Endoscopic surgery for malignant sinonasal tumours: an eighteen year experience*

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Abstract

Introduction: Curative resection of malignant tumours of the skull base is increasingly undertaken endoscopically. Hitherto the diverse histology, rarity and long natural history have made it difficult to accrue statistically robust cohorts for comparison with conventional craniofacial resection. It is now possible to make such a comparison in a large personal cohort.

Method: Data on all cases of sinonasal malignancy undergoing endoscopic resection with curative intent over an eighteen year period were collected prospectively and analysed for survival and prognostic factors.

Results: There were 140 cases, 68 men and 72 women, aged 20-92 years (mean 63 yrs). Follow-up ranged from 6-184 months (mean 60 months). Eighteen different histopathologies were represented with olfactory neuroblastoma (36), malignant melanoma (33) and adenocarcinoma (19) being the commonest. Additional radiotherapy was given in 95 cases and chemotherapy in 49. Overall survival is 84% at 5 years and 69% at 10 years. Overall disease-free survival was 77% at 5 years and 56% at ten. Overall and disease-free survival at 5 (and 10) years is, respectively, 97% and 90% for olfactory neuroblastoma, 79% and 68% for adenocarcinoma and 56% and 39% for malignant melanoma.

Conclusion: These results show that endoscopic resection is an alternative to conventional craniofacial resection in selected cases.

Key words: endoscopic skull base surgery, anterior skull base, esthesioneuroblastoma

Introduction

An endoscopic approach has become the standard of care for the majority of conditions requiring surgery both within the nose and sinuses and at the interfaces with the orbit and skull base. Whilst the use of endoscopic techniques for benign neoplasia were well established, their application to malignant tumours remained controversial mainly due to concerns that the ability to undertake an adequate resection might be compromised. This combined with the rarity of these tumours, occurring in <1/100,000 of the population, their diverse histologies, variable natural histories and ability to recur many years later have made it difficult to accrue large series with sufficient follow-up to make statistically robust comparisons with 'gold standard' treatments such conventional craniofacial resection. However, it is clear from the literature [1,2] that this situation is changing and there are a number of centres where experience with both endoscopic techniques and sinonasal malignancy have facilitated prospective collection of data on cohorts of reasonable size for such assessment. This paper documents one such cohort.

Diagnosis is often made late because these tumours are asymptomatic or produce non-specific symptoms in their early stages and although there are several staging systems, none are ideal or universally utilised. However, generally stage at presentation is highly predictive of survival [2,3] and despite maximum treatment of the primary tumour, local, regional and distant metastases can occur and may do so after many years.

Materials and methods

Data collection

This study considers all patients with >6months follow-up undergoing endoscopic resection with curative intent for sinonasal malignancy in a single centre by the first author over an 18-year period, from 1996 to 2014, complete data on whom have been collected prospectively by the author. The diagnosis was confirmed by dedicated head and neck histopathologists, expert in sinonasal neoplasia. All patients underwent preoperative contrast-enhanced computerized tomography (CT) and magnetic resonance imaging (MRI) enhanced with gadolinium diethylenetriamine penta-acetic acid contrast of the nose, paranasal sinuses, entire intracranial compartment and neck together with imaging of the thorax and abdomen. Regular postoperative follow-up was undertaken using a rigorous protocol [1]. Age, sex, stage, surgical management, pre- and post-operative treatment, recurrence and survival data were recorded.

Treatment

All patients deemed suitable after multi-disciplinary pre-operative assessment, underwent endoscopic surgery with curative intent, details of which have been previously published [4] (Table 1) Wide-field mucosal clearance was performed according to the extent of disease, with resection of skull base whenever this was involved or adjacent to the tumour. If skull base was involved, adjacent dura was resected and in cases of olfactory neuroblastoma or when dura was affected, the olfactory bulbs and tracts were removed. Intracranial spread was divided into 3 groups: 1) tumour adjacent to or involving the bone of the skull base; 2) tumour adjacent to ± microscopic involvement of the dura which was resected or 3) tumour extending through the full thickness of the dura into the anterior cranial fossa.

Orbital periosteum was resected endoscopically if adjacent to or involved by tumour. Orbital involvement was divided into 3 groups: 1) none where the lamina remained intact; 2) tumour adjacent to ± microscopic involvement of orbital periosteum when periosteum was resected or 3) spread of tumour through the full thickness of the orbital periosteum confirmed on histological examination after resection of it and adjacent fat.

