# Clinical features and outcomes of skull base osteoradionecrosis in nasopharyngeal carcinoma patients: a systematic review and meta-analysis

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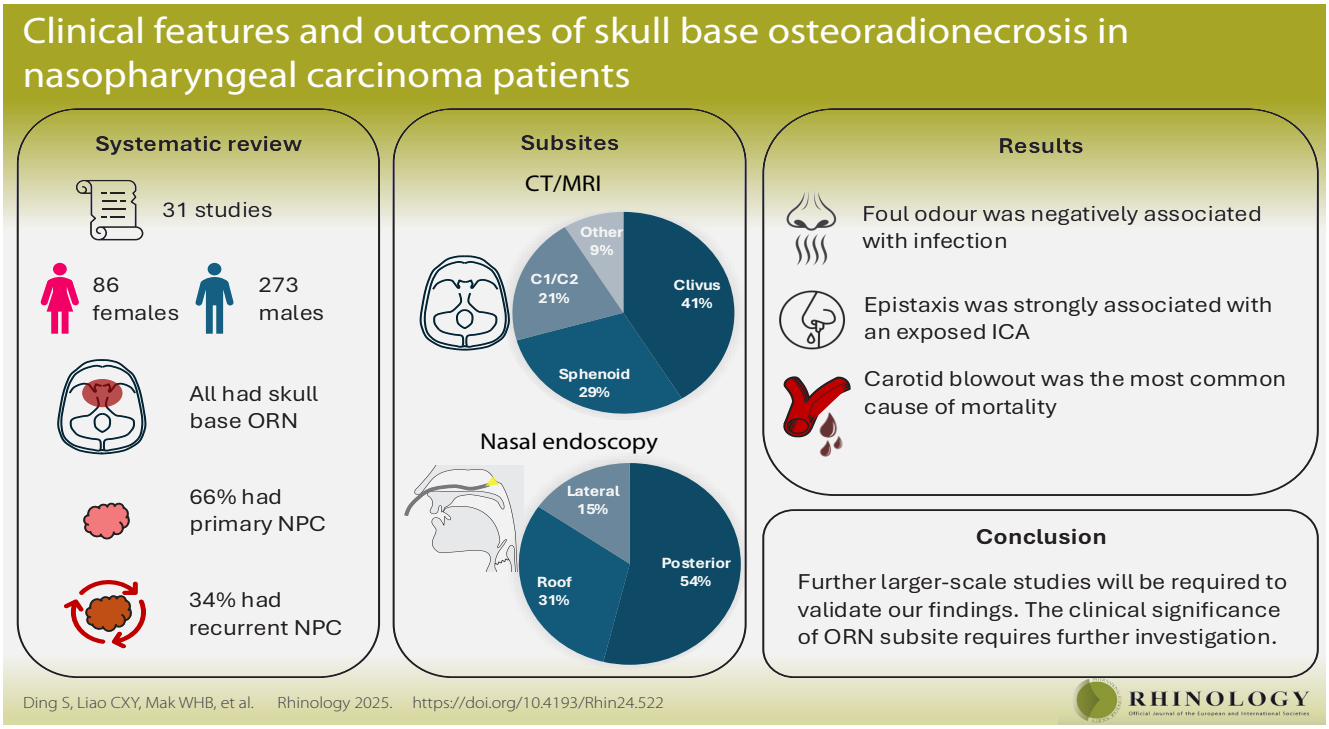


## Abstract

**Background**: Skull base osteoradionecrosis following radiotherapy for nasopharyngeal carcinoma is a potentially life-threatening complication. Assessing severity, prognosis and providing appropriate treatment for the condition can be clinically challenging. This systematic review evaluates factors associated with patient outcome.

**Methodology**: A literature search of PubMed, Embase, MEDLINE and Cochrane databases was conducted in August 2024. Data was extracted for patients with skull base osteoradionecrosis caused by nasopharyngeal carcinoma. Results were presented by narrative synthesis or with statistical analysis.

**Results**: 359 patients from 31 papers were included. The clivus and posterior nasopharyngeal wall were the most common subsites for osteoradionecrosis. We categorized subsites into posterior, roof and lateral areas. Subsite was not associated with ICA exposure or infection. Frequent symptoms include headache, foul odour and epistaxis. Foul odour was negatively associated with infection and epistaxis was highly associated with ICA exposure. The most common direct complication was CSF leak (18.2%), whereas the most common post-treatment complication was infection (43.8%). Carotid blowout was the most common cause of mortality (45.9%).

**Conclusions**: Foul odour and epistaxis may predict cases of skull base osteoradionecrosis complicated by ICA exposure and infection. Further research is necessary to assess the significance of ORN subsite as a prognosticator or guide to treatment.

**Key words**: nasopharyngeal, skull base, osteoradionecrosis, endoscopy, clivus

## Introduction

Osteoradionecrosis (ORN) describes the necrosis of bone after radiation damage [1], presenting as an area of exposed bone which does not heal and may also involve breech of skin or mucosal tissue [2]. Marx's "3Hs Theory" of hypovascularity, hypoxia and hypocellularity provides a classical description of events that lead to ORN [1]. Mandibular ORN following radiotherapy (RT) for head and neck cancer is the best described in the literature [3]. However, the skull base is another potential site for ORN, and is particularly associated with nasopharyngeal carcinoma (NPC) [4]. NPC is an epithelial tumour originating from the nasopharynx, rare in western parts of the world but prevalent in Southeast Asia [5].

Historical estimates of the rates of ORN in irradiated head and neck cancer patients were between 5-38%, however, advances in RT have reduced this to an estimated 2% risk [6]. Nevertheless, ORN still presents a substantial burden on patients and the healthcare system [7]. The clinical course is often unpredictable and may lead to potentially life-threatening outcomes if not treated appropriately [8].

Skull base ORN can be diagnosed through clinical history, nasal endoscopy and CT/MRI imaging of the skull base [9]. The most likely symptoms include foul odour, headache and epistaxis [9–13]. On nasal endoscopy, an area of exposed or sequestered bone in the nasopharynx can be observed [11,14–20]. There may be an associated infection [10,15,16,21] or exposure of the internal carotid artery (ICA) [9,11,15,17,20,22–26]. CT imaging at the level of the skull base would show a localized area of bony destruction and necrosis which may extend outwards and be associated with other findings, like pneumocephalus [27,28] or temporal lobe necrosis [29].

Treatments for skull base ORN can be divided into non-surgical and surgical modalities [4]. Besides general nasal care, like nasal irrigation, non-surgical treatments include systemic antimicrobials, hyperbaric oxygen therapy (HBO) [30] and the pentoxifylline-tocopherol-clodronate (PENTOCLO) treatment regimen [31]. Surgical treatment can be divided into endoscopic and open approaches. Endoscopic sequestrectomy of the necrosed bone is the mainstay of treatment for most cases of skull base ORN [4] but an open approach, such as a maxillary swing [25,26,29], transpalatal [25] or paramedian mandibulotomy [29] may be warranted in certain situations. The resulting defect is usually reconstructed, either with a local flap or a free flap. Surgery may also be performed for direct complications of ORN, such as for ORN associated craniocervical instability [19,32]. Prophylactic endovascular management of an exposed ICA or repair of a damaged ICA may be required if affected by ORN [11,20,22–24,29].

Skull base ORN is associated with a significant morbidity and mortality [4]. This may be a result of the disease process or a consequence of the high-risk nature of the surgery. Therefore, surgical intervention may not be desirable for milder cases of ORN. Surgery can pose a significant risk of infection, such as meningitis [19] and sepsis [23,33], and chronic issues such as choanal stenosis [10], fistulas [16] and CSF leak [29]. There is also potential for flap defects, haematomas and flap failure [26,29]. Endovascular treatment for ICA involvement is also associated with significant mortality due to carotid rupture and massive haemorrhage or in-stent thrombosis [24].

This systematic review aims to provide anatomical characterization of subsites affected by ORN, identify common features and to evaluate their significance on clinical outcome.

## Materials and methods

### Study selection

Inclusion criteria were as follows: 1) NPC patients with skull base ORN, 2) ORN subsite information, 3) Treatment and follow up details and 4) Articles available in English. ORN of other anatomical sites (such as mandibular ORN) or non-NPC patients were excluded. Systematic reviews, randomized control trials, case series and single case reports were considered in this study. Preprints and conference abstracts were excluded.

### Search strategy

An electronic search was conducted on PubMed, Embase, MEDLINE and Cochrane library databases. The literature search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [34]. The search strategy is listed in Table S1. Titles and abstracts were independently screened by two reviewers (S.D. and D.C.M.Y.) and selected for full-text review before inclusion.

### Data extraction

Data extracted revolve around five key themes:

1. General patient demographics, including age and sex.
2. Background information on NPC stage, treatment, recurrences and radiotherapy dose.
3. Clinical features of skull base ORN, including subsite, associated pathologies, symptoms and complications.
4. Treatment modalities for skull base ORN and rationale.
5. Time course and outcomes of ORN following treatment, including morbidity and mortality data.

Extracted information was collated and tabulated on Microsoft Excel. The data collected from different studies were compared and analysed wherever possible. Otherwise, data was presented using narrative synthesis.

