Pitfalls in the Staging of Cancer of Nasopharyngeal Carcinoma

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KEYWORDS

- Staging • Nasopharyngeal carcinoma • Nasopharynx • Epstein-Barr virus

KEY POINTS

- Although nasopharyngeal carcinoma (NPC) is the most common primary malignancy of the nasopharynx, it is an uncommon malignancy in much of the Western world.
- Over the last several years, there have been important changes in the terminology used for the histologic classification of NPC and important changes to the American Joint Committee on Cancer TNM staging of NPC.
- Accurate imaging assessment is critical for diagnose, to stage and plan the radiation treatment, and for ongoing follow-up and surveillance.
- This article emphasizes important nasopharyngeal anatomy landmarks and the imaging appearances and pitfalls of nasopharyngeal carcinoma, its patterns of spread, and posttreatment appearances.

INTRODUCTION

Although nasopharyngeal carcinoma (NPC) is the most common primary malignancy of the nasopharynx, it is an uncommon malignancy in much of the Western world where it has an incidence of less than 10 per 1 000 000. Over the last several years, there have been important changes in the terminology used for the histologic classification of NPC and important changes to the American Joint Committee on Cancer (AJCC) TNM staging of NPC. Imaging already plays a central role in the evaluation of nasopharyngeal disease because this region may be difficult to examine clinically. With NPC, our clinical colleagues depend on accurate radiologic assessment to diagnose, stage, and plan the radiation treatment and for ongoing follow-up and surveillance. This article emphasizes important nasopharyngeal anatomy landmarks and the imaging appearances and pitfalls of NPC and its patterns of spread and

posttreatment appearances. The updated histology and new AJCC TNM staging are presented, emphasizing key changes that are of relevance to the radiologist.

NASOPHARYNGEAL ANATOMY

The nasopharynx is the most superior portion of the tubular pharynx, located immediately caudal to the central skull base. The inferior limit of the nasopharynx is the soft palate, and it is at this level that the pharynx is deemed oropharynx. The posterior and lateral walls of the nasopharynx are in continuity with the posterior and lateral oropharyngeal walls, respectively. On axial imaging, the nasopharynx is located posterior to the nasal cavity, with which it communicates through the choanae (**Figs. 1** and **2**). The pharyngobasilar fascia of the superior constrictor muscle, which forms the wall of the nasopharynx, attaches the pharynx to the undersurface of the clivus.[1] There

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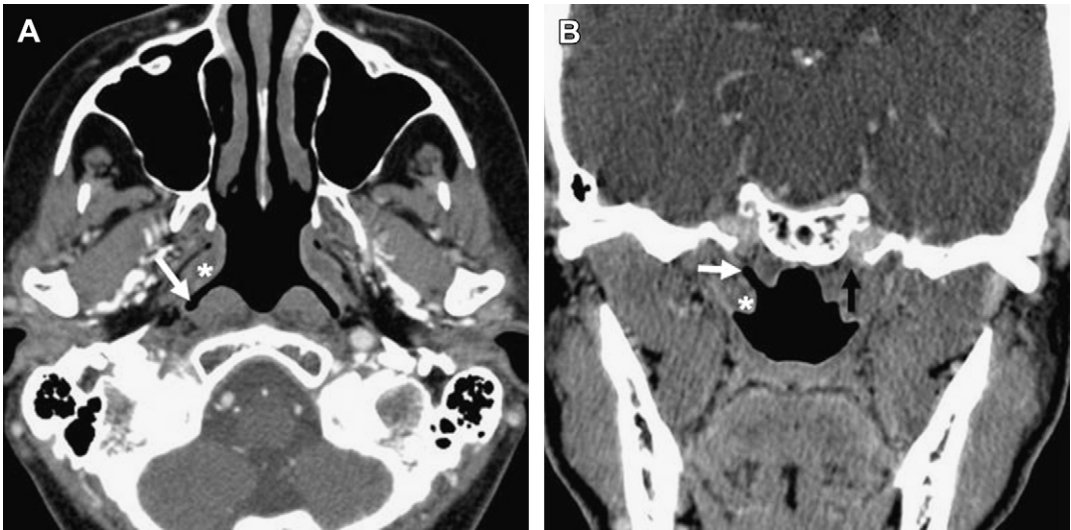*E-mail address:* christine.glastonbury@ucsf.edu

Fig. 1. Axial (*A*) and coronal (*B*) contrast-enhanced computed tomography images through the nasopharynx illustrating normal anatomic landmarks. The nasopharynx is posterior to the nasal cavity. The posterior wall in this adult has an undulating contour from the prevertebral longus capitis muscles, and the adenoidal tissue is almost completely atrophic. The lateral pharyngeal recess or fossa of Rosenmüller (*arrow*) is delineated by the lateral margin of these muscles. Note that in the axial plane the recess is posterior to the torus tubarius (*asterisk*), whereas the recess (*white arrow*) is superior to the torus tubarius (*asterisk*) in the coronal plane. The coronal plane best emphasizes the intimate relation of the nasopharynx to the central skull base and the foramen lacerum (*black arrow*).

is a small lateral hiatus or opening in this skull base attachment, known as the foramen of Morgagni, through which the eustachian (pharyngotympanic) tube and levator veli palatini muscle pass.[2] The levator veli palatini and the tensor veli palatini muscles are identifiable on magnetic resonance (MR) scans in the lateral wall of the nasopharynx and are responsible for opening the eustachian tube and for tensing and elevating the palate to prevent oronasal reflux (see **Fig. 2**). The eustachian tube communicates with the middle ear, allowing both middle ear aeration and drainage; its