When deemed necessary, standard post-operative 3-field external beam radiotherapy to a dose of 55-65 Gy was given between 1996-2009. Since 2010, IMRT has been employed. The decision to give radiotherapy was based on previous published clinical experience regarding the histopathology together with adjuvant mainly cisplatin-based chemotherapy in selected cases. Specifically radiotherapy has been shown to be of significant benefit in olfactory neuroblastoma, squamous cell carcinoma, SNUC and rhabdomyosarcoma [2,3] but of less proven value in adenocarcinoma, malignant melanoma and chondrosarcoma

Table 1. Potential limitations for an entirely endoscopic approach where a combined conventional and endoscopic CFR may be considered.

Tumour through dura infiltrating falx/sagittal sinus and/or frontal lobe
Tumour extension lateral to mid-point of orbit
Wide dural involvement, especially in proximity to optic chiasm
And/or orbital clearance
Tumour through orbital periosteum to involve orbital contents eg fat, muscle, neurovasculature
Type of malignancy eg type of tumour which can embolise within orbit such as squamous cell carcinoma

[2,5,6].

Statistical analysis

Data was analysed using SPSS version 14.0 (IBM, Chicago, IL, USA) by the second author. Outcome measures were overall survival (OS) and disease free survival (DFS), also stratified by orbital and intracranial involvement. They were evaluated by Kaplan-Meier curves and statistical significance was calculated by the Mantel-Cox test. Cox regression analysis was used to identify any independent factors affecting overall survival. Univariate analysis included sex, previous radiotherapy, chemotherapy and/or surgery, subsequent radiotherapy, chemotherapy and/or surgery, T staging, orbital and intracranial involvement and histological type of tumour.

Results

One hundred and forty patients were treated surgically with curative intent from 1996 - 2014, 68 male (49%) and 72 female (51%) aged 20-92 years (mean 63 yrs).

Eighteen different histopathologies were represented with olfactory neuroblastoma (ON) (36 cases), mucosal malignant melanoma (MMM) (33 cases) and adenocarcinoma (AC) (19 cases) being the commonest (Table 2). The site of origin was predominantly nasal cavity (89 cases: 64%) or ethmoids (43 cases: 31%) with 2 cases each arising in and confined to the frontal or sphenoid and 4 in the maxillary sinus, all regarded as amenable to endoscopic excision.

Table 3 shows T staging when applied to all tumours, the majority being T1/T2. Only one patient had neck involvement at presentation. None presented with distant metastases. In keeping with the most recent AJCC staging [7], all melanomas have been staged as T3 or greater. However, it should be noted that the AJCC staging is not designed for application to non-epithelial tumours or those of lymphoid tissue, soft tissue, bone

Table 2. ESS for Malignant Sinonasal Tumours Personal series 1996-2014.

Histology	N	Range of FU (months)	Mean	SE
Olfactory neuroblastoma	36	6-162	77.6	10.7
Malignant melanoma	33	6-167	68.6	7.6
Adenocarcinoma	19	2-99	33.1	5.1
Other histologies	52	3-184	59.7	6.1
Squamous cell carcinoma	9			
Haemangiopericytoma	8			
Chondrosarcoma	8			
Malignant schwannona	5			
Sinonasal undifferentiated carcinoma	5			
Lymphoma	4			
Rhabdomyosarcoma	2			
Leiomyosarcoma	2			
Transitional cell carcinoma	2			
Cylindric cell carcinoma	2			
Ewing's sarcoma	1			
Plasmacytoma	1			
Malignant fibrous histiocytoma	1			
Neuroendocrine carcinoma	1			
Adenoid cystic carcinoma	1			
TOTAL	140			

FU = follow up

Table 3. T staging of entire cohort [7] (n = 140).

	N	%
T1	57	41
T2	27	19
T3	41	29
T4	17	11

All N are M0 except one T3.

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dergone previous surgery, either via lateral rhinotomy (2 cases) midfacial degloving (2 patients), endoscopically (5 patients) or a craniotomy (2 patients). Of these 11, 3 had also received radiotherapy. Previous treatment did not adversely affect subsequent outcome (p > 0.1 for all treatments) though as the numbers are small, this may be a type II error.