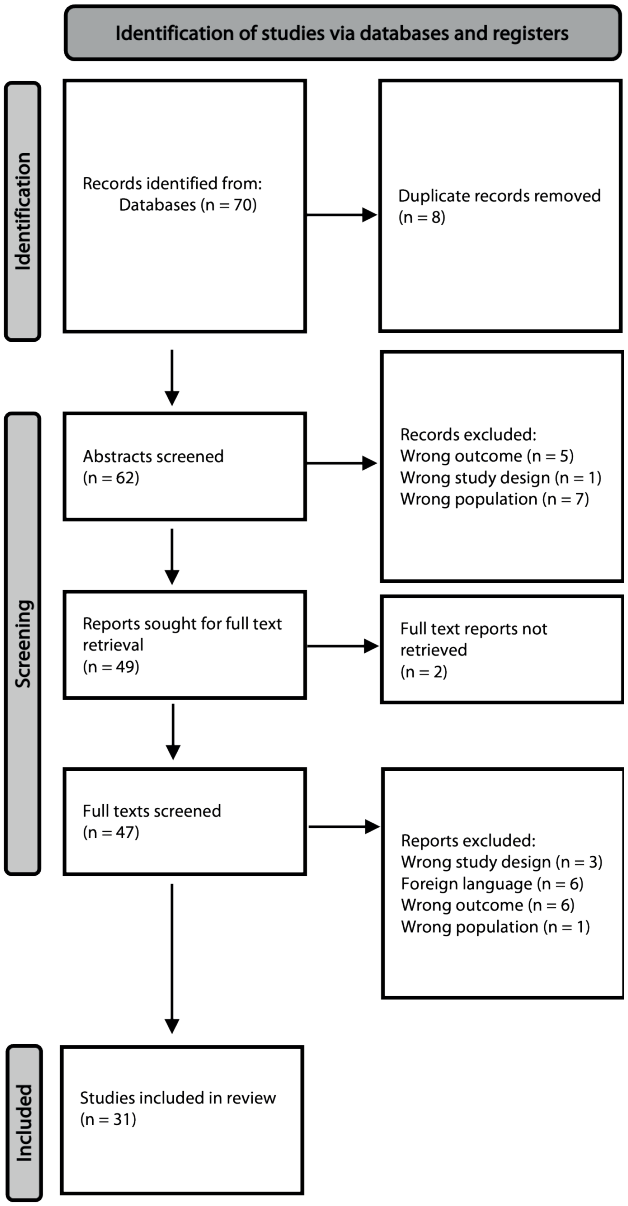


Figure 1. PRISMA flowchart.

### Statistical analysis

Comparisons between two groups of binary categorical data were performed using Fisher's exact test. When one of the variables contained more than two options, univariate logistic regression was used. Data was analysed using IBM SPSS Statistics (Version 29.0.2, IBM Corp.).

## Results

### Study characteristics

A flowchart of the literature search is illustrated in Figure 1. 70 articles were found using the specified search terms. Thirty-one studies were included following abstract screening and full-text review [9–29,32,33,35–42].

A total of 359 patients were included in this systematic review. 16 papers were retrospective case series, 13 were case reports and 2 were prospective case series. Study sizes ranged from one to 162 patients. The age range fell between 27 and 79 years old, with an average of 53 years. 273 patients were male (76.0%) and 86 were female (24.0%). Duration from last dose of RT to identification of skull base ORN ranged from 1.1 months to 504 months, with a mean duration of 52.2 months. Definitions for ORN varied between studies, and these are listed in Table 1.

### Background NPC data

Patient demographics and background NPC data of included studies can be found in Table S2. The number of patients by NPC stage were as follows: Stage I (n=31, 15.0%), stage II (n=71, 34.3%), stage III (n=61, 29.5%) and stage IV (n=44, 21.3%). 174 patients had primary NPC, whereas 89 patients had recurrent disease, of which seven patients underwent salvage nasopharyngectomy. 25 studies included information regarding treatment modality: Combined chemotherapy and radiotherapy treatment (CCRT, n=120, 46.2%), radiotherapy (RT) alone (n=130, 50.0%) and surgery (n=10, 3.85%). Types of radiotherapy treatment included external beam (not otherwise specified) (n=210), brachytherapy (n=38), intensity-modulated (n=3), stereotactic (n=3) and proton-beam therapy (n=1). The average total radiation dose received was 84.3Gy, ranging from 60Gy to 202Gy. In those with recurrence requiring further RT, the average total radiation dose was 132Gy.

### Subsites of skull base ORN on CT/MRI and nasal endoscopy

Subsites of skull base ORN can be localized on CT/MRI or on flexible nasal endoscopy. Subsite prevalence data can be found in Figure S1. 19 studies provided radiological data. The clivus was most discussed, followed by the sphenoid and the C1-C2 vertebrae. Eight studies presented nasal endoscopy data. The posterior wall of the nasopharynx was involved most, followed by the roof and lateral walls. The term "central" nasopharynx was assumed to be a reference to the posterior nasopharyngeal wall. Seven studies included both imaging and nasal endoscopy data [11,14–19] allowing direct comparison between the two modalities. We hypothesized that imaging should anatomically corroborate with nasal endoscopy. For example, the roof of the nasopharynx is formed by the sphenoid, so ORN affecting the roof should involve the sphenoid on imaging. As evidenced in Table 1, this was indeed the case for all seven studies [11,14–19].

### ICA involvement and association with ORN subsite

ORN can invade beyond the bone to surrounding structures. The internal carotid artery (ICA) was the most frequent structure affected (10/31 studies, 41.9%). Anatomically, the ICA runs superiorly, posteriorly and laterally to the fossa of Rosenmuller. We investigated whether there was any association between ICA

Table 1. Characteristics of osteoradionecrosis.

| Study | Mean time to ORN (months) | ORN definition | ORN subsite on imaging (n) | ORN subsite on endoscopy (n) | Affected structures (n) | Associated infections (n) | Symptoms of ORN (n) | Direct complications of ORN (n) |
|---|---|---|---|---|---|---|---|---|
| Kosaraju 2023 | 15 (11-19) | DNE Imaging | Pterygoid process (1) Clivus (1) | Roof (1) Lateral1 (1) | n/a | n/a | n/a | n/a |
| Pan 2023 | n/a | DNE + PE | Sella turcica (1) Sphenoid body (1) Pterygoid process (1) | n/a | n/a | Intracranial infection (1) | Headache (12) Foul odour (12) | n/a |
| Dai 2023 | n/a | DNE + PE | n/a | n/a | ICA (11) | n/a | n/a | n/a |
| Greenhill 2023 | 24 | DNE + PE | Clivus (1) | n/a | n/a | n/a | n/a | Pneumocephalus (1) |
| Sreenath 2023 | 17 | DNE Imaging | Sphenoid to C2 (1) Sphenoid to clivus (1) | n/a | n/a | n/a | n/a | n/a |
| Czech 2022 | 112 (4-232) | n/a | n/a | n/a | n/a | SBO (15) | Neck pain (11) Headache (10) Otalgia (5) Hearing loss (3) Foul odour (3) Oronasal secretions (3) Weight loss (3) Otorrhoea (2) | n/a |
| Cho 2022 | 8.7 (1.1-134.4) | DNE + PE | n/a | n/a | ICA (10) Foramen lacerum (10) | Sepsis (1) | n/a | Carotid blowout (3) |
| Duan 2022 | 19 | Imaging | n/a | n/a | n/a | Meningitis (1) | Headache (1) | Pneumocephalus (1) CSF leak (1) |
| Sagheer 2021 | 102 (24-180) | n/a | Posterior cranial fossa (1) | Posterior (1) | ICA (1) | Osteomyelitis (1) | n/a | Velopharyngeal insufficiency (1) |
| Daoudi 2020 | 84 (12-300) | DNE + PE | Sphenoid (4) Temporal bone (1) C1 (1) | n/a | ICA (3) | n/a | Headache (2), Asthenia (1), Epistaxis (1) | CN XII (1) |
| Chapchay 2019 | 2 | DNE + PE | Clivus (1) C1 (1) C2 (2) | Roof (1) Posterior (1) | n/a | Sepsis (1) Necrotising fasciitis (1) | Foul odour (1), Nuchal rigidity (1) | Dysphagia (1) |
| Hallak 2019 | 3 | n/a | Clivus (1) | Posterior (1) | ICA (1) | Abscess (1) | Headache (1), Otalgia (1) | n/a |
| Liu 2019 | 96 (6-504) | DNE + PE | Clivus (2) Pterygoid process (2) Petrous apex (1) Sphenoid body (1) Internal carotid canal C1-C2 Hypoglossal canal | Posterior (2) Lateral1 (2) Centre (1) | ICA (29) | n/a | Foul odour Headache, Recurrent bleeding | CN V (8), VI (3), IX/X (3), XII (2) Dysphagia (1) |
| Han 2018 | 45.57 (38.43-52.71) | DNE + PE | Clivus (11) Petrous apex (6) Sphenoid bone (2) Temporal bone (2) | n/a | n/a | n/a | n/a | n/a |
| Vlantis 2018 | n/a | n/a | n/a | n/a | ICA (2) | n/a | Recurrent epistaxis (1) | n/a |
| Huang 2018 | 82.6 (54-158.4) | DNE + PE | Maxillary sinus (26) Clivus (32) Petrous temporal bone (16) C1-3 (23) | n/a | Temporal lobe necrosis (21) | Local (16) CNS (28) | Pain (14), Recurrent epistaxis (20) | Blowout bleeding (20) |

