination with cyclophosphamide in two patients. Most patients also received a total dose of 50 Gy of preoperative fractionated radiation therapy.

CNS Metastases

CNS metastases (as opposed to direct intracranial extension) can occur in olfactory neuroblastoma. These lesions are

thought to arise when tumour cells violate the ependymal epithelium of the ventricles to gain free access to the ventricular fluid. Tumour cells then disseminate through the cerebrospinal fluid pathways to distant sites ⁽⁷¹⁸⁾. More than 17 patients have been identified from the literature had CNS metastases from olfactory neuroblastoma ^(718,719). The following trends from these treated patients comprise: 1) most patients in whom CNS metastases developed had Kadish stage C disease at diagnosis; 2) there was a highly variable time to onset of CNS metastases, ranging from 1–228 months after initial diagnosis olfactory neuroblastoma; 3) survival after CNS metastases was generally less than 2 years; and 4) the treatment regimen that appeared to result in the longest survival after CNS metastases included surgical resection of the metastatic lesion followed by radiation and/or chemotherapy.

Neck Metastases

Neck metastases are found at presentation in 5% of patients. Such patients should be treated by neck dissection or radiotherapy. It has been estimated from a review of the literature ⁽²³⁸⁾ that up to 23.4% may develop cervical lymph node metastases. Thus, treatment of the clinically negative neck may be warranted. In general, the reasons given for not considering an elective neck dissection is because these cervical nodes metastases may not develop for as long as 2 years or more. It would seem pragmatic to treat them when they are clinically apparent. However, nodal metastases are associated with the development of distant metastases – hence, should these patients undergo an elective neck dissection in advance of the development of metastatic neck disease? The relatively high frequency of occurrence of lymph node metastases is sufficient to refute the claim that olfactory neuroblastoma is a “low-grade” malignant tumour. Distant metastases synchronous at presentation have been reported in 6.6% (3/45) ⁽⁶⁸¹⁾.

Primary Tumour Recurrence

The assessment of recurrent olfactory neuroblastoma at the primary site must include CT and MRI. The appearances of the recurrent tumour do not differ from that imaged at initial presentation ⁽⁷¹⁹⁾. Enhanced CT and MRI images in the coronal plane are helpful in identifying small recurrences and/or intracranial extensions. The meta-analysis by Dulguerov et al. ⁽⁶⁸⁹⁾ found that the 5 year survival of 45% was associated with recurrent disease. Local recurrence in olfactory neuroblastoma occurs in approximately 30%. Craniofacial resection followed by radiotherapy is associated with fewer recurrences – around 10%. Salvage after local recurrence is possible in 33 – 50% of cases ⁽²³⁶⁾.

Regional and Distant Recurrence

Regional recurrence in the cervical lymph nodes, where the primary site is disease free, occurs in 15–20% of cases and is salvageable by treating these in a third.

Distant metastases with locoregional control are common (8%) and carry a very poor prognosis. The time to metastases varies from 1–20 months⁽⁶⁸¹⁾. Sites involved include the lung, liver, eye, parotid, central nervous system, bone, vertebrae, and epidural space.

Assessment of recurrence and further treatment

Median survival after recurrence is 12 months – therefore it is imperative to deal with the primary site initially to minimise the risk of metastatic disease⁽⁷¹⁰⁾.

There is a delayed neck metastatic rate of 16% and some consider that this is an indication for elective neck dissection in all cases of olfactory neuroblastoma. Patients with advanced local disease should probably undergo radiological examination of the neck and may be candidates for regional treatment⁽⁷⁰⁸⁾ that may include either treating the neck with radiotherapy or performing an elective neck dissection followed by radiotherapy.

The principle site for distant metastases in one series⁽⁶⁸¹⁾ was bone, vertebrae being the most common location (86%). Asymptomatic bone metastases were found in three patients at presentation coincidentally with a bone scan that was performed after bone marrow biopsies showed aplasia. Hence a bone scan and bone marrow biopsy should be considered if the likelihood of distant metastases is raised. The significant risk factor for developing distant metastases is the presence of cervical metastases at initial presentation.

There is a single case report of a woman with an olfactory neuroblastoma with epithelial and endocrine differentiation that transformed into a mature ganglioneuroma after chemoradiotherapy⁽⁷²⁰⁾.

Recommended Follow-up

Olfactory neuroblastoma is a neoplastic disease with a long natural history characterised by frequent local and regional recurrences after conventional treatment⁽⁷⁰⁸⁾, and so extended follow-up of patients is warranted. The mean time for recurrence is 5 years for evaluating most other cancers of the head and neck but this is not valid for olfactory neuroblastoma, there the survival data at 10, 15 and even 20 years is important in evaluating the result of treatment⁽⁷²¹⁾.

Girod et al.⁽⁶⁹⁵⁾ have gone so far as to suggest that MRI with gadolinium should be done 2–4 months after completion of all therapy, and should be repeated 4–6 monthly for 5 years and then annually for the patient's lifetime^(719,722). Continued clinical follow-up is indicated annually thereafter and any symptoms investigated. An annual chest radiograph should be performed to exclude the presence of metastases.

Discussion

Should the management of olfactory neuroblastoma include primary surgery followed by elective radiotherapy for the well-differentiated tumours and pre-treatment chemotherapy followed by surgery and radiotherapy for the poorly differentiated

tumours? Should all patients have life-long follow-up? What is the balance between the morbidity sustained by surgery and radiotherapy gauged against the addition of chemotherapy, which may only help the mortality in a small percent of individuals? There are now several QoL formats to assess life outcome measurements⁽⁷²³⁾, which are specific to skull base patients. As these patients may live quite a long time with or without disease, it is important to document patients long-term outcome and not just focus on the immediate surgical procedure performed⁽⁷²³⁾. Akin to most skull base tumours, prospective multi-centred studies are needed to clarify the best mode of treatment for these tumours taking both the surgical and histological staging into consideration.

Conclusions

- Olfactory neuroblastoma is an uncommon malignant neoplasm believed to arise from is thought to arise from the basal reserve cell, the olfactory stem cell that gives rise to both the neuronal and the epithelial sustentacular cells.
- The tumour shows varying biological activity, ranging from indolent growth to a highly aggressive neoplasm.
- The incidence of olfactory neuroblastoma is not as rare as is commonly reported, and probably represents > 5% of all malignant nasal tumours.
- Both the Kadish surgical stage and the Hyams' pathological stage are predictive of survival.
- Appropriate evaluation includes both computed tomography (CT) and magnetic resonance imaging (MRI).
- A combination of surgery and radiotherapy is the most frequently used approach, and the one that achieved the highest cure rates.
- The current recommended treatment strategy suggested is:
 - Kadish A – Surgery – and in selected cases combined with radiotherapy.
 - Kadish B – Radiotherapy before/or after surgery, to the primary tumour site and subclinical lymph nodes. Adjuvant chemotherapy may be added to this treatment depending on the degree of differentiation of the tumour.
 - Kadish C/D – Preoperative chemotherapy and/or radiotherapy followed by surgery. The use of adjuvant chemotherapy has yet to be further elucidated, as well as the timing of the surgery and the radiotherapy.

Table 7.10. Olfactory neuroblastoma: staging According to Kadish et al.⁽⁶⁸⁰⁾ and modified by Morita et al.⁽²⁴⁰⁾.

Type	Extension
A	Tumour limited to the nasal cavity
B	Tumour involving the nasal and paranasal sinuses
C	Tumour extending beyond the nasal and paranasal sinuses, including involvement of the cribriform plate, base of the skull, orbit or intracranial cavity
D	Tumour with metastasis to cervical nodes or distant sites

Table 7.11. Olfactory neuroblastoma: staging system after Dulguerov et al. ⁽²⁴¹⁾.

Stage	Characteristics
T1	Tumour involving the nasal cavity and/or paranasal sinuses (excluding the sphenoid sinus) sparing the most superior ethmoidal cells
T2	Tumour involving the nasal cavity and/or paranasal sinuses (including the sphenoid sinus) with extension to or erosion of the cribriform plate
T3	Tumour extending into the orbit or protruding into the anterior cranial fossa, without dural invasion
T4	Tumour involving the brain
N0	No cervical lymph-node metastases
N1	Any form of cervical lymph-node metastases
M0	No metastases
M1	Any distant metastases

Table 7.12. Olfactory neuroblastoma: distribution of patients and survival by treatment modality (1992 – 2008) according to Devaiah's meta-analysis ⁽⁷⁰⁰⁾.

Modality	Patients (n)	Frequency (%)	Survival (%)	Odds Ratio (OR)	Confidence Interval (CI)
Surgery alone	87	20 ± 22	48 ± 40	1.9	0.7 - 4.9
Surgery + Radiotherapy	169	44 ± 20	65 ± 25	1	
Radiation Alone	49	13 ± 19	37 ± 33	2.5	1.02 - 6.0
Surgery + RT + Chemo	48	7 ± 16	47 ± 37	2.1	0.68 - 16.5
Radiation + Chemo	26	0 ± 1	0		
Chemotherapy	6	2 ± 4	40 ± 55		

Table 7.13. Olfactory neuroblastoma: comparison of survival results (1992 – 2008) according to Devaiah's meta-analysis ⁽⁷⁰⁰⁾.

Treatment A	No	Treatment B	No	p-value
Surgery	279	No surgery	52	< 0.001
Open Surgery (endoscopic better)	214	Endoscopic surgery	40	.0019
Open Surgery (endoscopic better)	214	Endoscopic assisted	57	.0123

Table 7.14. Median Follow-up Times (months) for olfactory neuroblastoma ⁽⁷⁰⁰⁾.

Open	51.0
Endoscopic	54.5
Endoscopic assisted	44.0
Nonsurgical	17.0

Table 7.15. Olfactory neuroblastoma: comparison of survival results (2002 – 2008) according to Devaiah's meta-analysis ⁽⁷⁰⁰⁾.

Treatment A	No	Treatment B	No	p-value
Open Surgery (endoscopic better)	145	Endoscopic surgery	40	0.0018
Open Surgery (endoscopic better)	145	Endoscopic assisted	57	0.0133

7-3-2 Malignant Melanoma

Search Strategy

A Medline and Pubmed review of the literature was performed of all case series of malignant melanoma of the nasal cavity and paranasal sinuses focussing published from 1990 onwards. If a single centre had published more than one case series, then data from the most recent series was used.

Introduction

Malignant melanoma of the sinonasal mucosa is an uncommon disease, and survival is poor. Diagnosis is often delayed because the onset of symptoms is insidious and patients present with advanced disease. The rarity and long natural history of malignant tumours make it difficult to accrue cohorts to compare endoscopic resection with the established gold standard of craniofacial resection ⁽⁶³⁵⁾.

Incidence and Aetiology

Malignant melanoma (MM) is a rare disorder of the nasal cavity and paranasal sinus mucosa. Primary sinonasal tract mucosal malignant melanomas are rare, accounting for between 0.3% and 2% of all malignant melanomas and about 4% of head and neck melanomas ^(224-229,231). In the National Cancer Data Base report by the American College of Surgeons Commission on Cancer and the American Cancer Society of more than 84,000 melanomas seen from 1985 to 1994, only 1.3% were melanomas that arose from mucosal surfaces, of which 55% were of the head and neck. Sinonasal tract mucosal malignant melanomas were found to be equally common in men and women. A higher proportion of melanoma were identified in black patients (10.4%) ⁽²²⁸⁾. In general, the mean age for sinonasal tract mucosal malignant melanomas is 64.3 years being later in life than cutaneous malignant melanomas. Sinonasal tract mucosal malignant melanomas have a worse prognosis over 60 years ⁽²²⁸⁾. Tumours originating in the sinuses are less common than those arising in the nasal cavity, and they tend to grow asymptotically until late in the disease course ^(231,233). A third of patients present with neck metastases, which often preceded more distant metastasis, and distant metastasis, the latter are usually rapidly fatal ⁽²³⁴⁾.

Approximately 80% of MM are found within the nasal vault and 20% in the sinuses ^(225,229,230). The incidence is not increasing unlike cutaneous melanoma where there has been a significant increase over the past few years.

Melanocytes are derived from the neural crest and are widely distributed throughout cutaneous and mucosal surfaces. They are present in the nasal mucosa, the secretory glands, superficial and deep stroma of the septum and turbinates, and are particularly common in the supporting cells of the olfactory epithelium. Pre-existing melanosis in the nasal mucosa is uncommon, and is thought to be a risk factor for developing MM and this is supported by a higher incidence in the black

population. The aetiology is unclear although several series have found that possible occupational exposure to formaldehyde may be a factor^(232,724,725). The commonest site of origin is from the lateral nasal wall and in particular from the middle and inferior turbinates, followed by the nasal septum. However, patients may also have disease arising from the maxilla and ethmoid sinuses. Very often the disease is too extensive to determine the exact site of origin. MM of the nose is almost always a primary lesion.

Clinical presentation

Symptoms on presentation can include nasal obstruction, epistaxis, swelling of the nose or the presence of a visible mass at the vestibule, pain, and nasal discharge. Diplopia, epiphora and proptosis are late features. Patients with mucosal melanoma tend to present later in the disease course than do patients with cutaneous melanoma because their insidious onset of symptoms that are often associated with benign conditions that may be ignored early on.

Diagnosis and Imaging

CT typically shows a uniform soft tissue mass with erosion of surrounding bone. MRI also shows a soft tissue mass with some retained secretions in any obstructed sinuses. The main differential diagnosis on the basis of imaging is squamous cell carcinoma, adenocarcinoma or lymphoma. However, the clinical appearance of a black coloured lesion helps make the diagnosis unless it is a non pigmented melanoma. Imaging of the neck, chest and liver are indicated to stage the disease and look for metastases.

Positron emission tomography (PET) scans are possibly more sensitive in detecting metastases⁽⁷²⁶⁾.

Histology

Most are large epithelioid cells with abundant eosinophilic cytoplasm with round nuclei showing eosinophilic nucleoli or spindle cells. About a third of tumours have undifferentiated small round blue cells that may be mistaken for a lymphoma. There may be a variety of morphological tumour cell types. The majority of cells have cytoplasmic pigment.

The immunochemical profile of sinonasal malignant mucosal melanoma is identical to dermatological lesions with S-100 protein, HMB-45, melan-A, MITF (microphthalmia transcription factor), tyrosinase, vimentin and cytokeratin (Fontana-Masson stain). S-100 is not always present, so a series of markers are needed to make a diagnosis. PNL-2 shows promise as a more specific marker.

Staging

Staging the disease before treatment is essential for documentation and comparing the results of treatment. Thompson et al.⁽²³²⁾ suggested using the TNM classification as a predictor of biological behaviour. Ballantyne⁽⁷²⁷⁾ described a simple system

that has been used by many over the years because of its simplicity”

Stage I : disease confined to the primary site

Stage II: primary lesion with regional lymph node metastasis

Stage III: presence of systemic metastasis

The AJCC staging system is geared towards cutaneous melanoma. Prasad et al.⁽⁷²⁸⁾ advocated a staging system based on the degree of invasion of the mucosa and found this was a significant independent predictor of survival:

Level I: Melanoma in situ without invasion or with microinvasion

Level II: Invasion of the lamina propria only

Level III: Invasion into deep tissue

Treatment and Results

The primary therapeutic modality is surgical resection with wide local margins. Incomplete local control is a predictor of poor survival in mucosal melanomas⁽⁷²⁹⁾. Although no formal randomized trials have shown benefit from radiation therapy in sinonasal melanoma, some studies suggest radiotherapy may provide some improved local control but none show an increase in life expectancy. Postoperative radiation is often recommended for advanced disease but with little evidence to support its use with any improvement in survival rates. Chemotherapy is currently only used for disseminated disease and palliation and its benefit is uncertain.

Local recurrence is a major problem and Huang et al. had an average time from surgery to local recurrence of 5 months⁽⁷³⁰⁾. Regional recurrence is similarly a problem being 7.45 months in the same series⁽⁷³⁰⁾.

Prophylactic neck dissection in an N0 neck is not done as the incidence of node metastases is relatively low⁽⁷³¹⁾. Distant metastases have been reported between 10.3 months⁽⁷³⁰⁾ and 23.2 months⁽²³²⁾. Dauer et al.⁽²³⁴⁾ reported a median time between diagnosis and death of 19 months in their series of 61 patients with a cancer specific survival rate of 22.1% at 5 years. In a series of 115 patients reported by Thompson et al.⁽²³²⁾, 55% died of disseminated disease after a mean of 2.3 years although Bridger et al., who propose initial radical surgery and postoperative radiotherapy⁽⁷³²⁾, reported a mean survival time of 4.3 years in their series of 27 patients. The completeness of resection appears to be very important.

Nicolai et al.⁽³²⁷⁾ retrospectively analysed 17 patients with MM in a series of 184 skull base tumours. Fourteen sinonasal MM were removed endoscopically and 3 using a craniofacial endoscopic approach. The staging of these patients was not described. Nine of the endoscopic group recurred (64%) and 2 of the craniofacial endoscopic approach (67%) after a mean follow-up of 34.1 months. It is not possible to determine the

survival rates for MM from the data in the large mixed group of skull base tumours that they reported.

In MM of all mucosal sites in the head and neck, positive margins are associated with a greatly increased mortality⁽⁷³³⁾.

Whatever the therapy, median survival is poor. Beyond the negative risk factors of size, deep thickness, and invasion, a review from the Mayo clinic found statistically significant survival benefit from the primary lesion being located on the nasal septum, as opposed to the sinuses or lateral nasal wall⁽²³⁴⁾.

Mucosal melanomas of the sinonasal tract tend to be more aggressive and have a poorer prognosis than their cutaneous counterparts, having 22% to 46% 5-year survival rate^(232,730,732). The poor prognosis with MM is attributable to both local recurrence and distant metastasis. Several new biologic and immune modulator treatments are currently being investigated for use in patients with mucosal melanoma and the results of these treatments is eagerly awaited.

Surgery and/or radiotherapy

A retrospective review Lund et al. examined whether surgery combined with radiotherapy confers any survival benefit compared with radical local excision alone⁽⁷³⁴⁾. From a cohort of 72 patients treated between 1963 and 1996 within a single unit, complete data were available for 58 individuals who were examined. The authors came to the conclusion that overall survival was poor and did not appear to be improved by the addition of radiotherapy. Thompson et al.⁽²³²⁾ who advocated surgery and radiotherapy in a series of 115 patients concluded that “the specific type of therapy did not seem to influence the overall patient outcome”, as there was no significant difference between patients managed by surgery, surgery with chemotherapy, surgery with radiotherapy or all three.

A minority of workers have been proponents of radiotherapy although MM has historically been regarded as not being radiosensitive. Owens et al.⁽⁷³⁵⁾ treated 11 patients with adjuvant radiotherapy and found that it decreased local recurrence but did not significantly improve survival although the sample size was small. Wada et al.⁽⁷³⁶⁾ retrospectively studied 21 patients who received radiotherapy alone and 10 for gross residual disease after surgery. They reported a 29% complete response rate and a 58% partial response rate but their disease specific survival rates were in line with other studies. Other studies of mucosal MM of the head and neck suggest that radiotherapy increased the local and neck disease free period but does not increase survival⁽⁷³⁷⁾. Temam et al.⁽⁷³⁸⁾ treated 46 patients with paranasal sinus MM as well as 23 with MM of the oral cavity or pharynx. Patients with small tumours who received postoperative radiotherapy had better local disease free survival than patients with larger tumours who did not receive radiotherapy. Their conclusion that “postoperative

radiotherapy increases local control” is open to criticism given the bias in the staging of disease between those who did and did not receive radiotherapy. Both Nandapalan et al.⁽⁷³⁹⁾ and Patel et al.⁽⁷³¹⁾ found that radiotherapy did not provide any local control.

Bridger et al.⁽⁷³²⁾ reported favourable survival rates compared to most other series advocating wide local excision followed by radiotherapy (Table 7.16).

Brandwein et al. from Mount Sinai Medical University did a retrospective study as well as a meta-analysis of the English-language literature for cases of documented sinonasal melanoma from 1977 to 1995⁽⁷²⁴⁾. The population in this study included 10 men and 15 women aged 23 to 83 years (mean 65 years). Tumour sites included the inferior turbinate, superior nasal cavity, nasal cavity floor/palate, ethmoid sinuses, and maxillary sinus. They reported that in spite of advances in imaging, surgical techniques and adjuvant therapeutics, the mean survival for patients with sinonasal melanoma remains poor. They identified a total of 163 cases were identified from the literature: The 5-year median survival for all patients was 36 months.

In another large cohort of patients, the Mayo Clinic retrospectively reviewed 61 cases over a period from 1955 to 2003⁽²³⁴⁾. The most common treatment was surgical excision alone (48%). The cancer-specific survival rate (ie rate of death due to disease) was 48.9% and 22.1% at 3 and 5 years, respectively. Median time between diagnosis and death due to disease was 19 months. They concluded that wide local excision is the treatment of choice, and some patients ‘may’ benefit from postoperative radiotherapy. Local recurrence and distant metastasis are common and any improvement in survival is likely to depend on the development of better systemic therapies⁽⁷⁴⁰⁾. In a more recent prospective study by Lund et al.⁽⁶³⁵⁾, all 11 malignant melanoma tumours were removed endoscopically with the intention to cure the patient. Three patients had previously had a lateral rhinotomy. Following endoscopic resection 1 patient had a further endoscopic resection and another, a lateral rhinotomy and two patients had neck dissections (6 and 16 months). The survival at 5 years for this specific group was overall 80% of whom 36% were disease free patients. Lund et al. found that the endoscopic removal of MM is as effective as by other means but emphasised that craniofacial resection remains the “gold standard” for tumours that contact or traverse the skull base⁽⁶³⁵⁾.

Discussion

In general, the prognosis of paranasal sinus malignant melanoma is poor⁽²³²⁾ although lesions that affect the septum do better⁽²³⁴⁾. The 5 year survival rate is much worse than cutaneous malignant melanoma. This may relate to a delay in diagnosis because of its hidden site and the non-specific nature of its presenting symptoms.

The place of radiotherapy remains uncertain. The small size of most series and lack of randomization and the variation in treatment modalities used makes it difficult to extract any meaningful data from the literature. The pathology and its propensity to recur locally and metastasise remain the primary problem. Whether the primary lesion is removed endoscopically, via an external incision or midfacial degloving would appear to make little difference to the prognosis. There is some data to favour wide local excision over local removal⁽⁷³²⁾. Lund et al. came to the conclusion that the intention with endoscopic surgery is not limited but should always be done with the intention to cure the patient by removing the tumour with the same margin as might be achieved by an open procedure. Long term follow-up is mandatory up to 15 or 20 years to help compare different treatment modalities⁽⁶³⁵⁾.

Conclusions

- Patients with sinonasal MM often present late as it often has an insidious onset.
- The initial resection should be wide with intention to cure.
- The limited evidence at present suggests that the endoscopic removal of MM is as effective as by other means.
- Radiotherapy may help local control but does not affect survival.
- Local recurrence is a problem.
- Sinonasal malignant melanoma is associated with poor survival rates.
- Malignant melanoma of the septum is associated with a better prognosis than elsewhere in the nose and paranasal sinuses.

Table 7.16. Results of treatment of sinonasal malignant melanoma in the literature.

Authors	Number of patients	Primary treatment to local recurrence	Primary treatment to regional recurrence	Primary treatment to distant metastases	Survival free and disease free interval
Thompson et al. (2003) ⁽²³²⁾ (Ethos: Wide local excision + some radiotherapy/chemotherapy)	N=115	Unable to extract data	Unable to extract data	Unable to extract data	45% alive at a mean of 2.3 years, 22% alive at 5 years
Bridger et al. (2005) ⁽⁷³²⁾ (Ethos: Radical surgery and radiotherapy)	N=27	14.7 months (mean)	Unable to extract data	23.2 months (mean)	46% alive at 5 years, mean survival 52 months
Huang et al. (2007) ⁽⁷³⁰⁾ (Ethos: Surgery + some with radiotherapy/chemotherapy)	N=15	5 months (mean)	7.45 months (mean)	10.3 months (mean)	49.5% alive at 2 years, 33% at 5 years
Lund et al. (2007) ⁽⁶³⁵⁾ (all endoscopic resection, intention to cure, prospective)	N=11	Unable to extract data	Unable to extract data	Unable to extract data	80% alive at 5 years, 36% disease free
Dauer et al. (2008) ⁽²³⁴⁾ (Ethos: Wide local excision + some radiotherapy)	N=61	9 months (mean)	Unable to extract data	13 months (mean)	48.9% alive at 3 years, 22.1% at 5 years Median survival 19 months
Brandwein et al. (1997) ⁽⁷²⁴⁾	N=25	Unable to extract data	Unable to extract data	Unable to extract data	60% survival at a mean of 21 months 44% disease free at 5 years
Nicolai et al. (2008) ⁽³²⁷⁾ (Endoscopic resection, probable radiotherapy but not detailed)	N=14	Unable to extract data	Unable to extract data	Unable to extract data	18% disease free mean follow-up of 34.1 months

7-4 Bony and cartilaginous

7-4-1 Chondrosarcoma

Search strategy

A review of the literature was conducted on the PubMed database from 2000 until now. Search entries were “chondrosarcoma AND (endoscopic OR endoscopy) AND (nasal OR sinus)”, which yielded 29 references, and “chondrosarcoma AND proton therapy OR proton beam therapy”. This search was completed with the textbook of the WHO⁽³²⁸⁾.

Introduction and incidence

Chondrosarcomas are rare, slow growing malignancies of cartilage that mainly affect the pelvis and long bones. In general, chondrosarcomas affect older adults, and show a male predilection⁽³²⁸⁾. Skull base chondrosarcomas often arise from remnants of cartilage after ossification and constitute 0.15% of all intracranial and 6% of all skull base tumours⁽⁷⁴¹⁾. Chondrosarcomas are even more rare in the facial skeleton and the sinonasal tract, accounting for less than 16% of all sarcomas of the nasal cavity, paranasal sinuses and nasopharynx.

Histology

Histologically, chondrosarcomas are divided in three grades (Grade 1: well differentiated; Grade 2: intermediate differentiated; Grade 3: poorly differentiated), according to the degree of cellularity, nuclear size and atypia, mitotic activity⁽⁷⁴²⁾. Analyzed in a multivariate fashion, histological grade is the single most important predictor of local recurrence and metastasis, along with surgical stage (margins)⁽⁷⁴³⁻⁷⁴⁵⁾.

A subtype called mesenchymal chondrosarcoma is a small round cell neoplasm with focal differentiation, often with a pericytomatous vascular pattern. Mesenchymal chondrosarcoma is extremely rare, and affects young adults, more commonly women. Classical chondrosarcomas of the head and neck commonly involve the alveolar portion of the maxilla, the maxillary sinus, the nasal septum, the sphenopetrous area and clivus, whereas, mesenchymal chondrosarcoma involves the mandible and maxilla almost equally. While classical chondrosarcomas have a local evolution, mesenchymal CS exhibits high biological aggressiveness and metastatic potential⁽⁷⁴⁵⁾.

Clinical presentation and imaging

Imaging and clinical appearance of chondrosarcomas can be similar to that of chordomas. However, their site of origin, pattern of spread and their lack of epithelial markers or oncofetal antigens, distinguish them from chordomas.

Treatment

En-bloc excision is the preferred surgical treatment for intermediate- and high-grade chondrosarcoma, however, this option is rarely possible in the head and neck or skull base areas. For low-grade chondrosarcoma, extensive curettage may provide satisfactory local control⁽³²⁸⁾ but is not ideal. However, it should be noted that status of the surgical margins and grading, comprise the most important predictive factors⁽⁷⁴³⁻⁷⁴⁵⁾. Management of skull base chondrosarcomas is difficult because of their challenging location along the median and paramedian ventral skull base, often extending along the petroclival fissures. By virtue of their location, critical arteries, cranial nerves and cavernous sinuses surround chondrosarcomas. En bloc resection is not possible for these lesions.

Chondrosarcomas are relatively radio-resistant; therefore, doses > 60 Gy are needed to achieve local control after incomplete resection. Compared with other forms of radiation therapy, proton beam therapy has been used to increase the dose delivered to the tumour while elegantly sparing dosing to adjacent critical normal structures⁽⁷⁴⁶⁾. An extensive review of the literature led some authors to conclude that "The use of PT following maximal surgical resection shows a very high probability of medium- and long-term cure with a relatively low risk of significant complications" although there are no available prospective studies⁽⁷⁴⁷⁾. Others, reporting the use of a 68 Gy dose for chondrosarcomas (n = 22) reported an actuarial 5 year

local control rate of 94% for chondrosarcomas. Brainstem compression at the time of proton therapy (p = 0.007) and gross tumour volume > 25 ml (p = 0.03) were associated with lower local control rates⁽⁷⁴⁸⁾. Chemotherapy is possibly effective only for mesenchymal chondrosarcoma, and is of uncertain value for undifferentiated chondrosarcoma⁽⁷⁴⁹⁾.

Various external and endoscopic approaches have been described for the surgical resection of chondrosarcomas of the skull base. Despite extensive external approaches, total resection is difficult and subtotal resection is the most common scenario. Similarly, others have noted that complications are to be expected with the management of these lesions⁽⁷⁴⁴⁾. Conventional transcranial/transfacial skull base approaches are often associated with postoperative cranial neuropathies due to the need to obtain an adequate surgical exposure⁽⁷⁴⁴⁾. Gay et al. reported a series of 60 patients with either chordomas or chondrosarcomas, in which only 28 patients (47%) had total resection based on postoperative imaging⁽⁷⁵⁰⁾. However, 48 patients (80%) suffered new cranial neuropathies. They noted a significant difference in recurrence and survival rates when comparing total or near total resection with patients who underwent subtotal or partial resection⁽⁷⁵⁰⁾.

In a review of 64 patients by Sekhar et al, only 50% of patients had total resection but 41% of patients incurred additional neurologic deficits⁽⁷⁵¹⁾. Oghalai et al. reported a series of 33 patients in whom only 8 patients (28%) had total resection and 6 patients (18%) suffered surgical complications⁽⁷⁴⁴⁾.

Tzortzidis et al. reviewed 47 patients that underwent microsurgical resection over a 20 year period⁽⁷⁵²⁾. A gross total resection was obtained in 61.7% of patients and subtotal resection was obtained in 38.3% of patients. A postoperative complication rate, including CSF leaks and new cranial nerve palsies, of 18% was reported. Patients that underwent a gross total resection, especially as a primary procedure, demonstrated better local control and quality of life⁽⁷⁵²⁾.

Results

Chondrosarcomas, especially low-grade tumours, are associated with an excellent prognosis if the lesions are completely resected. (Table 7.17) Their tendency to present in well-differentiated form (Grade 1) explains why chondrosarcoma is the head and neck soft tissue malignancy with initially the best prognosis. However, overall 5 year survival, combined for the different grades, varies from 56% to 87% and this deteriorates markedly with time⁽⁴⁸¹⁾. Conversely, mesenchymal CS is a high-grade tumour with an unpredictable and generally very poor prognosis.

Discussion

Obviously, endoscopy may be used for sampling. Its role for the surgical resection is not well defined. A literature search

reveals a lack of randomized trials comparing open and endoscopic approaches in regard to completeness of surgical excision and outcome for either skull base or sinonasal lesions. There are various case reports of endoscopic removal of chondrosarcomas affecting: the septum^(291,742,753-756) and the posterior septum and sphenoid rostrum⁽⁷⁵⁷⁾. These reports suggest that small lesions without skull base or orbital involvement, especially if located at the level of the nasal septum, are amenable to an endoscopic resection. Others have described the techniques for the endoscopic removal of deep-seated lesions, including chondrosarcomas with other pathologies arising in the sphenoid sinus^(636,758,759), clivus⁽⁷⁶⁰⁻⁷⁶²⁾, petrous apex⁽³⁵¹⁾, and pterygopalatine fossa⁽⁷⁶³⁾. However, long-term follow-up is lacking.