Fig. 2. Sagittal fat-saturated postcontrast T1-weighted (*A*), axial T1-weighted (*B*), and axial fat-saturated postcontrast T1-weighted (*C*) images of the nasopharynx illustrating normal anatomy. (*A*) The sagittal projection demonstrates the normal adult contour of the nasopharynx. Note the sloping roof or vault, formed by the clivus (c) and sphenoid sinus (s). There is little adenoidal tissue in this adult patient. (*B*) Axial T1-weighed image shows the tensor veli palatine muscle (*white arrow*) in the lateral wall, innervated by a branch of the mandibular division of the trigeminal nerve. The levator veli palatini muscle (*black arrow*) is innervated by the pharyngeal plexus. Bright parapharyngeal fat (*asterisk*) is evident lateral to the nasopharynx. (*C*) Postcontrast imaging shows normal enhancement of the mucosa of the torus tubarius (*asterisk*) and of the mucosa lining the lateral recess (*arrows*). The prevertebral muscles are distinct from this mucosal enhancement.

opening in the superolateral aspect of the naso-pharyngeal wall is marked by the torus tubarius, an elevation of the wall of the nasopharynx formed by the eustachian tube cartilage. The foramen of Morgagni is an essential anatomic structure but is also a potential weak spot in the head and neck through which nasopharyngeal neoplasms or infections may spread directly to the skull base or laterally to the parapharyngeal fat.

The lateral pharyngeal recess (often known by its eponym, the fossa of Rosenmüller) is superolateral to the torus tubarius and the opening of the eustachian tube. On axial images, the lateral pharyngeal recess is located posterior to the torus tubarius and it is superior to the torus tubarius on coronal images (see **Fig. 1**). It is within the lateral recess (fossa of Rosenmüller) that most nasopharyngeal carcinomas arise.

The midline posterior nasopharyngeal wall connecting the two lateral recesses is superficial to the prevertebral longus capitis and longus colli muscles that attach to the basiocciput and upper cervical vertebrae. The posterior nasopharyngeal wall, as well as the roof or vault in younger patients, is the location of the nasopharyngeal

tonsillar tissue or adenoids. Adenoidal hypertrophy in response to infection may mimic neoplastic enlargement or a nasopharyngeal mass. However, reactive hypertrophy is never associated with invasion of the prevertebral muscles, and these structures are clearly delineated on MR imaging.

The overall shape of the nasopharyngeal cavity varies depending on the bulk of the prevertebral muscles and the adenoids. In older patients, the nasopharynx may appear enlarged but shallow with loss of muscle bulk and atrophy of the adenoids, whereas the nasopharyngeal cavity may be entirely obliterated in children by large adenoids.

EPIDEMIOLOGY OF NPC

There have been many changes to the terminology used for the classification of NPC. Currently, the World Health Organization (WHO) divides NPC into a histologic classification of 4 types, with epidemiology reflecting the different pathologic types (**Table 1**).[3–6] Broadly defined, NPC is defined as keratinizing (previously termed type I or squamous cell carcinoma), nonkeratinizing (NK), and basaloid squamous cell carcinoma

Table 1
Comparison of different histologic types of NPC

WHO Classification	Previous Terminologies	Epidemiology	Prognosis
Keratinizing	Type I, squamous cell carcinoma	~25% NPC cases Rare <40 y of age Men greater than women Weak EBV association Environmental risk factors	20%–40% 5-y survival
Nonkeratinizing		Overall ~75% NPC cases Most common fifth to seventh decades 70% men, 30% women Strong EBV association Genetic & environmental risk factors	
Differentiated	Type II, transitional carcinoma	~15% NPC cases	~75% 5-y survival
Undifferentiated	Type III, lymphoepithelial carcinoma	~60% NPC cases May occur in children	~75% 5-y survival
BSCC		Rare Sixth to seventh decades, mean age = 55 y Men greater than women Associated with excessive alcohol and tobacco use	Seems to be less aggressive than BSCC in other sites but overall poor prognosis

Abbreviations: BSCC, basaloid squamous cell carcinoma; EBV, Epstein-Barr virus.

(BSCC). NK NPC is further subdivided into differentiated (previously termed type II or transitional carcinoma) and undifferentiated (previously termed type III or lymphoepithelioma).

NK NPC is the most common form, with undifferentiated NK being approximately 4 times as common as the differentiated form. The subtypes of NK NPC share the same proposed epidemiologic and etiologic factors. Both are strongly associated with Epstein-Barr virus (EBV) infection, are most commonly found in Asian (particularly Chinese) men, and are most often found in patients from 40 to 80 years of age. Although pediatric NPC is relatively rare, undifferentiated NK NPC is the most common form.[7–9] The incidence rate of NPC at less than 20 years of age is higher for African Americans than for American Asians.[10] NK NPC is highly radiosensitive, which results in reasonably good 5-year survival statistics of approximately 75%.[4,7,11]

Keratinizing NPC was previously termed NPC type I and is the histologic type found in approximately a quarter of NPC cases.[5] It is graded as poorly, moderately, or well differentiated, with well differentiated being the least commonly occurring. Keratinizing NPC is not typically associated with EBV but is associated with cigarette smoking; prior radiation; and occupational exposures, such as to chemical fumes, smoke, and formaldehyde. Five-year survival is significantly lower for keratinizing NPC (20%–40%) and this is largely because of poor local control. The US statistics for relative survival at 5 years from diagnosis overall for all nasopharyngeal carcinomas varies from 47% to 78% depending on the tumor stage at presentation of stage IV to stage I, respectively.[11]

Another common malignancy to involve the nasopharynx is lymphoma arising in or secondarily affecting the adenoid tissue. Diffuse large B-cell lymphoma is the most common type to affect the Waldeyer ring and is weakly associated with EBV infection. Lymphoma mimics NPC on imaging and can be a diagnostic dilemma for the radiologist. However, lymphoma is more commonly midline in origin; when invading the skull base, it tends to expand the clivus rather than just infiltrate the marrow.