Table 1 *continued*. Characteristics of osteoradionecrosis.

| Study | Mean time to ORN (months) | ORN definition | ORN subsite on imaging (n) | ORN subsite on endoscopy (n) | Affected structures (n) | Associated infections (n) | Symptoms of ORN (n) | Direct complications of ORN (n) |
|---|---|---|---|---|---|---|---|---|
| Choi 2017 | 8 (6 -11) | DNE + PE | Clivus (4)<br>C1-2 (2)<br>C1-3/4 (2)<br>Sphenoid (1)<br>Pterygoid process (3) | n/a | ICA (4)<br>Medial pterygoid (3) | n/a | Foul odour,<br>Pain (4),<br>Bleeding (3) | CN X, XII palsy (1)<br>Carotid blowout (1)<br>CSF leak (1),<br>Torticollis (1) |
| Adel 2016 | 384 | DNE Imaging | Clivus (1) | n/a | n/a | n/a | Purulent rhinorrhoea (1)<br>Epistaxis (1)<br>Bilateral tinnitus (1)<br>Headache (1)<br>Neck pain (1) | Dysphagia (1) |
| Risso 2016 | 42 | DNE Imaging | Clivus (1)<br>Sphenoid sinus (1) | Posterior (1) | n/a | n/a | Headache (1) | CSF rhinorrhoea (1)<br>Tension pneumocephalus (1)<br>Oro-nasal fistula (1) |
| Brand 2015 | 48 | Imaging | Middle cranial fossa floor (1)<br>Sphenoid sinus (1) | n/a | n/a | n/a | n/a | CSF leak (1)<br>CN palsy, all except II & XI (1)<br>Pneumocephalus (1) |
| Kau 2015 | 48 (7-96) | DNE + PE<br>Bacterial culture of tissues | n/a | n/a | n/a | n/a | n/a | Diplopia - CN III (1), CN VI (2) |
| Tiruchelvaray 2012 | 180 | DNE + PE | n/a | n/a | n/a | Cervical osteomyelitis (1) | n/a | Craniocervical instability (1) |
| Tan 2011 | n/a | DNE + PE | Clivus (1) | n/a | n/a | n/a | n/a | n/a |
| King 2010 | 68 (6-168) | Imaging | Clivus (8)<br>C1 (9)<br>C2 (4) | Roof (3)<br>Posterior (9)<br>All walls (1) | n/a | Osteomyelitis (1) | Neck pain (8)<br>Headache (4)<br>Otorrhoea (1) | n/a |
| Liang 2009 | n/a | DNE + PE | n/a | n/a | n/a | COM (5)<br>Brain abscess (3)<br>Epidural abscess (1)<br>Meningitis (6)<br>CST (3) | Foul odour<br>Headache (6) | CSF leak (2)<br>Ptosis (2)<br>Hemiparesis (3)<br>Seizure (1)<br>Visual loss (1) |
| Wang 2006 | 26 | DNE + PE | n/a | n/a | n/a | n/a | Headaches (1) | CSF rhinorrhoea (1)<br>Temporal lobe necrosis (1) |
| Huang 2006 | 94 (7-180) | DNE + PE | Sphenoid<br>Clivus<br>Internal carotid canal<br>Temporal bone | n/a | ICA | n/a | Foul odour (15)<br>Headache (14)<br>Intermittent epistaxis (10) | n/a |
| Chen 2004 | 48 | DNE + PE | n/a | Roof | ICA | n/a | Epistaxis (1) | Carotid blowout (1) |
| Liu 2004 | 2 | DNE + PE | n/a | n/a | n/a | n/a | Headaches (1) | n/a |

Table 1 *continued*. Characteristics of osteoradionecrosis.

| Study | Mean time to ORN (months) | ORN definition | ORN subsite on imaging (n) | ORN subsite on endoscopy (n) | Affected structures (n) | Associated infections (n) | Symptoms of ORN (n) | Direct complications of ORN (n) |
|---|---|---|---|---|---|---|---|---|
| Chang 2000 | 116 (21-183) | DNE + PE | n/a | n/a | n/a | n/a | Foul odour (6), Epistaxis (4), Headache (3) | n/a |
| Wu 1999 | 12 | DNE + PE | Sphenoid body (1) | n/a | n/a | Ventricular fluid (1) | n/a | Tension pneumocephalus (1) |

Abbreviations: ORN, osteoradionecrosis; DNE, diagnostic nasal endoscopy; PE, pathological examination; ICA, internal carotid artery; SBO, skull base osteomyelitis; COM, chronic otitis media; OME, otitis media with effusion; CST, cavernous sinus thrombosis. 1 Lateral = Lateral to Fossa of Rosenmuller.

exposure and ORN subsite. ORN subsites were classified into lateral, posterior and roof areas (Figure 2) and compared between ICA affected (n=19) [15,17,20,24,26] and unaffected groups (n=14) [11,14,16,18,19]. Univariate logistic regression revealed no significant differences between the posterior (p=0.830, OR 1.250, 95% CI 0.164 - 9.538), lateral (p=0.548, OR 0.625, 95% CI 0.135 – 2.891) or the roof subsite (reference) and ICA involvement (Table 4).

### Microbiological data for ORN

Microbiology data for ORN was limited, despite possible involvement in its pathogenesis [43]. Available microbiology data are summarized in this paragraph. Czech 2022 analysed specimens from patients with confirmed skull base osteomyelitis (SBO) superimposed on ORN, finding that most samples were polymicrobial, most composed of bacteria typically found naso- or oropharyngeal flora, such as *Streptococci*, *Staphylococci*, and anaerobes. Rarer organisms isolated included *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA) and fungi (*Candida* spp. and *Aspergillus* spp.) (21). Tiruchelvaray described C1 to C2 osteomyelitis as a complication of ORN where microbial cultures grew Group B *Streptococcus*, *Staphylococcus aureus* and *Candida* spp. (*glabrata* and *krusei*) [32]. Overall, these findings suggest that in addition to commensals, skull base ORN can be complicated by drug-resistant bacteria and fungal infections.

### Associated infections

Twelve studies included information on ORN-associated infections. Amongst these, 49 patients had a local infection (55%), and 40 patients had a CNS infection (45%). Prevalence of specific infections are shown in Table 1, with osteomyelitis being the most common (n=18, 40%). ORN subsites were compared with infectious (n=6) [9,11,14,18,24,26,27,35–38] and non-infectious (n=60) ORN cases [15–17,19,42]. Univariate logistic regression revealed no significant differences between the posterior (p=0.998, OR 0.00, 95% CI 0.00), lateral (p=0.963, OR 0.929, 95% CI 0.150-5.733) and the roof subsite (reference) and presence of infection (Table 4).

### Symptomatic features of ORN

Prevalence of symptoms by number of studies can be found in Figure S1. Most common symptoms included headache, epistaxis and foul odour. Less frequent nasal symptoms include pain at the ORN site and purulent rhinorrhoea. Otologic symptoms were uncommon, and included otalgia, bilateral tinnitus, hearing loss and otorrhoea. Non-specific symptoms were also infrequent, and included nuchal pain or rigidity, weight loss and asthenia. Headache (n=56) was not significantly associated with the presence of infection (n=30) (p=0.269, OR 1.78, 95% CI 0.726-4.356), but foul odour (n=41) was negatively associated with presence of infection (n=23) (p<0.01, OR 0.116, 95% CI 0.36–0.37) (Table 4). Epistaxis (n=34) was significantly associated with ICA involvement (n=53) (p<0.001, OR 37.0, 95% CI 13.0-104.8) (Table 4).

### Direct complications of ORN

Complications extracted from 18 studies are listed in order of prevalence in Figure S1. Cerebrospinal fluid (CSF) leak was the most common complication, discussed in six studies. Cranial nerve (CN) palsies and pneumocephalus were the second most common, noted in five studies each. This number does not include CN-related pathologies that are not explicitly defined as such, like dysphagia, torticollis and tongue deviation, and is therefore likely to be an underestimation. Across the studies, all CNs were implicated in skull base ORN, apart from CN II (optic nerve). Multiple studies also mentioned carotid blowout (four studies) or dysphagia (three studies) as complications. Owing to the small sample sizes for complications, statistical analysis was not performed.