In a recent report by Frank et al., the endoscopic transnasal approach for chordomas and chondrosarcomas was reviewed⁽⁷⁶⁰⁾. Using this technique the mean hospital stay was five days and no perioperative complications, including CSF leaks or neurologic deficits, were noted. However, only two of the nine patients had skull base chondrosarcomas.

Conclusions

- Surgical resection (and occasionally for high grade tumours or positive margins postoperative radiotherapy) provides the best long term results.
- Tumour recurrence has been associated with advanced histological grading and adequacy of treatment. Therefore, the recurrence rate is directly proportional to the degree of resection as well as the histological grade.
- A total resection can be achieved with endoscopic endonasal approaches for most tumours in the median sinonasal tract.
- Skull base lesions are often adjacent to critical neurovascular structures; therefore, their removal is achieved in a piecemeal fashion regardless of the approach.
- An endonasal corridor offers the advantage of avoiding the manipulation of cranial nerves required by the external lateral approaches.

Table 7.17. Chondrosarcomas (CS) removed via an endonasal endoscopic approach in the literature.

Location	Series	Study Design	Total n° of patients	CS (n°)	Extent of resection	Follow-up range (mean)	Morbidity	Recurrence
Septum	Matthews ⁽⁷⁵³⁾	Case series	1	1	complete		none	
Septum	Giger ⁽⁷⁵⁴⁾	Case series	1	1	complete	3 yrs	none	
Septum	Coppit ⁽⁷⁴²⁾	Case series	2	2	complete		none	
Septum	Betz ⁽⁷⁵⁵⁾	Case series	2	1	incomplete	1 yr	none	Early recurrence removed
Septum	Jenny ⁽⁷⁵⁶⁾	Case series	1	1	complete		none	
Sphenoid	Carrau ⁽⁷⁵⁷⁾	Case series	1	1	complete		none	
Sphenoid	Castelnuovo ⁽⁷⁵⁹⁾	Case series	41	1				
Sphenoid	Tami ⁽⁷⁵⁸⁾	Case series	8	1				
Clivus and sphenopetrous	Frank ⁽⁷⁶⁰⁾	Case series	11	2				
Clivus	Zhang ⁽⁷⁶¹⁾	Case series	9	2	complete/ subtotal	3-39 MO		
Pterygopalatine area	Hu ⁽⁷⁶³⁾	Case series	1	1				

First author only given for each series

7-4-2 Osteosarcoma

Introduction

Osteosarcoma is a malignant tumour of bone that is thought to arise from a primitive mesenchymal bone-forming cell and is characterized by the production of osteoid. Osteosarcoma can occur in any bone but it most commonly occurs in the long bones of the extremities near metaphyseal growth plates⁽⁷⁶⁴⁾. Skull or jaw bones are rarely involved (8%).

Incidence and aetiology

In the United States, the incidence is 400 cases per year (4.8 cases per million persons < 20 yr). The incidence is slightly higher in African Americans than in Caucasians⁽⁷⁶⁴⁾. The incidence of osteosarcoma of the limbs increases steadily with age, nonetheless, a relatively dramatic increase in adolescence corresponds with the growth spurt. Osteosarcoma is the third most common cancer in adolescence. Head and neck osteosarcomas, however, differ from other localizations in that their

mean age ranges between 26 and 40 years of age; thus, they affect patients that are 10 or 15-years older than osteosarcomas of long bones⁽⁷⁷⁹⁾.

The exact cause of osteosarcoma is unknown. However, numerous risk factors have been identified. Rapid bone growth appears to predispose patients to osteosarcoma, as suggested by the increased incidence during the adolescence and the typical location of osteosarcomas near the metaphyseal growth plate of long bones. Exposure to radiation is the only known environmental risk factor. A genetic predisposition may be present. Presence of a constitutional mutation of the retinoblastoma *RB* gene (germline retinoblastoma) combined with radiation therapy, is associated with a particularly high risk of developing an osteosarcoma. Of note, the genetic locus retinoblastoma at band 13q14 has also been implicated in the pathogenesis of sporadic osteosarcoma. In addition, the Li-Fraumeni syndrome (germline *TP53* mutation) and Rothmund-Thomson syndrome (ie, autosomal recessive association of congenital bone defects, hair and skin dysplasias, hypogonadism, cataracts) are associated with an increased risk. Bone dysplasias, including Paget disease, fibrous dysplasia, enchondromatosis, and hereditary multiple exostoses, also increase the risk for osteosarcoma.

Histology

Numerous variants of osteosarcoma are named according to the cellular pattern of differentiation, conventional types (ie, osteoblastic, chondroblastic, fibroblastic types) and telangiectatic, multifocal, parosteal, and periosteal types. There is no correlation, however, between histological subtype and prognosis.

Treatment

The mainstay of therapy is removal of the lesion. Chemotherapy is also recommended to treat micrometastatic disease, which at the time of diagnosis is present but not detectable in most patients. Before the use of chemotherapy, osteosarcoma was primarily treated with surgical resection. Despite good local control of the disease, more than 80% of patients subsequently developed pulmonary metastases. This triggered the use of adjuvant (postoperative) systemic chemotherapy for the treatment of patients with osteosarcoma of the limbs⁽⁷⁶⁵⁾.

The most active chemotherapeutic drugs against osteosarcoma are doxorubicin, cisplatin, and high-dose methotrexate. In addition, other therapies are being studied, such as, anthracycline escalation using a cardioprotectant, muramyl tripeptide phosphatidyl ethanolamine (MTP-PE) and other immune enhancers (eg interferon), and monoclonal antibody against the Her2/neu antigen, which is overexpressed in some osteosarcomas^(766,767).

It is noteworthy that resection of metastatic pulmonary nodules is widely advocated. If osteosarcoma recurs as a solitary lung lesion more than 1 year after completion of therapy, surgical resection alone can be curative, as the likelihood of metastases to other sites is low⁽⁷⁶⁸⁾. Conversely, if the osteosarcoma recurs sooner than one year after therapy, chemotherapy is warranted, as the risk of other micrometastatic disease is high.

Osteosarcoma of the head and neck (OHN) is rare representing less than 10% of all cases, and exhibits a clinical behavior and natural history that are distinct from those of osteosarcoma of the trunk and extremity. In the head and neck area, metastases are rare, but lethality is associated with poor local control of the disease⁽⁷⁶⁹⁾. This phenomenon is observed with most sarcomas in the head and neck area where wide margins are often impossible and positive margins around critical neurovascular structures are common. Carrau et al. examined the role of skull base resection for a fifteen patients presenting with various sarcomas of the sinonasal tract⁽²⁸⁸⁾. Although not statistically significant, the authors suggested that resection of the skull base provide an additional margin that aims to achieve an adequate surgical resection and improve the prognosis in patients with sinonasal sarcomas that invade or approach the anterior skull base. Kassir et al. examined the role of adjunctive therapy in 173 patients with osteosarcoma of the head and neck⁽⁷⁷⁰⁾. The overall 5-year survival was 37%. Survival of patients with extracranial tumours was significantly worse than patients with mandibular and maxillary ($p < 0.001$). Interestingly, surgery alone was associated with significantly longer survival rates ($p < 0.03$) than surgery with adjuvant therapy. However, we expect a significant bias toward the use of adjunctive therapy for advanced tumours or those with positive surgical margins. Data regarding the adequacy of the surgical margins was not available for the majority of patients entered in the database; therefore, the differences may not adequately represent the effect of adjuvant therapy. Adjuvant treatment protocols for long bone osteosarcoma produced encouraging outcomes, however, its role in the management of osteosarcoma of the head and neck remains unproven. Adjuvant therapy should be entertained in view of the poor prognosis associated with osteosarcomas of the head and neck.

Overall, the main goal of treatment is to achieve local control through wide resection. For patients without distant metastases at the time of diagnosis, chemotherapy does not seem to improve survival, as opposed to postoperative radiotherapy for the cases with uncertain or positive margins⁽⁷⁷¹⁾. In a series of 119 patients, overall survival (OS) rates at 5 years and 10 years were 63% and 55%, respectively⁽⁷⁷¹⁾. Corresponding disease-specific survival (DSS) rates were 67% and 61%, respectively. Stratified analysis by resection margin status demonstrated that CMT compared with surgery alone improved OS and DSS for patients with positive/uncertain resection margins. A total of 44

(36.97%) patients experienced local disease recurrence (LR) and 25 (21%) developed distant metastases (DM) ⁽⁷⁷¹⁾. These outcomes are similar to those reported by Patel et al. ⁽⁷⁷²⁾.

Conclusions

- Osteosarcomas of the ventral sinonasal tract or skull base are extremely rare as they typically involve the outer face skeleton and/or maxilla.
- They usually require an open approach so the literature regarding the use of pure endoscopic endonasal surgery is sparse.
- In general, when the resection provided with an endonasal endoscopic approach is equivalent to that of an open approach then it is appropriate to use it.
- An endonasal endoscopic approach can also be used to complement open traditional approaches.

8. Pituitary Tumours

8-1 Introduction

Pituitary surgery is a distinct subspecialty of neurosurgery that demands precise knowledge of basic neurosurgical techniques and associated skills, together with specific knowledge, interest, and appreciation of pituitary pathophysiology, allowing the surgeon to make the right choice at the right moment. It is currently possible to manage many of the different pituitary syndromes with more than one option, including medical, surgical, and radiotherapeutic, alone or in various combinations. Pituitary surgery yields the best outcomes when performed in centers where the entire range of pituitary specialties is offered in an environment of effective teamwork. Such teamwork demands a “teamwork attitude”, which is not just the addition of the expertise of the single contributors, but rather a cultural and psychological attitude, with the single units working with a goal of true exchange and sincere collaboration, which allows cooperative effort for the benefit of the patient and positive feedback for physicians and surgeons. Pituitary surgery, perhaps more than other areas of neurosurgery, requires careful and specific postoperative management and long-term patient follow-up, which can make the difference between a satisfactory result and a poor result. A patient can be operated on successfully, but the outcome may not be as good as the surgical procedure if mutual exchange between specialists such as the endocrinologist, the otolaryngologist, the ophthalmologist, the neuroradiologist and the pathologist is not established.

To realize these goals, the neurosurgeon must know detailed anatomy, learned in the laboratory before working in an operating room; he or she must be experienced in neuroimaging, must know pathophysiology and the natural history of pituitary disease, and must be familiar with the various therapeutic options.

8-2 Treatment

Therapy for pituitary adenomas is targeted to achieve multiple goals, as follows:

1. Normalization of excess hormone secretion
2. Preservation or restoration of normal pituitary function
3. Elimination of mass effect
4. Preservation or restoration of normal neurologic function, usually visual acuity or visual field (or both) being more frequently affected
5. Prevention of tumour recurrence
6. Achievement of a complete pathologic diagnosis

Because pituitary tumours are biologically, endocrinologically, and pathologically a heterogeneous group of lesions (see Table

8.1 and Table 8.2), the role of surgery differs for the different pituitary tumour subtypes⁽⁷⁷³⁻⁷⁷⁵⁾. The primary role of surgery is established in the following conditions:

- Nonfunctioning pituitary tumours
- Cushing’s disease, because of the present inadequacy of pharmacologic agents
- Acromegaly, in combination with medical treatment (pre-operative and postoperative, if necessary)
- Thyroid-stimulating hormone-secreting adenomas

The role of surgery in prolactinoma is secondary, but still necessary in selected conditions.

Indications for surgery also include the following:

- Failure of or resistance to medical treatment or intolerable side effects of medical therapy
- Recurrences, in combination or in association with the other therapeutic options, medical or radiotherapeutic or both

Indications for surgery have changed over time and with the refinement of the surgical techniques. Extended transsphenoidal approaches sometimes can represent a valid alternative to transcranial options.

8-2-1 Surgical approaches

The surgical approach, with respect to the basic principles for resecting pituitary adenomas, can be performed by two main approaches, each of them with several subcategories:

1. Transsphenoidal
 - a. Microscopic
 - 1) Transnasal
 - 2) Sublabial
 - 3) Endonasal
 - b. Endoscopic
 - c. Combined or endoscope-assisted microscopic approach
2. Transcranial
 - a. Subfrontal unilateral
 - b. Frontolateral or pterional
 - c. Subfrontal bilateral interhemispheric

The success of the transsphenoidal approach is based on solid foundations: it is the least traumatic route to the sella, it lacks visible scars, it provides excellent visualisation of the pituitary gland and adjacent pathology, it offers a lower morbidity and mortality rate compared with transcranial procedures, and it requires only a brief hospital stay. Indications for transsphenoidal surgery today include more than 95% of the surgical indications in the sellar area and more than 96% of all pituitary adenomas⁽⁷⁷⁶⁾. The well-established indications for this route are as follows:

- Almost all adenomatous lesions⁽⁷⁷⁷⁾
- Non-neoplastic intrasellar cysts⁽⁷⁷⁸⁻⁷⁸¹⁾

- Craniopharyngiomas, preferably cystic, extra-arachnoidal⁽⁷⁸²⁾, and infradiaphragmatic⁽⁷⁸³⁾, with an enlarged sella⁽⁷⁸⁴⁻⁷⁸⁶⁾.

Absolute indications were established in the 1970s and are still valid today; they include the following⁽⁷⁸⁷⁾:

- Elevated surgical risk of the transcranial route
- The elderly
- Long-standing compression of the chiasm, not able to tolerate additional trauma
- Acute endosellar hypertension
- Most cases of pituitary apoplexy
- Pan-invasive, not radically removable adenomas
- Adenomas with downward development
- Microadenomas

To these classic guidelines for the transsphenoidal option, in more recent decades the following can be added:

- The extended transsphenoidal approaches to the sphenoid planum, for giant pituitary adenomas or for adenomas with predominant suprasellar component, suprasellar craniopharyngiomas, Rathke's cleft cysts, some tuberculum sellae meningiomas, and anterior cranial base CSF leaks^(11,23,788-800); to the clival area, for chordomas^(23,801-805); and to the parasellar compartment for invasive adenomas and chordomas^(4,23,803,806-813).

Transsphenoidal Approaches

One or another variation of the transsphenoidal approach represents the most physiologic and minimally traumatic corridor of surgical access to the sella, providing direct and superior visualisation of the pituitary gland and adjacent pathology^(804,814). The transsphenoidal approach represents a midline approach that has been performed since the 1960s by the operating microscope as visualizing tool, through transnasal transseptal, sublabial transseptal, or endonasal procedures (microsurgical transsphenoidal procedures). The transsphenoidal approach also can be performed by the endoscope as the sole visualizing tool during the entire surgical procedure, realizing a "pure" endoscopic endonasal transsphenoidal approach defines the condition of endoscope-assisted microsurgery.

Microscopic Transsphenoidal Approaches

Although many different transsphenoidal procedures and variations have been described, currently there are three basic microsurgical transsphenoidal approaches to pituitary tumours: the transnasal transseptal transsphenoidal approach, the sublabial transseptal transsphenoidal approach, and the endonasal transsphenoidal approach.

For the purposes of this document, the focus will be on the endonasal endoscopic approach.

Endoscopic Endonasal Transsphenoidal Approach

Endoscopic endonasal transsphenoidal surgery is a novel, minimally invasive transsphenoidal approach performed by the endoscope as a stand-alone visualizing and operating instrument, without the need of the transsphenoidal retractor^(10,74,815-818). It has the same indications as the conventional microsurgical technique^(819,820) and since the 1990s has enjoyed progressive acceptance among surgeons and patients for its minimal invasiveness and for the excellent surgical view it provides^(10,816,817,819,821-823). It requires specific endoscopic skills and is based on a different concept because the endoscopic view that the surgeon receives on the video monitor is not the transposition of the real image, as it would be looking through the eyepiece of a microscope, but is the result of a microprocessor's elaboration. It offers a closer view of the surgical target area, a wider angle of view and a better tumour interface image and understanding⁽³⁴¹⁾.

When the sphenoid recess and the anterior wall of the sphenoid sinus have been reached, a large opening of the anterior wall of the sphenoid sinus is performed, which extends beyond the sphenoid ostia to provide adequate sellar floor exposure. After opening the anterior wall of the sphenoid sinus, one or more septa can be identified. The surgeon should review the anatomy of the sphenoid sinus on the preoperative nasal and paranasal cavity CT scans and compare them with the intraoperative ones, particularly when the septa are implanted on one of the carotid prominences and the sphenoid sinus is of a presellar type. The insertion of the septum along the posterior wall of the sphenoid sinus may be a useful anatomic landmark to identify the sellar floor and to define the medial extent of the cavernous sinus. Even if in selected cases it is not necessary to remove all the sphenoid septa, their removal must allow exposure of all the crucial anatomic findings visible on the posterior wall of the sphenoid cavity.

From this step over, the surgeon might be willing to work using two instruments plus the endoscope, as he/she was using a microsurgical technique even though with the endoscope. The surgeon could proceed performing a bimanual dissection while a "tuned" coworker holds the endoscope moving it dynamically and, as requested, insert another surgical instrument. This so-called "3-4 hands technique" requires a good collaboration between two surgeons that should be perfectly tuned, one holding the endoscope and another handling two surgical instruments inside the surgical field⁽⁸²⁴⁾. The two surgeons have therefore the possibility to continuously pass between the close-up view, as during the dissecting maneuvers, and a panoramic view of the neurovascular structures. However, it is possible to fix the endoscope to an autostatic holder, that can be settled by a single surgeon. Anyway, there are not class 2 evidences that one of such two techniques is superior to the other, but from the neurosurgical point of view,

the dynamic technique is the best way to make microsurgery with the endoscope.

Usually, the sphenoid mucosa is displaced laterally as much as necessary to open the sellar floor, unless adenomatous infiltration is evident or suspected, and the mucosa is resected in such cases. Its preservation is thought to ensure adequate mucociliary transport, with its associated function in maintaining the physiology of nasosinus ventilation.

An adequate bony exposure of the sellar floor, sometimes confirmed by or neuronavigation is crucial to the success of the approach, particularly when dealing with large tumours.

The method of opening of the sellar floor depends on its consistency: if it is intact, opening is achieved by a microdrill or bone punches or both; if it is eroded or thinned, opening is achieved by a dissector, sometimes realizing an osteoplastic opening useful for sellar repair⁽⁸²⁵⁾.

The dura is incised in a midline position, in a linear or cross fashion, and a fragment of dura can be taken for histologic examination if it appears infiltrated⁽⁸²⁶⁾. When the dura is incised, the surgeon must keep in mind that the perisellar sinuses⁽⁸²⁵⁾, and particularly the superior and the inferior intercavernous sinuses, are compressed and usually obliterated by macroadenomas, making the dural incision bloodless. The situation is different with microadenomas, particularly in cases of Cushing's disease, in which it is possible to find the entire sellar dura covered by one or two venous channels that can bleed during tumour resection. Caution is necessary when incising the dura in microadenomas to avoid damaging a possibly ectopic carotid artery⁽⁸²⁷⁾, which may be located within the sella, especially in acromegalic patients.

Before removing an adenoma, the surgeon must keep in mind that the pituitary gland is an extra-arachnoid structure, situated below the diaphragma sellae. During the removal of a pituitary adenoma, the surgical manoeuvres must respect these structures, to avoid postoperative CSF leaks and other major complications. Concerning the removal of a microadenoma, a cleavage plane between the microadenoma and the residual anterior pituitary should be found, with the aim of delimiting the lesion^(828,829). When the microadenoma is not superficial, a small incision can be made in the normal pituitary gland on the same side of the microadenoma, and the lesion can be removed with the help of small ring curettes.

Concerning the removal of macroadenomas, the surgeon first must try to remove the tumour tissue from the interior of the sella and from any lateral extension, to avoid cumbersome obstruction of the surgical field by a down-hanging, inverted diaphragma sellae⁽⁸³⁰⁾.

It is also important to recognize the neurohypophysis, some-

times present in front of the dorsum sellae, where curettage or aspiration must be avoided, to prevent the development of postoperative diabetes insipidus.

The closer and orientable view offered by the endoscope enhances the possibility of a better tumour-gland discrimination, resulting in a lower percentage of new post-operative hormonal deficits⁽³⁴¹⁾.

After lesion removal, closure of the sellar floor is performed, especially when an intraoperative CSF leak has occurred, using a variety of techniques (intradural or extradural closure of the sella, packing of the sella with or without packing of the sphenoid sinus) and different autologous and synthetic materials^(31,345,831-833). Overpacking of the sella must be avoided to prevent compression of the optic system.

Besides the advantages offered by the advent of the endoscope, there are also several limitations. They include a learning curve to become confident with the unfamiliar anatomy of the nasal cavities and to acquire the necessary endoscopic dexterity. Nevertheless, after adequate experience, the operating time becomes the same or shorter than that required for transsphenoidal microsurgery, especially in case of recurrences. The endoscope offers only bidimensional vision on the video monitor. However, the sense of depth can be gained with the surgeon's experience, making the endoscope execute in and out movements, looking for many useful different anatomic landmarks and referring to the many protuberances and depressions in the sphenoid sinus, representing reflections and shadows corresponding to different structures. Dedicated microsurgical endoscopic instruments with secure grip, straight and not bayonet shaped, provided with different and variably angled tips are necessary to reach the surgical targets, particularly the targets that the angled endoscopes are able to show^(834;835).

Combined or endoscope-assisted microscopic approach

A way to combine the endoscope with the microscope in endonasal skull base surgery is the endoscope-assisted microsurgery, thus having the advantages offered by both the visual tools. The procedure is carried out with the microscope, so the nasal speculum is needed. The endoscope can be used at the beginning of the operation, to reach the posterior nasal septum and insert the speculum under direct visual control⁽⁸³⁶⁾. More usual is the intermittent use of the endoscope during the manoeuvres of tumour dissection, to check the completeness of the removal and to inspect the areas of the surgical field that are hidden from the microscopic view⁽⁸³⁷⁻⁸⁴⁰⁾.

Results

Until a few months ago it was not easy to find reliable articles that compare the results of the endoscopic endonasal surgery with those of the conventional microsurgical technique. However, more recent publications on endonasal endoscopic

surgery, which consider this aspect, report similar endocrinologic results to those obtained by traditional transsphenoidal microscopic surgery^(339,833,841-845). However, some publications point to a better endocrinologic outcome for functioning adenomas when using endoscopy compared with the results reported in the literature using the traditional technique^(846,847). In our experience^(11,848), the endoscopic technique, offering as it does better vision within the anatomy and “around-the-corner”, gives a better chance to achieve a more complete removal of the tumour, preserving at the same time the normal gland with better results from the endocrinological point of view as well.

Another undoubted advantage brought by the endoscope in skull base surgery is the exponential growth of peer-reviewed publications during the last decade, which caused a Renaissance of the endo/transnasal approach to the sellar area and to the skull base.

Complications

Complications of pituitary surgery depend on the surgical route employed to reach the sella. We refer to transsphenoidal (microsurgical and endoscopic) and transcranial complications. Microsurgical transsphenoidal surgery, with its lack of visible scars and lower mortality and morbidity compared with the conventional transcranial approaches, is appealing to patients and physicians. Serious complications of transsphenoidal surgery are uncommon and seem to be related to the size of the tumour and the experience of the surgeon.

For the endoscopic transsphenoidal approach, differences in the type of complications are noted compared with complications described with the microsurgical transsphenoidal approach. These differences arise from the different type of approach and from the absence of the nasal speculum in the endoscopic procedure. Oral complications are lacking. The absence of the nasal speculum avoids the development of other rare complications, such as separation of the intermaxillary suture or fracture of the hard palate, etc.⁽⁸⁴⁹⁾.

Series of endoscopic operations^(12,821,823) show an overall decreased incidence of complications compared with historical microsurgical transsphenoidal series⁽⁸⁵⁰⁾. There is not only a decrease in functional and esthetic nasofacial complications, but there is also a correlated decrease in all the other complications described in the literature. The explanation for the reduced complication rate might be found in the wider “overview inside the anatomy,” facilitated by the endoscope, and in the decreased surgical trauma of the endoscopic approach itself.

Transcranial approaches

There are conditions that limit and sometimes contraindicate the choice of the transsphenoidal approach in favor of the transcranial, either related to the anatomy of the surgical pathway

or to the morphology and consistency of the lesion. The size of the sella, the size and the pneumatization of the sphenoid sinus, and the position and tortuosity of the carotid arteries can increase remarkably the difficulty of the transsphenoidal procedure and the final surgical result and may determine the opportunity or even the necessity for the transcranial alternative.

Indications for transcranial surgery include the following^(777,783,851,852):

- i) tumours with extensive intracranial invasion, into the anterior cranial fossa or lateral or posterior extension into the middle and posterior cranial fossae
- ii) tumours with asymmetric suprasellar development, particularly if major vessel involvement is present
- iii) tumours with intracranial extension separated from the intrasellar portion by a narrow neck (dumbbell adenoma), showing an hourglass configuration
- iv) suprasellar tumours not completely resectable through the transsphenoidal route
- v) when preoperative MRI assessment, on the basis of long TR signal, suggests a firm consistency of the adenoma, preventing easy debulking with subsequent collapse and descent into the sella, when resected from below
- vi) when the sphenoid sinus is not pneumatized and the sella is small or does not make it easy to reach the suprasellar extension of the tumour
- vii) when coexisting vascular and tumoural surgical pathology is evident and a once-only surgical treatment of both conditions is chosen. The neurosurgeon can choose among: the unilateral subfrontal approach, pterional approach, and bilateral subfrontal interhemispheric approach.

Radiotherapy

As part of the armamentarium for the management of pituitary tumours, radiotherapy/radiosurgery should be mentioned. It consists of a way of treating brain disorders with precise delivery of a single high dose of radiation usually in a 1-shot session (radiosurgery – XRS) or in multiple sessions, usually in a 6-week period (fractionated radiotherapy – XRT). Treatment involves the use of radiation beams delivered onto the target. Through the use of three-dimensional, computer-aided planning and the high degree of immobilization provided by stereotactic head fixation devices, the treatment can minimize the amount of radiation to neighbouring neurovascular structures. For XRS, the patient’s head is secured to a stereotactic frame and positioned so that the tumour mass is centered in the spot where all the beams intersect. In this way, the tumour receives the maximum dose of radiation. Radiosurgical techniques including the Gamma Knife (GKRS), LINAC and Cyberknife.

Radiosurgery usually is proposed as a second-line therapy after failed surgery, if the tumour volume is small (< 3 cm⁽⁸⁵³⁾) and the distance of the adenoma surface to the optic pathways is

wide enough to allow a safe procedure (3-5 mm). It is indicated in some patients with recurrent adenomas that are known to be locally invasive in the cavernous sinus, bone, or dura or when the recurrence is clearly unlikely to be treated with re-do surgery^(854,855).

Table 8.1. Immunohistochemical classification of pituitary adenomas⁽⁷⁷⁴⁾.

• GH adenoma
• PRL adenoma
• GH/PRL
• ACTH adenoma
• TSH adenoma
• Gonadotropin secreting adenoma
• 'Null cell' adenoma
• Mixed histotypes
• Silent GH
• Silent ACTH
• Other silent
• Atypical (high proliferative index, increased Ki-67, etc.)
• Pituitary carcinoma

The appropriate candidates for such treatments are patients with a small residual tumour or with a tumour confined to the cavernous sinus, where the risk of injury to vision is minimized.

Table 8.2. Radiological and surgical classification of pituitary adenomas^(776,856).

Grading	Staging
Grade 1: Normal sella or focal deformity < 10 mm	O: No suprasellar extension
Grade 2: Enlarged sella, normal floor, > 10 mm	A: Up to the suprasellar cistern
Grade 3: Macroadenomas with focal erosion of the floor	B: Up to the recess of the III ventricle
Grade 4: Macroadenomas with diffuse erosion of the floor	C: Compression of the III ventricle
Grade 5: Macroadenomas with	D1: Extension to the anterior fossa metastases
	D2: Extension to the middle fossa
	D3: Extension to the posterior fossa
	E: Extradural, inside or beneath the cavernous sinus

9. Cranial tumours involving the skull base

9-1 Benign soft tissue tumour

9-1-1 Meningioma

Search strategy

A Medline and Pubmed review of the literature was performed to identify case series of inverted papillomas that were published from 1966 onwards. In those instances where a single centre had generated more than one case series from overlapping periods, data from the most recent series was used.

Introduction

Meningiomas are usually benign and account for 15% of primary intracranial tumours. Peak age at presentation is 40 – 60 years; females are more often affected. Their incidence is increased by radiation, with increasing age, and by the presence of neurofibromatosis type 2 (NF2)⁽⁸⁵⁷⁾. They originate from arachnoid cap cells and may be located anywhere that arachnoid cells are found. Meningiomas occur intracranially in 90%, 9% spinal, and 1% ectopic. Parasagittal and convexity are the most common cranial locations (50%). Anterior skull base meningiomas account for 40% of all intracranial meningiomas; tuberculum sellae, sphenoidal ridge, and olfactory groove, are the predominant locations⁽⁸⁵⁸⁻⁸⁶⁰⁾.

Meningiomas of the tuberculum sellae (TSM) arise from the tuberculum sellae, chiasmatic sulcus, limbus sphenoidale, and the diaphragm sellae, they may extend onto both optic canals⁽⁸⁶¹⁾. Olfactory groove meningiomas (OGM) arise in the midline along the cribriform plate, they may be symmetrical or extend to one side; approximately 15% grow into the ethmoid sinuses⁽⁸⁶²⁾.

Surgical resection is the primary treatment option for symptomatic lesions⁽⁸⁶³⁾. Meningiomas have a good long-term prognosis after treatment with a five-year survival of more than 90%, but may recur even after total removal⁽⁸⁶⁴⁾. Skull base meningiomas are difficult to access and require frequently complex surgical approaches for tumour removal, which may be associated with a higher morbidity⁽⁸⁶⁵⁻⁸⁶⁷⁾. Advances in neurosurgical techniques have contributed to reduce morbidity and mortality rates; nevertheless, these tumours remain challenging for neurosurgeons. Over the past decade, extended/expanded endoscopic endonasal skull base approaches have developed and a wide variety of skull base lesions is meanwhile the target of treatment; skull base meningiomas are placed in this group of lesions^(18,35,37,46,47,330,333,348,822,845,868-873).

Clinical presentation

Presenting symptoms have a wide variety and are dependent on tumour location; progressive enlargement of the tumour may lead to focal or generalized seizures or neurological deficits caused by compression of adjacent neural tissue^(859,860,863). Visual deterioration is the most common presentation of TS meningiomas followed by headaches⁽⁸⁶¹⁾. OG meningiomas may reach a considerable size before causing symptoms; meningiomas are most often slow-growing tumours⁽⁸⁶²⁾.

Diagnosis and Imaging

Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are standard radiological techniques for diagnosis, postoperative evaluation, and follow-up⁽⁸⁵⁹⁾. On CT scan, meningioma are typically isodense to slightly hyperdense, homogeneous, and sharply marginated with marked enhancement by injection of contrast medium. Peritumoural edema and calcifications may be variably present. Bony involvement and bony landmarks can be assessed by bone windows. Characteristic MRI features are isointensity to slight hypointensity on T1-weighted images; the appearance on T2-weighted images is variable, the presence of hyperintensity may indicate a softer tumour. Post-gadolinium enhanced images show a homogenous, usually intense mass with or without a dural “tail”. MRI provides information for invasion of dura and sinuses and displacement of neural and vascular structures. MR-angiography can be helpful to delineate the critical neurovascular relationships and MR-venography can demonstrate sinus patency. CT angiography is very valuable in demonstrate the osseous and vascular relationships that can guide surgical approaches. Conventional angiography may give more precise information about vascular tumour supply. Preoperative embolisation can be used to reduce tumour vascularisation in selected cases, however this rarely required and the risks associated need to be considered carefully^(874,875).