Hospital stay ranged from 3-8 days, mean 4.5 days and most patients were readmitted as a daycase for removal of packing at 10-12 days. Follow-up ranged from 6 – 210 months (mean 60 months). The first type of tumour treated endoscopically was malignant melanoma from 1996 onwards but from 1998 all histologies were considered. This is reflected in the numbers performed each year with 8 cases being undertaken between 1996-2000, 41 between 2001-2005, 54 between 2006-2010 and 37 between 2011 and mid-2014 when this analysis was undertake equating to 10 cases each year during the last decade.

There were few peri- or post-operative complications and all were resolved without significant morbidity. These comprised three cases (2%) who required further packing for bleeding in the immediate post-operative period and cerebrospinal fluid leakage (3 cases = 2%), which unusually occurred 9 months, 1 and 4 years after initial treatment. These were successfully treated endoscopically. Epiphora occurred in 8 cases (6%), all of whom had received combined surgery and radiotherapy, and six of whom underwent successful endoscopic dacrocystorhinostomies. One patient developed pituitary insufficiency 5.5 years after combined surgery and radiotherapy.

Ninety-five (68%) patients received post-operative radiotherapy and 49 (34%) had additional chemotherapy. The radiotherapy was given to 33 patients with ON, 20 patients with MMM, 14 adenocarcinomas and 27 of the 52 other individuals. This was combined with chemotherapy in 25 ONs, 4 cases each of squamous cell carcinomas, MMM and sinonasal undifferentiated carcinoma (SNUC), lymphoma, 2 cases each of poorly differentiated adenocarcinoma, rhabdomyosarcoma and leiomyosarcoma, one

or cartilage. This would include 38 patients in this cohort who are considered separately in terms of survival.

Orbital periosteum was resected and repaired in 12 (9%). In this series no involvement of muscle was encountered on frozen section and thus no formal orbital clearance was undertaken. Dura was resected and a skull base repair undertaken in 35 (25%) cases which included 20 olfactory neuroblastomas for purposes of staging.

Prior to referral to our unit, 115 patients were untreated and 25 patients had received and failed previous treatment. Eight patients had been treated with radiotherapy and 9 had received both chemotherapy and radiotherapy. Eleven patients had un-

Table 4. Five and 10 year % survival for whole group and individual histologies.

	N	Overall survival		Disease-free survival	
		5yr	10yr	5yr	10yr
Whole group	140	84%	69%	77%	56%
Olfactory neuroblastoma	36	97%	97%	90%	90%
Adenocarcinoma	19	79%	72%	68%	61%
Malignant melanoma	33	56%	0%*	39%	0%*

*Survival for MM at 91 months 24% (overall) and 17% (DFS)

case each of plasmacytoma and Ewing's sarcoma.

Fifteen cases (11%) have undergone additional endoscopic surgery, in 6 cases on multiple occasions, for local recurrence during the course of follow-up (MMM (11 cases), ON (2 cases), AC (2 cases) and chondrosarcoma (1 case)). These occurred within the surgical cavity at a wide range of locations of which 2 involved the skull base (ON [1], MM [1]) and one the orbit (CS). Local recurrence occurred within the first 12 months in most cases but one ON recurred at 39 months and one AC at 8 years. Four cases were converted to formal craniofacial resection at 6, 10, 12 and 13 months for ON (2 cases), AC and transitional cell carcinoma due to dural/intracranial recurrence deemed to be beyond what could be safely encompassed by an entirely endoscopic approach.

Routine initial staging and regular follow-up MRI included the neck, together with ultrasound and fine needle aspiration for any cervical lymphadenopathy. As a consequence, nine patients have had unilateral ipsilateral neck dissections performed (1 ON prior to ESS and 4 other ON cases at 10, 14, 18 and 26 months

and 4 cases of MMM between 5 and 50 months) and one patient with ON had bilateral neck dissections (ipsilateral at 2 and contralateral at 4 years) after the initial ESS. Of these patients, two thirds had no recurrent disease at the primary site. Additional radiotherapy to the neck was given to 4 patients. Distant metastases occurred in 13 patients, 7 MMMs, 2 poorly differentiated ACs and one case each of transitional cell carcinoma, adenoid cystic, ON and leiomyosarcoma; 11 have succumbed and 2 are alive but expected to die of their disease, both MMMs.