### Treatment modalities for managing ORN

Twenty-eight studies included treatment details. Treatments can

Table 2. Osteoradionecrosis treatment modalities.

| Study | Number of Cx/Sx/ Cx+Sx | Cx type (n, length) | Abx type (n) | Sx type (n) | Rationale for Rx |
|---|---|---|---|---|---|
| Kosaraju 2023 | 0/0/1 | Abx (1, 4w) | Cefepime (1) | Endoscopy + LF (1) | Non-surgical – Initial control<br>Surgical – To achieve adequate control |
| Pan 2023 | 0/12/0 | n/a | n/a | Endoscopy + FF (12) | Timely surgical intervention for patients with difficult to control skull base ORN with medication, recurrent intracranial infection or high fever. |
| Dai 2023 | 0/18/0 | n/a | n/a | Endoscopy (2) + LF (16);<br>ICA Rx (8) | Based on location + severity of ORN, patient preferences, consultations with radiation oncologists and surgeons |
| Greenhill 2023 | 0/1/0 | n/a | n/a | Endoscopy + LF (1) | "Mainstay" of treatment |
| Sreenath 2023 | 0/0/2 | Abx (2, 30d/90d)<br>HBO (1 – 40 dives) | n/a | Endoscopy + FF (2) | Non-surgical – Trialled<br>Surgical – If failed HBO, prolonged IV antibiotics and/or PENTOCLO. |
| Czech 2022 | 9/0/6 | Abx (15)<br>Anti-fungal (2)<br>HBO (5 – 40 dives) | n/a | Endoscopy (6) + LF (1); Spinal Rx (1) | Non-surgical – Abx based on culture data when available.<br>Surgical – As an effort to achieve source control, often in recurrent SBO cases |
| Cho 2022 | 8/7/0 | Abx (8)<br>HBO (n/a) | n/a | Endoscopy + LF (7);<br>ICA Rx (n/a) | No significant differences in age, underlying disease, disease extent between non-surgical and surgical groups. Therefore, unclear rationale for non-surgical vs surgical Rx. |
| Duan 2022 | 0/0/1 | Abx (1)<br>LP (1) | n/a | Open + LF + FF (1) | Non-surgical – Evidence of severe bacterial meningitis<br>Surgical – Extensive ORN revealed on CT/MRI, which was used to create a 3D printed model. |
| Sagheer 2021 | 0/2/0 | n/a | n/a | Endoscopy + FF (2) | FF – In large defects, multiple reoperation situations, LF may be inadequate. |
| Daoudi 2020 | 1/0/3 | PENTOCLO (1)<br>Abx (3) | n/a | Endoscopy; + LF (3);<br>ICA Rx (1) | Case by case basis by MDT.<br>Non-surgical – If well tolerated symptoms & low-risk of carotid rupture<br>Surgical – Symptomatic cases with major bone exposure on endoscopy<br>ICA Rx – Active bleeding or ICA considered at risk of rupture (irregular lumen shape, presence of pseudo-aneurysm, no longer covered by bone, exposed necrotic soft tissues. |
| Chapchay 2019 | 0/0/1 | Abx (1)<br>Anti-fungal (1) | n/a | Endoscopy; + FF (1) | Non-surgical – To improve patient condition<br>Surgical – Failure of healing after prolonged anti-microbial regime (several months). |
| Hallak 2019 | 0/0/1 | Abx (1) | Pip-Taz (until sensitivities), Co-amoxiclav (6w) | Endoscopy; + FF (1) | Surgical – Persistent deep ulcer on posterior wall of NP after 2 months, and, exposed clivus, deep extension of necrosis of soft tissues, threat of rupture of ICA |
| Liu 2019 | 0/59/0 | n/a | n/a | Endoscopy (59); + LF (5); ICA Rx (4) | Surgical – Argument that once there was sequestra, dead bone could not be revitalized and should be removed surgically. Non-surgical measures would only delay the treatment. |
| Han 2018 | 6/8/0 | Abx (6)<br>HBO (8) | n/a | Endoscopy (8) | n/a |
| Vlantis 2018 | 0/4/0 | n/a | n/a | Open + FF (4) | Surgical – Severe ORN, unresponsive to non-surgical measures, +/- exposed ICA<br>Muscle-only free flap – Bulk (to protect ICA) and better mucosalisation (e.g. vs radial forearm free flap which is susceptible to crusting & cacosmia). |

Table 2 *continued*. Summary of all included studies.

| Study | Number of Cx/Sx/ Cx+Sx | Cx type (n, length) | Abx type (n) | Sx type (n) | Rationale for Rx |
|---|---|---|---|---|---|
| Huang 2018 | 104/0/58 | PENTOCLO (162)<br>Nasal douching (162)<br>Abx (n/a) | n/a | Endoscopy (12);<br>Open (46);<br>+LF (12); +FF (46);<br>ICA Rx (8) | Non-surgical – All patients treated non-surgically first.<br>Surgical – Complications secondary to ORN that failed non-surgical treatment<br>Endoscopic – Limited debridement of sphenoid sinus, clivus & C1.<br>Open (maxillary swing) – Extensive debridement of ICA. |
| Choi 2017 | 0/0/4 | n/a | n/a | Open + FF (4) | Surgery (maxillary swing + muscular FF) – Patients with extensive ORN with high possibility of ICA rupture. |
| Adel 2016 | 0/1/0 | n/a | n/a | Endoscopy + LF (1) | Surgical – Prompt debridement of devitalised tissue and adequate coverage of exposed defect. |
| Risso 2016 | 0/0/1 | Abx (1) | Linezolid, Meropenem | Endoscopy + LF (1) | n/a |
| Brand 2015 | 0/0/1 | Abx (1) | Co-amoxiclav (1, 5d) | Endoscopy + LF + FF (1) | Surgical – Concurrent repair of CSF leak required, as persistent CSF leak may lead to ascending meningitis. |
| Kau 2015 | n/a | n/a | n/a | n/a | n/a |
| Tiruchelvaray 2012 | 0/0/1 | Abx (1)<br>Anti-fungal (1) | Vancomycin (1, 6w)<br>Linezolid (1, 6w)<br>Voriconazole (1, 6mo) | Spinal Sx | Non-surgical – Abx based on microbial cultures from transoral, transpharyngeal wall biopsy.<br>Surgery – To address cranio-cervical instability |
| Tan 2011 | n/a | n/a | n/a | n/a | n/a |
| King 2010 | 6/0/3 | Abx (9)<br>HBO (2) | n/a | Spinal Rx (3) | n/a |
| Liang 2009 | n/a | n/a | n/a | n/a | n/a |
| Wang 2006 | 1/0/0 | Abx (1)<br>Intraventricular drainage tube (1) | Vancomycin (1, 1mo) | n/a | Non-surgical – CSF fluid cultured Staph aureus, so Abx, and intraventricular drainage to decompress tension pneumocephalus.<br>Surgery – Was refused. |
| Huang 2006 | 5/9/0 | Abx (n/a)<br>HBO (2) | n/a | Endoscopy (8);<br>Open (1) | Non-surgical – Inaccessible areas of skull base ORN or difficult to reconstruct.<br>Surgical – ASAP if feasible and non-surgical treatment is not effective. |
| Chen 2004 | 0/1/0 | n/a | n/a | Endoscopy (1); ICA Rx (1) | Surgical – To manage massive haemorrhage from ruptured ICA and rapidly remove sequestrum. |
| Liu 2004 | 1/0/0 | HBO (1) | n/a | n/a | HBO – Considered to be "treatment" for ORN. |
| Chang 2000 | 4/0/2 | HBO (2, 40 dives) | n/a | Endoscopy (6) | Non-surgical – HBO if the initial non-surgical sequestrectomy did not work.<br>Surgical – Initial non-surgical sequestrectomy to control the disease. Further sequestrectomy if persistent disease. |
| Wu 1999 | 0/1/0 | n/a | n/a | Endoscopy + graft (1) | n/a |

Abbreviations: Cx, Non-surgical management; Sx, Surgical management; Cx+Sx, Non-surgical and Surgical management; Abx, antibiotics; HBO, hyperbaric oxygen therapy; LP, lumbar puncture; PENTOCLO, Pentoxifylline, Tocopherol & Clodronate combination; LF, local flap; FF, free flap; Rx, treatment; MDT, multidisciplinary team.

be split into three groups: Non-surgical treatment only (n=145), surgical treatment only (n=123), and conservative and surgical treatment together (n=84). Surgery was the most utilised treatment modality in 11 studies, non-surgical management in seven studies and non-surgical plus surgical management in 10 studies. Non-surgical treatments included antibiotic therapy (16