Histology

Meningiomas are well-demarcated and in general firm and rubbery lesions. They may have a globular or en plaque growth. Immunohistochemistry is of mesenchymal and epithelial cells, positive for both vimentin and epithelial membrane antigen. Histologically, the following variants are distinguished, classified by the World Health Organization (WHO) as Grade I: fibroblastic, transitional, psammomatous, meningotheliomatous (angiomatous). These variants are typical and represent more than 90% of meningiomas. Atypical meningiomas (WHO II) show hypercellularity, frequent mitosis, and necrosis. Malignant/anaplastic meningiomas (WHO III) are characterized by brain invasion, rapid recurrence, increased mitosis, and rarely metastasize^(859,860,876).

Treatment

Basically, there are three primary treatment options depending on tumour size and associated symptoms: Observation for asymptomatic, small lesions (many meningiomas tend to grow very slowly), surgical resection, and stereotactic radiosurgery (SRS)⁽⁸⁵⁸⁻⁸⁶⁰⁾.

SRS is increasingly used for meningiomas, particularly for residual, surgically inaccessible, or recurrent lesions. SRS has been proposed for some lesions as the primary treatment for skull base meningiomas. These are usually small and there is still remains significant controversy regarding this as primary therapy. SRS is not generally recommended as the primary treatment option for meningiomas compressing the visual system. Conventional radiation therapy or SRS in comparison is usually recommended for malignant or atypical variants⁽⁸⁷⁷⁻⁸⁸⁰⁾.

Complete surgical resection with an acceptable morbidity is the goal of treatment. The degree of surgical resection is closely related to progression free survival and overall outcome⁽⁸⁸¹⁾. The extent of resection for meningiomas has been typically classified according to the Simpson classification: Grade I, total tumour removal with excision of dural attachment and abnormal bone; Grade II, total tumour removal and coagulation of dural attachment; Grade III, gross total removal without resection or coagulation of dural attachment or extradural extensions; Grade IV, partial removal leaving tumour in situ; and Grade V, simple decompression (biopsy). A Simpson Grade I or II resection is the goal, recurrence after gross total removal occurred in 9 to 15%. A Simpson Grade III or IV resection has a recurrence rate in the range of 29 to 40%.

Standard surgical approaches for skull base meningiomas differ according to tumour location, size, and extension. Petroclival meningiomas (PCM) arise at the petroclival junction from the upper two-thirds of the clivus and medial to the trigeminal nerve. Conventional surgical approaches to these tumours include: retrosigmoid-suprameatal, combined petrosal, frontotemporal transcavernous, anterior transpetrosal, transmastoid translabyrinthine, postauricular translabyrinthine, transotic, transcochlear total petrosectomy. PCM are critically located adjacent to cranial nerves, brain stem, and vessels; surgery is demanding and major postoperative deficits are cranial nerve palsies^(866,867). Cavernous sinus meningiomas (CSM) arise primarily in this location or involve the CS secondarily; treatment for CSM is controversial. Conventional surgical approaches for this region used are the cranio-orbitozygomatic approach and the extended middle fossa approach with/without zygotomy. Surgical removal of CSM is associated with relatively high morbidity primarily due to cranial nerve palsies and risk of carotid artery injury⁽⁸⁸²⁻⁸⁸⁴⁾. OGM are most commonly approached conventionally by pterional, subfrontal, unilateral orbitocranial, bifrontal, or interhemispheric exposures. The resection of OGM has a lower morbidity (though little is available on cognitive outcomes) and the rate of total resections

range between 85 and 100%^(862,885-890). TSM may be accessed transcranially by the pterional, frontolateral, unilateral subfrontal, orbitofrontal, or bifrontal subfrontal approach. The rate of gross total resection ranges from 58 to 100%^(861,865,891-901). Furthermore, the supraorbital keyhole “eyebrow” craniotomy is used for resection of TSM^(334,902,903). The sublabial transsphenoidal or endonasal transsphenoidal approach with the operating microscope or with endoscopic assistance has also been reported to remove TSM^(789,837,894,904-906).

Results of endoscopic endonasal resection of skull base meningiomas

Since the advancement of endoscopic endonasal skull base surgery, skull base meningiomas have become an increasing focus of surgeons familiar with this technique. The concept to approach the tumour from below by removing bone and the base of the lesion allowing early devascularisation of the meningeal blood supply without brain retraction and minimizing the manipulation of neurovascular structures, in particular the optic apparatus has been the attraction. Specifically, the working trajectory is within the axis of the tumour facilitating tumour removal and critical structures like the optic nerves and optic chiasm can effectively decompressed minimizing the risk of devascularisation (preservation of critical perforators), and thereby, reducing the risk of visual deterioration.

Conceptually protection of neural structures can be optimized by approaching the tumour from the base without the need of crossing the plane of cranial nerves, thus reducing surgical manipulation of these critical structures and their small perforators that supply them. Basic principles of tumour removal and microsurgical dissection techniques are absolutely the same as for microscopic transcranial approaches. Specifically, this involves bimanual technique adhering to the principles of internal debulking, extracapsular dissection without excessive traction and avoiding grasping instruments.

Anatomically the limits in the sagittal plane are considered to extend from the posterior wall of the frontal sinus to the craniocervical junction and the anterior portion of the foramen magnum. The odontoid process represents the caudal limit. The lateral limits in the anterior skull base are related to the position of the optic nerves. In general, lesions extending between the midorbit (between the plane of the superior rectus muscles bilaterally) can be approached with this technique alone. Modular classification of approaches divided into the midline sagittal (rostro-caudal axis) and paramedian (coronal plane) have been reported. These extended/expanded approaches include the parasellar, the transplanum/transsterculum, the transcribriform, the lateral approaches to the petrous apex and the approach to the anterior portion of the foramen magnum and the craniocervical junction^(18,46,47,348,762,882).

At present, Kassam et al.⁽³⁴⁰⁾ have published the largest study of endoscopically resected anterior cranial base meningiomas comprising 35 patients. Mainly TSM (n = 13) and OGM (n = 15) were treated. All patients with visual decline showed postoperatively improved or resolution of visual function. A gross or near total resection (> 95%) was achieved in 92% (12/13) of TSM and in 66.7% (10/15) of OGM. Complications are listed in Table 9.1. Despite the excellent outcomes for the visual apparatus, this paper highlights the primary limitation of this technique – reconstruction. Postoperative cerebrospinal fluid (CSF) leak rate was 40% most frequently occurring in TS lesions. This series represents reconstruction prior to the development of the vascularised flaps. The authors note that the rate of CSF leaks decreased substantially (5%) over time with the use of vascularised nasoseptal flaps for skull base reconstruction (see reconstruction chapter). There was no associated mortality. One tumour progressed (2.8%) was noted in a patient with a recurrent parasellar/PCM that was initially debulked; this patient underwent two further endoscopic approaches.

De Divitiis et al.⁽³³²⁾ presents a series of 11 patients harbouring TSM and OGM. Total removal was accomplished in all OGM and 86% of TS lesions. Transient visual deterioration occurred in 43%, visual improvement was recorded in 57%. CSF leak rate was 27.3%. No permanent endocrinological deficit was noted. One patient died three weeks after a total resection of a TSM of a massive intraventricular haemorrhage after the insertion of a lumbar drainage for CSF leakage.

Kurschel, Mokry et al.⁽⁹⁰⁷⁾ have treated the same number of patients in his series. TSM also represent the largest proportion (n = 9) and were totally removed in 77.8%. Vision improved postoperatively in 80%; the CSF leak rate was 9%. One patient presented with a postoperative CSF infection (9%). A subtotally resected TSM recurred after 17 months and was removed via a transcranial approach (9%).

Wang et al.⁽⁹⁰⁸⁾ reports a series of seven patients with TSM. Total removal was performed in 86%, visual improvement occurred in 83%, and postoperative CSF leakage in 14.3%. Asymptomatic recurrence was observed in a subtotal resected meningioma after 15 months (14.3%).

Laufer et al.⁽⁵⁹⁾ lists five patients with TS and planum sphenoidale meningiomas treated endoscopically in their series comprising in all 10 patients with suprasellar lesions. The extent of resection for meningiomas alone is not defined. All patients with visual decline improved postoperatively. The rate for CSF leakage was 20% just as the occurrence of permanent DI.

In a series of 13 patients with midline skull base lesions, Ceylan et al.⁽⁷⁶²⁾ has removed two TSM endoscopically, one total, the other subtotal (> 80%). There was no associated mortality; no further detailed information regarding complications in these two cases is available.

Three further papers report the approach for meningiomas in specific locations. Liu et al.⁽⁸⁸⁴⁾ performed a biopsy for ten cavernous sinus lesions via an endoscopic endonasal approach. Out of them, two lesions turned out to be meningiomas. One intervention was followed by a CSF leak (50%). Kassam et al.⁽³⁴⁷⁾ presents an endoscopic endonasal transdorsum sellae approach to the retroinfundibular space and interpeduncular cistern by pituitary transposition in 10 patients. In this way, two PCM were partially resected; the patient with visual decline improved, one CSF leak was observed postoperatively (50%). The same author reports an expanded endoscopic endonasal approach via an anteromedial corridor to Meckel's cave in 40 patients⁽⁵¹⁾. In this series, seven meningiomas were secondarily but predominantly located in the Meckel's cave. Subtotal resection (> 95%) was performed in four patients, total in two, and partial (70-95%) in one. Cranial nerve palsies improved in two patients; there were no associated complications and no mortality.

In the reviewed studies, 82 patients harbouring skull base meningiomas were treated by an extended endoscopic endonasal approach^(51,332,340,347,762,884,908). It is not possible to pool the data and provide meaningful information. The studies involve an entirely heterogeneous group of lesions that have significant variables the most important of which are location of the lesions and prior treatment. This precludes providing summary data. However, a summary of key complications despite location can be provided. In the parasellar lesions that involved the operative apparatus, a transient visual deterioration was observed in three patients (6.5%). The most frequent postoperative endocrinological deficit was DI, transient in 4.9% (4/82) and permanent in 3.7% (3/82). One patient developed panhypopituitarism (1.2%, 1/82). Other complications represent an incidence of 1.2% (1/82) and include: CSF infection, foreign body granuloma/abscess, intraoperative bleeding/venous congestion requiring aborting the procedure, frontopolar artery compromise/pseudoaneurysm, intraventricular haemorrhage, pneumocephalus with the need of endoscopic exploration. The overall mortality rate was 1.2% (1/82; TSM). Follow-up so far as defined ranged from 1 to 51 months, which does not allow for long-term results.

Discussion

Surgical removal of skull base meningiomas remains a challenge to neurosurgeons despite technical advances, improved neurophysiologic monitoring, and intensified interdisciplinary teamwork; demanding complex cranial approaches are commonly required and critical adjacent neurovascular structures have to be preserved. A wide variety of surgical approaches have been used for individual meningiomas; each demanding special experience and each is associated with advantages and limitations. The use of the endoscope has clearly widened the spectrum of skull base surgery; either by endoscopic assisted or pure extended/expanded endoscopic endonasal approaches.

A Simpson Grade I and II resection (gross total) is the goal of surgery to avoid recurrence or to prolong time to recurrence for this usually slow-growing tumours^(864,881). Extended endoscopic endonasal series dealing with skull base meningiomas define the degree of resection commonly in percentages, in which a near total resection indicates more than 90 or more than 95% of tumour removal, a subtotal resection varies around 80% of tumour removal, and partial resection is stated in ranges. In these series, particularly the larger ones, the dural tail is considered as residual disease and the volume of this is quantified as a percentage of the overall tumour. Most reports of conventional meningioma surgery classify the extent of tumour removal according to the Simpson Grading system, thus making the comparison of results difficult. The advantage of endoscopic endonasal surgery for skull base meningiomas is the approach from below and the possibility to remove the base of the tumour and potentially infiltrated bony structures first, so that in principle a Simpson Grade I resection may be accomplished.

As discussed above, a review of the literature yields a heterogeneous population precluding meaningful comparisons. However, if a subgroup analysis is considered TSM represent the largest group of endoscopically treated meningiomas, comprising 41 patients. Reviewing the literature since 2000, there are eleven representative studies of transcranial approached TSM treating a total of 487 patients^(888,891-893,895-901). The mean percentage of total resection was 86.4% (range: 71–98%); this is similar to the endoscopic endonasal group (86.9% total and near total resection). Visual improvement occurred in mean 63% (range: 37.8–80%) and postoperative visual worsening was observed in mean 14.7% (range 4.1-30%) in the conventional group. The endoscopic group showed a 90.7% (39/43) rate of visual improvement after TSM removal, while 7.3% (3/41) had a transient visual deterioration. Mortality was mean 2.1% in the transcranial series and 2.4% (1/41) in the endoscopic group. The rate of CSF leak is significantly higher in endoscopically operated TSM. The majority of these endoscopic series report on results prior to the development of vascularized nasoseptal flaps, which have substantially reduced the rate^(345,832,909,910). The mortality and extent of gross tumour removal are comparable in both groups, but postoperative visual improvement is considerably higher for endoscopically approached TSM. The extended/expanded endoscopic endonasal approach maybe a consideration for a selected group of TSM due to the excellent postoperative recovery of visual function. All other subgroup analysis do not all for adequate numbers for comparison. Even in the TSM group there is a 10-fold difference in the series.

Five series of transcranial resected OGM were reviewed in the literature published during the last 10 years^(885-887,889,890). A total of 234 patients with OGM were operated, the mean rate of total removal was 90.7%, mortality rate was mean 1%. The overall complication rate was mean 25.5% (range 0-46.6%);

CSF leaks occurred in mean 9.4% (range 0-20%). Out of the 20 endoscopic endonasal resected OGM, 75% had a gross total resection, and there was no associated mortality. The CSF leak rate was 25%. Comparison of these two pooled series is very limited given little available data on key variables: mean size/volume of tumour, previous therapy and preoperative goals of surgery.

Of the complications seen after skull base meningioma surgery, permanent cranial nerve dysfunction may have a significant long-term impact on impair the quality of patient's life. In selecting an ideal approach to the tumour, the need to cross the path of a cranial nerve should be considered in selecting the trajectory. Lesions that are located lateral to cranial nerves are often best suited for lateral conventional approaches, whereas those that are medial to the cranial nerves maybe well suited for endonasal approaches. Thus, there will always be a role for both approaches with the selection being guided by the regional anatomy rather than surgeon's familiarity with one approach over another. Occasionally the same patient may benefit from surgery using both corridors. However, what is clear the need for incremental experience prior to selecting an endonasal approach and familiarity with vascularised reconstruction techniques. Recurrence rates of endoscopically treated skull base meningiomas cannot be evaluated because of short follow-up periods.

Conclusions

- Endoscopic endonasal surgery for skull base meningiomas is still in progress.
- Comparability of results of transcranial and endoscopically approached skull base meningiomas is poor for the present. First, considerable fewer patients are treated via an endoscopic approach. Second, not all skull base meningiomas are suitable for endoscopic endonasal surgery.
- The main complication of endoscopic endonasal meningioma removal is CSF leakage. The development of endoscopic reconstructive skull base techniques has reduced this rate.
- The main advantage of endoscopic endonasal skull base meningioma surgery may be the protection of cranial nerves, neural and vascular structures by approaching the lesions from the base.
- Tumour recurrence rates after endoscopic endonasal skull base surgery can be determined when long-term follow-up studies are available.
- Both, the transcranial and the endoscopic endonasal approach for skull base meningiomas requires experienced teams to achieve optimal treatment results.

Table 9.1. Removal of tuberculoma sellae meningioma via an extended endoscopic endonasal approach.

Series	No of patients	Meningioma location/no	Extent of resection	Postoperative visual function	CSF leak	Complications	Mortality	Recurrence/ months	Follow-up months mean/range
Lauter et al., 2007 ⁽⁹⁹⁾	5	TS 3 PSP 2	NA	improved 4/4 (100%)	1 (20%)	permanent DI 1 (20%)	none	none	8.6/5-12
De Divitiis-Cappabianca et al., 2008 ⁽¹³²⁾	11	TS 7 OG 4	total 6/7 near total (>90%) 1/7 total 4/4	improved 4/7 (57%) unchanged 3/7 (43%)	3 (27.3%)	transient DI 1 (9%) transient visual deterioration 3 (4.3%)	1 (9%)*	none	NA/1-51
Gardner, Kassam et al., 2008 ⁽³⁴⁰⁾	35	TS 13 OG 15 PS/petrous 5 PC/PS 2	total 11/13 near total (>95%) 1/13 subtotal 1/13 (78%) near total (>95%) 10/15 partial 5/15 range: 35-95% range: 63-89%	improved 23/23 (100%)	14 (40%)	permanent DI 2 (5.7%) transient DI 1 (2.8%) parhydropituitarism 1 (2.8%) frontopolar artery injury, pseudaneurysm, ICH 1 (2.8%) granuloma (telon), abscess 1 (2.8%) pneumocephalus 1 (2.8%) intraop. venous bleeding 1 (2.8%)	none	1 (2.8%)	NA/12-48
Kassam et al., 2008 ⁽³⁴⁷⁾	2	PC 2	partial 2/2	improved 1/1 (100%)	1 (50%)	transient DI 1 (50%)	none	none	NA
Ceylan et al., 2009 ⁽⁹²⁾	2	TS 2	total 1 subtotal (>80%) 1	NA	NA	NA	none	NA	NA/2-10
Kassam et al., 2009 ⁽⁵¹⁾	7	MC 7	total 2 subtotal 4 partial 1	not affected	none	none	none	NA	NA
Liu and Di, 2009 ⁽⁸⁸⁾	2	GS/PC 1 CS/PS 1	biopsy	normal	1 (50%)	none	none	none	NA
Wang et al., 2009 ⁽⁹⁸⁾	7	TS 7	total 6 subtotal 1	improved 5/6 (83%) unchanged 1/6 (16.7%)	1 (14.3%)	transient DI 1 (14.3%)	none	1 (14.3%) 15 months	23
Kunschel, Mokry et al., 2010 ⁽⁹⁷⁾	10	TS 8 OG 1 PSP 1	total 6 subtotal 1 partial 1 total 1	improved 4/5 (80%) unchanged 1/5 (20%)	none	CSF infection 1 (9%)	none	1 (9%) 17 months	14.3/2-48

Abbreviations: Nb = number, TS = tuberculoma sellae, OG = olfactory groove, CS = cavernous sinus, PS = parasellar, PC = petrosal, PSP = planum sphenoidale, MC = Meckel's cave, DI = diabetes insipidus, ICH = intracerebral haemorrhage, NA = not available.
*CSF leak, intraventricular haemorrhage

9-2 Cranial nerve lesions

9-2-1 Optic pathway and hypothalamic gliomas, schwannomas

Search strategy

A Medline and Pubmed review of the literature was performed to identify case series of inverted papillomas that were published from 1966 onwards. In those instances where a single centre had generated more than one case series from overlapping periods, data from the most recent series was used.

Introduction

Gliomas are primary brain tumours involving a wide heterogeneity with a topographically uneven distribution within the brain. Localisation of gliomas is a factor of particular importance not only for purposes of their classification, but also in their prognosis. Topographically, gliomas are classified as supra- and infratentorial⁽⁹¹¹⁻⁹¹³⁾. Among the supratentorial gliomas, optic pathway and hypothalamic gliomas (OPHG) are located in the supratentorial midline in close relation to the skull base, thus accessible by an extended endoscopic endonasal approach^(330,872,914,915).

Optic gliomas can arise anywhere along the optic pathway and may present with cerebrospinal fluid (CSF) dissemination. Management of OPHGs is still controversial and in evolution. Observation is usually indicated in patients with non-progressive disease, especially in patients with NF1⁽⁹¹⁶⁾. Surgical debulking is advocated in the case of progressive tumours with mass effect or obstructive hydrocephalus to relieve intracranial hypertension. Biopsy may be particularly indicated in non-NF1 patients to confirm diagnosis. Chemotherapy has shown to be an effective treatment modality and is used as first-choice therapy, especially for infants. Radiotherapy is reserved for children older than 5 years of age as an alternative treatment modality^(913,917-932).

When surgery is indicated for schwannomas, they can be accessed via complex transcranial or skull base approaches. Recently, an expanded endoscopic endonasal approach was used to remove schwannomas in the Meckel's cave⁽⁵¹⁾.

Incidence

OPHG are rare brain tumours and appear mostly in childhood, though there is also a peak in the adult population (913). The incidence of these tumours is about 25% higher in neurofibromatosis type 1 (NF 1), but manifests a more benign course in these individuals. This neurocutaneous disorder occurs in about 1/2500-3300 births and represents more than 90% of cases of neurofibromas^(912,935-937). The incidence of other associated brain tumours is also significantly higher^(917,918). The percentage of patients with optic pathway gliomas and diagnosed NF1 reported in the literature varies between 10 and 70%⁽⁹³⁸⁾.

Schwannomas are benign tumours; Schwann cells are derived from the neural crest cells. They account for about 7% of intracranial tumours, 5% are multiple with a higher incidence in NF 2. Intracranially, they are most commonly found on the superior vestibular nerve in the internal acoustic meatus, the second most common site is the trigeminal nerve (5%), and these are located in the middle fossa (50%), posterior fossa, or both^(912,933-935). Neurofibromatosis (including NF 1 and NF 2) is a common genetic disorder, inherited in an autosomal dominant fashion with a predisposition to nerve sheath tumours. Neurofibromatosis of the skull base is a syndrome that may occur in an isolated fashion or as a component of NF 1. Treatment in general is symptomatic^(916-919,921,925,927,935,936,939).

Clinical presentation

Clinical presentations of intracranial schwannomas depend on their localisation. The most common site of origin is the superior vestibular nerve in the internal acoustic meatus; patients present with hearing loss, tinnitus, and disequilibrium. The second most common site is the trigeminal nerve; symptoms include pain and dysaesthesia (trigeminal neuralgia). Skull base schwannomas may have an intra- or extradural extension, or both^(917,919,933-936,940).

Optic gliomas may cause a painless proptosis as an early sign of an expanding lesion of one optic nerve. Gliosis of the optic nerve might be seen on fundoscopy. Chiasmal lesions cause rather nonspecific visual field defects and can become symptomatic by mass effect, causing hypothalamic and/or endocrinologic dysfunction, and hydrocephalus^(911,913,920,930). Hypothalamic gliomas infiltrating the anterior hypothalamus usually present with a diencephalic syndrome, which is characterized by cachexia associated with hypoglycemia, hyperactivity, over-alertness, and an almost euphoric effect. Twelve to 40% of children with chiasmal tumours and NF 1 will present endocrinological disturbances like precocious puberty^(916,926,927). However, small series and case reports refer to clinically silent tumours and report spontaneous tumour regression. Natural history and histopathologic mechanisms are still subject of current studies and are not yet entirely understood^(916,926,927).

Diagnostic criteria

NF 1 and NF 2 are rather inhomogeneous diseases as are their clinical manifestations. NF 1 is a common autosomal dominant disorder diagnosed by several clinical criteria advised by the National Institutes of Health Consensus Development Conference^(919,925). Two or more of the following characteristics have to be present to confirm diagnosis: 6 or more café au lait spots, more than 2 neurofibromas of any type, or one plexiform neurofibroma (usually not evident until the age of 10-15 years), hyperpigmentation of the axilla or intertriginous areas, more than 2 iris hamartomas (Lisch-nodules), distinctive osseous abnormality, such as sphenoid dysplasia or thinning of long bone cortex, and a first degree relative with NF 1. Lear-

ning disabilities are found in about 40–60% of the patients (925,927,940).

Imaging

Computed tomography (CT) shows best structures within the orbit and delineates bony relationship for OPHGs. Magnetic resonance imaging (MRI) is superior in demonstrating tumour extension and chiasmal and hypothalamic involvement as well as cerebral and spinal tumour dissemination. OPHGs are typically contrast enhancing on CT or MRI, whereas most low-grade gliomas do not enhance on imaging and are usually hypointense on CT and T1-weighted MRI.

Schwannomas are isointense to hypointense on T1-weighted MRI, enhance after contrast medium application, and are rarely calcified (912,941,942).

Histology and genetics

In the 1990s, the NF-1 gene and the protein product called neurofibromin was identified. Recent investigations suggest that this protein acts as a tumour suppressor or cell growth repressor. Defects in the genetic expression and protein synthesis cause irregular cell growth and result in tumour disposition (927,943-945). Histologically, most optic gliomas and hypothalamic gliomas are typically low-grade gliomas, mostly consistent with pilocytic astrocytomas, but also fibrillary, and pilomyxoid astrocytomas can occur, the latter tending to have a more aggressive behaviour (911,916,920,926,927). Recent studies have shown that the histological diversity and malignancy of optic gliomas is much more inhomogeneous than previously supposed and the importance of biopsy is emphasized (921-924,939).

Schwannomas are usually macroscopically firm and encapsulated covered by epineurium. They contain no axons and show histologically a biphasic pattern of typical Antoni A areas (composed of fusiform cells, reticulin, and collagen) and Antoni B areas, containing stellate round cells in stroma. Immunohistochemistry is S100 positive (912,917).

Treatment

Gliomas

Optic gliomas may show involvement of only one optic nerve, both optic nerves, and/or the optic chiasm. In this region, they can extend to the hypothalamic/thalamic region. Large series show that about 70% of optic gliomas involve the anterior third ventricle, the optic chiasm and the optic tract. Only 30% of the tumours involve the prechiasmatic portion (913,919).

Treatment options for OPHGs include clinically cautious observation in patients with minor or no symptoms. Surgical debulking, radiation, and chemotherapy are given for progressive neurologic deficit and progressive tumour growth, either as monotherapy or in combination. Adjuvant chemotherapy is increasingly used as first-line treatment for OPGHs (911,920,946). In general, treatment strategies should follow the principle of maximum benefit and the least risk of neurologic and clinical deterioration for the individual patient (916-918,926-929,932,946,947).

If surgery is indicated in case of progressive disease with intracranial hypertension, mass effect or hydrocephalus, the approach has to be adapted to tumour localisation and required extent of resection. Transcranial pterional, transventricular, or interhemispheric approaches are used for resection. There are various papers published in the past decades describing these approaches (931,948-951). More often, biopsy may be required to confirm histology prior adjuvant treatment, especially for non NF 1 patients. Open or stereotactic procedures have shown to be associated with a considerable risk of morbidity (921,932).

So far, various pathological entities are reported to be approached by an extended endoscopic endonasal transsphenoidal technique (11,51,333,762,868,873,914,947,952,953). A few studies of endoscopic skull base surgery report the approach for gliomas. Rudnik et al. (914) mention the biopsy of an optic glioma via an endoscopic endonasal approach. De Divitiis et al. (330) describe a subtotal removal of a chiasmatic astrocytoma in their series; vision remained unchanged in this patient. Kassam et al. (872) report on a diagnostic biopsy for a low-grade optic glioma in a paediatric patient without complications. Cavallo et al. (915) list in their report of cystic sellar lesions the total removal of a chordoid glioma. This procedure was performed without complications (Chordoid gliomas are rare grade II tumours originating from the third ventricle with both glial and chordoid features. Gross total resection is the treatment of choice, but is often difficult because of the location and adherence to the hypothalamus) (948). In a study cohort of 58 non-adenomatous lesions, Kurschel et al. (907) performed a subtotal removal for a chiasmatic optic glioma (pilocytic astrocytoma) and a biopsy for a hypothalamic glioma (fibrillary astrocytoma II). Visual function improved postoperatively in the patient with optic glioma, but diabetes insipidus occurred due to pituitary stalk involvement. No further morbidity or mortality was observed (Table 9.2).

Schwannomas

The treatment of choice for symptomatic lesions is surgical resection. Depending on location and extension of schwannomas different surgical approaches are used for removal. These procedures include transmaxillary, presigmoid, retrosigmoid, frontotemporal, trans-sylvian transtentorial, and subfrontal approaches (933,934).

Series dealing with endoscopically treated skull base schwannomas are shown in Table 9.3. The largest study group is reported by Kassam et al. (51) and consists of six patients harbouring schwannomas, all were located within the Meckel's cave, therefore primarily originating from the trigeminal nerve. Five lesions could be removed totally (83.3%); complications included one transient VIth nerve palsy. Esposito et al. (953) describe a case report of an intrasellar schwannoma as an extremely rare location for this pathology. The tumour could be removed subtotally without new endocrinological or other complications. In their case study, Kanaan et al. (954) identify

another rare location of a schwannoma originating from the olfactory nerve. This lesion was subtotally removed as well. Kurschel et al. ⁽⁹⁰⁷⁾ included two patients with schwannomas in their study. One patient presented an extended schwannoma, which had to be treated by staged procedures via different transcranial approaches. Extended endoscopic endonasal surgery performed twice provided additional partial resection;

the small residual tumour was treated radiosurgically and showed no progression. The other patient had a trigeminal schwannoma extending into the infratemporal fossa, which was totally removed. Both procedures had no associated complications.

Table 9.2. Gliomas treated via an endonasal endoscopic transsphenoidal approach.

Series	Total no of patients	No of gliomas	Histologic diagnosis	Extent of resection	Complications	Follow-up range/months
Rudnik et al., 2005 ⁽⁹¹⁴⁾	70	1	optic glioma	biopsy	none	NA
de Divitiis et al., 2007 ⁽³³⁰⁾	20	1	optic glioma	subtotal removal	none	NA
Kassam et al., 2007 ⁽⁸⁷²⁾	25	1	optic glioma	biopsy	none	24
Cavallo et al., 2008 ⁽⁹¹⁵⁾	76	1	chordoid glioma	total removal	none	NA
Kurschel et al., 2010 ⁽⁹⁰⁷⁾	58	2	hypothalamic glioma (II) optic glioma	biopsy subtotal removal	none DI	15-33

Abbreviations: NA = not available, no = number, DI = diabetes insipidus

Table 9.3. Schwannomas treated via an endonasal endoscopic transsphenoidal.

Series	Total no of patient	No of schwannomas	Histologic diagnosis (localisation/origin)	Extent of resection	Complications	Follow-up range/ months
Esposito et al., 2004 ⁽⁹⁵³⁾	case report	1	schwannoma (intrasellar)	subtotal removal	none	12
Kanaan et al., 2008 ⁽⁹⁵⁴⁾	case report	1	schwannoma (olfactory)	subtotal removal	none	NA
Kassam et al., 2009 ⁽⁵¹⁾	40	6	schwannoma (trigeminal)	total removal 5 subtotal removal 1	transient VI th nerve palsy 1	NA
Kurschel et al., 2010 ⁽⁹⁰⁷⁾	58	2	schwannoma* schwannoma (trigeminal)	partial removal 1 total removal 1	none	35-37

Abbreviations: NA = not available, no = number

*schwannoma extending from the left posterior fossa to the ipsilateral maxillary sinus involving the left middle and infratemporal fossa, and the intra- and intrasellar area.