Ninety six patients are alive and well, 16 alive with recurrence, 20 dead of disease and 5 have died of intercurrent disease. Three have been lost to follow-up. Those alive with local recurrence comprise MMM (9), AC (2), ON (2), chondrosarcoma (2) and squamous cell carcinoma (1). Thirteen patients with MMM, 2 ACs and 1 each of transitional cell carcinoma, ON, adenoid cystic carcinoma, SNUC and leiomyosarcoma have died of disease. Of those 15 undergoing further endoscopic surgery for local recurrence, control thus far has been achieved in 10 (but not in 5 of the melanomas). Of those undergoing formal craniofacial resection, 3 have survived but the patient with transitional carcinoma succumbed 11 months later. Of those undergoing neck dissection, all ON patients are alive but all MMM patients have died.

Overall crude survival is 84% at 5 years and 69% at 10 years. Overall disease-free survival was 77% and 56% at 5 and 10 years. Overall and disease-free survival at 5 years is, respectively, 97% and 90% for ON, 79% and 68% for AC and 56% and 39% for MMM (Table 4). Mean survival times are shown in Table 5.

When overall survival and disease-free survival for ON, AC, MMM and the rest of the group are compared, ON has the best outcome, followed by AC, the miscellaneous group of mainly non-epithelial histologies whilst MMM, as anticipated comes last (Figures 1-4).

Table 5. Mean overall and disease-free survival for whole group and individual histologies.

	N	Mean overall survival (months)	SE	CI	Mean disease-free survival (months)	SE	CI
Whole group	140	141	7.21	26.7-1551	120	7.5	105.1-134.6
Olfactory neuroblastoma	36	162	4.5	153.4-171.2	150	7.9	134.2-165.2
Adenocarcinoma	19	130	13.5	103.5-156.7	118	14.1	90.5-145.8
Malignant melanoma	33	58	8.0	42.4-73.9	47	7.3	32.7-61.4

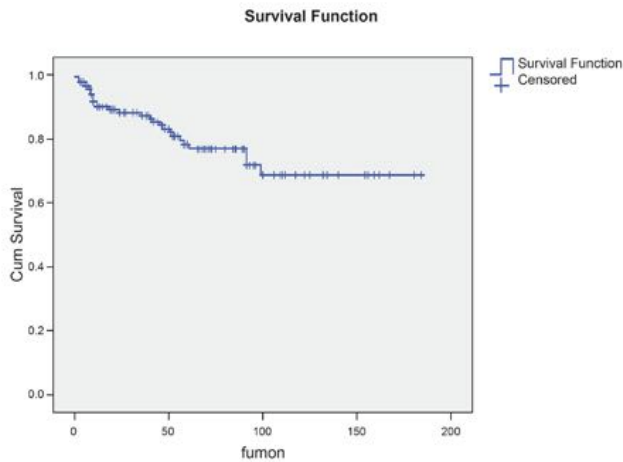SE:standard error; CI: confidence interval

Figure 1. Kaplan-Meier graph of overall survival of 140 cases of sinonasal malignancy.
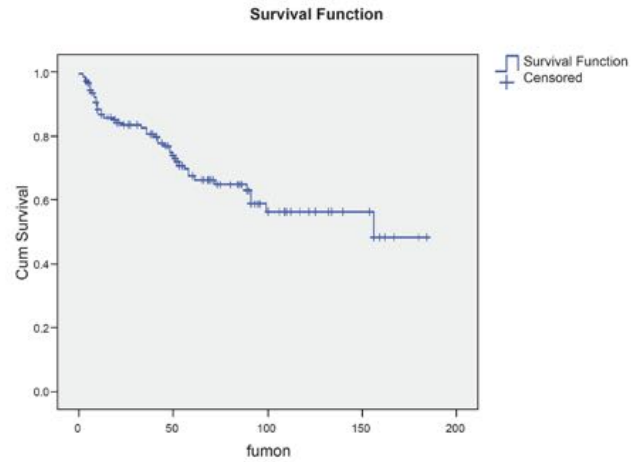

Figure 2. Kaplan-Meier graph of disease-free survival of 140 cases of sinonasal malignancy.
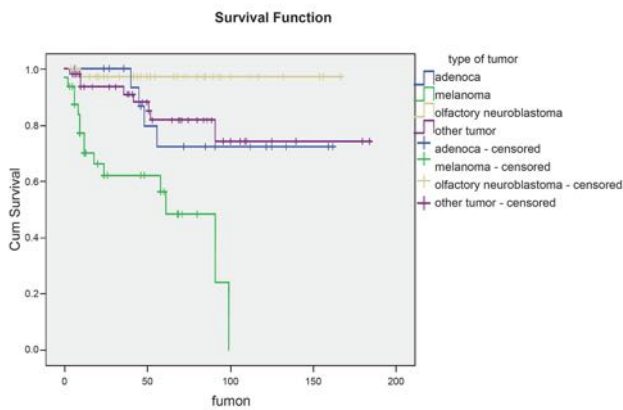