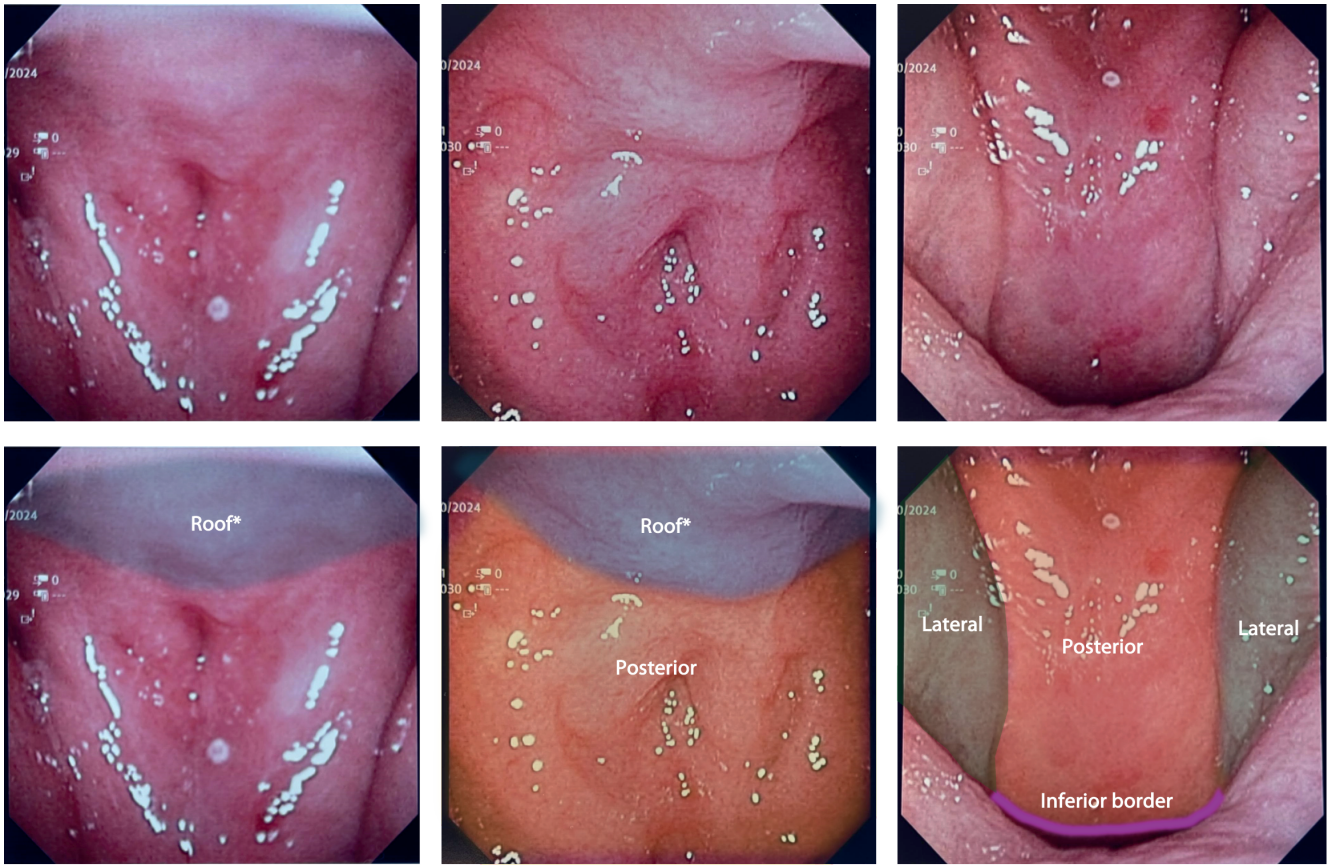


Figure 2. Classification of the nasopharynx into posterior, roof and lateral subsites. *Roof= Continuation the posterior septum to the sphenoid rostrum.

studies), HBO (eight studies), antifungal therapy (three studies) and PENTOCLO (two studies). Most studies (26/31) included surgical patients. Of these, most were endoscopic (n=158, 21 studies) and a minority required an open approach (n=56, 5 studies). Free flaps (n=74, 10 studies) were used more often than local flaps (n=50,12 studies). Six studies discussed ICA treatment. In cases where ICA occlusion was safe, endovascular embolization with coils were usually employed [11,23,24,29]. When ICA occlusion was not possible, surgical bypass [11,23,29] or a covered stent [24] were used. Occasionally, ICA resection [22] or ligation [29] were performed (Table 2).

### Post-treatment ORN outcomes

Follow-up times after treatment for ORN ranged from 0.5-530 months (mean = 33.3 months). Details on post-treatment outcome of 260 patients from 25 studies were included (Table 3). Overall, 158 patients improved, 37 patients had complications, and 65 patients died within the follow-up period. Improvements included symptom resolution, flap success, improvements on imaging and blood markers and stable disease. Infection was the most prevalent post-treatment complication (43.8%) and included SBO recurrence, parapharyngeal abscess, aspiration pneumonia, meningitis and delayed neck healing. Nasal complications were second most prevalent (40.6%), and included nasal adhesions and stenosis, ulcer formation, sinus infection, chronic rhinorrhoea and post-nasal drip. Carotid blowout complicated 9.4% of cases and pharyngeal complications occurred in 6.3%. Complications visualized by endoscopy include residual exposed bone, mucosal defects, re-exposure of the ICA and rarely flap haematomas and failure. In a cohort of patients treated for SBO, all had persistent abnormalities of the skull base on imaging [21]. Sixty-five patients from eight studies provided mortality data. Carotid blowout was the most common cause of death (45.9%), followed by tumour spread or recurrence (17.6%). Other causes included infection or sepsis (n=7), organ failure (n=2) and non-ICA related haemorrhage (n=2), ischaemic stroke (n=1), temporal lobe necrosis (n=1) and cerebral oedema (n=1) (Appendix 1 - 2).

### Statistical analyses for predictors of outcome

Fisher's exact test was performed on binary variables that may be associated with outcome (improved or dead). ICA involvement (p=0.175, OR 0.357, 95% CI 0.672-11.669), associated infection (p=0.070, OR 1.400, 95% CI 0.876 - 2.237) and antibiotic use (p=1.00, OR 1.333, 95% CI 1.005 – 1.769) were not associated with differences in outcome (Table 4). Univariate logistic regression was performed on clinical features with more than two categories. There was no statistically significant associa-

Table 3. Osteoradionecrosis outcomes post-treatment.

| Study | Follow-up in months (mean, range) | Outcome measures | Number of Ip/Mb/ Mt | Ip details [n(%), time] | Mb details [n(%), time] | Cause of Mt [n(%), time*] |
|---|---|---|---|---|---|---|
| Kosaraju 2023 | n/a | n/a | n/a | n/a | n/a | n/a |
| Pan 2023 | 3-12 | Symptoms; Endoscopy | 11/1/0 | Headaches & foul odours relieved [12(100%), 0mo] | NP adhesion & posterior nasal stenosis [1(8%), 3mo] | n/a |
| Dai 2023 | 3.68 (0.5-16) | Symptoms | 15/0/3 | Pain score decreased; foul odour decreased [n/a, 0mo] | n/a | Non-ICA related haemorrhage [2(67%), 1mo]; Multiple organ failure [1(33%), 6mo] |
| Greenhill 2023 | 12 | n/a | 1/0/0 | Doing well [1(100%), 1y] | n/a | n/a |
| Sreenath 2023 | 49.2 (46.8-50.6) | Symptoms; 2° interventions (revision surgery, hospitalisation) | 1/1/0 | Pain resolved [1(50%), 1mo]; Pain improved [1(50%), 1mo]; No 2° interventions [2(100%), 1mo] | Sinus infection [1(50%), 1mo] | n/a |
| Czech 2022 | 127 (13-530) | Blood markers; endoscopy; Imaging | 0/15/0 | Cure of SBO [7(47%), 127mo]; ESR/CRP normal [3(30%)], downtrend [6(60%)], stable elevated [1(10%)] Restored mucosal barrier [2(14%)] | SBO recurrence [8(53%), 127mo] Residual mucosal defects [12(85.7%)]; Residual exposed bone [4(29%)] Imaging abnormalities of skull base [15(100%)] | n/a |
| Cho 2022 | n/a | n/a | 5/3/7 | Stable disease: [2(25%)C; 6(86%)S] | 2y blowout rate: [3(38%)C; 0(0%)S] | Massive haemorrhage from carotid rupture [3(43%)] Sepsis [1(14%)]; Cancer recurrence [1(14%)] Unknown cause [2(29%)] |
| Duan 2022 | 12 | Symptoms; CT/MRI imaging | 0/0/1 | Resolved nasal drip & swallowing of sweet-tasting fluid [1(100%)] Pneumocephalus absorbed [1(100%)] | Facial numbness [1(100%)] | Tumour progression [1(100%), 1y] |
| Sagheer 2021 | 36 (24-48) | Symptoms; Complications | 0/2/0 | Resolved VPI [1(50%), 2.5y] | Dysphagia [1 (50%), 2.5y] Post-nasal drainage [1(50%), 4y] Parapharyngeal abscess [1(50%), 2y] | n/a |
| Daoudi 2020 | 24 (10-38) | n/a | 2/0/2 | Healed [2(50%)] | n/a | Mortality [2(50%), 2y] ICA rupture [1(50%), 2y] Sepsis [1(50%), 2y] |
| Chapchay 2019 | 48 | Endoscopy | 0/1/0 | No recurrent malignancy or ORN [1(100%)] | Fistula, chronic supraglottic oedema, adynamic pharyngeal constrictors [1(100%)] | n/a |
| Hallak 2019 | 4 | Endoscopy | 1/0/0 | Graft integration; closed defect; No inflammatory signs [1(100%)] | n/a | n/a |
| Liu 2019 | 27 (1-108) | Symptoms; imaging; endoscopy | 32/0/26 | Resolution of headache, foul odour, epistaxis No imaging evidence of recurrence Good epithelialisation | n/a | Haemorrhage from ICA rupture [24(92.3%)] Ischaemic stroke [1(3.8%)] Pneumonia [1(3.8%)] |
| Han 2018 | n/a | n/a | 9/-/- | n/a | n/a | n/a |
| Vlantis 2018 | 2.9-34.8 | Symptoms; Endoscopy | 0/4/0 | Improved speech, cacosmia & nasal crusting [4(100%)] | Temporary ICA re-exposure [1(25%)] Choanal stenosis [3(75%)] | n/a |

Table 3 *continued*. Osteoradionecrosis outcomes post-treatment.