Discussion

Currently, only a small number of cases treated by an extended endoscopic endonasal transsphenoidal approach has been reported for both, gliomas and schwannomas ^(51,330,872,914,915,953,954). Follow-up periods are not defined or too short to draw conclusions concerning recurrence rates. Conventional transcranial approaches for gliomas located close to the anterior midline skull base have a well-defined risk profile ^(929,931,932,948-951). The same can be applied to anterior skull base schwannomas when approached transcranially ^(933,934). Based on the current literature, there is no significant evidence that endoscopically treated gliomas and neurofibromas/schwannomas have a better outcome or a lower complication-rate compared to traditional transcranial approaches. Preliminary results are encouraging concerning a low risk of neurologic deterioration, but this so-called minimally invasive technique has to prove its effectiveness in the future by including more patients with a longer follow-up.

Conclusions

- Cranial nerve lesions, OPHGs, and other gliomas located close to the skull base can be approached by an extended endoscopic endonasal procedure.

- Depending on the aim of surgery, biopsy, partial, subtotal, or total removal can be achieved.
- Preliminary reports suggest a low complication rate.
- These results are based on a few case reports and represent for the present no evidence.

9-3 Craniopharyngiomas

Introduction

Craniopharyngiomas are a usually benign central nervous system tumour. Despite its benign histology, craniopharyngiomas tend to adhere and infiltrate surrounding structures. This characteristic accounts for their aggressive behavior and potentially significant morbidity and mortality. Because of their frequent location in the sellar and supra-sellar region, these tumours can compress the optic apparatus, pituitary stalk and gland, floor of the third ventricle, hypothalamus, and cerebral vasculature of the circle of Willis. Although complete resection remains the goal of primary surgery, this may not be warranted if it is associated with significant morbidity. In circumstances where adherences to critical neurovascular structures preclude complete resection, adjuvant treatment may be indicated. Although such lesions were traditionally resected through tran-

scranial approaches, the more recent description and evolution of the expanded endonasal approaches (EEA) has created a new paradigm in endoscopic transsphenoidal surgery opening a new corridor to the suprasellar space^(331,334,335,337,952,955-958).

Because most craniopharyngiomas are infrachiasmatic midline tumours, the endonasal approach offers the advantages of accessing the tumour without the need for brain or optic nerve retraction with a direct visualisation through a midline subchiasmatic surgical route.

Incidence and aetiology

Craniopharyngiomas occur at a rate of 1.3 per million person-years⁽⁹⁵⁹⁾. Overall, they account for 2-5% of all primary intracranial neoplasms⁽⁹⁶⁰⁾. Craniopharyngiomas can be diagnosed at any age. However, they typically present a bimodal age distribution with a first peak between 5-14 yrs old and a second peak in adults of ages 50-74^(955,959). They represent the most common sellar lesion in children, accounting for 5.6-15% of intracranial tumours in children⁽⁹⁶¹⁻⁹⁶³⁾.

Craniopharyngiomas are benign epithelial tumours that arise along the path of the craniopharyngeal duct, a canal connecting the stomodeal ectoderm with the evaginated Rathke's pouch. To date, the exact pathogenesis of these tumours remains uncertain. Some authors have proposed that these tumours arise from neoplastic transformation of embryonic squamous cell rests of the involuted craniopharyngeal duct⁽⁹⁶⁴⁾. Others have suggested that craniopharyngiomas result from metaplasia of adenohypophyseal cells in the pituitary stalk or gland^(965,966).

Clinical presentation

As craniopharyngiomas grow, they may exert mass effect on vital structures of the nervous system including the visual apparatus, the brain parenchyma, ventricular system, blood vessels and hypothalamic-pituitary axis. Clinical presentations depend to the tumour's size, location and growth potential and may result in neurologic, visual or hypothalamic-pituitary axis dysfunction. Headache, nausea/vomiting, visual disturbances, growth failure (in children), and hypogonadism (in adults) are among the most commonly reported^(967,968).

Hydrocephalus can occur in any age population and results from the obstruction of the foramen of Monro or of the Aqueduct by the tumour^(969,970).

Pituitary dysfunction is a common clinical manifestation. Reported rates for pituitary hormone deficits include 35-95% for GH, 38-82% for FSH/LH, 21-62% for corticotrophin (ACTH), 21-42% for TSH, and 6-38% for antidiuretic hormone (ADH)⁽⁹⁶⁸⁾.

Diagnosis/imaging

Most craniopharyngiomas are located within the sellar/parasellar region adjacent to the optic chiasm. In rare cases, ectopic

locations have been described including the pineal gland, the cerebellopontine angle, the temporal lobe, or completely within the third ventricle⁽⁹⁶⁷⁾.

The diagnosis of a craniopharyngioma is usually made after detailed analysis of MRI and CT scans. The CT scan is valuable for evaluation of the bony anatomy and to assess the various components of the mass and identify the presence of calcifications⁽⁹⁷¹⁾. On CT imaging, the cystic components typically appear hypodense, calcification appears as hyperdense, and the solid portions and cyst capsule enhance following contrast administration⁽⁹⁶⁷⁾. The MRI is useful to assess the precise localization of the lesion in relation to adjacent critical neurovascular structures. This imaging modality also gives more information regarding the various components of the tumour. Craniopharyngiomas are purely or predominantly cystic in 46-64% of cases^(955,969,972), purely or predominantly solid in 18-39%^(955,969,972,973), and mixed in 8-36%^(969,972). Protein, cholesterol and methhemoglobin may result in high signal on T1-weighted images. CTA or MRA may be valuable as part of the pre-operative evaluation if clarification of the anatomic relation of the tumour to the blood vessels is required⁽⁹⁷⁴⁾.

Pre-operative imaging enables surgeons to plan the safest and most effective surgical strategy as well as to anticipate intra-operative difficulties⁽⁹⁷⁵⁾. Differential diagnosis should include Rathke's cleft cyst, congenital inclusion cyst, and cystic pituitary adenomas.

An endocrine work-up and ophthalmological examination are essential for a complete pre-operative work-up. In addition, body composition, growth, and weight curves may be useful in paediatric patients since they may serve as indicators of hypothalamo-pituitary dysfunction.

Staging

Since craniopharyngiomas vary in location and extent of growth, many classification systems have been proposed to classify these tumours and guide surgical planning. Authors have proposed various classifications for craniopharyngiomas depending on their relation to the sella turcica, diaphragm sellae, optic chiasm, and third ventricle. Yasargil initially categorized these lesions in purely intra-sellar-infradiaphragmatic (type a); intra- and suprasellar, infra- and supradiaphragmatic (type b); supradiaphragmatic, parachiasmatic, extraventricular (type c); intra- and extraventricular (type d); paraventricular in respect to the third ventricle (type e) and purely intraventricular (type f)⁽⁹⁷⁶⁾. Using similar anatomical landmarks, Hoffman categorized craniopharyngiomas in prechiasmatic, retrochiasmatic, subchiasmatic and intraventricular⁽⁹⁷⁷⁾. These lesions have also been graded depending on their vertical projection. As such, a grade I craniopharyngioma (intrasellar and/or infradiaphragmatic), grade II (suprasellar cistern with or without an intrasellar component), grade III (located along the lower half of the third ventricle), grade IV (located in the upper half of

the third ventricle), and type V (reach the septum pellucidum or lateral ventricles)⁽⁹⁷⁸⁾. Other groups have stratified surgical resection in relation to hypothalamic involvement varying from no hypothalamic involvement (grade 0) to hypothalamic involvement in which this structure is not identifiable (grade 2)⁽⁹⁷⁹⁾. The tumour's relationship with these afore mentioned structures are critical, particularly for transcranial approaches.

However, for EEA approaches, a key anatomical consideration is the tumour's relationship with the pituitary stalk⁽⁹⁸⁰⁾. This classification proposed by Kassam et al, uses the relationship to the stalk to determine the specific EEA module required to create a corridor to the tumour. Type I Craniopharyngiomas are pre-infundibular, located immediately anterior to the pituitary stalk in the suprasellar space, guarded inferiorly by the diaphragm, superiorly by the displaced chiasm, posteriorly by the pituitary stalk and laterally by the carotid arteries (980). They push the suprasellar arachnoid and the attached superior hypophyseal artery (SHa) against the retro-tubercular dura. Pre-infundibular lesions are the most accessible craniopharyngiomas to approach through an endonasal route. Type II Craniopharyngiomas are transinfundibular lesions that grow within the long axis of the infundibulum, widening it circumferentially⁽⁹⁸⁰⁾. Such lesions often create a component in the subchiasmatic space and extend rostrally through the tuber cinereum and into the anterior third ventricle. In these cases, the stalk forms the capsule of the tumour. Type III craniopharyngiomas are those that are retro-infundibular, located posterior to the pituitary stalk⁽⁹⁸⁰⁾. These lesions are considered the most challenging to access via the endonasal route. Such craniopharyngiomas are bounded anteriorly by the pituitary stalk and posteriorly by the mamillary bodies and basilar apex. The tumour may extend rostrally (type 3a), through the membrane of Lilliequist, to ultimately encroach on the anterior third ventricle. It may also extend caudally (type 3b) to fill the interpeduncular fossa, potentially encroaching on the posterior circulation. Laterally, retroinfundibular craniopharyngiomas are bounded by the oculomotor nerve as it travels forward toward the cavernous sinus and the posterior communicating arteries as they travel between the posterior cerebral artery (P1) and the ICA. Type IV craniopharyngiomas are pure intraventricular tumours⁽⁹⁸⁰⁾. These tumours may best be approached by a transcranial route as the endonasal corridors are often limited by the stalk and chiasm. Since craniopharyngiomas are rarely only located in any one of these spaces, finding the predominant location of their solid component will identify the primary surgical target and guide operative strategies.

Histology

Craniopharyngioma are histologically benign grade I tumours according to the WHO (World Health Organisation) classification⁽⁹⁸¹⁾. Rarely, craniopharyngiomas may present a malignant transformation, potentially induced by radiation therapy^(982,983).

Histologically, two subtypes have been described, the adamantinomatous and the papillary. However, transitional or mixed forms have also been reported⁽⁹⁸⁴⁻⁹⁸⁶⁾. The adamantinomatous type predominantly affects young patients during the first two decades of life^(985,987,988). This subtype of craniopharyngioma may have cystic and/or solid components, necrotic debris, fibrous tissue, and calcifications. The fluid of the cystic portion is mostly composed of desquamated squamous epithelial cells⁽⁹⁶⁰⁾. The diagnosis of this subtype requires the presence of adamantinomatous epithelium represented by palisading of a single cell layer bordering clusters of loose stellate cells or wet keratin (clusters of desquamated squames)⁽⁹⁸⁹⁾.

Adamantinomatous craniopharyngiomas often have an adherent interface between the mass and adjacent neurovascular structures, rendering difficult the intra-operative identification of a tumour-normal tissue interface.

On the other hand, the papillary subtype has been almost exclusively described in adults^(985,988). Its cellular structure is similar to that of the oropharyngeal mucosa⁽⁹⁹⁰⁾. Macroscopically, papillary craniopharyngiomas are generally well circumscribed lesions. They are either purely solid or mixed with solid and cystic components^(988,991,992). Calcifications are rarely present^(985,988,989,992). In addition, infiltration of adjacent brain tissue is less frequent than in the adamantinomatous subtype⁽⁹⁸⁵⁾.

Treatment

Surgery

Currently, surgical removal with possible adjuvant external beam irradiation is the treatment of choice. Although the goal in primary resections should be complete tumour removal, this may not always be possible with acceptable morbidity^(957,967,968,993). Traditionally, craniopharyngiomas have been removed using various open skull base approaches including the anterior midline route (subfrontal), the anterolateral routes (supraorbital, pterional, orbitozygomatic), and the intraventricular (transcallosal-transventricular; transcortical-transventricular; translamina terminalis) approaches^(334,957,958).

In the last two decades, transsphenoidal approaches, performed either under microscopic or endoscopic visualisation, have been used to treat intrasellar or intra-suprasellar subdiaphragmatic craniopharyngiomas^(785,994). Initially, the endonasal route was often considered contraindicated in patients with a normal pituitary function from the need to traverse the sella to reach the suprasellar space. More recently, the introduction of the expanded endonasal approaches for craniopharyngiomas has enabled safe and effective treatment of these lesions by directly accessing the suprasellar space via a transtuberular/transplanum approach. The panoramic view obtained with the endoscope and its magnification may allow for the removal of craniopharyngiomas with supradiaphragmatic components^(956,995). The specific EEA performed should be

tailored to the tumour's location. Particular attention must be paid on dura closure technique to avoid postoperative CSF leak. Therefore, at the very beginning of the procedure, a Hadad-Bassagasteguy (nasoseptal) flap is raised from the widest nasal cavity using a standard technique^(31,344,996). The general technical nuances for endoscopic craniopharyngioma surgery are described in literature for each specific tumour type^(46,347,980).

Overall, endoneurosurgical resection of craniopharyngiomas uses the same techniques as those used in microneurosurgery including internal debulking of the solid part and/or cystic evacuation followed by fine and meticulous dissection of the tumour from the surrounding neurovascular structures^(980,995). A reliable skull base reconstruction is mandatory at the end of the procedure due to the large dural opening, extensive dissection of arachnoid cisterns and/or third ventricle, and associated CSF leak. Skull base reconstruction with vascularized tissue has proven to decrease the incidence of postoperative CSF leak and the correlated morbidity consequences^(31,345,346,996). A nasoseptal flap is the preferable vascularized tissue in the nasal cavity. It is elevated from the nasal septum in the beginning of the procedure and stored in the nasopharynx till the end of the procedure. Once the resection is completed, a collagen matrix membrane is used for inlay reconstruction followed by the vascularized nasoseptal flap in an onlay fashion. The reconstruction is then followed by an oxydized cellulose polymer (Surgicel[®]), a dural sealant agent (DuraSeal[®]) and a Foley balloon to buttress it. Antibiotics are given until the packing is out^(31,345,346,996).

Complementary treatments

When gross total removal cannot be safely performed during initial surgery, post-op external radiation is generally recommended. In instances where there residual tumour is quite small and without mass effect, it may be reasonable to perform serial MRIs every 3 to 6 months and wait until definitive tumour growth is documented before proceeding with stereotactic radiosurgery or stereotactic radiotherapy. When facing a near total removal (NTR) or a subtotal removal (STR), the inherent risks of radiotherapy must be balanced against the high risk of tumour progression and its negative impact on overall mortality^(957,979,987,997-999).

Adjuvant radiotherapy with stereotactic radiosurgery, stereotactic radiotherapy or conventional external beam radiotherapy appears to have resulted better long term control rates reducing the recurrence/progression rates after subtotal removal ranging to 0-30% (mean 17.2%)^(952,967,998).

Tumour recurrence should be managed on an individual basis. Endoscopic endonasal approaches are very viable surgical options for recurrent craniopharyngiomas that have been operated via craniotomy or even transphenoidally previously^(335,952).

In such circumstances, the goals of the procedure should be adapted to each patient, aiming for effective but safe reversal of compression of neurovascular structures and removal of as much tumour as is safely possible. Overall satisfactory surgical results for recurrent and residual craniopharyngiomas may be enhanced with adjuvant therapies. Other treatment options include complementary radiation treatments, intracavity irradiation or instillation of the antineoplastic agent bleomycin, surgical cyst controlling procedures and/or mass debulking, and systemic chemotherapy⁽⁹⁶⁷⁾.

Results

Large surgical transsphenoidal series have reported gross total removal (GTR) rates ranging from 7% to 89%, these series have used the microscope and/or endoscope^(331,335,337,967,973,1000-1003) for visualisation. Cavallo et al. recently reported their combined experience with the EEA in the treatment of recurrent and residual symptomatic craniopharyngioma. Of the 22 patients operated in this series, 9 patients (40.9%) underwent gross total removal (GTR), 8 patients (36.4%) had near-total removal (NTR) (more than 95% removal), and 4 patients (18.2%) had subtotal removal (STR) (more than 70% removal). Only one patient had a partial removal of less than 50%⁽⁹⁵²⁾. In this series, post-operative CSF leakage occurred in 13.6% of cases. Furthermore, pre-operative visual deficits normalized in 22.2% and improved in 61.1% of patients. Surgical results of craniopharyngiomas removal through the supraorbital approach have presented GTR rates ranging from 40% to 74%^(903,1004,1005). Gross total removal rates obtained following a sub-frontal, pterional, transtemporal route for craniopharyngiomas varies from 9.5 to 90%^(893,955,970,976,977,979,1006-1009). When reviewing specifically the series of EEA (pure endoscopic approaches) for the removal of craniopharyngiomas, overall GTR /STR (residual tumour less than 25%) was reported in 92.4% of cases, specifically with a 60.4% of complete removal (no residual). These data seem to be at least equivalent to the GTR rates of the transcranial series (9.5 to 90%)^(893,955,970,976,977,979,1006-1009). Unfortunately, radical resection (independent of approach) does not preclude recurrences. In fact, recurrences occur between 0-50% (mean 21.4%) of cases following GTR^(952,955,970,976,997,1002,1006). Near total removal rates are reported ranging from 18 to 53%, with subsequent recurrence/progression rates varying between 0-62%^(334,337,952). In cases in which a STR or a partial removal was achieved, tumour recurrence rates vary between 25-100% (mean 65%)^(952,955,967,970,976,997,1006). Following surgery, pituitary deficits rarely improve. Overall, the rates of individual hormone deficits following craniopharyngioma removal range between 88-100% for GH, 80-95% for FSH/LH, 55-85% for ACTH, 39-95% for TSH, 25-86% for ADH⁽⁹⁶⁷⁾. The highest rates of post-operative hypopituitarism are reported in surgical series aiming for GTR⁽⁹⁷⁶⁾. Hypothalamic damage may result in a hypothalamic syndrome characterized by hyperphagia, obesity, disorder of thirst and water/electrolyte balance, behavioral and cognitive impairment,

loss of temp control, and disorder of sleep. In series that specifically assessed hyperphagia, this symptom occurred post-operatively in 20-40% of cases following an EEA^(335,1000) and in 61%-85% after a conventional transcranial approach^(994,1000). In a recent series of craniopharyngiomas removed via the EEA, this complication was avoided⁽³³⁷⁾. This well-recognized complication of craniopharyngioma surgery is most likely related to direct hypothalamic injury or indirect injury to vessels vascularizing the hypothalamus.

Visual outcome seems to be worse after transcranial surgery in comparison to transnasal approaches⁽¹⁰⁰⁰⁾. Visual deterioration rates following conventional craniopharyngioma removal range from 14.7 to 56.5 %^(955,973,976,979). Visual deterioration after an endoscopic endonasal surgery occurs in 0-10 %^(331,334,335,337,1000). Improvement in vision and/or normalization is noted in 33-68% of cases treated by a transcranial approach^(955,973,976,979). However, visual improvement and/or normalization occurs in 61-94% of patients treated by an EEA^(331,334,335,337,1000). It should be noted that adjuvant radiotherapy following surgical removal of craniopharyngiomas may contribute to additional delayed visual compromise. The cumulative probability of a visual defect at 10yr follow-up after surgical removal and irradiation varies between 36-62%^(969,974,1010).

Discussion

To date, the surgical management of craniopharyngiomas remains challenging, whether they are removed through a conventional transcranial approach or an EEA, using the microscope and/or the endoscope for visualisation. In our opinion, the magnification and direct visualisation provided by the endoscope has enabled better identification of the limits

between the tumour and the normal surrounding tissue, permitting the potential for safer and more radical tumour removal. The EEA offers several advantages, which include minimizing brain retraction, early exposure of the lesion, good visualisation of the pituitary gland, stalk and the critical vascular structures, minimal optic apparatus manipulation. Perhaps one of the greatest advantages is to approach these midline lesions via a midline corridor is the early and clear visualisation of the critical subchiasmatic perforators that supply the optic apparatus and the stalk. Although the endoscope might help achieve a safer and more radical tumour removal, its use in the endonasal approaches cannot change the pathological entity, its tendency to recurrence, or the fragility of invaded or associated structures. Furthermore, not all craniopharyngiomas can be safely removed by the EEA. Therefore, when a craniopharyngioma cannot be removed through an EEA, an open route may be considered as in intraventricular lesions or a combination of endonasal and open approaches (lateral extensions into the middle fossa).

Despite the promising results obtained with the EEA for removal of craniopharyngiomas, preservation or improvement of function and low complication rate, larger series with longer follow-up are required before definitive conclusions are drawn concerning the disease control.

Conclusions

- Craniopharyngiomas are benign lesions (WHO grade I), however they have the tendency to infiltrate adjacent neurovascular structures and present an overall aggressive behavior.

Table 9.4 Large series (n ≥ 10) reporting purely endoscopic EEA treatment of craniopharyngioma in an adult population.

Reference	Population	Removal	Post-operative visual outcome of patients with pre-op visual deficit	Post-operative endocrinological outcome	Complications
Cavallo ⁽⁹⁵²⁾	22 reoperation series ONLY for residual or recurrent tumours	GTR/NTR: 17 STR: 4 Partial: 1	Resolution: 4/18 Improved: 12/18 Unchanged: 2/18	Unchanged: 20 New deficit: 2	CSF leak: 3, all required operative repair
Gardner et al. ⁽³³⁷⁾	16 (M:10;F:6) 5 recurrent tumours	GTR/NTR: 11 STR: 4 Partial: 1	Resolution: 6/14 Improved: 7/14 Stable : 1/14	Improved: 1 Unchanged: 12 New deficit: 2 Lost to FU : 1	CSF leak: 11, 10 required operative repair Vascular injury: 1 (p1 perforator)
Cavallo et al. ⁽⁹¹⁵⁾	18 (M:10;F:8) 5 recurrent tumours	GTR/NTR: 13 STR : n/s Partial : n/s	Improved: 12/13 Worsened: 1/13	Improved: 0 New deficit: 2	Pneumocephalus required operative repair
De Divitis et al. ⁽³³¹⁾	10 (M:6;F:4) 3 recurrent tumours	GTR/NTR: 7 STR: 2 Partial: 1	Improved: 5/6 Worsened : 1/6	Improved: 0 Unchanged: 7 New deficit : 3	CSF leak: 2, all required operative repair
Frank et al. ⁽³³⁵⁾	10 (M:4;F:6) 2 recurrent tumours	GTR/NTR: 7 STR: 1 Partial: 2	Resolution: 4/8 Improved: 2/8 Stable: 2/8	Improved: 0 Unchanged: 1 New deficit: 9 (mostly DI)	CSF leak: 3, 2 required operative repair

GTR/NTR: gross total removal/near total removal
STR: subtotal removal, CSF: cerebrospinal fluid

- Currently, surgical resection with or without adjuvant external radiation treatment is currently the treatment of choice.
- Although the goal in primary resections should be complete tumour removal, this should not be attempted at the cost of neurovascular damage and subsequent long-term morbidity.
- The endonasal route provides the advantage of accessing the tumour via a midline approach minimizing the need for brain or optic nerve manipulation with a direct visualisation through a linear surgical route
- This is particularly valuable in the preservation of key perforators the most important of which is the superior hypophyseal artery
- The infundibulum is the key anatomical landmark that helps guide the modular exposure of EEAs for craniopharyngioma resection.
- The EEA enables near total and subtotal tumour removal in more than 90% of cases, results that favorably compare with transcranial results, with preservation or improvement of function (visual and pituitary) acceptable complication rates.
- The rate of CSF leak is higher following EEA in comparison to transcranial approaches; however, the development of vascularized reconstruction techniques has reduced this further.

9.4 Chordomas

Introduction

Chordomas are rare, slow-growing, locally aggressive, and destructive tumours. They are classified as low-grade malignancies with a high tendency of local progression. Chordomas are located at the end of the spinal axis: sacrococcygeal region (50%) and less often in the vertebral bodies (15%)⁽¹⁰¹¹⁻¹⁰¹⁶⁾. Approximately 35% involve the clivus (spheno-occipital bone, nasal) originating from the midline with varying degrees of lateral extension; rarely primarily intradural intracranial occurrence is reported^(1011-1013,1015,1017-1020). Metastatic dissemination is possible (10–20%) to lung, bone, liver, and lymph node as well as seeding along the surgical pathway^(1015,1016,1021,1022).

Local tumour control is the basic goal of treatment for clivus chordomas. Radical surgical removal is recommended as primary modality while minimizing surgical morbidity^(1015-1017,1021,1023,1024). Several conventional skull base approaches are described in literature for chordoma removal as well as endoscopic endonasal approaches^(10,18,305,306,750,760,805,1013,1023,1025-1029). Regardless of which surgical approach is used, total removal is achieved in only 49.2–79% of cases^(750,1013,1017,1023,1024,1029-1032).

Adjuvant therapies are proton beam radiotherapy (PBRT), Gamma Knife radiosurgery (GKRS), or LINAC based stereotactic radiotherapy^(1011,1031,1033-1044).

Combination of radical surgery and high-dose radiation therapy is regarded as the best treatment. The proximity to critical

structures such as major vessels, cranial nerves, and brain stem makes the removal of chordomas challenging for skull base surgeons^(1013,1015,1016,1022,1023).

Incidence and aetiology

The incidence is < 1.1 per 100,000 per year. Chordomas account for less than 0.1% of all cranial base tumours and for 1-4% of all primary malignant bone tumours^(1014,1015,1022,1024). They originate from embryonic remnants of the primitive notochord. Chordomas may occur at any age, though there is a peak at 50–60 years. The male-to-female ratio is 2:1^(1013,1015,1016,1019,1022,1045,1046).

Clinical presentation

Symptoms vary with lesion location and extension and may be caused by hydrocephalus, brain stem compression, and/or cranial nerve displacement or involvement. At presentation, the most common clinical findings are headaches and diplopia due to cranial nerve palsy. Other reported symptoms include decreased and/or blurred vision, facial pain, anosmia, dysphagia, ataxia, hemiparesis, IXth, Xth, XIth, VIIth, and VIIIth nerve dysfunction^(306,760,805,1013,1015,1016,1022-1024,1030,1047,1048).

Diagnosis and imaging

Skull base chordomas extend primarily along the anteroposterior axis. They are well delineated and displace adjacent structures, advanced tumours show invasiveness and bone destruction. Both, computed tomography (CT) scan and magnetic resonance imaging (MRI) exhibit the lesion and contribute to the diagnosis. CT scan demonstrates best bone erosion, osteolysis, and intralesional calcifications; typically, there is no surrounding sclerosis. MRI is particularly reliable to evaluate tumour extension. Most chordomas are isointense or hypointense on T1-weighted images; high signal correlates with haemorrhage or mucinous collections. T2-weighted images demonstrate usually a high signal. Gadolinium enhancement is mostly heterogeneous with a honeycomb appearance. Rarely MR angiography or conventional angiography is required to depict vessel displacement or encasement^(1015,1016,1022).

Histology

Macroscopically, chordomas are soft, grey, gelatinous, and lobulated neoplasms; extraosseous parts tend to have a pseudocapsule^(1011,1015,1016,1022,1049). Microscopically, chordomas are composed of vacuolated physaliphorus cells with mucin; immunohistochemistry shows expression of epithelial markers including cytokeratin and epithelial membrane antigen as well as mesenchymal markers (S100)^(1022,1050-1053). Ki-67 Li has a close relationship with tumour volume-doubling time and with poor prognosis⁽¹⁰³⁰⁾. The invasive nature of these tumours is evidenced by the fact that islands of tumour cells can be found surrounded by normal appearing bone⁽¹⁰¹¹⁾. Three groups are classified: the conventional (= typical) type is the most common chordoma and is characterized by the absence of cartilagi-

nous or additional mesenchymal components; the chondroid type occurs in 5–15% and contains chordomatous and chondromatous features and appears to have a more favourable long-term outcome; and the dedifferentiated chordoma with a frequency of 2–8% has a poor prognosis⁽¹⁰¹⁵⁾. Malignant change into undifferentiated spindle cell tumour, malignant fibrous histiocytoma, or chondrosarcoma may occur over time^(1045,1054,1055). Analyses of large series suggest the existence of two different subgroups of patients with different patterns of disease: one group with aggressive tumours and a high incidence of recurrence within 5 years of treatment, and another group with a much more indolent course and long-term survival^(1017,1022,1031-1033,1043,1056).

Treatment

Radical surgical resection, with or without adjuvant radiotherapy, seems to give the best perspective of progression free survival^(10,305,750,760,805,1013,1015,1022,1030,1033,1037,1041).

Surgery

A multitude of open microscopic approaches for skull base chordomas is used. Primarily, these lesions are removed via anterior, lateral or combined approaches; they may be performed in staged procedures. Among them, there are fronto-orbitozygomatic, transbasal, transmaxillary, transmandibular, transoral, transsphenoidal, transcoclear, and subfrontal-infratemporal approaches^(305,750,760,805,1013,1016,1017,1022-1024,1027,1029-1032,1047,1048,1057). Since the last decade endoscope-assisted and fully endoscopic endonasal techniques were established as shown in Table 9.5.

The first fully endoscopic endonasal procedure performed in 1 case was reported by Jho and Carrau et al.⁽⁸⁰¹⁾. A subtotal removal was achieved without complications resulting in postoperative neurologic improvement; GKRS was accomplished 10 days after the intervention.

Stammberger et al.⁽⁶⁵⁸⁾ treated 43 patients with invasive/destructive tumours of the paranasal sinuses and the anterior skull base by endoscopic endonasal surgery. Out of them, 3 patients had chordomas. 1 of them recurred and underwent a further endoscopic removal followed by a GKRS treatment. No complications occurred in these patients.

Again, Jho⁽¹⁰²⁸⁾ reported on a series of 160 patients, 7 demonstrated clivus chordomas. A total removal was obtained in 5 patients and a subtotal in 2. Six patients underwent subsequent GKRS of the tumour bed. The complication rate of cerebrospinal fluid (CSF) leaks was 6% in the total patient group.

In their large study of 100 endoscopically treated patients, Cappabianca and deDivitiis et al.⁽⁸²²⁾ performed a biopsy in two clivus chordomas.

Rudnik et al.⁽⁹¹⁴⁾ published a series of 70 patients treated endoscopically. Out of them, 1 chordoma was partially removed and postoperatively irradiated.

Solares et al.⁽⁶⁴²⁾ presented a series of 6 patients with clivus lesions approached endoscopically; 3 had chordomas and two out of them had undergone prior treatment. Total removal was performed in 2 patients (67%) and partial in 1 (33%). There were no complications, deaths or recurrences over a median follow-up period of 13 months.

Frank et al.⁽⁷⁶⁰⁾ treated 11 patients, 9 chordomas and 2 chondrosarcomas by endoscopic endonasal procedures. Total tumour removal was achieved in 33%, subtotal in 56%, and partial resection in 1 patient. Four recurrences were observed over a mean follow-up of 27 months. Individualized adjuvant or further surgical treatment was performed.

Dehdashti et al.⁽¹⁰⁵⁸⁾ and Carrabba et al.⁽³²⁹⁾ published a series comprising 12 patients with chordomas. Gross total removal was obtained in 58%. Five patients had undergone prior microscopic surgery and/or radiation therapy. The endoscopic procedure was followed by intensity modulated radiation therapy in nine patients after a median follow-up of 16 months. CSF leaks occurred in 4 patients in both reports; no mortality or recurrences occurred.

Zhang et al.⁽⁷⁶¹⁾ presented 9 patients with clivus lesions, 7 harbouring chordomas. Three of them had prior treatments; 2 were operated via a midface degloving approach and 1 patient was operated twice followed initially by GKRS in another institution. A total removal was achieved in 6 patients and a subtotal removal in 1. Postoperative adjuvant radiotherapy was not administered routinely. One chordoma recurred after 5 months.

Arbolay et al.⁽¹⁰⁵⁹⁾ performed an extended endoscopic approach in 12 patients. Two clivus chordomas were removed without complications. Both patients showed complete relief of symptoms.