Other uncommon malignancies that involve the nasopharyngeal mucosa include adenoid cystic carcinoma (ACC) and small cell undifferentiated neuroendocrine carcinoma (SCNEC). There is a rare nasopharyngeal papillary adenocarcinoma (NPPA) that most often presents as an exophytic obstructing nasopharyngeal mass. This slow-growing low-grade neoplasm does not typically metastasize and is cured by complete excision. There are no known viral or environmental etiologic factors for ACC, SCNEC, or NPPA.[12]

AJCC SEVENTH EDITION STAGING

The seventh edition of the AJCC, published in January 2010, brought important changes to the way in which NPC is staged and these were largely simplifications of the prior system.[3,13] With regard to staging the primary tumor site (T stage), it has been determined that tumors extending to the oropharynx or nasal cavity (previously staged as T2a) did not have a worse prognosis than tumors confined to the nasopharynx (T1) and so are now staged as T1 (Box 1, Fig. 3).[3,13] Parapharyngeal space extension, which is posterolaterally spread through the pharyngobasilar fascia to the parapharyngeal fat, denotes T2 stage (Fig. 4). T3 and T4 designations remain unchanged from the prior AJCC staging system (Figs. 5 and 6).

Additional changes were made to the regional lymph node status staging (N stage), which clarified the status of retropharyngeal nodes. It was unclear before the seventh edition how to stage retropharyngeal nodal metastasis in the absence of jugular chain adenopathy. Some institutions would determine this to be N1 disease, whereas others would determine it to be N0. It has now been clarified that unilateral or bilateral retropharyngeal nodal metastases, less than or equal to 6 cm in greatest dimension, are now considered N1 disease (see Box 1, Fig. 6). No other changes were made to the nodal staging system in the current edition. The most difficult designation for radiologists remains the determination of N3b, that is, the presence of supraclavicular adenopathy. This stage is a clinical stage, determined by the anatomic boundaries of the triangle of Ho; but in the authors' practice, a low level IV or VB node, or any node on the same slice as the clavicle on cross-sectional imaging, should be specifically described as a potential supraclavicular node because it may upstage the nodal status to N3b, stage IVB (see Box 1, Fig. 7, Table 2).[3] The M designation remains unchanged as M0 for no distant metastasis and M1 for the presence of metastasis. MX is commonly used when metastatic disease status is unknown.

When looking at the overall anatomic stage/prognostic groups (stage 0–IV), the only changes made were to reflect the removal of the separate designations, T2a and T2b, again resulting in the simplification of NPC staging (Table 3).

Box 1
AJCC seventh edition nasopharynx staging

Primary tumor (T)

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma in situ

T1: Tumor confined to the nasopharynx or extends to oropharynx and/or nasal cavity without parapharyngeal extension

T2: Tumor extends to parapharyngeal fat

T3: Tumor involves bone of skull base and/or paranasal sinuses

T4: Intracranial extension and/or involvement of cranial nerves, orbit, hypopharynx, and/or extension to the infratemporal fossa or masticator space

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Unilateral nodes 6 cm or less in greatest dimension and/or unilateral or bilateral retropharyngeal nodes 6 cm or less in greatest dimension

N2: Bilateral nodes 6 cm or less in greatest dimension

N3: Metastasis in a lymph node more than 6 cm in greatest dimension or extension to supraclavicular fossa

N3a: Nodes 6 cm or more in dimension

N3b: Nodal metastasis in supraclavicular fossa

Distant Metastasis (M)

M0: No distant metastasis

M1: Distant metastasis

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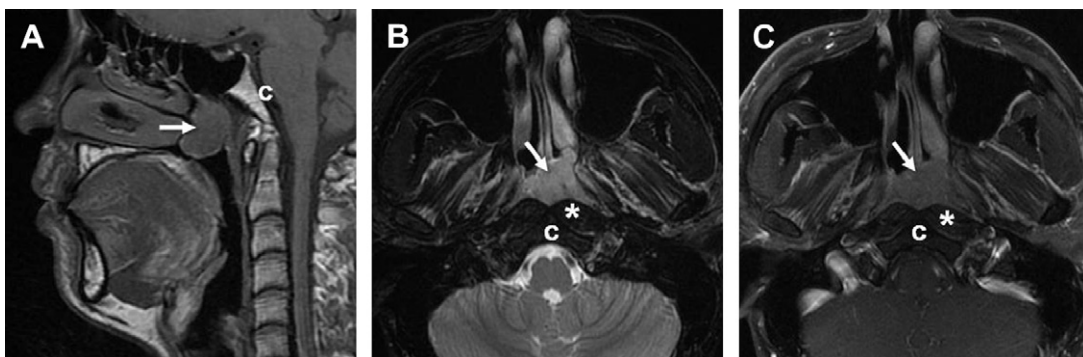