| Study | Follow-up in months (mean, range) | Outcome measures | Number of Ip/Mb/Mt | Ip details [n(%), time] | Mb details [n(%), time] | Cause of Mt [n(%), time*] |
|---|---|---|---|---|---|---|
| Huang 2018 | 36.2 (2-68) | Symptoms; Pain-status | 58/8/24 | No recurrent CNS infection or bleeding [58(100%)]<br>Weaned from morphine to paracetamol [10(17.2%)]<br>No analgesia requirement [48(82.8%)] | CSF leak [3(37.5%)]<br>Flap haematoma [1(12.5%)]<br>Aspiration pneumonia [2(25%)]<br>Delayed neck healing [2(25%)] | Intracranial invasion [8(33.3%)];<br>Distant metastasis [3(12.5%)];<br>Aspiration pneumonia [2(8.3%)];<br>Unrelated events [11(45.8)] |
| Choi 2017 | 3 | Symptoms; endoscopy | 3/1/0 | Pain alleviated, absent bleeding & foul odour [4(100%)]<br>No flap failure or infection [4(100%)]<br>Mucosalisation at 3mo [3(75%)] | Chronic inflamed flap & watery rhinorrhoea [1(100%)] | n/a |
| Adel 2016 | n/a | n/a | n/a | n/a | n/a | n/a |
| Risso 2016 | 0.5 | Symptoms; imaging | 1/0/0 | No rhinoliquorrea [1(100%)]<br>CT/MRI - Resorption of pneumocephalus [1(100%)] | n/a | n/a |
| Brand 2015 | 3 | Symptoms; endoscopy | 1/0/0 | No nasal symptoms [1(100%)]<br>No crusting or CSF leakage [1(100%)] | n/a | n/a |
| Kau 2015 | 21 (6-120) | n/a | 0/0/3 | n/a | n/a | Carotid artery rupture [1(33.3%)]<br>Sepsis [1(33.3%)]<br>Liver failure [1(33.3%)] |
| Tiruchelvaray 2012 | n/a | n/a | n/a | n/a | n/a | n/a |
| Tan 2011 | n/a | n/a | n/a | n/a | n/a | n/a |
| King 2010 | 38.8 | Symptoms | 8/1/0 | No local tumour recurrence [8(100%)] | Meningitis [1(100%), 14mo] | n/a |
| Liang 2009 | n/a | n/a | n/a | n/a | n/a | n/a |
| Wang 2006 | n/a | n/a | n/a | n/a | n/a | n/a |
| Huang 2006 | n/a | Symptoms | 9/2/6 | No foul odour, bleeding or headache [9(100%)S] | Headache, recurrent epistaxis [2(33.3%)C] | Temporal lobe necrosis [1(11.1%)S, 6mo]<br>Cerebral oedema [1(11.1%)S, 4y]<br>Aspiration pneumonia [1(16.7%)C, 4y]<br>ICA rupture & haemorrhage [3(50%) C] |
| Chen 2004 | 3 | Symptoms | 1/0/0 | No bleeding or neurological deficits [1(100%)] | n/a | n/a |
| Liu 2004 | 2 | Imaging | 1/0/0 | No increased uptake with FDG-PET [1(100%)] | n/a | n/a |
| Chang 2000 | 14.7 | Symptoms; Endoscopy | 5/1/0 | Symptom free [6(100%)] | Ulcer at NP [1(16.7%)] | n/a |
| Wu 1999 | 6 | n/a | 1/0/0 | Stable condition [1(100%)] | n/a | n/a |

Abbreviations: Ip, Improvement; Mb, Morbidity; Mt, Mortality; SBO, skull base osteomyelitis; NP, nasopharynx; mo, months; y, years; 2°, secondary; VPI, velopharyngeal insufficiency. *Mortality follow-up time is two years unless otherwise specified. C Non-surgically-treated group; S Surgically-treated group.

Table 4. Results from statistical analyses.

| Fisher's exact tests for association between two variables | | | | | | |
|---|---|---|---|---|---|---|
| **Comparison arm 1** | **Comparison arm 2** | | | **1 vs 2 OR (95% CI)** | | **p-value** |
| Symptoms (and possible associations) | | | | | | |
| Headache | Infection | | | 1.778 (0.726 - 4.356) | | 0.269 |
| Foul odour | Infection | | | 0.116 (0.36 – 0.369) | | <0.01 |
| Epistaxis | ICA involvement | | | 36.975 (13.042 – 104.828) | | <0.001 |
| Mortality (and possible associations) | | | | | | |
| ICA involvement | Mortality | | | 0.357 (0.672-11.669) | | 0.175 |
| Infection | Mortality | | | 1.400 (0.876 – 2.237) | | 0.070 |
| Antibiotic use | Mortality | | | 1.333 (1.005 – 1.769) | | 1.000 |
| **Univariate logistic regression analysis for association between variables and outcome** | | | | | | |
| **Variable*** | | **Coef (B)** | **SE** | **OR (Exp(B))** | **95% CI** | **p-value** |
| **Subsite (and possible associations)** | | | | | | |
| Subsite (ICA) | Roof | Reference | Reference | Reference | Reference | Reference |
| | Posterior | 0.223 | 1.037 | 1.250 | 0.164-9.538 | 0.830 |
| | Lateral | -0.470 | 0.781 | 0.625 | 0.135-2.891 | 0.548 |
| Subsite (infection) | Roof | Reference | Reference | Reference | Reference | Reference |
| | Posterior | -19.331 | 9748 | 0.00 | 0.00 - | 0.998 |
| | Lateral | -0.074 | 0.929 | 0.929 | 0.150-5.733 | 0.963 |
| Subsite (mortality) | Roof | Reference | Reference | Reference | Reference | Reference |
| | Posterior | -0.511 | 1.390 | 0.600 | 0.039-9.156 | 0.713 |
| | Lateral | 1.099 | 1.291 | 3.00 | 0.239-37.672 | 0.395 |
| **Improvement outcome (and possible associations)** | | | | | | |
| Treatment (improvement) | Non-surgical | Reference | Reference | Reference | Reference | Reference |
| | Surgical | 0.46 | 0.466 | 1.585 | 0.636-3.947 | 0.323 |
| | Non-surgical + surgical | 0.762 | 0.71 | 2.143 | 0.532-8.625 | 0.283 |
| Surgical approach (improvement) | Endoscopic | Reference | Reference | Reference | Reference | Reference |
| | Open | 1.099 | 1.563 | 3.00 | 0.140-64.262 | 0.482 |
| | None | -0.242 | 1.174 | 0.785 | 0.079-7.844 | 0.837 |
| Flap type (improvement) | None | Reference | Reference | Reference | Reference | Reference |
| | Local | -0.446 | 0.929 | 0.631 | 0.104-3.951 | 0.631 |
| | Free | 1.335 | 1.286 | 3.8 | 0.306-47.211 | 0.299 |

Abbreviations: OR, Odds ratio; CI, Confidence interval; Coef (B), coefficient B; SE, standard error of the coefficient; Exp(B), exponential value of B
*Dependent variable is in brackets ( ).

tion between outcome and ORN subsite, treatment, surgical approach or flap type (Table 4). Low numbers of paired data between variables precluded the utility of correlation analysis for detecting associations between treatment and outcome (Appendix 3 and 4). Due to the limited sample size, further studies will be required to consolidate these findings.

## Discussion

### Classification of subsites involved in skull base osteoradionecrosis

We classified ORN subsite separately based on observations on radiology and nasal endoscopy. The clivus and posterior nasopharyngeal wall were the most frequently mentioned subsite on imaging and nasal endoscopy respectively. Both radiology and nasal endoscopy should be utilized when evaluating the location of ORN. CT/MRI is useful for detecting surrounding areas of involvement, including bony structures, vessels and sinuses [44]. Nasal endoscopy provides direct visualisation of nasopharyngeal boundaries, identify exposed sites of bone and corroborate radiological findings [45]. There are classification systems for

localising skull base pathologies, but to our knowledge, none exist for the nasopharynx. Anatomically, the boundaries of the nasopharynx are closely opposed to bony structures. The roof and posterior walls are imperceptibility merged and formed by the sphenoid sinus, clivus and anterior aspect of the first two cervical vertebrae. The pterygoid plates indirectly oppose the lateral walls of the nasopharynx, separated by the pharyngeal fascia. Based on these anatomical relations, we grouped subsites into three categories: posterior (clivus, cervical vertebrae); roof (sphenoid) and lateral (pterygoid plates and muscles). Using this system, we found anatomical consistency between imaging and nasal endoscopy. Future work will be required to elucidate whether this subsite classification system may help to dictate treatment.

### Determinants of osteoradionecrosis severity

There is currently no universal staging system for ORN severity. The most used staging systems characterize ORN severity using a variety of clinical, radiological, anatomical and response measures [46]. However, these generally focus on mandibular ORN rather than skull base ORN. In this study, we investigated severity by looking at four factors: ICA involvement, associated infection, symptoms and direct complications. The ICA was assessed in 42% of studies and used as a marker for disease severity in several studies [17,22–24]. ICA exposure indicates threatened carotid blowout syndrome and implicates a high risk of bleeding [47]. Skull base ORN has been shown to be a significant predictor of carotid blowout syndrome [47,48], especially with extensive skull base erosion [49]. In this study, no statistically significant differences between subsite and ICA involvement were found. This contrasts with another study which found an association between clival exposure and carotid blowout, although the patient cohort was NPC rather than NPC ORN [49]. Recurrent epistaxis is a well-known marker of impending ICA compromise [11,26,49] and this was reinforced by our results. Microbiology data from skull base ORN studies were sparse. The role of microbiota in the pathogenesis of ORN is not clear. It has been suggested that there is a greater abundance and diversity of microbiota that disrupt metabolic pathways, increase osteoclastic activity and impair healing in ORN patients [43]. Additionally, our findings suggest that skull base ORN can be complicated by multi-drug-resistant bacteria and fungal species. Prompt identification of these infections and specialist input by a multi-disciplinary team are essential for positive outcomes [50]. We found a similar prevalence of patients with associated local and CNS infections, with osteomyelitis being the most common. Local infections in skull base ORN share parallels with native vertebral osteomyelitis and carry a poor prognosis [21]. Headache, foul odour and epistaxis were the most frequently discussed symptoms, consistent with other studies [4,11,12,29]. It has been suggested that ORN patients with a CNS infection are more likely to have a persistent headache [12]. Our study showed a non-significant increase in the likelihood of headache in the presence of infection. Interestingly, we found that foul odour was negatively associated with the presence of infection. To the best of our knowledge, this finding has not been reported in other studies. This suggests that foul odour is likely to be a poor predictor for ORN-associated infections, but an underlying pathophysiological explanation for this association is debatable. Further investigation is warranted to determine its representability in this population cohort. CSF leak was the most common direct complication in this study. CSF leakage may also predispose to CNS infections in this patient cohort [54]. CSF leaks not only complicate ORN but may also recur as a complication after ORN repair, months after surgery [55]. Cranial nerve palsy (CNP) was another commonly mentioned complication. It has been noted that patients with existing CNP who go on to have skull base ORN show a rapid progression of the CNP [33]. Furthermore, the CNP often persists post-treatment [26,33].