Ciarpaglini et al.⁽¹⁰²⁰⁾ reported the case of an intradural clivus chordoma, which was subtotally removed by an endoscopic endonasal procedure without complications. Four months after the procedure there was no evidence of recurrence. No further radiation was applied.

Fraser et al.⁽³³⁶⁾ operated on 7 patients with clivus chordomas by 10 endoscopic endonasal procedures. In 5 patients, a total removal was obtained. One patient underwent twice palliative endoscopic tumour debulking and died finally of disease. Another patient underwent 2 further endoscopic procedures followed by PBRT resulting in progression free survival. PBRT was administered in 3 patients. No CSF leaks occurred.

Hong et al.⁽¹⁰⁶⁰⁾ treated 12 patients endoscopically with gross total resection in 7 patients (59%), subtotal removal in 4 (33%) and partial removal in 1 patient (8%). Ten patients underwent intensity modulated radiation therapy postoperatively. One patient with recurrent tumour had a second endoscopic procedure followed by an intensity modulated radiation therapy as well. Overall, 1 death of disease and 2 recurrences are described. Follow-up period ranged from 6 to 36 months.

The largest study published by Stippler et al. ⁽³⁰⁶⁾ reviewed 20 patients with clivus chordomas including eight recurrent lesions treated in other institutions. 5 patients had undergone prior radiation therapy. Total resection was achieved in 45%; 2 patients had scheduled staged endoscopic procedures and in another 2 patients, further microscopic open approaches accomplished tumour removal. Eight patients obtained GKRS or PBRT following surgical procedures. One patient died of disease over a mean follow-up of 13 months and 5 recurrences were observed.

Overall, 87 patients harbouring clivus chordomas were treated via an endoscopic endonasal procedure. Approximately a fourth (n = 23) had undergone any kind of previous treatment. A gross total resection was performed in 58.3% (49/84), a subtotal in 34.5% (29/84), and a partial resection in 4.8% (4/84); in 2.4% (2/84) biopsy was the aim of surgery. As far as data are available, the rate of postoperative CSF leakage was 14.7% (10/68), 16 recurrences occurred, and 7.8% (6/77) died of disease during the follow-up period.

Radiotherapy

Chordomas are increasingly treated with radiotherapy in an attempt to gain local tumour control ^(1015,1016,1022). PBRT (particularly with three-dimensional planning) proved to be superior to conventional radiotherapy and represents the most promising adjunctive treatment particularly in combination with radical surgical removal ^(1036,1037). Actuarial 5-year survival rates of 100% are reported with acceptable risks ^(1022,1036,1043,1061).

The use of stereotactic radiosurgery is increasingly reported for skull base chordomas either as primary or adjuvant treatment. Data suggest that radiosurgery may be part of the commonly required multimodal management for local tumour control ^(1018,1034,1038,1040,1042).

Implantation of iodine-125 seeds in brachytherapy has been anecdotally reported as an adjunctive treatment in the management of skull base chordomas, it has been used with partial success ^(1035;1039).

Prognosis and outcome

Outcome of clivus chordomas varies greatly. Factors associated with poor prognosis include tumour volume (> 70cm³), increasing age, recurrence after surgical resection and postoperative radiotherapy, and possibly female sex ^(750,1015,1018,1022,1036,1046,1062). Clivus chordomas have reported 5- and 10-year survival rates of 70–75% and 40–63% for younger patients and 30% and 11% for older patients ^(1013,1015,1022,1024,1030). However, chordomas arising under the age of five are reported to have a poor prognosis ⁽¹⁰¹³⁾. Specific histological, pathological, and molecular features of chordomas have shown to be related to outcome and biological behaviour of these lesions. Expression of human telomerase reverse transcriptase (hTERT) messenger (m)RNA in chordoma cells identifies those tumours that exhibit unusually fast rates of growth ⁽¹⁰²⁵⁾.

Discussion

Clivus chordomas are rare tumours challenging by their location, extension, and biological behaviour. Radical surgical removal is regarded as the primary treatment modality while paying particular consideration of minimizing complications. High recurrence rates, local destructive growth, and the difficulty to accomplish complete tumour removal emphasise the importance of adjuvant therapies. Surgery in combination with high-dose radiation therapy, particularly PBRT has shown to be effective for tumour control ^(750,1013,1015,1016,1022,1030,1036,1037).

Surgery for clivus chordomas requires often complex and even staged procedures. The most frequent associated complications are CSF leakage and cranial nerve deficits ^(750,1013,1016,1022,1024). There are a few representative series dealing with surgery of skull base chordomas in the current literature; often the results for both, chordomas and chondrosarcomas are reported, although the latter are a distinct entity and known to be associated with a better prognosis ^(1030,1063). Overall, there are 3 studies reporting on 169 patients with skull base chordomas ^(1013,1024,1030). The mean follow-up period ranges from 49.9 to 96 months. Mean 43% (36-50%) had undergone previous surgery and/or radiotherapy. The extent of surgical resection varies, gross total removal (> 90%) was achieved in 71 to 76.2%. Complications occurred in 13.5 to 76%, surgery-related mortality was mean 2.9% (1.9-4.2%). The comparability with endoscopically approached skull base chordomas is poor for the following reasons: mostly case reports and small case series are reported for endoscopically endonasal approached chordomas; data on previous treatment, histological features or follow-up periods are not consistently available, all of which are of importance in terms of surgery, postoperative complications, and outcome and survival, respectively. However, preliminary results suggest a lower complication rate in the endoscopic endonasal group with 14.7% postoperative CSF leakage and no new cranial nerve deficits or other neurological sequelae resulting in no permanent disability. CSF leakage is one of the most common complications in the conventionally approached skull base chordomas as well as for endoscopic surgery in general; the endoscopic endonasal removal of chordomas requires experience with this technique and the development of effective closure techniques has reduced this main problem ^(832,910). Moreover, so far no surgical mortality is reported for endoscopic endonasal approaches at approximately equal removal rates. However, lateral tumour extensions beyond the reach of endoscopic surgery will still require conventional lateral approaches to complete tumour removal and optimise local tumour control.

Conclusions

- Endoscopic endonasal removal of skull base chordomas requires experience with this technique. The advancement in endoscopic closure techniques has resulted in a comparatively low rate of postoperative CSF leakage.

- So far, no new postoperative cranial nerve or neurological deficits and no surgical mortality are reported following endoscopic endonasal chordoma resection.
- Local tumour control by surgery and high-dose radiotherapy is the best strategy for these critically located lesions. This can be achieved by staged and/or combined (endoscopic/conventional) approaches.
- Long-term observations are of particular importance to estimate the efficacy of treatment in skull base chordomas.

No sufficient follow-up data are available for endoscopically treated chordomas to answer this question.

- Further reports of endoscopically approached skull base chordomas should include a unified grading system of tumour removal and detailed information regarding previous treatment, histological features, and follow-up period.

Table 9.5. C1vrus chordoma removed via an endoscopic endonasal approach.

Series	Total (n)	CH (n)	Previous treatment	Extent of resection	CSF leak	Further treatment months	Follow-up,	Mortality	Recurrence	DOD
Jho et al., 1997 ⁽⁸⁰¹⁾	1	1	1 FEBR (n=1)	subtotal I (100%)	none	GKRS (n=1)	NA	none	NA	none
Stammberger et al., 1999 ⁽⁶⁵⁸⁾	43	3	NA	NA	none	EC + GKRS (n=1)	7 - 75	none	1 (33%)	none
Jho, 2001 ⁽¹⁰²⁸⁾	160	7	NA	total 5 (71%) subtotal 2 (29%)	NA	GKRS (n=6)	NA	NA	NA	NA
Cappabianca et al., 2002 ⁽⁸²²⁾	100	2	NA	biopsy 2	none	NA	NA	none	NA	NA
Rudnik et al., 2005 ⁽⁹¹⁹⁾	70	1	NA	partial 1	none	URT (n=1)	NA	none	NA	NA
Solares et al., 2005 ⁽⁶⁴²⁾	6	3	unspecified treatment (n=2)	total 2 (67%) partial 1 (33%)	none	IMRT (n=1) PBRT (n=1)	8 - 24 (mean 13)	none	none	none
Frank et al., 2006 ⁽⁷⁶⁰⁾	11	9	MA (n=2) MA + URT (n=2)	total 3 (33%) subtotal 5 (56%) partial 1 (11%)	1 (11%)	EC + MA (n=1) PBRT (n=4) CMVRT (n=1)	15 - 69 (mean 27)	none	4 (44%)	3 (33%)
Dehdashi et al., 2008 ^(329,1058)	12	12	MA (n=2) MA + SRT (n=3)	gross total 7 (58%) subtotal 5 (42%)	4 (33%)	IMRT (n=9) (median 16)	4 - 26	none	none	none
Zhang et al., 2008 ⁽⁷⁶⁰⁾	9	7	MA (n=2) EC + GKRS + MA (n=1)	total 6 (86%) subtotal 1 (14%)	none	NA	3 - 39 (mean 21)	none	1 (14%), 5 months)	none
Arbolay et al., 2009 ⁽¹⁰⁵⁹⁾	12	2	none	total 1 (50%) subtotal 1 (50%)	none	NA	NA	NA	NA	none
Ciaraglini et al., 2009 ⁽¹⁰²⁰⁾	1	1	none	subtotal 1	none	none	4	none	none	none
Fraser et al., 2009 ⁽¹³³⁶⁾	7	7	NA	total 5 (71%) subtotal 2 (29%)	none	2 EC + PBRT (n=1) PBRT (n=3) EC (n=1)	mean 18	none	3 (43%)	1 (14%)
Hong et al., 2009 ⁽¹⁰⁶⁰⁾	12	12	NA	gross total 7 (59%) subtotal 4 (33%) partial 1 (8%)	NA	IMRT (n=10) EC + IMRT (n=1)	6 - 36	none	2 (16%)	1 (8%)
Stülpner et al., 2009 ⁽³¹⁶⁾	20	20	8 recurrent chordomas URT (GKRS, PBRT) (n=5), not otherwise specified	total 9 (45%) near total 4 (20%) subtotal 7 (35%)	5 (25%)	URT (GKRS, PBRT) (n=8) MA (n=3) EC (n=2)	1 - 54 (mean 13)	none	5 (25%)	1 (5%)

Abbreviations: n = number, CH = chordoma, CSF = cerebrospinal fluid, DOD = death of disease, NA = not available, FEBR = fractionated external beam radiation, GKRS = Gamma Knife radiosurgery,

MA = microsopic approach, EC = endoscopic endonasal surgery, URT = unspecified radiation therapy, IMRT = intensity modulated radiation therapy, PBRT = proton beam radiotherapy,

CMVRT = conventional megavoltage radiation therapy, SRT = stereotactic radiation therapy.

10. Sinus and skull base lesions in the paediatric population

Introduction

Paediatric tumours of the sinonasal tract and the skull base are as a histologically diverse group of neoplasms as in adults. Tumours in this region are rare in childhood, oncological manifestations and prognosis differ to the adult. Hemangioma and tumours of neural derivations are the most common benign tumours, sarcoma the most common malignant ones⁽¹⁰⁶⁴⁾. Depending on tumour extension, location, and involvement of neural and/or vascular structures, there is a wide range to presenting symptoms. Age at presentation allows often drawing conclusions about tumour type or lesion⁽¹⁰⁶⁵⁻¹⁰⁷¹⁾.

Some lesions are especially common in children, like juvenile nasopharyngeal angiofibroma and fibro-osseous lesions and some behave differently from the same lesion in adulthood like ossifying fibroma that has a more aggressive variant called 'juvenile ossifying fibroma' that occurs in children.

Surgical treatment

A variety of surgical approaches is used for tumours of the sinonasal tract and skull base in children: subfrontal, subcranial, orbitozygomatic, transfacial/transmaxillary, uni- or bilateral fronto-orbital including nasal bone removal, transpalatal, transoral, transsphenoidal, midfacial degloving, and facial translocation⁽¹⁰⁶⁵⁻¹⁰⁷²⁾.

Commonly, benign lesions are located extradurally, it is recommended to choose an extradural route for the approach; total resection will provide cure in these cases⁽¹⁰⁶⁵⁻¹⁰⁷²⁾. Skull base tumours and tumours closely located to the cranial base not always require extensive surgery, but biopsy to confirm diagnosis; they may correspond well to chemo- and/or radiotherapy in childhood.

Extended endoscopic endonasal skull base surgery has a cruising radius in the rostro-caudal direction from the crista galli to the foramen magnum and laterally to the midorbit. Therefore, most paediatric skull base lesions seem to be suitable for endoscopic endonasal surgery^(46,47,330,333,868,873,1073).

Associated complications correspond to those reports for adult skull base surgery such as infection, CSF leak, oedema, stroke, infarction, haemorrhage, new neurological deficit, inadequate tumour removal, tumour recurrence, cranial nerve palsies, and visual deterioration. Paediatric patients have additionally the involved risk of interference with facial growth, eruption of dentition, and resulting cosmetic deformities^(1065-1072,1074).

One of the most commonly endoscopically treated paediatric tumour is the juvenile nasopharyngeal angiofibroma with series up to 50 patients. This tumour is discussed separately in Section 6.

Kassam et al.⁽⁸⁷²⁾ reported the largest series of endoscopically treated skull base lesions in the paediatric population comprising 25 children with a mean age of 13.5 years (range 3-18). Pathological entities varied widely and surgical interventions depended on the individual situation and included biopsy, partial, subtotal, and total removal, CSF fistula repair, and optic nerve decompression. Two children, 3 and 4 years old, required a sublabial incision to enable the introduction of endoscope and instruments; all others were treated through a binary endonasal approach. There was no associated mortality. Complications consisted of CSF leaks in two patients (8%). One recurrence of a prolactinoma was observed after 1 year (4%). Staged endoscopic procedures had no additional morbidity.

Kanaan et al.⁽⁹⁵⁴⁾ described an endoscopic endonasal two-staged removal of an olfactory schwannoma. There were no associated complications.

A study by Locatelli et al.^(1075,1076) involved 11 children with different skull base lesions treated by an endoscopic endonasal procedure. Depending on type of lesion, total removal, biopsy, CSF fistula repair, marsupialisation, and evacuation were performed without complications. In 2004, the same author published a paper in which he described five endoscopically endonasal treated recurrent cystic craniopharyngiomas⁽¹⁰⁷⁷⁾. Cysts were marsupialised, a stent was placed from the cyst to the sphenoid sinus, and tumour was partially resected according to the individual situation. One child underwent a combined transcranial approach. One recurrence was reported after 2 years (20%); no further complications are listed with a follow-up longer than 48 months.

Castelnuovo et al.⁽¹⁰⁷⁸⁾ reviewed a series of 11 children with nasal meningo- and meningoencephaloceles ranging in age from 1 to 15 years, who underwent removal of the coele and multilayer closure by an endoscopic endonasal procedure without associated complications.

De Divitiis et al.⁽¹⁰⁷⁹⁾ discussed the role of endoscopic transsphenoidal surgery in children and presented three children treated by this approach. One craniopharyngioma and one pituitary adenoma were totally removed; one nasal meningocele was repaired; there were no reported complications.

The reviewed case reports and case series of paediatric sinonasal and skull base lesions approached by an endoscopic endonasal route include around one 100 patients of which 67 are skull base lesions. Treatment was successful in the majority corresponding to the individual surgical goal. Staged endoscopic procedures were tolerated without additional morbidity. A sublabial incision was occasionally used to facilitate the introduction of the endoscope in children under the age of five. Two recurrences are reported (2/67, 3%), one pituitary adeno-

ma and one recurrent cystic craniopharyngioma. Follow-up was mainly short or not defined. Complications consisted of CSF leaks in two patients (2/67, 3%); both (pituitary adenoma, suprasellar epidermoid) underwent a successful endoscopic repair. There was no associated mortality and no new or permanent postoperative deficit.

Discussion

Several points have to be considered when nasal, sinus and skull base lesions in the paediatric population are discussed (1065-1072,1074).

1. These lesions are infrequent.
2. The factor growth and development have a significant impact on the management, not only the surgical procedure but also decision about radiotherapy. Cosmetic deformities and functional deficiencies concerning vision, lacrimal duct, nasal septum and airways, alignment, taste, deglutition, and speech formation may be a direct consequence of treatment or may be aggravated by growth.
3. The paediatric skull base is incompletely developed and differs anatomically from the adult. Nasal sinus development is age dependent; the sphenoid sinus is usually recognizable by age 4 and is fully developed by puberty.
4. Intraoperative blood loss may be critical for small children.
5. Adjuvant therapy particularly radiotherapy is limited by age to avoid severe long-term sequelae favouring gross total resection.

Comparisons with non endoscopic techniques

There are few representative studies in the literature dealing with paediatric skull base lesions (1065,1066,1068-1070). All authors commonly stated that a multidisciplinary team approach is mandatory to obtain good postoperative results. All used a broad spectrum of standardized skull base approaches according to tumour location and type of lesion. These five reports include 225 paediatric patients. Pathological categories showed a high variability. The overall perioperative mortality rate was low with 0.9%. Tumour removal was total in 73 to over 90%. Survival rates were noted at 50 to 90% at 2 and 5 years, respectively. Postoperative complications occurred in mean 35% (range: 9.5-57%), of those mean 20.5% turned out to be permanent (range: 1.5-37%).

Even though comparability of endoscopically and conventionally approached sinunasal and skull base lesions is difficult due to the heterogeneity of lesions, complication rate of endoscopic endonasal surgery is very low with 3% and currently no reported permanent deficits. Extend of tumour removal seems to be comparable in both groups. Lesions extending in lateral

and posterior locations and with ventrally displaced critical neurovascular structures limit the extended endoscopic endonasal approach. Combined endoscopic and traditional approaches may be used in that case to complete resection. The concept of combined and/or staged procedures for large paediatric skull base lesions has the advantage that gross tumour removal may be obtained without critical intraoperative blood loss. All staged endoscopic procedures have been well tolerated by the paediatric patients. Postoperative care after CSF leakage may be difficult in paediatric patients. The pedicled nasoseptal flap may not be a viable option for EEA reconstruction in children < 10 years of age (345). This flap is a reliable option in patients > 14 years of age, as their septa are comparable to adults (345). Patients 10 years to 13 years of age require careful consideration of facial analysis and preoperative radioanatomic evaluation on an individual basis (1080). Bed rest and instructions to avoid coughing and sneezing are not always understood or followed by a child. Small nares in young children may not permit the passage of endoscopic instruments without risk of injury. It has been shown that in these cases a sublabial incision provides sufficiently access to the nasal cavity. Potential risks of this approach are upper lip and incisor paresthesias, dental injury, or alteration of the anterior nasal spine (1075). However, endoscopic endonasal surgery has several advantages: recovery is quick, there is no need of brain retraction and no need of postoperative nasal packing, visualisation of the surgical field is superior, and neurovascular structures may be particularly preserved by this technique. All these facts are supported by the low morbidity rate of endoscopically treated paediatric skull base lesions (345,872,910,954,1075-1085). Follow-up periods are too short to determine definitive recurrence rates or long-term efficacy.

Conclusions

- Endoscopic endonasal skull base surgery is applicable for a wide variety of paediatric sinunasal and skull base lesions.
- Endoscopic endonasal procedures for children may be scheduled staged if necessary. Staged procedures have been well tolerated.
- Postoperative complication rate is low with so far no permanent morbidity and no mortality.
- Special conditions of paediatric anatomy, physiology, and growth have to be considered when these lesions are approached.
- Teamwork and expertise in endoscopic endonasal surgery is required for the treatment of paediatric skull base lesions.

11. Outcome measures, prognostic factors, quality of life and staging

Search Strategy

The presented data are taken from a PubMed search using the keywords 'outcome' or 'prognosis' or 'Quality of life / (QoL)' and 'staging' referring to 'skull base / skull base surgery / craniofacial surgery' and focusing on articles, which were published in the English literature of the last 20 years.

11-1 Outcome measures

11-1-1 Benign tumours

The outcome of endoscopic endonasal surgery for benign tumours of the paranasal sinuses and the skull base is generally evaluated by reporting the relative number of recurrences in a cohort of patients, followed up for a defined time. Data may be compared to historical cohorts or parallel subgroups of patients subjected to classical types of surgery^(329,415,465,526,564,841,1086-1088). Recurrence rates are supplemented by complication rates and at times by data on other aspects such as operation time, blood loss, need for nasal packing or length of hospital stay^(525,605,606,1089).

11-1-2 Pituitary tumours

Evaluation of surgery for pituitary tumours is primarily focussed on endocrinological and ophthalmologic outcome, while the persistence of residual tumour on postoperative MRI may be reported.

More recently, aspects of patient comfort have been considered in addition without mention of preventive lumbar drains or nasal packing, hospitalization, obstruction, epistaxis and olfactory disturbances⁽¹⁰⁹⁰⁻¹⁰⁹⁵⁾. Generally, impaired nasal physiology may be an issue in selected case series, especially following turbinate ablation, posterior septectomy or use of extensive mucosal (e.g. bilateral nasoseptal) flaps for reconstruction^(31,372,1058,1096).

11-1-3 Malignant tumours

The role of endoscopic endonasal techniques in malignant tumours of the sinuses and skull base in contrast, is mostly defined by retrospective chart analysis presenting data primarily on survival (e.g. 5 years, 10 years disease free survival rate / overall survival rate; patient being alive with disease / dead of disease / dead of intercurrent disease / lost to follow-up), control of disease (local / regional control, distant metastases; need for additional treatment modalities) and surgical complications. Sometimes additional data e.g. on operative time, estimated blood loss, postoperative discomfort (morbidity) as well as length of hospitalization and follow-up time are provided referring to one or more cohorts of patients (exclusively endoscopic / endoscopic assisted / nonendoscopic resections) suf-

fering from comparable types and sizes of tumours according to established staging systems^(239,327,419,630,631,634,635,638-641,734,1088,1097).

According to the literature, endoscopic surgery is usually performed on relatively well-selected, localized cases. Improved cosmetic outcome following endonasal interventions is sometimes mentioned⁽⁶³⁸⁾ but it is rarely evaluated. The same holds true for postoperative development of atrophic rhinitis, which may be potentiated by adjunctive radiotherapy^(640,711,1098,1099).

11-2 Need for a multicentre database

Outcome research on endoscopic surgery for tumours of the sinuses and skull base faces challenges: the rarity of tumours, the variability of their size and localization, the multitude of tumour entities and diversity of treatment strategies. Prospective multi-institutional trials are required to obtain meaningful data⁽¹¹⁰⁰⁾. The TNM system should be supplemented with specifications taking into account endoscopic accessibility of the tumour.

According to literature, outcome in endonasal tumour surgery is favourable. However, there exists a publication bias in favour of reports on successful surgery, which has been noted in other disciplines⁽¹¹⁰¹⁾. In endonasal skull base surgery, the mandatory learning curve of the surgeon calls for specific training programs addressing technical demands and also crisis management^(12,329,526,824,1102,1103). In addition, advanced skull base techniques should be undertaken only in centres where all other surgical approaches can be performed if required⁽⁶⁵⁸⁾. Constant training of the multidisciplinary skull base team should help to keep the rate of complications minimal^(1026,1105).

11-3 Prognostic factors

11-3-1 General Considerations

The prognosis varies according to the diversity of patho-histologic and individual features (type of tumour, size, location, grade and growth pattern, regional and distant spread; general health status of the patient) and also to differing treatment strategies. Some of these factors are constitutive elements of the TNM classification system^(640,734,1104,1105).

In the case of malignant disease, involvement of the orbita, dura, retromaxillary fossa, intradural extension or brain infiltration all have a significant negative impact on survival^(342,481,631,689,1106-1110). One of the most important negatively prognostic signs is a positive surgical margin at the first extirpative procedure^(608,1111). Size of the tumour (bulk), sphenoid sinus

involvement, limited invasion of the dura and brain tissue, site of orbit invasion (anterior vs. posterior), age and sex have been a matter of debate^(659,1107,1108,1112-1114). In general, a higher rate of recurrence is observed for more advanced disease, regardless of the surgical technique⁽⁴²⁰⁾.

Concerning endoscopic surgery, the analysis of these data indicates that one's strategy should be to perform a complete removal, and this strategy has to be based on the staging of the tumour. However, 'en bloc' versus piecemeal resection does not make a prognostic difference⁽¹¹¹⁵⁾.

Some tumours have special prognostic features: malignant melanoma generally has a very poor overall survival⁽⁷³⁴⁾. In olfactory neuroblastomas, histopathological grading according to Hyams can predict the outcome^(682,707,1116). On the other hand, e.g. in inverted papillomas no prognostic factor of local control has been defined⁽⁴¹⁶⁾, whereas younger patients and smokers show a trend to recurrence of these tumours⁽³⁸²⁾. In chordomas, tumour bulk matters: tumour volume of more than 70 ml is associated with a worse prognosis⁽⁷⁶⁰⁾.

Eligibility for the endonasal approach and T-staging do not parallel each other⁽⁶⁵⁹⁾ (Figures 9 and 10).

11-4 Quality of life (QOL)

Quality of life in patients with sinus or skull base tumours has been specifically addressed in the literature primarily related to non-endoscopic and craniofacial surgery⁽¹¹¹⁷⁾. The specific merits of endonasal tumour surgery in terms of QOL have not yet been addressed.

There are a few reports in the literature, which have implemented specific, mostly rhinologic questionnaires to address specific complaints in tumour patients^(1090,1118,1119); others make use of the Karnofsky index only^(239,329,703).

Concerning self esteem of patients, it should be kept in mind that moderate scarring in the midface (lateral rhinotomy) is surprisingly well accepted⁽¹¹²⁰⁾. Ultimately survival is ranked by the patients much above aesthetic appearance⁽¹¹²¹⁾. However, complaints of being disfigured may become a prominent issue following major craniofacial procedures⁽¹¹¹⁹⁾.

QOL in general improves postoperatively, especially after a longer (> 6 month) postoperative time⁽¹¹²²⁾. Less invasive surgical techniques are paralleled by more favorable postoperative QOL scores⁽¹¹²²⁾. Generally, the operating surgeons tend to overrate their patients' QOL, whereas caregivers' perceptions correlate with patients' scores⁽¹¹²³⁾.

Besides the external appearance, nasal obstruction, intranasal crusting, anosmia, neuralgia, local numbness, pain, mucocoele formation, eating disorders, epiphora, diplopia and impaired field of vision or diplopia may contribute to an impaired QOL^(399,1119,1122,1124). The same holds true for increasing age, malignant disease, recurrence and adjunctive radiotherapy, whereas reversible postoperative complications do not have a lasting influence^(1117,1122,1125).

In general, there are a lot of QOL instruments available. Most of them, however, are not targeted at sinonasal and skull base tumours (Tables 11.1-11.3). As a consequence, there is general agreement, that global QOL instruments should be supplemented with disease-specific tools, which differ from those used for head and neck cancer patients^(723,1126,1127). To some extent, the same holds true for all available QOL question-

Table 11.1. Short-list of general QOL instruments.

Instrument	Special Features	Reference
Short Form 36 Health Survey (SF-36)	36 items (8 scales)	Ware (1993) ⁽¹¹²⁹⁾ www.sf-36.org
Short Form 12 Health Survey (SF-12)	12 items	Ware et al. (1996) ⁽¹¹³⁰⁾ www.sf-36.org/tools/sf12.shtml
Glasgow Benefit Inventory (GBI)	18 items	Robinson et al. (1996) ⁽¹¹³¹⁾
European Quality of life 5 dimensions (EQ-5D)	5 dimensions	Rabin and de Charro (2001) ⁽¹¹³²⁾ www.euroquol.org
Child Health Questionnaire (CHQ)	50 items (CH-50PF)	Solans et al. (2008) ⁽¹¹³³⁾
CHQ-50PF (parent form)	87 items (CH-87CF)	
CHQ-87CF (child form)		
European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC-QLQ-C30)	30 items	King (1996) ⁽¹¹³⁴⁾ http://groups.eortc.be/qol/questionnaires_qlqc30.htm
Functional Assessment of Cancer Therapy - General (FACT-G); Head and Neck (FACT-H&N)	27 items (FACT-G) 11 items (FACT-H&N)	List et al. (1996) ⁽¹¹³⁵⁾
University of Washington Quality of Life Scale (UWQLS)	9 items	Hassan and Weymuller (1993) ⁽¹¹³⁶⁾
Hospital Anxiety and Depression Scale (HADS)	14 items	Bjelland et al. (2002) ⁽¹¹³⁷⁾

Table 11.2. Validated QOL instruments addressing sinonasal diseases^(1128,1138,1139).

Instrument	Special Features	Reference
Rhinosinusitis Outcome Measure (RSOM-31)	31 items	Piccirillo et al. (1995) ⁽¹¹⁴⁰⁾
Rhinosinusitis Quality of Life Survey (RhinoQol)	17 items	Atlas et al. (2005) ⁽¹¹⁴¹⁾
Sino-Nasal Outcome Test (SNOT-22)	22 items (modification of the RSOM-31)	Hopkins et al. (2006) ⁽¹¹⁴²⁾

Table 11.3. Disease-specific QOL instruments addressing skull base diseases.

Instrument	Special Features	Reference
Questionnaire 'craniofacial tissue-integrated prosthesis'	Assessment of appearance and functional deficits related to implant-supported prostheses (20 items)	Sloan et al. (2001) ⁽¹¹⁴³⁾
Midface Dysfunction Scale (MDS)	Assessment of midface function (4 items: vision, smell, taste, crusting)	Palme et al. (2009) ⁽¹¹¹⁷⁾
Youth Quality of Life Instrument – Facial Differences; Youth Quality of Life Instrument – Craniofacial Surgery module	Assessment of QOL in adolescents with congenital and acquired craniofacial differences	Edwards et al. (2005) ⁽¹¹⁴⁴⁾
Skull Base Quality of Life Questionnaire	General assessment of QOL in patients undergoing anterior skull base surgery (35 items)	Gil et al. (2003, 2004b) ^(1122,1125)

naires addressing rhinitis and rhinosinusitis⁽¹¹²⁸⁾ Table 11.2. A few other questionnaires may address at least some of the specific needs of extended sinus surgery – the Glasgow Benefit Inventory (GBI) may be mentioned, which was designed to provide an overall view of patient benefit across different ORL interventions. Nonetheless none of the existing health instruments for measurement of quality of life address all the unique and individual perceptions of the health status of our sinus and skull base tumour patients.

11-5 Staging

Staging should be correlated to prognosis and help in selecting the best strategy (such as neoadjuvant chemotherapy) and surgical approach (endoscopic versus CFR, medial maxillectomy, extended skull base approach, etc.). The TNM-classification of malignant tumours according to the standards of the UICC-AJCC is not often used⁽¹¹⁴⁵⁾ because it correlates poorly with prognosis^(1146,1147) and does not allow one to predict eligibility for endoscopic removal. For instance, a tumour ranked T3 involving the palate will require maxillectomy and is not amenable to endoscopic surgery, whereas a T4b tumours, which includes circumscribed dural involvement may be addressed endoscopically together with cases with major brain invasion⁽¹¹⁴⁶⁾.

However, similar systems specifically related to the endonasal surgical accessibility and probability of recurrence in benign disease are often absent or relate to pre-endoscopic surgical strategies. Existing systems usually address insufficiently the specific danger points of endoscopic endonasal surgery. Moreover, in relation to the diversity of tumour growth and therapy, they may appear generally inadequate when dealing

with the multitude of stringent or combined (endonasal / transoral / transfacial / endocranial) approaches and (endoscopic / non-endoscopic / microscopic) techniques. The Krouse system for inverted papilloma groups together extrasinus extension and secondary malignancy as T4 lesions^(362,1148). However, in general, a relationship between T-stage of Krouse and rate of recurrence has not consistently been demonstrated in the literature⁽⁴³²⁾. It should be noted that a T3 tumour may involve the sphenoid, which is accessible to an endoscopic approach possibly with a transpterygoid approach, the maxillary sinus, which may require a medial maxillectomy, or the frontal sinus, which can be very difficult to deal with endoscopically in the case of a large sinus.