Figure 3. Kaplan-Meier graph of overall survival comparing adenocarcinoma, malignant melanoma, olfactory neuroblastoma and the remaining other tumour histologies.
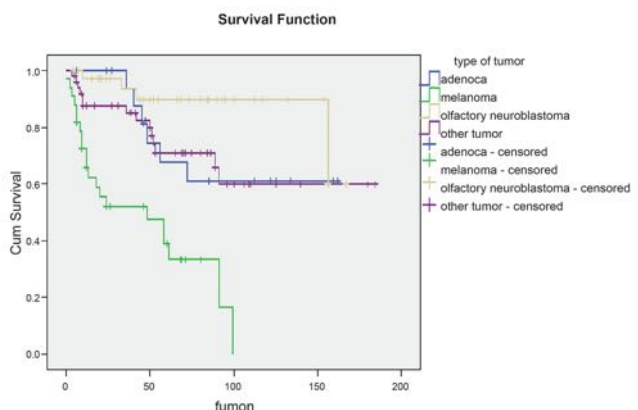

Figure 4. Kaplan-Meier graph of disease-free survival comparing adenocarcinoma, malignant melanoma, olfactory neuroblastoma and the remaining other tumour histologies.

A Cox regression analysis on the entire cohort shows T stage to be the most significant prognostic factor affecting overall survival followed by previous surgery and orbital involvement (Mantel Cox p = 0.002, respectively). In addition to T stage, for AC and ON both extent of intracranial and orbital involvement are significant but for MMM none of these factors are significant.

Discussion

Since endoscopic techniques have been applied with curative intent, there have been many publications though the vast majority have been characterised by small numbers, mixed histologies and short follow-up. In 2010, the European Position Paper on the Endoscopic Management of Tumours of the Nose, Paranasal Sinuses and Skull Base [1] summarised the literature to date and called for collaboration in the prospective collection of data on these rare cases. Although this has met with some success,

there are still relatively few publications of large cohorts with long-term follow-up. This paper builds on previous publications from a single centre, which have also allowed comparison with alternative open approaches such as craniofacial resection (CFR) and lateral rhinotomy. In keeping with these and the experience of other units [4,8-13], one may conclude that endoscopic approaches may be undertaken in cases of appropriate histology and extent with the expectation of equivalent results and in many cases, reduced morbidity and hospital stay.

This cohort, in common with others, comprises a wide range of histologies but is sufficiently large to include larger groups of individual tumour types such as ON, AC and MMM, which may be analysed separately and demonstrate that ON has the most favourable outcome and MMM the worst. In a recent study in which ON treated with endoscopic surgery was compared to

CFR, there was significantly improved OS in the endoscopic group with 5-year survival of 100% compared to 76.5% in the CFR group directly attributable to the less advanced disease being treated endoscopically, as might be expected [3]. When tumours of similar stage were compared, survival was equivalent. A meta-analysis of 361 cases of ON reported a significantly higher survival rate for endoscopic versus open surgery, related to tumour extent [14]. Similarly in a series of 35 patients, Song et al reported significantly higher 5-year disease free survival in those who underwent endoscopic resection when compared to open surgery [15].

The same situation has been demonstrated for AC and MMM in literature reviews and a number of recent endoscopic series [5,8,16-21]. However, in the case of sinonasal MMM, endoscopic resection may even confer survival benefit irrespective of tumour extent [6]. Since 1996, endoscopic resection had been employed irrespective of tumour extent yet when this was compared to open approach resection, there was a significantly improved overall survival in the endoscopic patients (Mantel-Cox p = 0.013). They had a longer median overall survival (59 month compared to 18 months for open approaches), longer local control (50 months v 18 months and longer median disease free survival (36 months v months versus 16 months). The precise explanation for this difference is unclear but may relate to the reduced morbidity of the endoscopic surgery compared to open procedures in elderly patients with an immunologically capricious disease and has been observed by others [22].