Fig. 3. A 29-year-old Asian man with 4 months of recurrent sneezing and trace epistaxis and a nasopharyngeal mass evident on ear, nose and throat examination. Sagittal T1-weighted (*A*), axial fat-saturated T2-weighted (*B*), and axial fat-saturated postcontrast T1-weighted (*C*) MR images demonstrate an asymmetric exophytic mass (*arrow*) that likely arose from the left fossa of Rosenmüller. There is no evidence of infiltration of the prevertebral muscles (*asterisk*) or parapharyngeal fat, and the clivus (c) has preserved signal intensity. There was no adenopathy in the neck on MR imaging and the whole-body positron emission tomography–computed tomography was negative. This NPC is T1N0M0 (stage I), EBV positive, and undifferentiated. It was treated with radiation alone.
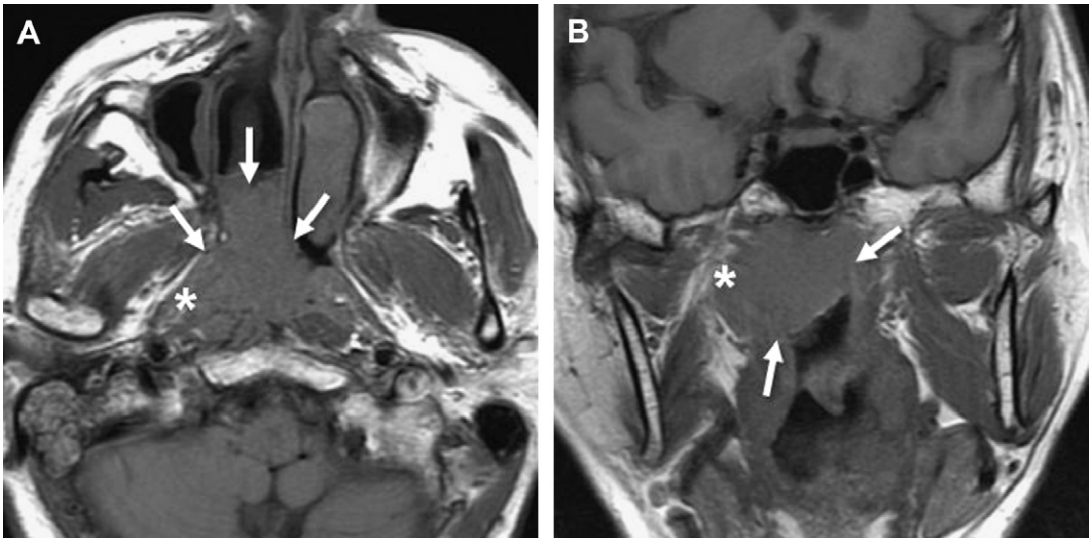
Fig. 4. Axial (*A*) and coronal (*B*) T1-weighted MR images in a 60-year-old man with nasal congestion of several months duration. The images demonstrate an asymmetric nasopharyngeal mass (*arrows*) that extends anteriorly through the right choana to the posterior right nasal cavity. There is lateral extension of the mass to the right para-pharyngeal fat (*asterisk*), indicating T2 disease. The mass infiltrates the right prevertebral muscle but does not invade the skull base. This undifferentiated NPC was staged as T2N1 (stage II disease) and treated with chemoradiation.

TRENDS IN NPC TREATMENT AFFECTING STAGING

NPC, particularly nonkeratinizing NPC, is typically a very radiosensitive tumor. Additionally, given its approximation to the skull base and pattern of spread, it is generally not amenable to surgical resection. For this reason, radiation has been the primary mode of therapy and is often augmented with systemic chemotherapy. Keratinizing NPC is
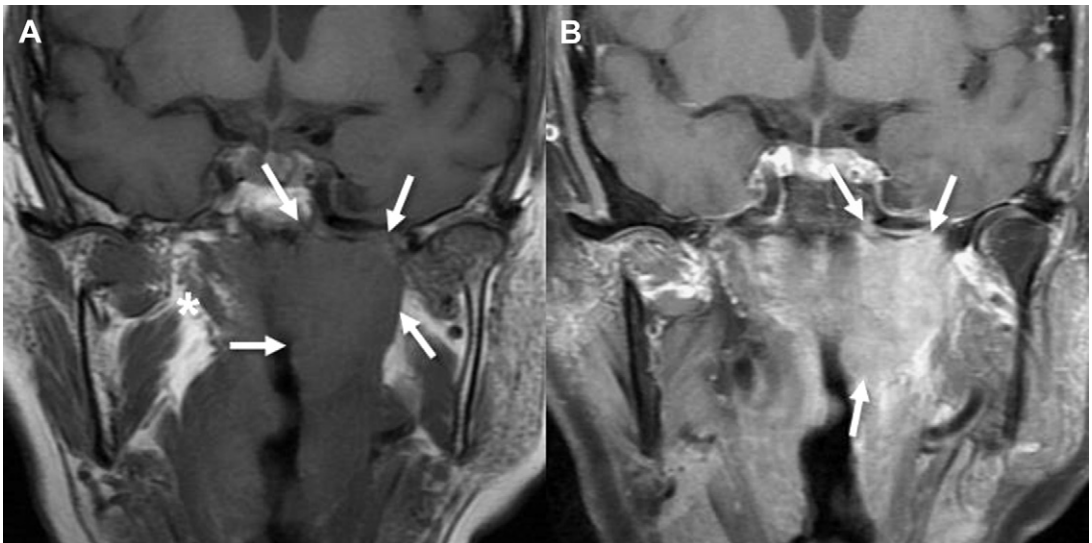