Positive comparative reports on endonasal surgery have occasionally been criticized because of selection bias in favour of less aggressive or more easily accessible lesions⁽¹²³⁾. However, in the case of inverted papilloma, because some tumours are large but based on a narrow pedicle, it is recommended that staging of this tumour be based on the site of tumour attachment, not on the global tumour extent and volume^(360;361). Criteria of success and failure should also be precisely defined – e.g. in surgery for angiofibroma, failure has been occasionally been defined as the need for reintervention, caused by symptomatic residual tumours⁽⁵⁹⁸⁾.

In recent years, alternative T-classification systems have been designed for specific malignant and benign tumours. Classification systems tend to rank either or both prognostic information with data, which help for the decision making. These systems are referred to in the individual sections.

12. Reconstruction

12-1 Endonasal skull base surgery reconstruction

Introduction

A major obstacle preventing advancement of expanded endonasal approaches (EEA) is the ability to reconstruct the resulting defect. Size and complexity of skull base defects have increased with the expansion of the indications for endoscopic skull base surgery.

Overall goals of reconstruction after EEA are similar to the traditional open skull base surgery and include separation of the cranial cavity from the sinonasal tract, protection of neurovascular structures, preservation or restoration of cosmesis, preservation or rehabilitation of function and avoidance of dead spaces. Separation of the cranial cavity from the sinonasal tract prevents postoperative cerebrospinal fluid (CSF) leaks, pneumocephalus and intracranial infections, such as ascending bacterial meningitis and abscesses; and protects cranial nerves and major vessels against desiccation and infection.

Early reconstructive techniques were based on the experience with the endoscopic repair of defects following spontaneous CSF leaks and accidental or iatrogenic trauma. Multiple reports have validated that small CSF fistulas can be reconstructed with a wide variety of free grafting techniques achieving success in more than 95% of patients^(62,344,1073,1149-1153). When applied to the larger and more complex defects produced by EEA these techniques proved to be inadequate. Subsequent refinements of free grafting techniques, such as multilayer repair or pie crusting techniques, reduced the CSF leak rate but its incidence still remained unacceptably high^(62,344,711,909,1150,1151).

A rapid and reproducible drop in postoperative complications followed the adoption of vascularized flaps for the reconstruction of skull base defects after traditional open approaches. Emulating this evolution, multiple pedicle flaps have been developed for the reconstruction of skull base defects resulting from EEA.

The Hadad-Bassagasteguy flap (HBF) has had a profound impact on the advancement and acceptance of EEA. With the introduction of the HBF, the incidence of post-EEA CSF leaks plunged to < 5%^(31,345,996,1080,1154,1155). Other more recently developed vascular pedicle flaps provide alternatives to address skull base defects of various sizes and locations when the HBF was available, or to complement the HBF. Various reports provide details about the anatomy, technique and application of these flaps^(346,1156-1160). This is a brief summary of these reports describing the surgical technique as well as their indications and drawbacks.

12-1-1 Vascularized Flaps

Hadad-Bassagasteguy flap

The Hadad-Bassagasteguy flap (HBF) comprises the nasal septal mucoperichondrium and mucoperiosteum and is posteriorly based on the nasoseptal arteries. These vessels are branches of the posterior nasal artery, which is one of the terminal branches of the internal maxillary artery.

Harvesting of the HBF include the use of two parallel incisions along the axis of the nasal septum. An inferior incision is made over the maxillary crest and a superior incision is made 1 to 2 cm below the most superior aspect of the septum to preserve the olfactory epithelium. A vertical incision at the muco-cutaneous junction joins these two horizontal incisions anteriorly. Posteriorly, the superior incision extends laterally over the rostrum of the sphenoid sinus at the level of the inferior aspect of the sphenoid ostium, while the inferior incision extends along the posterior free border of the nasal septum and then laterally along the arch of the posterior choana. A strip of mucosa that is between the sphenoid rostrum incisions contains the posterior septal arteries and forms a relatively long and narrow pedicle that facilitates a long reach and wide arc of rotation. Maximal length of the flap is obtained by placing the anterior vertical incision at the muco-cutaneous junction. A wider flap can be harvested by placing the inferior incision at the lateral nasal floor. All incisions can be modified according to reconstructive or oncologic needs. A subperichondrial elevation of the flap frees its paddle and pedicle so it can then be stored in the nasopharynx or inside the antrum.

The use of this vascularized flap to reconstruct the skull base defects has dramatically changed the postoperative CSF leak rates allowing the expansion of endoscopic skull base procedures^(345,996,1154,1155). Pinheiro et al. correlated the dimensions of the HBF with that of skull base defects⁽¹¹⁶¹⁾. On the whole, the HBF provides an area of vascularized tissue of approximately 25 cm^(1153,1161). Its potential dimensions are adequate to cover anterior skull base/cribriform, planar/sellar or clival defects when addressed independently. The surface area of the HBF is usually sufficient to cover two contiguous areas of the skull base such as the cribriform plate and planum sphenoidale or the sella and clivus. A special consideration, however, is the use of the HBF in children. Shah et al. correlated the dimensions of the HBF with that of skull base defects in children of different ages⁽¹⁰⁸⁰⁾. As a rule of thumb the cranium to face ratio needs to be near 1:1 before the dimensions of the nasal septum are adequate to cover a large skull base defect. This ratio is reached around the 12 years of age⁽¹⁰⁸⁰⁾. Pre-operative imaging can be use to estimate both the dimensions of the defect and the flap; thus, anticipating any potential mismatch

^(1080,1161). Postoperative imaging provides a way to examine the adequacy of the reconstruction by establishing the position of the flap in respect to the defect ⁽³²⁶⁾. Migration of the flap away from the defect or the presence of a dead space between the flap and the defect strongly suggest the need for re-exploration or at least careful observation of the patient. Similarly, lack of contrast enhancement suggests ischemia of the flap and may warrant re-exploration or removal of the nasal packing to relief the pressure.

The HBF has become a mainstay reconstructive option after EEAs due to its versatility, wide arc of rotation, generous size and relative ease of harvesting. To this date, more than 400 nasoseptal flaps have been performed at one institution with loss of only two flaps and an overall postoperative CSF leak rate of less than 5% ^(345,996). Loss of the flap occurred in patients who had undergone extensive radiation therapy to the area of the posterior choana, a phenomenon that has been noted by others ⁽¹¹⁵⁴⁾.

Tumour involving the septum, pterygopalatine fossa or sphenoid sinus rostrum precludes the use of a HBF. In addition, some patients may have suffered disruption of the blood supply to the septal flap due to prior posterior septectomy or large sphenoidotomies. Other nasal and regional pedicled flaps represent alternatives for those patients in whom the HBF is not a suitable option or not available. These flaps can also complement the HBF.

Posterior pedicled inferior turbinate flap

The posterior pedicle inferior turbinate flap (PPITF) is based on the inferior turbinate artery, which is a terminal branch of the postero-lateral nasal artery (PLNA), which in turn arises from the sphenopalatine artery (SPA) ⁽¹¹⁵⁷⁾. Harvesting of the PPITF requires the identification of the SPA as it exits the sphenopalatine foramen, then following it inferiorly to identify the PLNA. Two parallel incisions are made following the axis of the inferior turbinate. One is made at the lateral nasal wall, just above the inferior turbinate and the inferior one is made along its caudal margin or even at its lateral aspect. A vertical cut made along the anterior head of the turbinate connect the other two incisions. Its medial mucoperiosteum is elevated, providing about 4.97 cm² of surface area ⁽¹¹⁵⁷⁾. Due to the postero-lateral position of its pedicle, the PPITF is better suited for caudal defects, such as those in the sella or clivus. Its use, however, is limited by its size and configuration. It is a long but narrow flap and significantly smaller than the HBF although a wider flap can be designed by placing the inferior incision on the medial side of the turbinate, or even at the nasal floor. To increase its coverage, it is feasible to raise bilateral PPITFs, or another pedicled flap can be used in conjunction with an inferior turbinate flap to address larger defects.

Posterior pedicled middle turbinate flap

The posterior pedicle middle turbinate flap (PPMTF) is suitable for the reconstruction of defects at the cribriform plate, fovea ethmoidalis, planum sphenoidale or sella turcica ⁽¹¹⁶⁰⁾. Its blood supply comes from the middle turbinate branch of the sphenopalatine artery that courses through the posterior attachment and constitutes its pedicle.

Its harvesting begins with a vertical incision at the most anterior aspect of the middle turbinate. A horizontal incision is made at its medial surface just below the skull base and parallel to its vertical attachment. The mucoperiosteum is elevated in a superior to inferior direction exposing the turbinate bone medially and laterally. Piecemeal removal of the turbinate bone exposes the lateral mucosal attachment that is then released using another horizontal incision. Further elevation of the flap posteriorly exposes the pedicle that can be mobilized and released from all surrounding attachments. A complete release allows a wider arc of rotation and greater length ⁽²²⁾.

A significant limitation of the PPMTF is the technical difficulty involved with its dissection. This is even more challenging in the presence of anatomical variations such as concha bullosa, paradoxical turbinate or hypoplasia ⁽¹¹⁶⁰⁾. As is the case with the PPITF, the surface area of the PPMTF is somewhat limited at 5.6 cm². However, the dimensions of the middle turbinates vary significantly and this should be taken into consideration. Its superior position allows it to reach defects of the planum sphenoidale, sella and fovea ethmoidalis area better than the PPITF. Nonetheless, the turbinate needs to be longer than 4 cm to reach the sella. As previously suggested, this can be estimated using the preoperative imaging.

Transpterygoid transposition of emporoparietal fascia flap

The temporoparietal fascia flap (TPFF) is a pedicled flap based on the anterior branch of the STA. Its blood supply comes from the superficial temporal artery (STA), which is one of the terminal branches of the external carotid artery. It has been used as a reconstructive option in variety of defects in the head and neck, including intraoral defects, oronasal and naso-cutaneous fistulas, as well as skull base defects after traditional craniofacial resections. A transpterygoid corridor allows the transposition of the TPFF into the nasal cavity; therefore, allowing its use to defects created from EEAs ⁽¹¹⁵⁶⁾.

A large maxillary antrostomy facilitates the identification of the SPA and the posterior nasal artery, which are then coagulated and/or ligated at their exit from the sphenopalatine foramen. These arteries are dissected proximally into the pterygopalatine fossa removing the posterior wall of the maxillary sinus. A wide communication with the infratemporal fossa (ITF) is opened as the lateral wall of the maxillary sinus is also removed. The soft tissues of the pterygopalatine fossa are mobilized to expose the anterior aspect pterygoid plates. This

bone is then reduced using a high-speed drill to enlarge the tunnel for the TPF transposition.

Harvesting of the TPF follows a conventional hemi-coronal incision. Then, the superficial layer of the deep temporal fascia is incised vertically and elevated away from the underlying temporalis muscle. This dissection is extended inferiorly to elevate the periosteum from the lateral aspect of the zygomatic arch. Transposition of the TPF into the infratemporal fossa follows a tunnel created by separating the temporalis muscle from the lateral orbital wall and from the pterygomaxillary fissure. This connects the temporal fossa, the infratemporal fossa and the transpterygoid approach. Further dilatation of this tunnel can be achieved using large percutaneous tracheotomy dilators over a guide wire. The TPF is then tied to the guide wire and pulled into the nasal cavity. Its long vascular pedicle along with large surface area allows the reconstruction of large defects of planum, sella, clivus and craniovertebral junction.

Potential drawbacks of the TPF flap include the potential for damage to the frontal branch of the facial nerve, alopecia, and ischemic necrosis of scalp. These, however, are rare.

Trans-frontal pericranial flap

The pericranial and galeopericranial flaps are the most commonly used reconstructive options for traditional anterior cranial base procedures. These are pedicled axial flaps based on the supraorbital and supratrochlear arteries, which yield a very large surface area⁽¹¹⁶²⁾. Their use after endoscopic skull base techniques requires introduction of the externally harvested flap into the nasal cavity through a bony window at the upper aspect of the nasion⁽³⁴⁶⁾.

The pericranial flap can be harvested via a standard coronal incision or using an endoscopic assisted technique⁽³⁴⁶⁾. This latter technique involves the use of several 2 cm incisions that are made along the coronal plane of the scalp to allow the endoscopic assisted dissection of the flap. The supraorbital and supratrochlear arteries are located by Doppler ultrasound, and are included in a 3 cm-wide pedicle. A 1 cm glabellar incision is made and a subperiosteal tunnel is developed to communicate with the subperiosteal plane of the flap dissection. This incision is obviated if the flap is harvested via a coronal incision. A bony window through the nasion allows the transposition of the flap through the naso frontal recesses into the endonasal surgical field. A Draf III frontal sinusotomy is needed as part of the corridor and to secure the drainage of the frontal sinuses. Given its pedicle location, the endoscopic assisted pericranial flap is best suited for the reconstruction of cribriform and planar defects but it can be extended to cover defects of the sella and clivus.

Oliver pedicled palatal flap

The Oliver modification of the palatal flap (OPPF), transposes the vascularized mucoperiosteal tissue of the hard palate into

the nasal cavity through the greater palatine foramen^(1158,1159). A mucosal incision is made around the hard palate extending to within 2 to 5 mm of alveolar ridge laterally and at the limit of the hard palate posteriorly. The mucoperiosteum of the hard palate is raised subperiosteally preserving one of the greater palatine neurovascular bundles. Using a drill or rongeurs, the greater palatine foramen is enlarged to allow the passage of the flap. Intranasally, a wide maxillary antrostomy allows the removal of the posterior wall of the maxillary sinus to expose the junction between the sphenopalatine and descending palatine arteries within the pterygopalatine fossa. A horizontal incision placed 2.5 to 3 cm posterior to the pyriform aperture allows the elevation of nasal floor mucosa. The bony canal of the pterygopalatine canal is opened and the descending palatine artery is released from the canal. Then, the flap is passed into the nasal cavity and mobilized to cover the defect.

It yields a large surface area that ranges between 12 to 18.5 cm². Its long pedicle allows a large arc of rotation that can reach multiple areas of the skull base. Radiologic and cadaveric studies revealed that the pedicle length of the OPPF is adequate to potentially reconstruct the defects of the planum, sella and clivus^(1158,1159).

The OPPF is an excellent alternative when previous EEA and/or open skull base surgery have eliminated all other reconstructive options. One potential complication of the flap is the persistence of an oronasal fistula. To avoid this complication, the nasal floor mucosa is elevated and preserved with a differential flap. Another potential problem is that the OPPF introduces oral bacterial flora into the surgical field.

Discussion

Complications brought by the communication between the cranial cavity and the sinonasal tract can be avoided with a repair that promotes rapid and complete healing of the defect. Vascularized tissue provides the best means to achieve this goal. An ideal flap should be simple to design, resist trauma, produce little or no morbidity, provide an adequate surface area and have an arc of rotation that allows its transposition without the tendency to return to its original position. In general, local flaps, obtained from areas that are adjacent to the defect are preferable to regional flaps and these are preferable to flaps that are obtained from distant areas or that require a microvascular transfer (Table 12.1). Consequently, the HBF is the preferred, although not the only option, for the reconstruction of the anterior, middle and posterior large skull base defects. Its surface area allows the reconstruction of two adjacent areas. Middle and inferior turbinate flaps are best suited for limited defects, usually confined to a single area of the skull base. Defects of the cribriform plate, fovea ethmoidalis, planum sphenoidale or the sella can be successfully repaired with the middle turbinate flap, while the inferior turbinate flap is a better option for the

reconstruction of more posterior and inferior defects such as the clivus. In patients with more extensive defects, the pericranial flap and the TPF can be used as previously described. Anterior defects, such as those resulting from a trans-cribiform skull base resection, are an ideally suited for a reconstruction with the trans-frontal pericranial flap. Posterior defects of the clivus or defects of the middle cranial fossa are best addressed with TPF. If these flaps are not available, the Oliver palatal flap provides coverage for defects of the planum, sella and clivus down to the level of foramen magnum.

Free tissue grafting yields adequate and reproducible results in patients who present small defects, such as those produced with trans-sellar surgery^(832,1163). Free tissue grafts are still an option for the repair of large skull base in select patients. Others have reported good outcomes using these techniques; therefore, the endoscopic surgeon should weigh the possible morbidity and technical difficulty of a vascularized flap against his or her own outcomes when using free tissue grafts. Other factors to consider are the need for perioperative radiation and the need to protect the ICA.

Besides the technical aspects of the skull base reconstruction, a thorough understanding of the dynamics and physiology of the CSF, as well as the intricacies of the nasal and skull base healing are critical to achieve optimal outcomes^(871,1164,1165). CSF is produced by a combination of an active transport system in the choroid plexus, capillary ultrafiltration, and metabolic water production. Its reabsorption by the arachnoid villi is a pressure-dependent phenomenon that occurs when the pressure of CSF is 3-6 cm of H₂O higher than that of the venous pressure⁽¹¹⁶⁴⁾. Factors that affect this delicate balance between production and reabsorption of CSF include prior intracranial infection, prior trans-cranial surgery or radiation therapy^(996,1165). Size of the defect and size of the corridor (i.e. paediatric patients), extensive arachnoid dissection and the direct open-

ing of a cistern or ventricle also affect the ability to achieve an adequate repair; therefore, can impact the outcome^(996,1165). Identification of any of these factors warrant considering the use of postoperative CSF diversion or medications that reduce the production of CSF (e.g. acetazolamide or furosemide).

A subject of some controversy is the use of autologous bone/cartilage grafts or rigid allografts to support the reconstruction or to prevent brain herniation⁽¹¹⁶⁶⁻¹¹⁶⁸⁾. In general, allografts are associated with a relative high incidence of infection and/or extrusion⁽¹¹⁶⁸⁾. Autologous material have less of a tendency to get infected but their rate of resorption is significant⁽¹¹⁶⁸⁾. Patients in whom bone replacement may be of functional or cosmetic importance may better benefit by replacement with vascularized bone⁽¹¹⁶⁷⁾. This is even more important when perioperative radiation is necessary. Currently the concern for delayed brain herniation seems more theoretical than practical, as the phenomenon is extremely rare and not found in large series^(327,340,996,1154,1155).

12-2 Transnasal endoscopic closure of skull base defects

Search strategy

PubMed/MedLine search using following key words: Endonasal, endoscopic, cerebro spinal fluid leak, CSF-Leak (over 900 hits), followed by individual selection of relevant papers from hit list.

Introduction

Cerebrospinal fluid rhinorrhea because of its potentially disastrous sequelae (i.e. ascending meningitis, encephalitis, intracranial abscesses, neurological deficits, death) is a dangerous condition, regardless of its background. Attempts to identify and consequently close CSF-leaks are numerous throughout neurosurgical and rhinological history.

Table 12.1. Reconstructive Techniques for skull base repair.

Reconstructive Technique	Size of Defect		CSF Flow		ICA Exposure	Radiotherapy
	Small	Large	Low	High		
Free Tissue: Layered Grafting	2 (AMPS)	1 (AMPS)	2	0	1	1
Free Tissue: Obliteration	2 (PS)	1 (PS)	2	1	1	1
Local Flap: H-B Pedicled Nasoseptal	1 (AMPS)	2 (AMPS)	1	2	2	2
Local Flap: Pedicled Inferior Turbinate	2 (PS)	0	1	2	1	2
Local Flap: Pedicled Middle Turbinate	2 (AS)	0	1	2	1	2
Regional Flap: Oliver Palate Island	1 (AMPS)	2 (AMPS)	1	2	2	2
Regional Flap: Trans-pterygoid Temporoparietal Fascia	1 (MPS)	2 (MPS)	1	2	2	2
Regional Flap: Trans-Frontal Pericranial	1 (A)	2 (A)	1	2	1	2

0 = not recommended 1 = possible 2 = recommended

A= anterior fossa M=middle fossa P= posterior fossa S= sella

Historical review

Charles Miller in 1826 for the first time described a spontaneous CSF-leakage in a child with hydrocephalus⁽¹¹⁶⁹⁾. In 1899, Sir St. C. Thomson investigated a series of CSF-fistulae of different aetiologies and coined the term “Cerebrospinal Rhinorrhea”⁽¹¹⁷⁰⁾. One of the first documented successful surgical closures of a CSF-leak was performed in 1926 by Walter Dandy, closing a dural tear with fascia lata via a frontal craniotomy⁽¹¹⁷¹⁾. Dohlman from Sweden in 1948 reported an extracranial approach via a nasoorbital incision to close a defect in the ethmoidal roof, using a nasoseptal mucosal flap⁽¹¹⁷²⁾. The first to use a strictly endonasal approach was Oskar Hirsch from Austria, who in 1952 closed a CSF-leak in the sphenoid sinus, using a mucosal perichondrial flap from the nasal septum, via a transseptal-transsphenoidal approach⁽¹¹⁷³⁾.

Since the late 1980s, a clear tendency towards exclusively endoscopic transnasal approaches can be seen in literature^(1174,1175) (Table 12.2).

As stated by Wormald and McDonough in 1997⁽¹¹⁷⁶⁾, CSF-leaks traditionally have been managed by neurosurgeons via a frontal craniotomy, with a success rate of between 60 and 80 %^(1177,1178) but have also been associated with significant morbidity due to frontal lobe retraction and anosmia⁽¹¹⁷⁹⁻¹¹⁸¹⁾.

Initially, the endoscopic spectrum of indications included post-traumatic CSF-leaks, iatrogenic and spontaneous CSF-rhinorrhea associated with either malformations of skull base, (meningo)encephaloceles, empty sella and/or increased intracranial pressure.

With improved skills, techniques and instrumentation, surgeons in the early 1990s were able to reach all of skull base bordering the sinuses and achieve amazingly high success rates with primary closure between 88% and 94%^(1178,1182-1188). Two topographical areas however remained a significant challenge for endoscopists to reach - or could not be reached at all, respectively: the lateral recess of the sphenoid sinus and the posterior table of the frontal sinus. For the latter, the “median drainage” procedure type III described by Wolfgang Draf, allowed for endonasal access to the posterior table of the frontal sinus at least in the mid- and para-midline region⁽¹¹⁸⁹⁾.

Intrathecal fluorescein

In 1972, Messerklinger combined nasal endoscopy and intrathecal application of Sodium fluorescein to diagnose CSF-leaks⁽¹¹⁷⁴⁾. Blue light and a blocking filter over the endoscope’s eyepiece allowed to identify fluorescein-stained CSF in a very high dilution of 1:10 million parts. Blue light induces fluorescence, giving fluorescein-stained CSF a neon-greenish appearance. If the blocking filter is added, all visible light will be blocked except that from fluorescein. This will precisely guide the endoscopic surgeon to the site of the lesion(s). One major

advantage of fluorescein is that it stains insufficiently healed defects. If over a dural defect, the arachnoid and the sinus mucosa have formed a scar, this may be a barrier preventing free flow of CSF, but not ascending infections. Fluorescein impregnates those scars rendering them visible during blue-light endoscopy – an advantage, no other technique can offer. The blue light blocking filter technique helps furthermore to visualize whether or not a CSF-tight closure has been achieved intraoperatively^(1174,1188,1190). The intrathecal fluorescein test can give a false negative result, when for instance the defect site is blocked by oedema of the mucosa, haematoma, or brain-herniation; the injection technique can be faulty, timing and patient positioning be inadequate or the CSF-circulation interrupted. Intrathecal fluorescein cannot however, yield false positive results.

Only a 5 % aqueous sodium fluorescein solution should be used, sterile and free of pyrogens. *No other potentially neurotoxic substances like stabilizers and/or preservatives must be added.* Intrathecal application is an off-label use of fluorescein for which informed consent must be obtained from the patient. Recommendations are to inject 0.05 to maximally 0.1 ml per 10 kg body weight; in no case however, more than 1.0 ml, not even in a massively overweight patient must be applied^(1188,1190,1191).

Fluorescein is injected via a standard lumbar puncture. In cases with evident CSF-flow, a few hours or immediately prior to surgical intervention, in unclear or intermittently leaking cases, usually the evening before an intervention. Even in massive rhino-liquorrhoea sodium fluorescein is washed out after several hours only and therefore even in long-lasting operations can safely be identified over 3–4 hours. Fluorescein not escaping through a dural defect, is bound to plasma proteins and filtrated via the kidneys over 1–2 days, giving the urine a neon-coloured appearance over this time⁽¹¹⁸⁸⁾.

Complications of intrathecal fluorescein

Intrathecal fluorescein application for identification and localisation of CSF-leaks, but as well for exclusion of the latter, is well a proven and helpful technique with a very small risk spectrum. There are reports however in literature, associating significant complications with its use like grand mal seizures, opisthotonus, cranial nerve palsies, even a case of death following application of an excessively high dose (15–20 ml) of undiluted fluorescein has been reported. According to Wolf et al. these complications can be traced back to three conditions: Too much fluorescein applied (volume), wrong concentration (over 5%), wrong fluorescein preparation (other than sodium fluorescein)^(1190,1192,1193). There are many reports in literature confirming the safety of correctly applied intrathecal fluorescein. Wolf et al. report on 925 patients undergoing intrathecal fluorescein applications during 1971–1995. There were only three complications (0.3 %), all grand mal seizures. All three patients experienced the complications in the late 1970s, when

application of fluorescein was via a suboccipital puncture. After this technique was suspended in favour of lumbar puncture, no further complications have occurred since then (1174,1175,1186,1188,1190,1192-1205).

In cases of scheduled dural resection however, fluorescein offers little advantages with the exception of a better evaluation of a water tight closure at the end of the procedure (344,345).

Laboratory testing for CSF

In unclear situations, laboratory techniques may help to differentiate non-CSF-related nasal secretions from true CSF. Quantifying the glucose content of the suspected nasal fluid nowadays “is not acceptable and should be confined to the past” (1206). For many years, beta-2-transferrin was the accepted gold standard. This protein is involved in ferrous ion-transport and also found in perilymph and aqueous humor. The mobility of beta-2-transferrin in electrophoresis is slowed down due to the low content of sialic acid. This results in a test sensitivity of 10 % CSF-content in the fluid (1207). However, certain conditions may cause abnormal transferrin-metabolism causing beta-2-transferrin to be present in the blood as well. This could lead to potentially false positive results, especially in chronic liver disease, genetic variant forms of Transferrin, errors of glycogen metabolism, neurologic-psychiatric disease and some forms of carcinoma (1208,1209). A detection of beta-2-Transferrin in nasal fluid can therefore only be considered a proof of CSF-rhinorrhea, when a simultaneous test for beta-2 from the peripheral blood is negative.

Testing for beta-2-transferrin today has largely been replaced with beta-trace testing: This protein is a prostaglandin T2 synthetase with an extremely high specificity for CSF. Above that, the test is much simpler to perform and can give reliable results after 30 minutes already (1210). The disadvantage of laboratory testing is that fluid must be present at the time of examination.

Grafting Materials (Table 12.2)

A variety of materials, both autologous and heterogeneous ones, have been used to close CSF-leaks and dural defects. In literature, there is a preference for autologous materials as these avoid all potential risks of heterogeneous grafts like prion-associated diseases, HIV, hepatitis and other transmissible disease entities (344,345,1178,1182,1211-1215).

From the immediate surroundings of a smaller defects, mucoperiosteal flaps can be rotated over a fistula, if for instance an olfactory filum has been resected. Free flaps of mucoperiosteum/mucoperichondrium can be used as well and are usually harvested from adjacent or opposite sites of the septum, middle and/or inferior turbinates (1184,1213,1216,1217).

Fascia lata according to literature is a preferred autologous grafting material. It is easy to harvest and large grafts can be

obtained. It can be combined with rotational flaps, pedicled flaps, free mucoperiosteal flaps, cartilage and/or fat, if required. Fascia lata heals very well and its texture and consistency is very similar to dura.

Fascia temporalis is easy to harvest as well but is thinner and weaker than fascia lata. Cartilage can be harvested either from the nasal septum, the ear concha or tragus and ribs.

Bone (from the nasal septum or a turbinate, for instance) is rarely used in endoscopic approaches and appears to be resorbed rapidly.

Fat can be used as fat plug according to the “Bath-Plug Technique”, or as obliteration material in combination with fascia, for instance in the lateral recess of the sphenoid sinus. Heterogenous materials like bovine or human lyophilized dura have been used widely, but since the evidence of prion-associated diseases, should not be used anymore routinely (1176,1218).

Synthetic material like Goretex patches, porous polyethylene implants or bone substitute material like hydroxyapatite are episodically mentioned in literature. Contact of the latter with brain surface or other neurologically sensitive structures should strictly be avoided, however (871,1219-1224).

Surgical techniques (Table 12.2)

For all kinds of defect closures it is recommended, that no vital nasal or sinus mucosa is “buried” under any graft or flap, to avoid any mucocele formation, possibly even extending intracranially. For any overlay technique, the receptor site therefore must be denuded of its mucosal layer in the area to be covered by the graft/flap.

Underlay technique

The (free) graft is placed between dura and bone of skull base. It is recommended to create the underlay one third larger in diameter than the actual defect, to compensate for shrinking of the graft during healing.

Overlay technique

Here, the graft is placed between the bone and the mucosa. The latter should not be covered by the graft.

Underlay and overlay techniques frequently are combined, especially when large dural defects exist or result from surgery, respectively.

Fat plug technique

A fat lobule of adequate size is “squeezed” gently through the dural defect such, that it slightly expands above the dura and thus stabilizes itself. This technique has proven very effective to stop the CSF-flow, whilst preparing other steps for closure like overlay grafts and/or mucoperiosteal flaps. Wormald and McDonogh have described a “fat bath-plug technique”, placing

a suture through the fat lobule prior to insertion, a piece of cartilage or fascia lata is then guided up the suture to stabilize the “squeezed through” fat lobule in the defect site^(1176,1218).

For meningoencephaloceles, which cannot be “pushed back” intracranially, the herniated contents should be resected to the level of the defect proper. Only then, a reliable closure with the techniques mentioned above can be expected. Prior to resection of meningoencephaloceles, it must be well established by imaging that no vitally important or other eloquent neural structures are in the herniated masses. This especially applies for cleft patients and herniations through the lateral recess of the sphenoid^(16,1194,1225-1229).

Large surgical defects

With the surgical advances over the past decade, large lesions affecting the dura as well as intradural tumours were approached transnasally endoscopically. This necessitated the development of additional techniques to provide a predictable, reliable and safe closure. This especially applied to defects in the lateral recess of the sphenoid, the clival region and for situations, where all bone and dura from the planum sphenoidale to the posterior wall of the frontal sinus had to be resected on both sides, leaving behind dural defects as large as 4 x 2.5 cm, possibly more.

Hadad et al. in 2006 reported on a novel reconstructive technique using a vascular pedicled nasoseptal flap, for which almost all of the mucoperiosteum/perichondrium of the nasal septum can be harvested from one side, pedicled on strong sphenopalatine arterial branches⁽²⁶⁾. This flap when applied directly or placed over traditional fascia grafts, would provide very strong support and rapid epithelialization, especially in the critical areas mentioned above. A variety of modifications of this flap have been described recently. The flap can be extended over the nasal floor, or it can be brought to the opposite side through a window in the posterior septum. Similar flaps can be pedicled based on the anterior ethmoidal artery and its branches as well^(31,344,346,1080,1156,1161).