Generally the complication rate and overall morbidity of endoscopic procedures compares favorably with the open procedures such as CFR [3,11,23,24] and those that do occur, such as CSF leaks or epiphora are readily amenable to endoscopic repair. The late development of a CSF leak in 3 of our cases is unusual as only one occurred in association with a recurrence. However, late failure of endoscopic skull base repair has been reported, albeit rarely [25]. Advances in endoscopic techniques allow repair of large anterior skull base defects and are associated with low complication rates even though the extent of surgery is comparable to that of open procedures [1,4,26-28]. It is also possible to commence additional radiotherapy and/or chemotherapy within a few weeks of surgery which may be considered advantageous [29,30]. However, the use of radiotherapy may lead to a loss of smell which otherwise would be less affected than with conventional CFR [31].

In ON, radiotherapy has been shown to reduce local recurrence and improve prognosis so is recommended in all cases, irrespective of extent [32-35]. It is also well-established in squamous cell carcinoma, SNUC and rhabdomyosarcoma but evidence for its role in other tumours such as AC and MMM [5,6,22,36,37] is less

robust. Notwithstanding this, post-operative radiotherapy is often given and there is increasing use of intensity-modulated radiotherapy (IMRT) in the expectation of reducing damage to adjacent structures [38,39].

The TNM staging system may be applied to sinonasal tumours but it was largely designed for squamous cell carcinoma and modifications of this and other systems have been proposed for individual tumors such as ON and MMM [2,7,40,41]. The 7th edition of the AJCC Cancer staging manual recommends all mucosal malignant melanomas are staged T3 or greater in recognition of their aggressive behaviour [7]. Thus nearly two thirds of our patients are smaller tumours i.e. T1and T2, and the majority of the T3 tumours are MMMs in contrast to some other series of more extensive lesions.

Stage at presentation has been shown to be highly predictive of survival and the outcomes from our series support this with the exception of malignant melanoma [3,5,6,11,21,24,42,43]. In ON a meta-analysis of 26 studies (390 patients) showed significantly better 5-year survival for Kadish stage A tumours (72%) compared to stage B (59%) or stage C (47%) [32]. Lund et al. reported a 61% 5-year and 42% 10-year overall survival in 42 patients who underwent CFR for ON [33]. The vast majority of patients in this series are T1-3 and would therefore be anticipated to do as well as those undergoing CFR, as has been demonstrated in this analysis.

All patients with the exception of one ON in this series were N0 at presentation, though 9 developed cervical lymphadenopathy during follow-up. Cervical metastases are reported in approximately 10% of cases of sinonasal malignancy and confer a significantly worse prognosis. This was most common in ON and MMM and for this reason, imaging of the neck is undertaken pre- and post-operatively as part of routine follow-up [44]. Distant metastases to brain/dura, lung, liver, bone, spinal cord, liver and skin are rare at presentation but can occur, especially in the terminal stages of disease [2].

From a surgical perspective, the degree of intracranial extension and orbital involvement have been shown to be independent prognostic factors [24] and are also the determinants of whether an entirely endoscopic approach is possible. However, it should be noted that a combination of endoscopic and open techniques, is an alternative in tumours with moderate intracranial involvement [45,46].

Clearly it is still necessary to retain the open approaches in one's armamentarium for those tumours which present with extensive involvement of the orbit and intradural compartment or for those, as in 4 cases in this series, who develop further disease not amenable to a further endoscopic removal and who subse-

quently underwent conventional CFR.

Sinonasal malignancy may recur many years after initial treatment. The longest time to local recurrence in this cohort was 8 years (a case of AC) and in our entire series of ON 233 months [2]. This was not apparent during the early reported series of endoscopic patients but now that cohorts with follow-up of substantial duration are available, up to 16 years in this series, this problem can be shown to occur, confirming that life-long follow-up is required irrespective of the treatment.

This series supports the contention that endoscopic resection offers equivalent results to conventional external procedures. The lower complication rate and peri-operative morbidity together with shorter hospital stay make an endoscopic approach which adheres to oncologic principles a more than acceptable alternative in appropriate cases. However, all other aspects of pre- and post-operative care remain unchanged and life-long follow-up is mandatory with clinical examination and MRI. Prospective collection of data is also fundamental to our understanding of the natural history and management of these rare diseases.

Author contributions
VJL undertook the surgery and WIW undertook the statistical analysis of data. Both wrote the paper.

Conflict of interest
There are no conflicts of interest to declare, financial or otherwise. No funding was received.

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