Fig. 5. A 73-year-old woman with a 2-month history of throat pain and a nasopharyngeal mass on clinical exam-ination. Coronal T1-weighted (*A*) and coronal fat-saturated postcontrast T1-weighted (*B*) MR images show a left nasopharyngeal mass (*arrows*) that extends almost down to the oropharynx. Superiorly, the mass infiltrates the skull base around foramen lacerum with subtle but real loss of the normally T1 hyperintense fatty skull base marrow. Postcontrast imaging shows enhancement of the mass and of the skull base involvement without clear intracranial extension that would have designated this as T4 tumor. The WHO II NPC tumor was staged as T3 N1, which is stage III disease. The patient is currently undergoing treatment with chemoradiation.
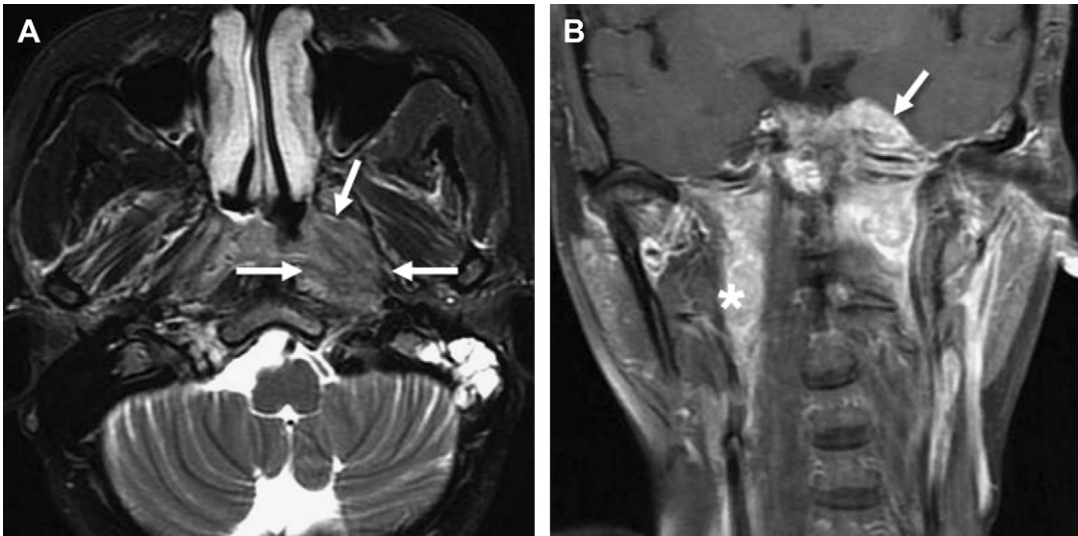
Fig. 6. Axial fat-saturated T2-weighted (*A*) and coronal fat-saturated postcontrast T1-weighted (*B*) MR images in a 44-year-old Asian woman with left-sided hearing loss and a nasopharyngeal mass on clinical examination. Axial imaging (*A*) shows an endophytic mass centered in the left fossa of Rosenmüller (*arrows*) that infiltrates the left prevertebral muscle and the lateral nasopharyngeal wall. Note T2 hyperintense secretions in the left mastoid air cells from the obstructed eustachian tube. Coronal imaging (*B*) shows that although this is not a large primary mass, it has extended cranially through the left foramen lacerum and skull base so that it is involving the left cavernous sinus (*arrow*) and the Meckel cave. Intracranial extension indicates this is T4 disease. Although there was no palpable neck adenopathy, there is a pathologically enlarged retropharyngeal node (*asterisk*) indicating N1 disease. This NPC is staged as T4, N1, or stage IVA.
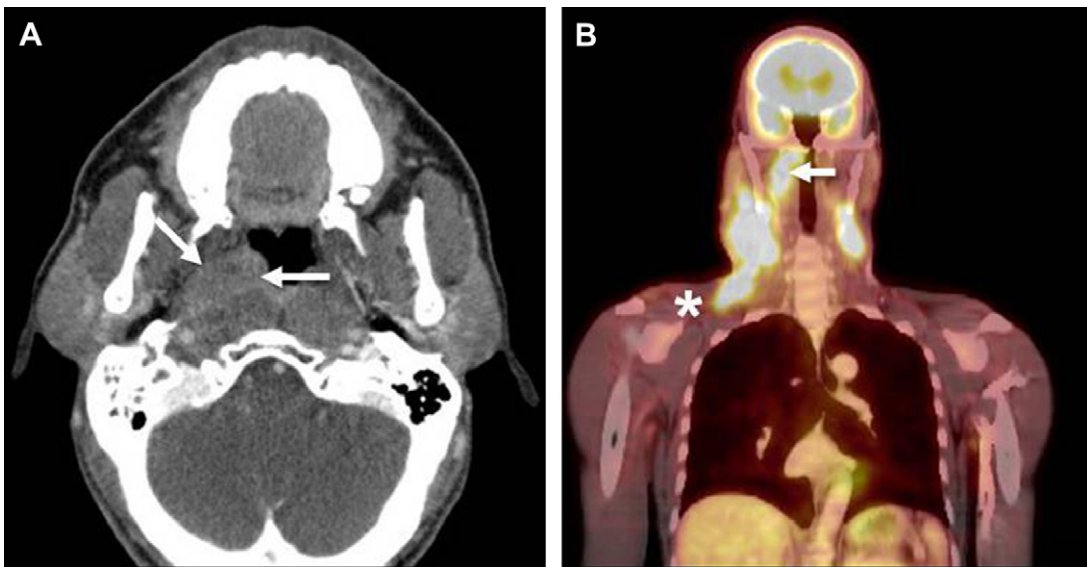

Fig. 7. Axial contrast-enhanced computed tomography (CT) (*A*) performed as part of a positron emission tomography (PET)-CT and coronal fused PET-CT (*B*) in a 49-year-old construction worker from China with a 3-year history of enlarging right neck mass and new left mass. The axial image shows minimal enhancement of a right nasopharyngeal mass that seems to invade the parapharyngeal fat. The fused PET-CT reveals intense uptake in the primary undifferentiated NPC (*arrows*) and intense uptake in bilateral neck nodes. Note the low location of the right adenopathy (*asterisk*) indicating supraclavicular nodal involvement. This NPC was staged as T2N3b, which is stage IVB, and the patient was treated with chemoradiation.

Table 2
Final tumor stage using the AJCC staging system for nasopharyngeal carcinoma, seventh edition

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T1/T2	N1	M0
	T2	N0	M0
Stage III	T1/T2	N2	M0
	T3	N0/N1/N2	M0
Stage IVA	T4	N0/N1/N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

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also treated with chemoradiation, whereas BSCC of the nasopharynx may be treated initially with surgical resection if possible.

External beam radiation therapy (EBRT) with opposed lateral fields has been the traditional form of radiation therapy for NPC. This therapy has many limitations because it is difficult to maximally irradiate the tumor while sparing vital adjacent tissues, such as the temporal lobes and brainstem.[14] Other tissues, such as the parotid glands, are almost impossible to spare with this traditional radiation therapy technique. Radiation parotitis results in xerostomia, which is the most common cause of significant morbidity in this group of patients and can be irreversible with a high dose (>40–50 Gy) to most of the gland. Intensity modulated radiation therapy (IMRT) is a form of 3-dimensional conformal radiotherapy

that allows high-dose radiation delivery to specific tissues and, therefore, improves tumor coverage. At the same time, the irradiated area is carefully contoured so as to spare normal adjacent tissues and, thus, reduce radiation-associated toxicity.[14,15] In many institutions, IMRT is replacing EBRT as the treatment of choice for NPC. This change to treatment has not so much affected staging as affected treatment planning and now requires more detailed understanding on the part of the radiation oncologist of the anatomic structures of the skull base and deep face. The head and neck radiologist can play an important role in treatment planning in concert with the radiation oncologist and specifically checking or redelineating the gross total volume (GTV) contours to ensure correct coverage of the primary tumor and nodal metastases.