Attempts have been made to endonasally suture dural grafts to the vicinity of defects and/or the remaining dura, to prevent displacement intra- and postoperatively. Special U-clip anastomotic suture devices, originally developed for cardio-vascular anastomosis, have been used⁽¹²³⁰⁾.

Packing (Table 12.2)

A variety of recommendations can be found in literature regarding packing of the surgical field. The spectrum reaches from no packing material at all to resorbable material like Oxycell, non resorbable ones like iodinated gauze, nasal packs like Merocel or RapidRhino-sponges, coated or uncoated, with or without inflatable balloons for additional support, to posterior nasal packings with either gauze or Foley catheters. No standardized recommendations are given in literature as to

how long the various packings should remain in situ, though non-resorbable materials – depending on the size and site of the defects – are usually removed at around one week postoperatively^(81,1188).

There is no uniformity in recommendations regarding duration of bed-rest – if any – postoperatively. At the Graz ENT-Department, traditionally 4-8 days of bed-rest had been recommended until the mid-1990s. Since then, duration of bed-rest was gradually shortened and nowadays is at 1-2 days for the same indications, without any noticeable increase of recurrences or complications. It appears therefore, that the importance of bed-rest has been overrated in the past⁽¹¹⁸⁸⁾.

Few authors mention details of recommendations given to patients postoperatively like not blowing their nose, bending forward, lifting (heavy) items, refraining from physical activities, sports etc. and the recommended duration of these precautions.

Lumbar Drains

Here too, no uniform recommendations are given in literature. Indications remain vague. As can be seen from Table 12.2, the spectrum reaches from no lumbar drain applied in a series of 8 patients⁽¹²³¹⁾, 24 lumbar drain applications in 32 patients (75%)⁽¹²²¹⁾ to 16 lumbar drains in 16 patients (100%)⁽¹²³²⁾. Eleven of 32 authors listed in Table 12.2, do not give any information on whether or not lumbar drains have been used in their cases. As –cum grano salis– indications, defect localizations and size of the lesions are comparable in the different studies, and reported closure rates are equally favourable, a statistical advantage of intralumbar drains cannot be established from the literature.

In Table 12.2, 35 publications are listed from the years 1991–2009, with all together 1123 patients. The methods of diagnosis of CSF-leaks include diagnostic endoscopy, CT- and MRI-scanning, contrast cisternography, glucose and beta-2-transferrin, beta-trace and intrathecal fluorescein applications. Eight authors do not list their diagnostic techniques. Four authors tested for glucose in the nasal fluid, 13 for beta-2-transferrin. Intrathecal fluorescein was used by 19 authors in altogether 368 patients. Twelve authors do not comment on whether or not they used fluorescein, only one author⁽¹²¹⁹⁾ clearly states that no fluorescein was used in his series. No fluorescein related complications were reported in any of the papers.

There is a wide spectrum of grafting materials and combinations, which appear not to have any significant impact on outcome. From 13 papers it cannot be seen, which technique for defect closure was used (i.e. underlay, overlay, or combinations), 21 authors used fibrin-glue in either all⁽¹¹⁸⁸⁾ or some of their patients. Twelve authors do not comment on whether or not they had used fibrin-glue. From only two series it is evident, that no glue had been used^(1183,1187).

Thirteen authors used lumbar drains in either all ^(1213,1232) of their patients or selectively. Altogether, lumbar drains were documented in 186 patients (i.e. 16.5 % of 1123 patients) with a duration of 1–8 days. Four authors indicate the use of lumbar drains, but do not give numbers or percentages.

Duration of postoperative bed-rest is either not mentioned, not quantified or ranges are given between 0.5 and 7 days (10 papers).

All together, 122 recurrent CSF-leaks are documented, which include patients who had to be re-operated several times. Recurrence occurred between postoperative day 2 and 18 months postoperatively, with the predominance of recurrence in the first weeks and months after surgery. Sixteen authors list the site of the recurrent leakage, which was in the sphenoid sinus in with 13 authors. This clearly points towards the difficulty in approaching lesions in the lateral sphenoidal recess, especially with meningoencephaloceles through the so-called Sternberg's canal ⁽¹²²⁹⁾.

Twenty four authors report primary closure rates of 90 % and better, 7 authors of 87.5 - 89.6 %, one author ⁽¹²³³⁾ 67 %, one author ⁽¹¹⁸²⁾ 50 % in sphenoid sinus leaks, Secondary closure rate, i.e. after revision, was 100 % in 19 papers, 6 papers list secondary success rates between 93.4 and 97 % and in six papers, no mention is made of a secondary closure rate. No details are given in those cases, whether or not craniotomy or other approaches were performed.

Thirty-two papers list follow-up time from 1 - 312 months. 9 papers do not mention any postoperative complications, 15 papers clearly state that no complications occurred. Complications documented in these 1123 patients include mucocele (n = 1), synechia (n = 8), fever (n = 2), headache (n = 1), transient diabetes insipidus (n = 2), pneumocephalus (n = 3), hydrocephalus (n = 4), meningitis (n = 13) and one death ⁽¹²¹²⁾. This patient is reported to have developed a hypertensive crisis with subarachnoidal haemorrhage on the fourth postoperative day and died of pneumonia and sepsis four weeks later.

Conclusions

- Endoscopic transnasal closure of CSF-leaks, minor and major, is a well proven concept with a high primary closure success rate, superior to that of craniotomy approaches.
- Almost all autologous grafting materials work well. Reports on allogenic material are episodic. Literature documents a clear trend towards autologous material, especial-

ly fascia lata. This is easy to harvest, and large grafts can be obtained. It can easily be combined with other materials like cartilage and/or fat. In texture and consistency, it is very similar to dura. Being autologous, it avoids all potential risks of heterogenous grafts like prion-associated diseases, HIV, hepatitis.

- Fibrin-glue: Good results are reported with and without its use; it appears to be advantageous to stabilize grafts and flaps during surgery.
- Fat-plugs have proven very helpful in individual situations.
- In meningo(encephalo)celes, resection of herniated tissue to the level of the defect proper is essential.
- For all grafting with the exception of underlay, the receptor site should be free of mucosa to avoid trapping of the latter.
- Intrathecal fluorescein is widely used globally, though an off-label application. It can be extremely helpful in diagnosis of CSF-leaks, especially in intermittent leakage or when insufficiently healed scars between mucosa and arachnoidea prevail. Fluorescein is not required when dural resection is scheduled anyway. Intrathecal fluorescein application has an extremely low complication rate, provided the correct amount and formula are used.
- For laboratory testing, glucose cannot be accepted as a standard anymore, beta-2-transferrin is replaced by beta-trace protein examination in many centres.
- Indications of lumbar drains remain unclear, no consensus can be found in literature. In comparable indications, authors routinely using lumbar drains do not have (statistically) better outcome than authors not using lumbar drains as frequently or at all.
- Techniques of postoperative intranasal packing vary greatly in literature as well as recommendations regarding duration.
- Importance of postoperative bed-rest apparently was overrated in the past. No clear recommendations / consensus can be found in literature.
- No clear recommendations can be obtained from the literature for patients' postoperative precautions, like not blowing their nose, bending forward, lifting heavy items, physical activity, nor the duration of these precautions.
- Novel techniques of graft fixation, like U-clip sutures, are being evaluated at present, their value and reliability need to stand the test of time.
- Sufficient experience in endoscopic CSF-leak repair is considered mandatory before surgeons should go for larger dural resections and/or transdural surgery.

Table 12.2. Endoscopic repair of CS Fleaks in the literature.

Author(s)	n	DG	Loc	n	ET	n	Na-Fl
Muscatello et al. 2009 ⁽¹²³¹⁾	8	CT, MR β2-transferrin	SPS	8	SP TR IA	3 2 3	yes
Nyquist et al. 2009 ⁽¹²²¹⁾	32	β2-transferrin MR/CT cisternog Na-Fl MR/CT	CP ER CP/ER SPS Sella Clivus FS	9 7 2 6 4 3 1	IA MEC/MC	9 23	32
Tabaee et al. 2009 ⁽¹²³³⁾	13	β2-transferrin CT/MR CT cisternog	SPS	13	MEC	13	9
Alameda et al. 2008 ⁽¹²¹²⁾	19	History clinical exam endoscopy CT β2-transferrin	CP ER NK O SPS	9 5 1 1 3	IA MEC SP TR	1 7 10 1	19
El-Banhawy 2008 ⁽¹²³⁴⁾	55	clinical exam endoscopy CT/MR	CP ER SPS	9 11 35	TU SP IA TR MEC	33 6 9 4 3	NK
Harvey et al. 2008 ⁽⁸⁷¹⁾	106	NK	Sella SPS ER CP FS O	42 20 19 15 7 3	IA SP TR CO	70 18 11 7	NK
Kassam et al. 2008 ⁽³⁴⁵⁾	75	NK	NK	NK	TU	75	NK
Sautter et al. 2008 ⁽¹²²²⁾	9	endoscopy CT/MR β2-transferrin	SPS	9	IA SP	5 4	4
Ismail et al. 2007 ⁽¹²²⁰⁾	21	β2-transferrin CT/MR CT/MR cisternog	SPS	21	IA MEC MC SP O	3 1 3 12 2	NK
Cappabianca et al. 2006 ⁽¹²¹⁹⁾	15	NK	Sella	15	IA	15	none
Bolger et al. 2005 ⁽¹²²⁵⁾	9	NK	SPS	9	MEC O	6 3	NK
Gendeh et al. 2005 ⁽¹²³²⁾	16	gluc CT/MR	CP ER SPS	5 2 9	IA SP TR TU	5 7 3 1	13

Legend: B: Bone; BP: bath plug; BR: bed rest; C: cartilage; CG: composite graft; CISTERNOG: cisternorgaphy; CM: collagen matrix; CO: congenital; COMP: complication; CP: cribriform plate; DP: dural patch; ER: ethmoid roof; FS: frontal sinus; FSC: fascia; FT/F: fat; FUP: follow-up; GLUC: glucose; IT: iatrogenic; LD: lumbar drain; LOC: localization; MC: meningocele; MEC: meningoencephalocoele; MP: mucoperichondrium/periosteum; MSL: muscle; MT: middle turbinate; MU: mucosa; Na-Fl: sodium fluorescein; NK: not known; NOS: not otherwise specified;

	Glue	Material	n	LD(d)	BR (d)	REC	PC (%)	SC (%)	Comp	n	FUP
Muscatello	8	CM/MP	6	no	NK	1	87.5	100	none	0	20.6 mths
		B/CM	1								
		SD/C	1								
Nyquist	NK	SD/F/FSC	small	24	NK	2	93.8	NK	NK	NK	90.5 wks
		Medpor,Titanium,	defects								
		B/flaps	large								
			defects								
Tabae	12	B/FSC	3	8	4.5d	2	94	100	meningitis	1	4.7y
		FSC/TG	3						facial paraesthesia	2	
		B/F	1								
		C/FSC	3								
		B	1								
		F/SD	1								
		TG/SD	1								
Alameda	NK	C	9	15	5	1	94	100	mucocoele	1	23 mths
		FSC	5						death	1	
		FT	8						other	1	
		MP	4								
		MU	11								
El-Banhawy	NK	TG	55	NK	NK	3	94.4	100	synechia	8	28 mths
Harvey	yes	Duragen/MU(flaps)	NK	no	NK	11	89.6	93.4	meningitis	2	19.9 mths
		O	NK						pneumoc	1	
Kassam	NK	Hadad Flap	75	yes	NK	8	89.4	NK	NK	NK	NK
Sautter	7	Allograft/MU	5		6.5d	2	97.8	100	diabetes ins	2	21.1mths
		Allograft/MU/B	2								
		Allograft/MU/C	2								
Ismail	21	acellular dermis	21	21(4)	yes	2	90.5	100	none	0	16 mths
Cappabianca	15	TissuDura	15	NK	NK	1	93.3	100	meningitis	1	1-12 mths
Bolger	NK	B/FSC/FT	9	NK	NK	0	100		none	2	14mths
Gendeh	NK	BP/TG	5	16	NK	2	87.5	NK	none	0	18 mths
		BP	5								
		FSC/F	2								
		DP/MP/TG	1								
		FSC/MP/F	3								

Legend: O: other; Obl: obliteration of sinus; OLAY: overlay; PC: primary closure; PCH: perichondrium; PNEUMOC: pneumocephalus; PS: prior surgery; REC: recurrence; SC: secondary closure; SD: synthetic dura; SG: septal graft; SP: spontaneous; SPS: sphenoid sinus; TG: turbinate graft; TR: trauma; TU: tumour; ULAY: underlay.

Table 12.2. Endoscopic repair of CSFleaks in the literature.

Author(s)	n	DG	Loc	n	ET	n	Na-Fl
Mirza et al. 2005 ⁽¹²³⁵⁾	72	β2-transferrin CT,MR	NK	NK	NK	NK	8
Tabaee et al. 2005 ⁽¹²¹⁵⁾	24	NK	ER CP SPS FS	10 8 6 5	IA TR SP	14 5 5	24
Zuckermann et al. 2005 ⁽¹²²⁴⁾	50	NK	NK	NK	SP TR IA O	10 6 14 30	NK
Al-Sebeih et al. 2004 ⁽¹²¹¹⁾	8	β2-Transferrin	CP ER SPS	2 1 5	MC MEC SP	2 2 4	NK
Briggs et al. 2004 ⁽¹¹⁸³⁾	52	CT/MR	NK		IA SP MEC TR PS	11 11 12 13 5	52
Landeiro et al. 2004 ⁽¹²³⁶⁾	10	endoscopy gluc CT cisternog Na-Fl CT/MR	ER SPS CP	5 2 3	TR IA SP	7 2 1	8
Lindstrom et al. 2004 ⁽¹²¹⁶⁾	36	clinical examination β2-transferrin CT/MR cisternog	CP SPS ER FS	15 13 9 3	IA SP TR	22 12 6	10
McMains et al. ⁽¹²³⁷⁾ 2004	92	β2-transferrin	SPS ER CP FS O	36 27 24 3 2	IA SP TR MEC/MC O	40 19 18 11 4	65
Pasquini et al. 2004 ⁽¹²²⁷⁾	4	CT/MR	SPS	4	MEC	4	4
Lopatin et al. ⁽¹²¹³⁾ 2003	21	CT CT/MR cisternog gluc endoscopy	CP ER SPS	6 6 9	SP	21	NK
Tosun et al. 2003 ⁽¹²³⁸⁾	24	endoscopy CT cisternog Na-Fl	SPS	24	IA TR SP TU	9 7 7 1	1
Wormald et al. 2003 ⁽¹²¹⁸⁾	33	NK	SPS FS CP ER	9 3 10 11	IA SP MEC/MC TR	9 7 11 6	33

Legend: B: Bone; BP: bath plug; BR: bed rest; C: cartilage; CG: composite graft; CISTERNOG: cisternogaphy; CM: collagen matrix; CO: congenital; COMP: complication; CP: cribriform plate; DP: dural patch; ER: ethmoid roof; FS: frontal sinus; FSC: fascia; FT/F: fat; FUP: follow-up; GLUC: glucose; IT: iatrogenic; LD: lumbar drain; LOC: localization; MC: meningocele; MEC: meningoencephalocele; MP: mucoperichondrium/periosteum; MSL: muscle; MT: middle turbinate; MU: mucosa; Na-Fl: sodium fluorescein; NK: not known; NOS: not otherwise specified;

Glue	Material	n	LD(d)	BR (d)	REC	PC (%)	SC (%)	Comp	n	FUP
NK	B	48	NK	0.5d	7	90	97	headache	1	5 y
	FSC	18								
	C	6								
19	FSC	22	NK	7d	8	67	96	meningitis	2	2.5 y
	C	16								
	TG	1								
	O	2								
yes	FSC	NK	yes	NK	7	85	100	NK	NK	15 mths
	Alloderm	NK								
8	FSC	8	NK	NK	1	87.5	100	none	0	15 mths
	FT	5								
	C	NK								
0	BP	47	NK	NK	5	90	100	none	0	27mths
	MU	5								
10	MP	6	5(4)	4	1	90	NK	none	0	NK
	F/MP/F	1								
	B/MP	3								
36	MU	NK	yes	NK	4	90.7	100	NK	NK	4.9 y
	MU(flap)	NK								
	B	NK								
	FSC/MSL	NK								
	F	NK								
	Flap	NK								
NK	MU(turb)	59	NK	NK	24	87	94	none	0	25 mths
	FSC	7								
	C	4								
	MU(septum)	3								
	B	3								
	NK	24								
1	B/MP	1	NK	3	0	100		none	0	18 mths
	F/MP	1								
	SD/F/MP	1								
	F									
21	F	NK	21(5-8)	NK	1	95.2	NK	none	0	9-42 mths
	FSC	NK								
	TG(flap)	NK								
	SG(flap)	NK								
	C	NK								
	MSL	NK								
10	F	15	16(1-5)	NK	2	92	100	NK	NK	36 mths
	MP	3								
	MU(flap)	2								
	B(turb)	1								
	O	6								
NK	BP(wormald)	33	NK	NK	2	94	100	NK	NK	28mths

Legend: O: other; Obl: obliteration of sinus; OLAY: overlay; PC: primary closure; PCH: perichondrium; PNEUMOC: pneumocephalus; PS: prior surgery; REC: recurrence; SC: secondary closure; SD: synthetic dura; SG: septal graft; SP: spontaneous; SPS: sphenoid sinus; TG: turbinate graft; TR: trauma; TU: tumour; ULAY: underlay.

Table 12.2. Endoscopic repair of CSFleaks in the literature.

Author(s)	n	DG	Loc	n	ET	n	Na-Fl
Lund 2002 ⁽¹²⁰²⁾	36	β 2-transferrin	NK	NK	CO	7	6
		CT/MR			TR	10	
		CT cisternog			SP	12	
		Na-Fl			IA	5	
					O	2	
Marshall et al. 2001 ⁽¹²¹⁴⁾	53	endoscopy	NK	NK	NK	NK	yes
		β 2-transferrin					
		CT/MR					
		Na-Fl					
Bibas et al. 2000 ⁽¹²³⁹⁾	4	CT/MR	CP	2	SP	3	4
			ER	1	TR	1	
			SPS	1			
Zweig et al. 2000 ⁽¹¹⁵³⁾	48	endoscopy	SPS	19	IA	26	2
		CT cisternog	CP	9	TR	10	
		Na-Fl	ER	15	SP	12	
					TU	2	
					O	3	
Casiano et al. 1999 ⁽¹¹⁸⁴⁾	33	CT/MR	CP	13	IA	27	NK
		Na-Fl	ER	14	TR	2	
			FS	2	SP	4	
			SPS	4			
Marks 1998 ⁽¹¹⁸⁷⁾	18	NK	ER	5	TR	2	NK
			SPS	7	IA	8	
			CP	6	SP	8	
Hughes et al. 1997 ⁽¹¹⁷⁸⁾	17	CT	ER	6	IA	9	5
		β -transferrin	SPS	5	SP	6	
			CP	6	TR	2	
Stammberger et al. 1997 ⁽¹¹⁸⁸⁾	72*	CT, MR	SPS	11	TR	51	69
			SPS/ER	4	IA	5	
			CP	8	SP	5	
			CP/ER	1	MEC/TU	10	
			ER	22	Mycosis	1	
			FS	12			
			ER/FS	13			
			ER/FS/SPS	1			
Kelley et al. 1996 ⁽⁸⁰²⁾	8	endoscopy	SPS	8	NK	NK	yes
		clinical exam					
		imaging NOS					
Anand et al. 1995 ⁽¹¹⁸²⁾	12	CT	CP	8	IA	6	NK
			O	3	IA/MEC	1	
			SPS	1	MEC	1	
					TR	3	
					TU	1	
Hosemann et al. 1991 ⁽¹¹⁸⁵⁾	18	endoscopy	ER	13	IA	11	NK
		gluc	CP	2	TR	6	
		CT	SPS	3	SP	1	

Legend: B: Bone; BP: bath plug; BR: bed rest; C: cartilage; CG: composite graft; CISTERNOG: cisternogaphy; CM: collagen matrix; CO: congenital; COMP: complication; CP: cribriform plate; DP: dural patch; ER: ethmoid roof; FS: frontal sinus; FSC: fascia; FT/F: fat; FUP: follow-up; GLUC: glucose; IT: iatrogenic; LD: lumbar drain; LOC: localization; MC: meningocele; MEC: meningoencephalocoele; MP: mucoperichondrium/periosteum; MSL: muscle; MT: middle turbinate; MU: mucosa; Na-Fl: sodium fluorescein; NK: not known; NOS: not otherwise specified;

Glue	Material	n	LD(d)	BR (d)	REC	PC (%)	SC (%)	Comp	n	FUP
1	MT/FSC/C (ASB) MU/F(obl SPS) FSC/Skin graft (cran)	NK	12	NK	5	85	NK	none	none	32.4 mths
NK	TG FSC/F TG	29 19 5	yes	NK	5	90	94	NK	NK	NK
2	MSL/C/MSL MU FSC/MU PCH/MU	1 1 1 1	NK	NK	2	50	100	none	0	162 mths
yes	C F MU MP FSC TG O	5 15 12 14 7 5 8	24(4)	NK	3	95	100	pneumocephalus meningitis hydrocephalus	3 5 4	26 mths
NK	MP (flap) MP (graft) TG CG	10 21 2 11	no	3-5	1	97	100	NK		29 mths
no	MU (MT) B/M (MT) CG (MT)	9 4 5	11	NK	1	94.5	NK	NK	NK	23 mths
1	MU FSC/F	12 5	no	NK	1	94	94	none	0	15.7 mths
72	MU Lyodura/MU Lyodura/TG/MU TG/MU	1 44 22 5	NK	NK	4	94.5	NK	none	none	19-65 mths
NK	MU/F and/or FSC	8	6(3)	3	1	88	100	none	0	2.3 y
12	FSC	12	7	NK	1	92	100	other	1	312 mths
18	TG	18	NK	NK	1	94.5	100	fever NOS	2	17 mths

Legend: O: other; Obl: obliteration of sinus; OLAY: overlay; PC: primary closure; PCH: perichondrium; PNEUMOC: pneumocephalus; PS: prior surgery; REC: recurrence; SC: secondary closure; SD: synthetic dura; SG: septal graft; SP: spontaneous; SPS: sphenoid sinus; TG: turbinate graft; TR: trauma; TU: tumour; ULAY: underlay.

12-3 Peri-operative use of antibiotics with skull base surgery for tumours

Search strategy

The following section is based on a PubMed search using the keywords ‘antibiotic’ or ‘prophylaxis’ matching with ‘skull base’, ‘endonasal surgery’ or ‘skull base surgery’ and focusing on articles, which were published in the English literature of the last 20 years.

Generally, antibiotic prophylaxis is advised in case of a high risk of infection and also if infection may lead to severe disease or even fatal outcome. In skull base surgery, infection becomes a major issue as the temporarily open communication of the sinuses with the intracranial cavity may provide access for contamination. Cranio-facial procedures leading to large operative cavities preceded by external skin incisions call for distinct and individual protocols for peri-operative use of antibiotics in contrast to endonasal surgery for simple inflammatory disease or major endoscopic ablative skull base surgery leading to multiple transbasal passages of instruments and grafts⁽¹²⁴⁰⁾; on the one hand, use of prophylactic antibiotics in routine functional endoscopic sinus surgery for chronic sinusitis and also in the management of small CSF-leaks encountered during the procedure, is neither supported nor advised against^(1241,1242). Traditional craniofacial surgery, on the other hand, is expected to lead to a significant wound infection rate. General complication rates have been reported to range around 40 %^(657,1243,1244). Fortunately, this scale of complications has decreased over the years and this decline is mostly attributed to the reduced number of postoperative infections due to the consequent administration of a broad-spectrum perioperative antibiotic regime in addition to other measures e.g. the preference to utilize vascularised tissues for reconstruction procedures⁽¹²⁴³⁻¹²⁴⁶⁾.

Skull base surgery for tumours usually leads to “Type II – surgical wounds” (“clean-contaminated wounds” due to disruption of the nasal mucosa)^(1247,1248) in contrast to e.g. “Type I – wounds” of neurosurgical craniotomy⁽¹²⁴⁹⁻¹²⁵¹⁾. According to general principles, antibiotic prophylaxis should be started ½ hour prior to any incision – specific indication provided. Prolongation of medical therapy depends on the duration of surgery in relation to the pharmacology of the antibiotic drug and also on specific features relating to the patient and the wound area^(1252,1253). Preoperative nasal swabs are not helpful to determine antibiotic therapy^(1246,1254). The rate of infection

does not seem to be dependent on prior irradiation, age or specific pathology⁽¹²⁴⁴⁾.

Literature focusing on the specific needs of endonasal skull base surgery is still rare and the evidence is low. The discussion on optimum therapy is analogous with that for classical craniofacial interventions but the choice of antibiotic and duration of treatment varies from case series to case series in craniofacial surgery and is often not explained. Exclusive administration of a broad-spectrum cephalosporin may be described as ‘first choice’; alternative regimens are based on cephalosporin + vancomycin, cephalosporin + aminoglycoside, cefuroxime + metronidazole, aminoglycoside + vancomycin, ciprofloxacin + teicoplanin or triple antibiotic therapy like “CMV” = ceftazidime + metronidazole + vancomycin^(481,1243-1245,1255-1257). Antibiotic treatment is initiated before surgery and is continued for at least 48 hours – prolongation for around 10 days is advocated depending on the duration of nasal packing or as an adjunctive measure in transient CSF-leakage^(478,1244,1255). Antimicrobial therapy may be supplemented by irrigation of the surgical cavity intraoperatively applying bacitracin or streptomycin⁽¹²⁵⁵⁾.

Postoperative bacterial meningitis may be anticipated in < 2 % of major endonasal skull base procedures, irrespective of antibiotic prophylaxis^(342,1247). According to the literature, monotherapy is preferred referring to e.g. cefazoline or ceftazidime. Alternative single-agent antibiotic regimes are based on amoxicillin-clavulanate, in case of suspected allergy vancomycin or clindamycin may be administered^(342,639,1098,1111,1240,1247). Certain high risk patients are subjected to an exceptional two drug therapy with ceftazidime + amikacin⁽¹²⁴⁷⁾.

Calculated antibiotic therapy may be given for 24-48 hours only^(845,1240,1247). Other regimens initiate therapy starting 3 days before surgery and extend it for 7 to 14 days while nasal packing is in place^(327,639,1096,1155). As a supportive measure, soaking of all reconstruction materials in antibiotic solution prior to insertion is advised^(640,711). Intraoperatively, frequent saline irrigation is done and use of vascularised flaps for reconstruction is preferred. In the postoperative period, special cleaning and debridement is undertaken and gentamycin nasal spray is sometimes advocated beginning 2 weeks after surgery. Postoperative CSF-leaks should be addressed immediately^(342,1240).

13. Adjunctive therapy for sinonasal and skull base tumours

13-1 Radiotherapy

13-1-1 External radiotherapy

Interpretation of results of treatment in general and radiotherapy in particular for sinonasal cancers is very complicated due to the high variety of histology, biological behaviour, the site and the extent of the disease. Moreover, due to the low incidence of these tumours, large series of homogenous patients are very rare to non-existent. This all makes comparison and analysis of the role of individual treatments difficult.

It is generally accepted that most sinonasal cancers are radiosensitive and that radiotherapy results in a success rate of about 35% as single-modality treatment^(173,1258). The radiosensitivity largely depends on the histology and growth rate of the tumour.

However, there is a consensus that the primary treatment of choice for most sinonasal cancers is, whenever possible, complete surgical resection followed by postoperative radiotherapy – with or without chemotherapy^(173,1259). The added value of radiotherapy to the surgical resection can be estimated at 10% on local control rates as well as improvement in survival (ranging from 5% to 50%) after 5 years^(1258,1260-1265).

To list specific data on treatment techniques is difficult since the treatment itself is also determined by variables such as the histology and the extension, both of which also determine the outcome. Specifically, in the large stage III/IV carcinomas multimodal treatment improves the outcome⁽¹²⁶¹⁾ and this is irrespective of the surgical margin status. In inoperable/unresectable cases the results with radiotherapy as single treatment modality are poor as expected, but may still reach 15 to 20%⁽¹²⁶⁶⁾.

The classical radiotherapy regimen consists of repeated doses of 1.8 to 2.0Gy, 5 days per week, during 6 to 7 weeks resulting in a total dose of 60 to 70Gy.

Radiotherapy has side effects including acute and late toxicity and long term complications^(174,1260,1263,1267-1271). The most important and most relevant traditional side effects for sinonasal cancers can be loss of smell, which is present in almost 100% of patients, possibly due to a combination of causes, mucositis with dryness and crust formation of the nasal mucosa, orbital complications including conjunctivitis, keratitis, retinopathy, optic neuropathy with vision loss and brain necrosis. Hypopituitarism may rarely occur resulting in clinical hormonal disturbances⁽¹²⁷²⁾. A secondary concern related to the toxicity of radiotherapy is underdosage in regions of risk, compromising the long term local control and survival rates.

To reduce these complications, improvements in radiotherapy have been developed and now are already integrated in the treatment regimens in most western countries. Three dimensional radiotherapy (3D-CRT)⁽¹²⁷³⁻¹²⁷⁵⁾ was the first major improvement and currently intensity modulated radiotherapy (IMRT) has become the ‘gold standard’ for radiotherapy. Using intensity-modulated radiotherapy (IMRT), the high-dose areas, which can be sculpted around the target volumes, with steep dose fall-off immediately outside these regions.

IMRT reduces significantly the risk for acute and chronic ocular toxicity and therefore prevents irreversible late optic nerve damage^(1274,1276-1282) (Table 13.1). However, these new developments in radiotherapy have not yet been shown to offer an improved oncological outcome^(1267,1273,1276-1279,1281).

13-1-2 Intraoperative Brachytherapy

Intraoperative high-dose-rate brachytherapy has been reported in a limited number of patients with locally advanced and/or recurrent paranasal sinus cancers. There are some results, but the application is confined to a limited number of centers^(1283,1284).

Table 13.1. Acute and chronic toxicity and optic neuropathy associated with IMRT.

Reference	N	acute tox(grade 3/4)*		chronic tox(grade 3/4)**		optic neuropathy***	
Duthoy 2005 ⁽¹²⁷⁶⁾	39	8	(21%)	6	(15%)	3	(8%)
Combs 2006 ⁽¹²⁷⁷⁾	46	2	(4%)	0	(0%)	0	(0%)
Dirix 2007 ⁽¹²⁷⁹⁾	21	0	(0%)	0	(0%)	0	(0%)
Daly 2007 ⁽¹²⁷⁸⁾	36	6	(17%)	2	(6%)	0	(0%)
Hoppe 2008 ⁽¹²⁸⁰⁾	37	3	(8%)	0	(0%)	0	(0%)
Madani 2008 ⁽¹²⁸²⁾	84	4	(5%)	6	(7%)	1	(1%)
Total	263	23	(9%)	14	(5%)	4	(2%)

*Acute toxicity according to the Common Toxicity Criteria (CTC version 3.0) published august 2006, available on internet at

http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf. Grade3/4 indicates at least severe toxicity affecting active daily life.

**chronic toxicity indicating adverse events occurring greater than 90 days after radiation therapy, according to the RTOG/EORTC morbidity scoring scheme available on internet at <http://www.rtog.org/members/toxicity/late.html>

***visual acuity impairment not caused by other ocular toxicity.

13-2 Chemotherapy

13-2-1 Systemic chemotherapy

There is evidence that adjuvant chemotherapy concurrent with radiotherapy (concurrent chemoradiotherapy) can be beneficial for the patient in specific indications. Survival is improved by 40%⁽¹²⁸⁵⁻¹²⁸⁷⁾.