### Factors determining outcome in ORN patients

Our study did not find any statistically significant associations between clinical outcome (improved versus deceased) and subsite, ICA involvement, infection, treatment, antibiotic use, surgical approach or flap type. This may be due to the limited amount of data that was extractable. The association between infection and mortality almost reached significance (p=0.07). This was unsurprising, as infection was one of the frequent causes of mortality in our study. Surgical (OR 1.585) and non-surgical and surgical approaches together (OR 2.143) gave a higher chance of improvement compared to non-surgical approaches, but neither reached statistical significance (p = 0.323 and p = 0.283 respectively). This is in keeping with multiple studies (9,23). An open surgical approach (OR 3.00 vs endoscopy, p = 0.482) and use of free flaps (OR 3.80 vs no flap, p = 0.299) were also associated with non-significant improvements, consistent with results from another systematic review [4].

### Limitations

Our study has several limitations. Firstly, our study was limited by small sample sizes for multiple variables, low numbers of paired data and missing values. This limited the power of the study, prevented significant associations from being drawn and meaningful multivariate analysis from being conducted. Larger-scale studies will be necessary to validate our findings. Furthermore, included studies had highly variable follow-up times, ranging from 2 weeks to 530 months, preventing outcome analysis within a standardised timeframe. Future studies should account for follow-up duration to distinguish between short-term and long-term outcomes.

## Conclusion

The most affected subsite in skull base osteoradionecrosis was

the posterior nasopharyngeal wall and clivus. No significant association between subsite and clinical outcomes were found in this study. Carotid involvement, associated infection and treatment modality could not individually predict clinical outcome. Further work with multivariate analysis would be useful in this regard (Appendix 5).

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## Authorship contribution

SD and DCMY were responsible for study conception and study selection. SD performed the literature search, statistical analysis and writing of the manuscript. CXYL, WHBM, HKC, CPLC, CCFL were collaborators on developing and critically editing the manuscript. SMWC, JYKC offered senior advice and critical appraisal of the manuscript. DCMY was integral in providing the direction of the study.

## Conflict of interest

None declared.

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## SUPPLEMENTARY MATERIAL

Figure S1. Subsite prevalence data of of skull base ORN.

Table S1. Search strategy for databases.

| Database | Search terms | Results |
|---|---|---|
| PubMed/Medline | Skull base AND osteoradionecrosis AND nasopharyngeal carcinoma | 48 |
| EMBASE | 1. exp osteoradionecrosis/<br>2. exp nasopharynx carcinoma/<br>3. exp skull base/<br>1 and 2 and 3 | 17 |
| Cochrane | Skull base AND osteoradionecrosis AND nasopharyngeal carcinoma | 2 |

Table S2. Patient demographics and NPC background data.

| Study | Design | Number of NPC ORN patients (M:F) | Median age (range) | NPC stage before ORN (I/II/III/IV) | NPC Tx (CRT/RT/Sx) | Type of RT (number) | Mean total RT dose Gy (range) | Number pNPC/r NPC (number of SNP =) |
|---|---|---|---|---|---|---|---|---|
| Kosaraju 2023 | Retrospective case series | 1:0 | 55 | n/a | 1/0/0 | IMRT (1) | 145.3 | 0/1 |
| Pan 2023 | Retrospective case series | 8:4 | 58 (45-75) | n/a | n/a | n/a | n/a | n/a |
| Dai 2023 | Prospective case series | 13:5 | 57 (34-72) | n/a | n/a | n/a | n/a | n/a |
| Greenhill 2023 | Case report | 1:0 | 65 | n/a | n/a | n/a | n/a | n/a |
| Sreenath 2023 | Retrospective case series | 2:0 | 53 (30-71) | n/a | 2/0/0 | SBRT (1) | n/a | n/a |
| Czech 2022 | Retrospective case series | 9:6 | 62 (27-78) | 3/4/1/6 | 13/2/4 | n/a | 116 (66-188) | 8/3 |
| Cho 2022 | Retrospective case series | 11:4 | 62.9 ± 11.6 | n/a | n/a | n/a | 67.5 (63-72)1<br>50 (24-67.5)2 | 9/4 |
| Duan 2022 | Case report | 0:1 | 37 | 0/0/0/1 | 1/0/0 | n/a | 128 | 0/1 (SNP=1) |
| Sagheer 2021 | Retrospective case series | 0:2 | 48 (35-61) | n/a | 2/0/1 | Proton beam RT (1) | n/a | 0/1 (SNP=1) |
| Daoudi 2020 | Retrospective case series | 3:1 | 53.5 (31-74) | n/a | 4/0/0 | n/a | 118 (70-202) | 2/2 |
| Chapchay 2019 | Case report | 1:0 | 64 | 0/0/0/1 | 1/0/0 | IMRT (1) | 70.4 | 1/0 |
| Hallak 2019 | Case report | 1:0 | 65 | 0/0/1/0 | 1/0/0 | n/a | 69.96 | 1/0 |
| Liu 2019 | Retrospective case series | 44:15 | 53 (36-79) | n/a | n/a | n/a | n/a | 36/23 (SNP=2) |
| Han 2018 | Retrospective case series | 11:3 | n/a | n/a | 10/4/0 | EBRT (14) | 72.14 (70-76) | n/a |
| Vlantis 2018 | Retrospective case series | 3:1 | 45 (38-53) | 2/1/0/1 | n/a | n/a | n/a | 1/3 |
| Huang 2018 | Retrospective case series | 125:37 | 58.2 (43-72) | 20/62/54/26 | 68/94/0 | EBRT (162) BT for rNPC (7) | 78.6 (68-94) | 114/48 |
| Choi 2017 | Retrospective case series | 3:1 | 62.5 (45-74) | n/a | 2/2/3 | n/a | 111.5 (68.4-126) | 1/3 |
| Adel 2016 | Case report | 1:0 | 65 | 0/0/1/0 | 0/1/0 | n/a | n/a | 1/0 |

Table S2 *continued*. Patient demographics and NPC background data.

| Study | Design | Number of NPC ORN patients (M:F) | Median age (range) | NPC stage before ORN (I/II/III/IV) | NPC Tx (CRT/RT/Sx) | Type of RT (number) | Mean total RT dose Gy (range) | Number pNPC/r NPC (number of SNP =) |
|---|---|---|---|---|---|---|---|---|
| Risso 2016 | Case report | 1:0 | 36 | 0/0/1/0 | 1/0/0 | SBRT for rNPC (1) | 93 | 0/1 |
| Brand 2015 | Case report | 1:0 | 37 | n/a | 0/1/0 | n/a | n/a | 0/1 |
| Kau 2015 | Retrospective case series | 3:0 | 61 (47-70) | 0/0/0/3 | 3/0/0 | n/a | 70 | 3/0 |
| Tiruchelvaray 2012 | Case report | 0:1 | 63 | 0/1/0/0 | 0/1/0 | EBRT (1) | 76 | 1/0 |
| Tan 2011 | Case report | 1:0 | 70 | n/a | 1/0/0 | n/a | n/a | n/a |
| King 2010 | Retrospective case series | 6:3 | 53 (37-65) | n/a | 8/1/1 | IMRT (1)<br>BT (8)<br>SBRT (1)<br>EBRT (9) | n/a | 5/4 (SNP=3) |
| Liang 2009 | Retrospective case series | 7:3 | 57 (43-69) | 1/2/0/5 | n/a | n/a | 112.8 (70-197) | 5/5 |
| Wang 2006 | Case report | 1:0 | 45 | 0/0/1/0 | 0/1/0 | n/a | 70.2 | 1/0 |
| Huang 2006 | Retrospective case series | 10:5 | 43 (32-67) | n/a | 0/15/0 | EBRT + BT (15) | 68-72[1]<br>68-84[2] | 9/6 |
| Chen 2004 | Case report | 1:0 | 55 | 0/0/1/0 | 1/0/0 | 3D EBRT + BT (1) | 73.8 | 1/0 |
| Liu 2004 | Case report | 1:0 | 59 | 1/0/0/0 | 0/1/0 | EBRT + BT (1) | 64 | 1/0 |
| Chang 2000 | Prospective case series | 3:3 | 54.5 (44-64) | 4/0/1/1 | 0/6/0 | EBRT + BT (6) | 76.5 (64.8 – 119.8) | 5/1 |
| Wu 1999 | Case report | 1:0 | 59 | 0/1/0/0 | 1/1/1 | n/a | 138 | 0/1 |

Abbreviations: NPC, nasopharyngeal carcinoma; M, male; F, female; ORN, osteoradionecrosis; Tx, treatment; CRT, chemotherapy and radiotherapy; RT, radiotherapy; Sx, surgery; pNPC, primary NPC; rNPC, recurrent NPC; SNP, salvage nasopharyngectomy for recurrent NPC; SBRT, stereotactic body radiation therapy (Cyberknife); EBRT, external beam radiotherapy (not otherwise specified); BT, brachytherapy. [1] Initial average radiotherapy dose for primary tumour. [2] Average radiotherapy dose for recurrent tumour.