T1N0M0 disease is typically treated with radiation alone. The current standard of care for treatment of NPC when there is evidence of T2-T4 or N1-N3 disease is concurrent chemoradiation followed by adjuvant chemotherapy or induction chemotherapy followed by chemoradiation.[16] Accurate TNM staging is, thus, important for treatment planning.

PATTERNS OF NPC DISEASE SPREAD

It is important to understand the potential patterns of tumor spread with any head and neck malignancy to anticipate and detect subtle findings that might upstage a tumor and potentially change therapy. NPC tends to behave with a fairly predictable pattern of local and nodal spread, although there seems to be much variability from patient to patient in the relationship of the T stage of the

Table 3
Pitfalls in staging of NPC

Pitfall	Recommendation
Failure to recognize parapharyngeal fat involvement, understaging as T1 instead of T2	Look for loss of normal fat density and precontrast T1 fat signal from the parapharyngeal fat
Indeterminate skull base invasion on CT	Perform MR imaging with close attention to precontrast coronal and sagittal T1-weighted images
Failure to recognize perineural and intracranial extension	Closely evaluate the skull base foramina on precontrast T1-weighted and postcontrast, fat-saturated, T1-weighted MR images
Underevaluating for distant metastatic disease	Recommend PET-CT to evaluate for distant metastases when N2 or N3 disease is present

Abbreviation: PET-CT, positron emission tomography–computed tomography.

primary tumor and the presence, size, and extent of nodal metastases (**Fig. 8**).

Because NPC most often arises in the fossa of Rosenmüller, small tumors can present with obstruction of the adjacent opening of the eustachian tube and stasis of secretions in the middle ear (serous otitis). Obstruction of middle ear drainage is not ubiquitous with NPC but is common. Unilateral serous otitis or the observation of unilateral middle ear/mastoid fluid on adult head imaging necessitates evaluation of the nasopharynx for a primary nasopharyngeal mass.

From this early stage as a small T1 tumor, NPC may enlarge in an exophytic fashion to fill the nasopharynx and may extend anteriorly into the nasal cavity through the choanae or inferiorly to the oropharynx. Any of these patterns of growth are considered T1 using the AJCC TNM staging system.[3] This growth is radiographically very similar to both benign lymphoid hypertrophy and
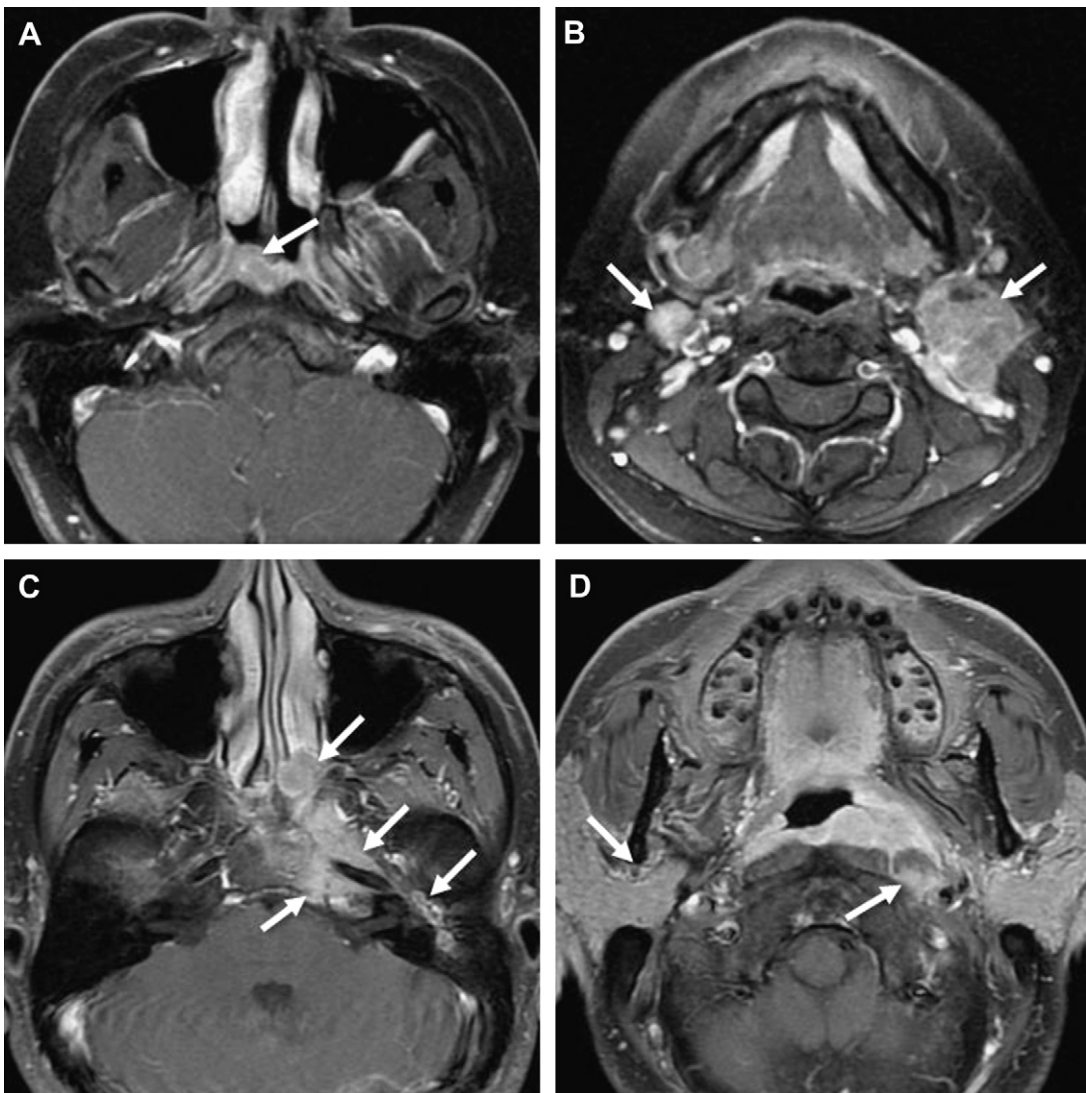