In the context of palliative treatment of metastases, both radiotherapy and chemotherapy may be indicated depending on the tumour histology, the location and number of metastases and the related symptoms.

13-2-2 Concurrent chemoradiotherapy

There are some positive, preliminary data on concurrent chemoradiotherapy in paranasal sinus malignancies. Experience is limited to advanced squamous cell carcinoma⁽¹²⁸⁸⁾ and sinonasal undifferentiated carcinoma⁽¹²⁸⁹⁾.

13-2-3 Local chemotherapy

Local application of 5-Fluorouracil (5-FU) in the treatment of adenocarcinoma of the sinuses was introduced by Sato et al.⁽¹²⁹⁰⁾: Minimally invasive transantral clearance followed by topical chemotherapy with 5-FU has also been used in the Netherlands by Knegt et al.^(652,1291) with excellent success. After an extended ethmoidectomy through a Caldwell-Luc approach, the cavity was packed with ribbon gauze impregnated with 5% 5-FU cream. On a regular weekly or twice weekly basis, the gauze was removed and debriding of necrotic tissue was performed under general anaesthesia or under local anaesthesia with analgesia and sedation. The cavity was then packed again with 5-FU impregnated gauze. Five year disease specific survival rates and local control rates of 78% and 87% have been reported⁽⁶⁵²⁾. This treatment however is not always well tolerated by the patients and has a high morbidity rate: orbital inflammation (40%) and CSF leakage (8%). These results have not been reproduced by many authors⁽¹²⁹²⁾.

13-3 Specific tumours

13-3-1 Adenocarcinoma

These are not highly radiosensitive but postoperative radiotherapy is part of the standard treatment protocol in many centres. There is a positive effect of cisplatin containing chemotherapy in 40% in intestinal type adenocarcinoma⁽¹²⁹³⁾.

13-3-2 Malignant melanoma

The use of radiotherapy is still somewhat controversial but may prevent local recurrence^(734,1294). Historically a treatment protocol using a reduced number of high dose fractions was frequently used. Now the standard radiotherapy protocol is 60-70Gy using daily 2 Gy fractions. Local control rates are good, but recurrence usually occurs. Yanagi et al.⁽¹²⁹⁵⁾ reported on proton beam irradiation with good results in a series of 72 patients with mucosal malignant melanoma. Results were

superior to conventional radiotherapy with 5 year disease survival of 39.6% and local control rate of 84.1%. Chemotherapy is mostly used in the palliative setting of disseminated disease although response rates are poor⁽¹²⁹⁴⁾.

13-3-3 Olfactory neuroblastoma

Standard treatment of olfactory neuroblastoma includes surgery and radiotherapy^(235,254,689). Radiotherapy specifically reduces the local recurrence rates. Only for Kadish C cases there are arguments for chemotherapy⁽²³⁵⁾. There are preliminary reports of minimally invasive approaches with a combination of endoscopic surgery and gamma knife radiosurgery documenting a good post-operative quality of life^(239,703).

13-3-4 SNUC (sinonasal undifferentiated carcinoma)

The optimal management remains unclear since most series contain less than 20 patients and long term follow-up is only rarely reported. Because of the frequency of positive lymph nodes at presentation (up to 30%) and the frequency of distant metastasis, there is an important role not only for radiotherapy but also for chemotherapy in the initial treatment plan^(257,1296-1298).

13-3-5 Neuroendocrine carcinoma

The proposed treatment plan for neuroendocrine carcinoma is a combination of chemotherapy, radiotherapy and surgery^(254,1299).

13-3-6 Small cell carcinoma

Small cell carcinoma treatment consists of a combination of chemotherapy, radiotherapy and surgery⁽²⁵⁴⁾.

13-3-7 Squamous cell carcinoma

Due to the frequency of cervical lymph node metastases, irradiation of the neck should be considered in the initial treatment plan for advanced squamous cell carcinoma.

13-3-8 Adenoid cystic carcinoma

In cases of adenoid cystic carcinoma, radiotherapy should be used after surgery since it reduces local recurrence rates⁽¹⁷⁶⁾.

13-3-9 Pituitary Tumours

As pituitary adenomas are located close to critical neural structures in the sellar and suprasellar regions such as optic nerve, chiasm, cavernous sinus with its brain nerves or pituitary gland, side-effects of conventional radiation treatment include impairment of neurocognitive function, visual dysfunction from optic neuropathy, stroke, and damage to other cranial nerves. Recent review papers on stereotactic radiosurgery⁽¹³⁰⁰⁻¹³⁰³⁾ found Gamma knife associated with a less-radiation exposure, thus reducing the risk for new endocrine deficits or cognitive decline. The most common adverse effect of SRS in patients with pituitary tumours is hypopituitarism with an incidence of 0 to 36%. Growth control of pituitary adenomas

(functioning and non-functioning) is extremely high (82 to 98%) but normalization of hormone overproduction can vary considerably⁽¹³⁰⁴⁾. GKRS can be recommended as adjunctive therapy for this type of tumour in case surgical treatment is incomplete.

13-3-10 Meningiomas

Many meningiomas cannot be completely resected without significant morbidity. Due to the delicate anatomy and the high rate of cranial nerve injuries with aggressive surgery, stereotactic radiosurgery is an important adjunctive therapy after subtotal tumour removal. Review articles^(1300,1305,1306) found 5-year progression-free survival (PFS) in 87% to 98% of cases. Furthermore, even the 10-year tumour control rate for WHO Grade I tumours was 87%. The 5-year control rates for Grades II and III was approximately 30% and 10%, respectively. Treatment-related complications occurred in 2.5% to 13% of cases. Typical toxicities include symptomatic oedema following treatment or transient injury of adjacent cranial nerves. Vascular complications occur rarely. The success of SRS has led to a shift in the treatment paradigms from radical surgery to a combined approach, especially for large tumours in eloquent regions with a planned sub-total tumour resection and radiosurgery. Mathiesen⁽¹³⁰⁷⁾ established the term “Simpson grade 4 gamma”. Thus, tumour control with acceptable morbidity can be achieved for residual or recurrent meningiomas⁽¹³⁰⁸⁾.

13-3-11 Haematological disorders and sarcomas

The treatment of haematological and lymphoid malignancies such as Natural Killer, T-cell lymphoma, Hodgkin and non-Hodgkin lymphoma localization within the paranasal sinuses and plasmacytoma is out of the scope of this overview.

The treatment of sarcomas, such as rhabdomyosarcomas and chondrosarcomas, will not be discussed in detail.

All patients with head and neck malignancies should be seen in a multidisciplinary clinic before deciding treatment protocols.

13-4 Stereotactic Techniques

Definition

Stereotactic radiosurgery (SRS) is a therapeutic modality that involves radiosurgical techniques including the Gamma Knife (GKRS), LINAC and Cyberknife. SRS combines stereotactic localization techniques with radiation physics to deliver energy (Gamma rays and X-rays) to an imaging defined target. The specific benefit is achieved by an inherent steep radiation fall-off thus protecting adjacent brain tissue from radiation induced injury. SRS is usually limited to smaller tumours (< 3cm diameter). The technique represents a conformal (usually single fraction) radiation delivery that can also be offered to patients with significant comorbidity. SRS has shown to be associated with a low risk of complications. Short hospitalisation compared with other techniques is a further advantage. There is growing evidence that a combination of judicious subtotal

surgery followed by SRS is beneficial for otherwise untreatable tumours. SRS can and should be considered for the treatment of circumscribed residual and recurrent tumours not exceeding 3 cm diameter⁽⁸⁵³⁾.

Malignant Sinonasal Tumours

Olfactory neuroblastoma

There are promising reports of minimally invasive approaches with a combination of endoscopic surgery and Gamma Knife Radiosurgery documenting a good post-operative quality of life^(239,703). Due to a rare incidence of olfactory neuroblastoma, patient numbers as well as long term results are still limited in the recent literature and need to be further investigated in the future.

Other Malignant Tumours

The histological variety of malignant sinonasal tumours is extremely high and therefore no large series of these tumours has been published to date. Accordingly, SRS studies in respect of these tumours do not exist. However, malignant brain tumours such as metastasis are frequently treated by GKRS. Large prospective studies (class 2 data) and retrospective studies (class 3 data) have been published. They provide evidence for the use of GKRS⁽¹³⁰⁹⁻¹³¹¹⁾. Therefore, GKRS has emerged as the sole initial management, or as a boost before or after whole brain radiation therapy (WBRT), as a widely practised treatment modality for brain metastasis. We conclude that GKRS can and should be considered for the treatment of remaining malignant sinonasal tumours after surgery.

Pituitary Tumours

Pituitary adenomas are often located close to critical neural structures in the sellar and suprasellar regions such as optic nerve, chiasm, cavernous sinus with its brain nerves or pituitary gland. Side-effects of conventional radiation treatment include impairment of neurocognitive function, visual dysfunction from optic neuropathy, stroke, and damage to other cranial nerves. SRS delivers a high dose of radiation, highly focused, in a single session. Instead of fractionated radiation, SRS requires 1 day versus 6 weeks. Recent review papers^(1300-1303,1312) found GKRS associated with a less-radiation exposure, thus reducing the chance of new endocrine deficits or cognitive decline. The most common adverse effect of SRS in patients with pituitary tumours is hypopituitarism with an incidence of 0 to 36%. Growth control of pituitary adenomas (functioning and non-functioning) is extremely high (82 to 98%) but normalization of hormone overproduction can vary considerably⁽¹³⁰⁴⁾. GKRS can be recommended as adjunctive therapy for this type of tumour.

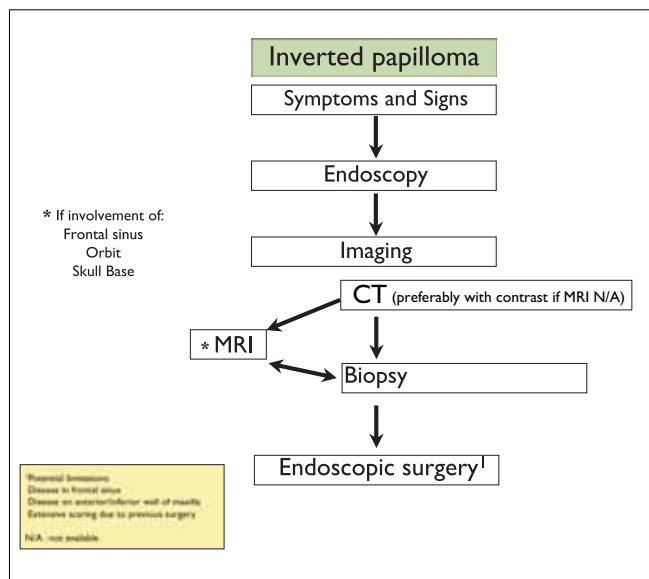
Meningiomas

Many meningiomas cannot be completely resected without significant morbidity. Due to the delicate anatomy and the high rate of cranial nerve injuries with aggressive surgery, SRS

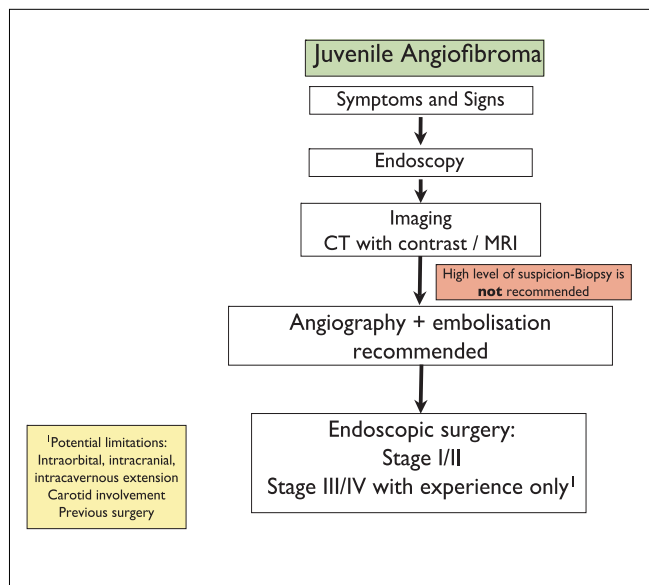
is an important adjunctive therapy after subtotal tumour removal. Radiosurgery is associated with a low risk of complications and a short hospitalisation compared with EBRT (external beam radiation therapy)⁽¹³¹³⁾. Review articles^(1300,1305,1306) found 5 year progression-free survival (PFS) in 87% to 98% of cases. Furthermore, even the 10 year tumour control rate for WHO Grade I tumours was 87%. The 5 year control rates for Grades II and III was approximately 30% and 10%, respectively. Treatment-related complications occurred in 2.5% to 13% of cases. Typical toxicities include symptomatic oede-

ma following treatment or transient injury of adjacent cranial nerves. Vascular complications occur rarely. The success of SRS has led to a shift in the treatment paradigms from radical surgery to a combined approach, especially for large tumours in eloquent regions with a planned sub-total tumour resection and radiosurgery. Mathiesen et al.⁽¹³⁰⁷⁾ established the term “Simpson grade 4 gamma”. Thus, tumour control with acceptable morbidity can be achieved for residual or recurrent meningiomas⁽¹³⁰⁸⁾.

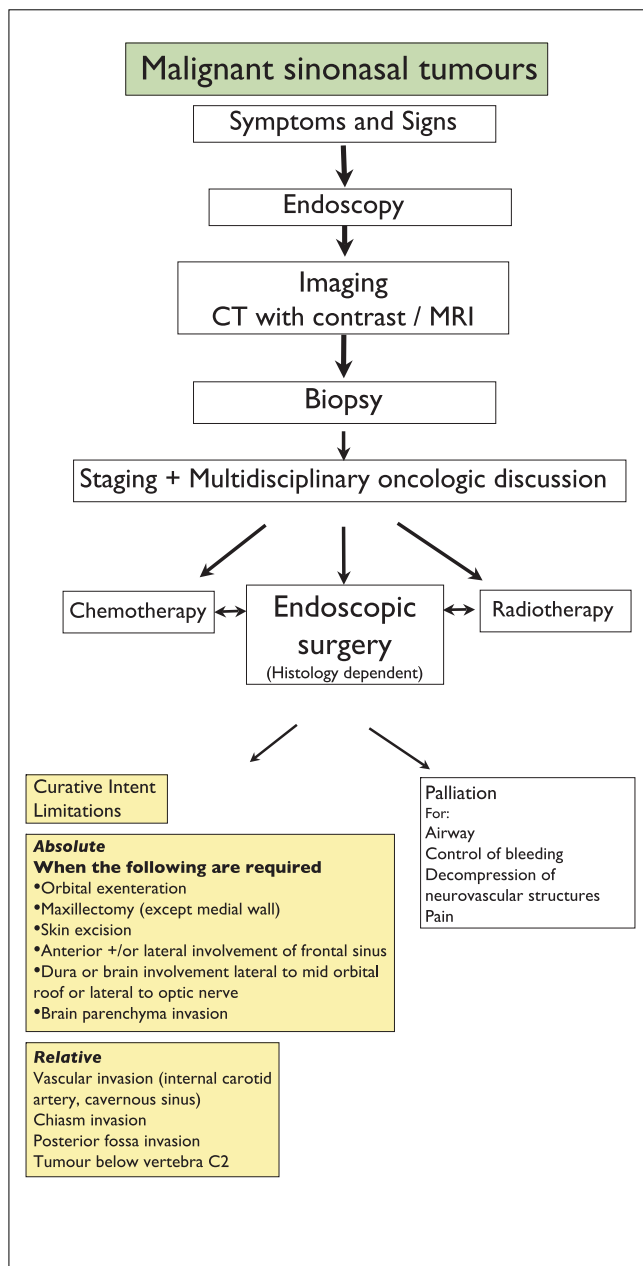
14. Management algorithms



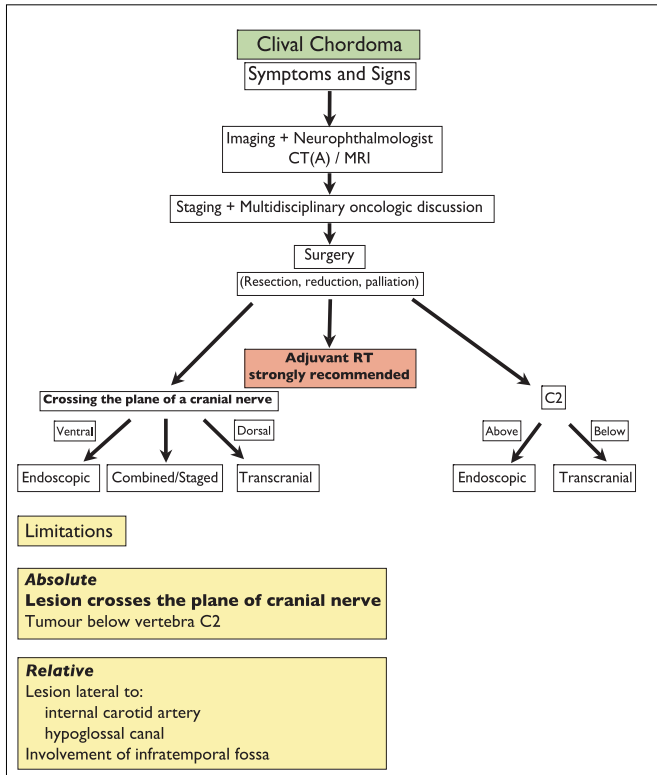
14.1. Management algorithm for inverted papilloma.



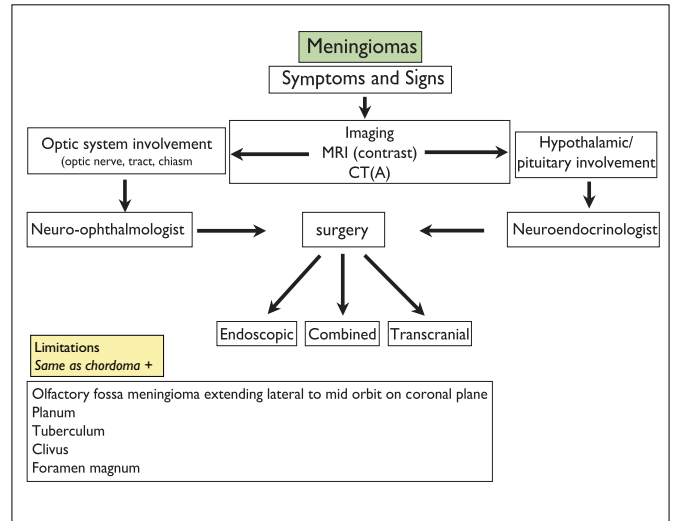
14.2. Management algorithm for juvenile angiofibroma.



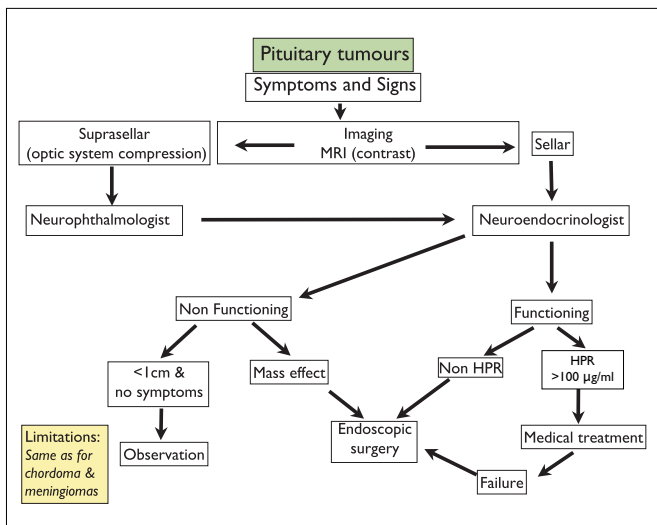
14.3. Management algorithm for malignant sinonasal tumours



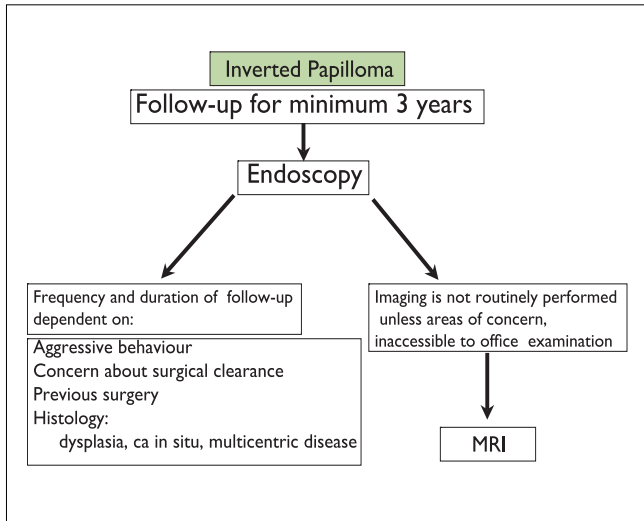
14.4. Management algorithm for clival chordoma.



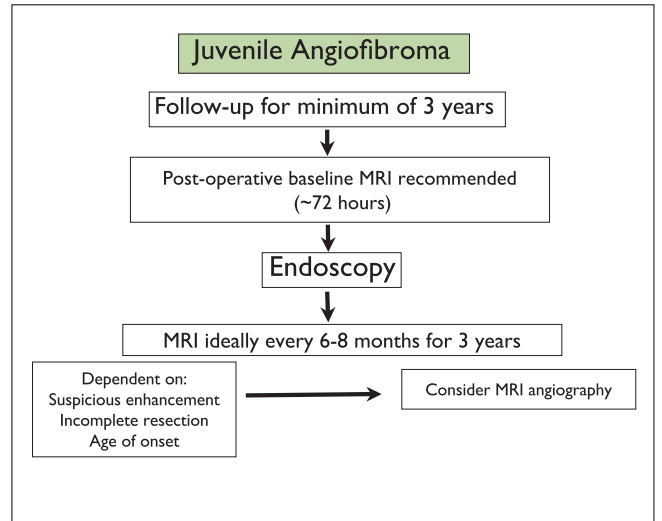
14.5. Management algorithm for meningioma.



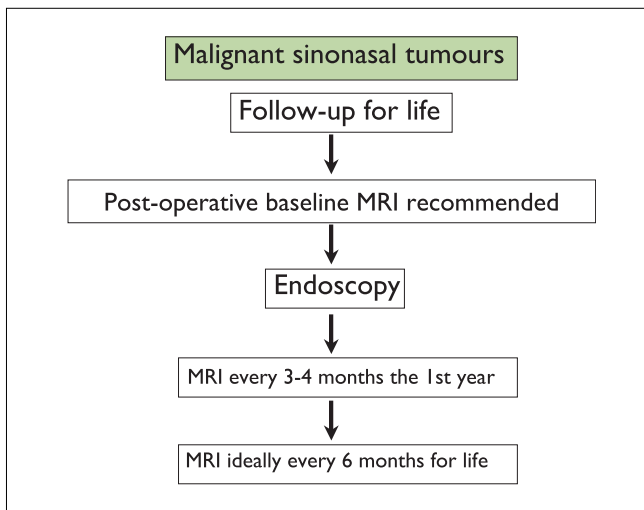
14.6. Management algorithm for pituitary tumours.



14.7. Follow-up algorithm for inverted papilloma.



14.8. Follow-up algorithm for juvenile angiofibroma.



14.9. Follow-up algorithm for malignant sinonasal tumours.

15. Research needs and future priorities

Although the introduction of endoscopic technology has had a profound impact on the management of sinonasal tumours, it is of utmost importance to realize that the endoscope is simply an enabling technology that may be utilized in any surgical corridor. The primary benefit of the endoscope is enhanced visualisation. Due to the optical properties of the endoscope, there is no loss of light and “line-of-sight” problems are avoided. Angled endoscopes allow visualisation around corners, minimizing displacement of normal tissues. The use of the endoscope for the removal of benign tumours such as inverting papillomas and angiofibromas has been introduced in the early 1990’s^(391,405,426,554,560,599,1314) and is now readily accepted by most sinus surgeons^(125,527,589,595,1148,1315,1316). Published series have demonstrated that endoscopic excision of properly selected tumours is associated with improved local tumour control and decreased morbidity compared to standard open approaches^(354,416,420,432,606,1317). The application of endonasal endoscopic techniques to the management of malignant sinonasal tumours has been much more controversial^(327,342,635,1097,1318). The primary concern is adherence to oncological principles: complete en bloc excision with adequate margins of the neoplasm. Secondary concerns include visualisation, the ability to achieve haemostasis and deal with vascular complications, and reconstruction.

Changes in clinical practice should be rooted in methodologically sound evidence. Surgical research as a whole has been criticized for a lack of randomized controlled trials (RCTs),

considered the “gold standard” of clinical research, and a reliance on less rigorous study designs such as the case series. The value of evidence based medicine is that it helps us to unravel the truth: High levels of evidence leading to high strength of recommendation will give us the confidence that what we consider to be the truth will also be the truth in the next decades. In general, surgical trials are the most difficult to perform and thus getting to high levels of evidence and thus a high strength of recommendation remains a challenge⁽¹³¹⁹⁾.

For the moment, the levels of evidence in endoscopic tumour surgery is mainly level 3 (case series) (Table 15.1) and level four (expert opinion). In the next decade, we have to reach to higher levels of evidence. Because of the paucity of the patient numbers, joint efforts will be crucial.

The main questions we have to tackle are:

1. The epidemiology of sinonasal tumours
2. Gathering data on large series of benign tumours, especially the more uncommon ones
3. Does clinical staging help to decide on the management of benign and malignant tumours?
4. Can histology/new molecular biology techniques predict tumour behaviour?
5. What are the treatment effects of endoscopic management in larger series of benign and malignant tumours?
6. What are the limits of endoscopic surgery?
7. Is “en bloc” resection necessary in sinonasal tumours?

Table 15.1. Case series of endoscopic surgery for sinonasal malignancy.

Author	Histology	N	Mean follow-up	Survival
Stammberger, 2000 ⁽⁶⁵⁸⁾	Olfactory neuroblastoma	6	57 months	100% 1 CFR
Goffart, 2000 ⁽⁶³³⁾	mixed	66	26 months	66%
Roh, 2004 ⁽⁶³⁴⁾	mixed	13	26 months	86% DFS
Shipchandler, 2005 ⁽⁶³⁷⁾	scc	7	31 months	91%
Poetker, 2005 ⁽⁴¹⁹⁾	mixed	16	17 months	recurrence rate 31%
Bockmuhl, 2005 ⁽¹³²²⁾	adeno, scc, on	29	65 months	78% 5yr survival
Castelnuovo, 2006 ⁽⁶⁹⁹⁾	mixed	18	25 months	61% 19.8 mnths
Bogaerts, 2008 ⁽⁶⁵⁹⁾	adeno	44	36 months	81% overall 73% local control
Dave, 2007 ⁽⁶⁴⁰⁾	mixed	17	? months	94% local control
Lund, 2007 ⁽⁶³⁵⁾	mixed	49	36 months	88% overall 68% DFS
Nicolai, 2007 ⁽⁶³⁹⁾	mixed	16	47 months	87% DFS
Podboj, 2007 ⁽⁶³⁶⁾	mixed	16	67 months	87% DFS
Gardner, 2008 ⁽³⁴⁰⁾	meningioma	34		
Nicolai, 2009 ⁽³²⁷⁾	mixed	184	34 months	91 % for EEA
		134		
	exclusive endoscopic approach (EEA)			

8. Can tumour-free margins be achieved during endoscopic resection with the same degree of accuracy as conventional open approaches?
9. And finally: are we able to organize randomized controlled trials to evaluate the possibilities of endoscopic management of malignant tumours compared to open treatment with regard to survival but also quality of life?

In the next decade we aim at reaching higher levels of evidence by combined efforts. The first goal will be to organize a large database of cases with benign and malignant tumours of the nose and sinuses. We will indicate which data of these cases are needed such as the sort of imaging, the history of the patient, the management, pre and postoperative evaluation and a tissue bank containing formalin and fresh frozen tissues of these patients. We now have series of relatively large numbers of patients with benign tumours like inverted papilloma (125,354,1320) and juvenile angiofibroma (562,568,589,595,1315,1321). Combining data on these benign lesions will enable to further predict optimal management based on staging and behaviour of the tumour.

The next step will be to combine efforts to have larger series of well defined patients with malignant tumours like adenocarcinoma, olfactory neuroblastoma and malignant melanoma with sufficient numbers for meaningful statistical analysis.

The final step will be to perform multicentre randomized controlled trials to compare management using an endoscope (“endoscopic”) compared to management not using an endoscope (conventional). An interesting issue is the necessity and possibility of “en bloc” resection in both “endoscopic” and conventional techniques. Questions, which could and should be answered are the survival rates in both groups in relation to morbidity and to determine the most relevant stratification variables.

The possibilities of grading tumours based on new molecular biology techniques and finally the tailoring of the treatment based on the behaviour of the tumour will further refine decision-making in the future.

16. Sinonasal and skull base tumour database

The indications of transnasal endoscopic surgery have been recently expanded to include the management of sinonasal malignancies. The increasing expertise in endoscopic surgery allows treatment by either an exclusive endoscopic approach or a craniendoscopic approach. It is therefore imperative to collect data on a multi-institutional basis according to agreed parameters, such as histological classification with TNM, and pre- and post-therapeutic clinical-radiologic assessment.

The sinonasal and skull base tumour database website has been developed to implement a complete visual database that details the clinical history of patients, and allows archiving of endoscopic and radiologic images. After choosing selected information, it is possible to carry out statistical analyses and to make detailed reports. The website permits collection of large series of patients, particularly of rare neoplasms, which will increase our knowledge of their biological behaviour.

Data will be stored on a secure central server that is password protected and uses an SSL certificate. The website has 8 sections: demographics, symptoms, extent of disease, radiology, histopathology, treatment, follow-up and statistics.

In the first section demographic data, histological diagnosis, pre-operative treatment, date of surgery, post-operative therapy, and outcome can be entered. Different histological diagnoses are listed according to the classification of the World Health Organization Classification of Tumours Pathology and Genetics of Head and Neck Tumours 2005 with minor modifications.

Nasal symptoms (blockage, rhinorrhea, epistaxis, pain, crusting) ocular symptoms (pain, swelling, displacement, visual dis-

turbance, epiphora) and neurologic symptoms (headache, paraesthesia, cranial nerves deficit) are found in the second section.

In the third section (extent of disease) the site of findings, intra-operative data, and analysis of surgical specimen together with radiologic data are summarized. In this section, endoscopic images may also be archived. In the fourth section, the radiologic images are collected. In the fifth section, all histopathological data, surgical assessment, and operative findings are stored. In sixth section information related to surgery, such as the name of the surgeon(s), the procedure performed, and complications are archived. The seventh section (follow-up) includes an evaluation of any post-therapeutic symptoms, and details of recurrence. In the last section, with the statistical analyses included in the webpage it is possible to evaluate the distribution of symptoms and extent of disease, to obtain survival curves according to the Kaplan-Meier method, and to study the impact on survival of different variables.

The website includes the possibility to generate an Excel file that includes all patient data so that single institutions may have their personal back-up and can analyze data on personal basis. Doctors from the same institution may work at the same time on the database. The complete database will not be visible to all institutions, but only to an independent statistical supervisor.

This is a unique opportunity for an international and interdisciplinary collaboration that will result in benefit for a wide range of patients with rare and life-threatening disease.

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