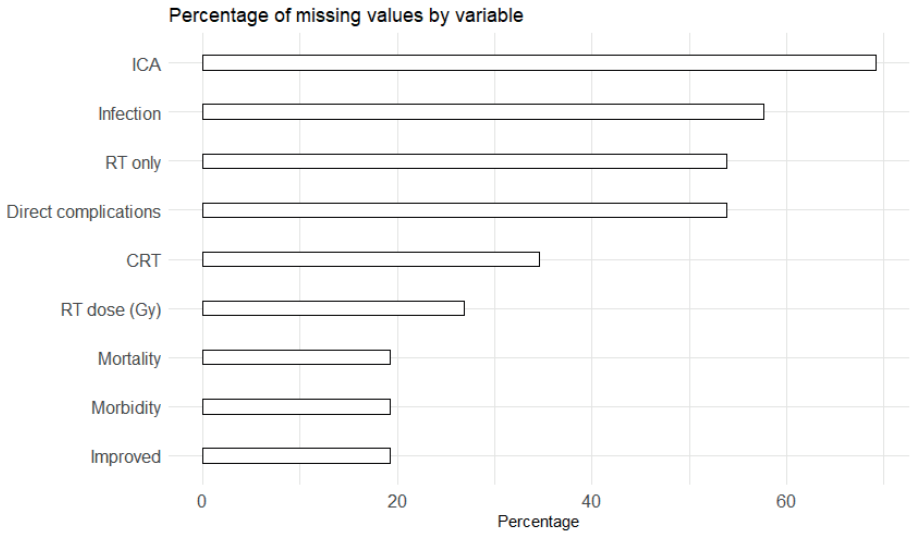
**Appendix 1. Extracted data used for correlation matrix analysis.**

| Study # | CRT | RT only | RT dose (Gy) | ICA | Infection | Direct complications | Improved | Morbidity | Mortality |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | | 145.3 | | | | | | |
| 2 | | | | | 1 | | 11 | 1 | 0 |
| 3 | | | | 11 | | | 15 | 0 | 3 |
| 4 | 2 | | | | | | 1 | 1 | 0 |
| 5 | 13 | 2 | 116 | | 15 | | 0 | 15 | 0 |
| 6 | | | 117.5 | 10 | 1 | 3 | 5 | 3 | 7 |
| 7 | 1 | | 128 | | 1 | 2 | 0 | 0 | 1 |
| 8 | 2 | | | 1 | 1 | | 0 | 2 | 0 |
| 9 | 4 | | 118 | 3 | | 1 | 2 | 0 | 2 |
| 10 | 1 | | 70.4 | | 2 | | 0 | 1 | 0 |
| 11 | 1 | | 69.96 | 1 | 1 | | 1 | 0 | 0 |
| 12 | 10 | 4 | 72.14 | | | | | | |
| 13 | 68 | 94 | 78.6 | | 44 | 20 | 58 | 8 | 24 |
| 14 | 2 | 2 | 111.5 | 4 | | 4 | 3 | 1 | 0 |
| 15 | 1 | | 93 | | | 3 | 1 | 0 | 0 |
| 16 | | 1 | | | | 3 | 1 | 0 | 0 |
| 17 | 3 | | 70 | | | 3 | 0 | 0 | 3 |
| 18 | | 1 | 76 | | 1 | 1 | | | |
| 19 | 1 | | | | | | | | |
| 20 | 8 | 1 | | | 1 | | 8 | 1 | 0 |
| 21 | | 1 | 70.2 | | | 2 | | | |
| 22 | | 15 | 146 | 1 | | | 9 | 2 | 6 |
| 23 | 1 | | 73.8 | 1 | | 1 | 1 | 0 | 0 |
| 24 | | 1 | 64 | | | | 1 | 0 | 0 |
| 25 | | 6 | 76.5 | | | | 5 | 1 | 0 |
| 26 | 1 | 1 | 138 | | 1 | 1 | 1 | 0 | 0 |

CRT = Chemoradiotherapy for NPC treatment; RT only = Radiotherapy only for NPC treatment; RT dose (Gy) = Mean radiotherapy dose from study; ICA = Internal carotid artery involvement by osteoradionecrosis; Infection = Local or CNS infection associated with osteoradionecrosis; Direct complications = Complications directly occurring as a result of osteoradionecrosis; Improved = Resolution of symptoms, imaging, blood markers and/or control of the disease following treatment for osteoradionecrosis; Morbidity = Complications arising during/after treatment for osteoradionecrosis; Mortality = Death following treatment of osteoradionecrosis due to the disease process.

**Appendix 2. Heterogeneity of data.**

This bar chart shows the percentage of missing values by variable. The variables least reported by the studies include ICA involvement and presence of CNS infection. The lack of data on these two variables means statistical findings related to these two variables are more likely to be unreliable.




**Appendix 3. Correlation matrix analysis.**

After excluding of extreme values and missing values, a correlation matrix was generated by calculating the Pearson Correlation Coefficient between each variable. "RT only," "CRT," and "RT dose" represent distinct treatment parameters and therefore do not require correlation assessment among themselves. Similarly, "improved", "morbidity", and "mortality", are mutually exclusive outcome measures that also do not require correlation assessment among themselves. Values greater than zero represent positive correlation, whereas values below zero represent negative correlation. A magnitude greater than 0.8 represents strong correlation. Some correlations could not be calculated (N/A) due to insufficient paired data.

| | ICA | Infection | Direct complications | Improved | Morbidity | Mortality |
|---|---|---|---|---|---|---|
| **CRT** | 0.58 | 0.83 | 0.02 | 0.31 | 0.84 | -0.01 |
| **RT only** | -1 | 1 | 0.76 | 0.68 | -0.02 | 0.94 |
| **RT dose (Gy)** | 0.28 | 0.11 | -0.19 | 0.42 | 0.24 | 0.43 |
| **ICA** | 1 | N/A | 0.55 | 0.67 | 0.17 | 0.51 |
| **Infection** | N/A | 1 | N/A | -0.28 | 0.98 | -0.16 |
| **Direct complications** | 0.55 | N/A | 1 | 0.3 | 0.4 | 0.17 |

**Appendix 4. Pairwise observations analysis.**

After performing the correlation matrix analysis, the number of pairwise observations between variables was assessed. A greater number of pairwise observations reduces uncertainty in the correlation estimates, while a lower number increases uncertainty.

The pairwise complete observations analysis shows that some variable pairs have very few complete cases (as low as 2-4 pairs), which means that their correlation estimates should be interpreted with caution. Notably, the ICA variable has the fewest complete pairs with other variables.

| | ICA | Infection | Direct complications | Improved | Morbidity | Mortality |
|---|---|---|---|---|---|---|
| CRT | 5 | 8 | 8 | 14 | 14 | 14 |
| RT only | 2 | 5 | 6 | 9 | 9 | 9 |
| RT dose (Gy) | 6 | 8 | 11 | 15 | 15 | 15 |
| ICA | 8 | 3 | 4 | 8 | 8 | 8 |
| Infection | 3 | 11 | 5 | 10 | 10 | 10 |
| Direct complications | 4 | 5 | 12 | 10 | 10 | 10 |

**Appendix 5. Conclusions drawn.**

Considering the results in the correlation matrix and the pairwise observations analysis, the following conclusions can be drawn:

1. CRT is strongly correlated with infection (0.83, 8 pairs) and morbidity (0.84, 14 pairs)
2. RT only is inversely correlated with ICA involvement (-1, 2 pairs), however, this was only from two pairs of data, so the correlation is likely to be erroneous.
3. RT only is strongly correlated with infection (1, 5 pairs) and mortality (0.94, 9 pairs).
4. RT dose does not have any strong correlations with any other variable.
5. ICA involvement does not have any other strong correlations with any other variable.
6. Infection has a strong correlation with morbidity (0.98, 10 pairs).
7. Direct complications do not have any strong correlations with any variables.

Note that for a correlation coefficient of $r = 0.8$, using a two-sided test with a 5% significance level ($\alpha = 0.05$) and 80% power ($\beta = 0.2$), a sample size of $N = 10$ is required to detect a meaningful correlation. Consequently, most of the above correlations are likely underpowered. The pairwise complete observations analysis shows that some variable pairs have very few complete cases (as low as 2-4 pairs), which means that their correlation estimates should be interpreted with caution. Notably, the ICA variable has the fewest complete pairs with other variables.