Fig. 8. Variability of N staging in relation to tumor T staging. Axial fat-saturated postcontrast T1-weighted MR images from patient 1 (*A, B*), a 25-year-old woman who presented with N2 neck adenopathy (*arrows in B*) found to be caused by a small (T1) exophytic primary right NPC (*arrow in A*). Note in particular the very large, heterogeneous left level II node. By comparison, axial fat-saturated postcontrast T1-weighted MR images from patient 2 (*C, D*), a 43-year-old man with a locally infiltrative left NPC (*arrows in C*) that spread superiorly through the skull base to involve multiple cranial nerves (T4). This patient had only one retropharyngeal node (*arrows* in *D*) evident on imaging, N1.
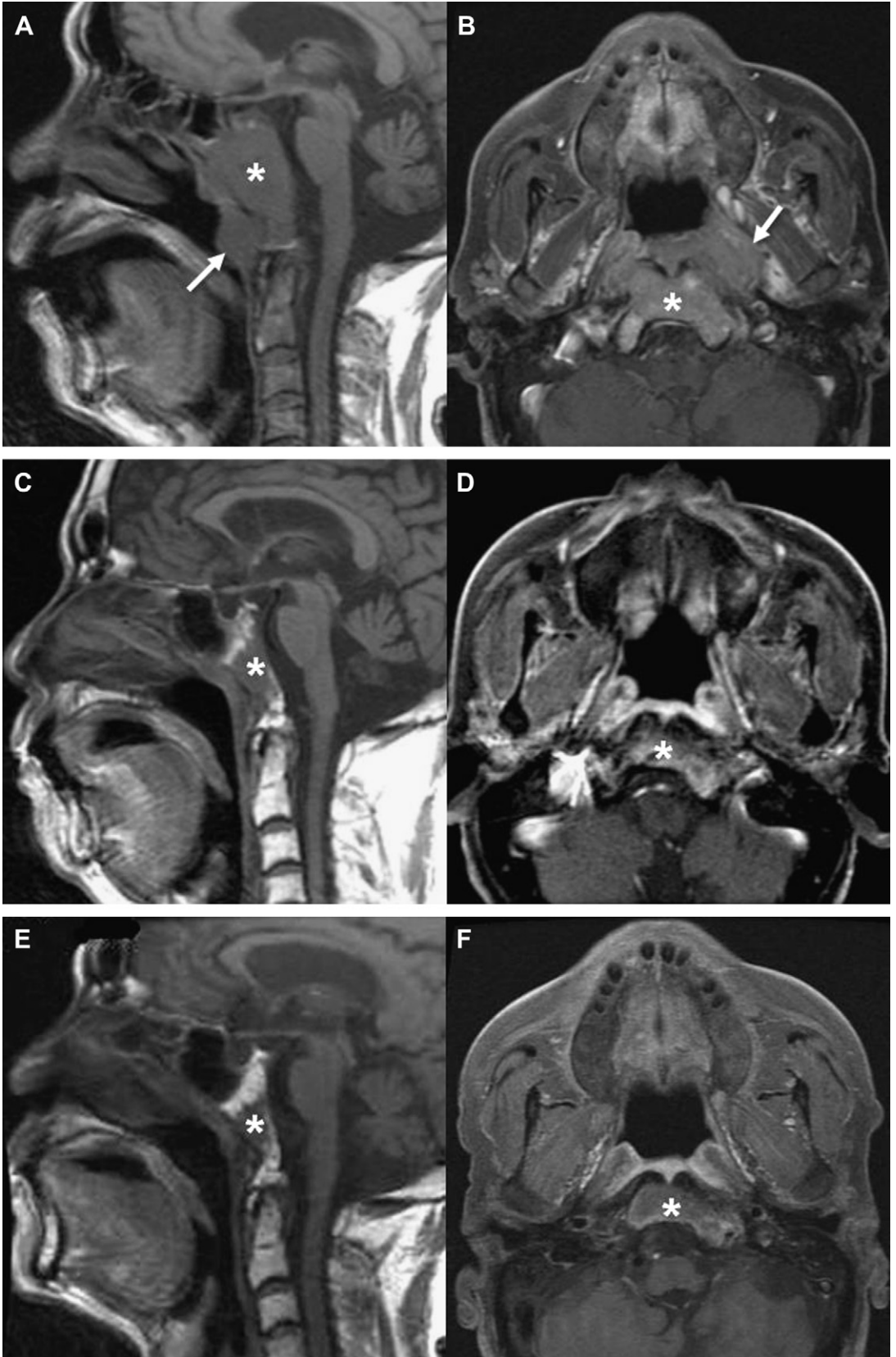
lymphoma involving the nasopharyngeal adenoids. Lymphoid hypertrophy can usually be distinguished from NPC by the striated appearance of normal lymphoid crypts on T2-weighted or postcontrast T1-weighted imaging, whereas NPC shows more homogenous mild enhancement.[17] NPC tends to be more asymmetric than lymphoma because it most often arises from the lateral aspect of the nasopharynx and not the midline tonsillar tissue.[18] Both NPC and lymphoma, but not lymphoid hypertrophy, may infiltrate posteriorly into the prevertebral muscles through the deep layer of deep cervical fascia. This infiltration does not change the staging for NPC but should heighten concern for invasion of the skull base and for metastatic nodal disease through retropharyngeal lymphatics.

Invasion of bone of the skull base can be imperceptible on computed tomography (CT) but denotes T3 stage. It is, thus, preferable that MR imaging be used for NPC staging.[3,19,20] In the authors' experience, the T1-weighted images in 3 planes, but particularly the coronal and sagittal plane, are excellent for evaluation of the normally hyperintense (fat signal) skull base marrow. When tumor abuts the skull base, loss of the fat signal indicates bone infiltration. Once this is determined, it is important to consider more extensive intracranial disease spread through the skull base foramina along cranial nerves or along the internal carotid artery. This disease spread is also best seen with MR imaging and designates T4 tumor.

NPC may also spread laterally from the nasopharynx through the pharyngobasilar fascia or through the foramen of Morgagni to the parapharyngeal fat with or without skull base invasion. Parapharyngeal fat involvement, which is well seen on either CT or MR imaging owing to the fat's low CT density and high T1 signal intensity on MR imaging, denotes T2 tumor. Further lateral spread through the superficial layer of the deep cervical fascia into the masticator space, however, upstages the tumor to T4 and is an independent prognostic factor for overall survival and local relapse-free survival.[21] Because the masticator muscles are supplied by the mandibular division

of the trigeminal nerve and are located inferior to the greater sphenoid wing, it is important to look for involvement of the foramen ovale for intracranial spread once masticator space involvement is determined. This involvement will not change tumor staging because intracranial spread is also T4, but it is important for radiation planning.

Nasopharyngeal tumors commonly spread to the retropharyngeal lymph nodes (RPN) first and then the upper jugular (level II) and spinal accessory (level V) nodal groups. RPN metastasis is now designated as N1 disease whether unilateral or bilateral. Nodal involvement follows an orderly spread down the neck to levels III and then level IV and supraclavicular nodes.[22–25] Metastatic nodal disease is often bilateral.[26] N0 disease is distinctly uncommon, and probably in the range of 4%, when staging is performed with MR imaging, which is more sensitive for detection of retropharyngeal adenopathy.

NPC has a strong tendency for systemic metastases to the bone, chest, and/or liver, with up to 5% of patients having distant metastasis at presentation. M1 tumor staging determines stage IVC disease.[7,27] Up to 30% of patients will have distant recurrence after radiation therapy.[15,28] National Comprehensive Cancer Network (NCCN) practice guidelines recommend positron emission tomography–computed tomography (PET-CT) to evaluate for distant metastases when N2 or N3 disease is present.[16]

PITFALLS IN NPC STAGING

For many institutions and practices, the greatest change to a treatment plan occurs when a tumor is designated as T2 (or more), and not T1, because chemotherapy is added to the treatment regimen. The presence of T2 disease portends a greater likelihood of distant treatment failure (ie, recurrence with metastatic disease). Thus if a T1 tumor is suspected clinically it is very important for the radiologist to look carefully for imaging features that may upstage the tumor

Fig. 9. A 66-year-old man diagnosed with T4N1 NPC (moderate to poorly differentiated nonkeratinizing) demonstrating expected changes to the skull base with treatment. All images are sagittal T1-weighted and axial fat-saturated postcontrast T1-weighted MR images. (A, B) These images were, at the time of diagnosis, demonstrating a large mass (arrow) centered in the left fossa of Rosenmüller and infiltrating the skull base (asterisk). Bilateral, left-greater-than-right cavernous sinus infiltration was also present. (C, D) These images were obtained 7 months later on completion of chemoradiation, showing almost complete resolution of the left nasopharyngeal mass. Note that the skull base shows ongoing low signal intensity (asterisk) with some enhancement, although loss of fullness of this infiltrative tumor. Surveillance images (E, F) were obtained 6 years later and show no evidence of a recurrent mass but residual loss of fat signal in the clivus (asterisk), which has minimal enhancement. The patient was asymptomatic and had a normal PET study. He remains well 30 months later.

such as parapharyngeal fat involvement (T2) and skull base involvement (T3).

The use of IMRT mandates that the radiation oncologist have a more precise knowledge of the local extent of disease to ensure that the tumor is encompassed in the radiation GTV. MR imaging is clearly the best imaging modality for evaluating intracranial and skull base involvement, which can be underestimated or completely occult on CT.[17,19,20] In addition, MR imaging, with its improved soft tissue contrast as compared with CT, makes the detection of abnormal RLN easier. In the authors' practice, the most common staging errors seen are understaging of the primary or lymph nodes when CT or, less often, positron emission tomography (PET)-CT is used without MR imaging. As described previously, fluorodeoxyglucose (FDG)-PET is of the most value when there is concern for distant metastatic disease at presentation (N2-N3 disease) or at the time of recurrence when distant metastases are more commonly found.[27,29,30]

PITFALLS IN NPC SURVEILLANCE AND APPEARANCE OF RECURRENCE

The NCCN guidelines recommend a baseline scan to be obtained within 6 months of completion of chemoradiation and only in those patients with T3-4 and/or N2-3. Further imaging is only recommended "as indicated based on signs/symptoms."[16] In the authors' practice, a baseline imaging scan is obtained at 2 to 3 months because it is perceived to be valuable for detecting subclinical residual adenopathy and also serves as a baseline to detect future more subtle recurrences.[31] Because the original tumor should have been staged with MR imaging, this modality is typically also used to establish a post-treatment baseline. The baseline scan should show significant decrease in size of the presenting primary mass, and it is not uncommon to find residual soft tissue that may represent granulation tissue and fibrosis (**Fig. 9**). If the pretreatment study showed infiltration of the parapharyngeal space, the pterygopalatine fossa, orbits, or the skull base, abnormal signal intensity may persist. The initial scan may also show significant posttreatment edema of the pharyngeal mucosa. There should be no residual enlarged lymph nodes, however; if these are found on the new baseline scan, a neck dissection is typically performed.[16] There is no defined surveillance protocol following successfully treated NPC. If further imaging studies are obtained after the baseline evaluation, any nasopharyngeal, deep face, or skull base soft tissue MR imaging signal abnormality should remain stable over this period or show further reduction in volume. The nasopharynx tends to lose its normal contours and develop a fibrosed appearance on MR imaging with effacement of the lateral pharyngeal recess primary site. This atrophic nasopharyngeal appearance also stabilizes over time, and any progression of soft tissue as compared with the baseline study must be considered recurrence until proven otherwise. Any new enlarged nodes must also be viewed with suspicion and fine-needle aspiration or biopsy is recommended.
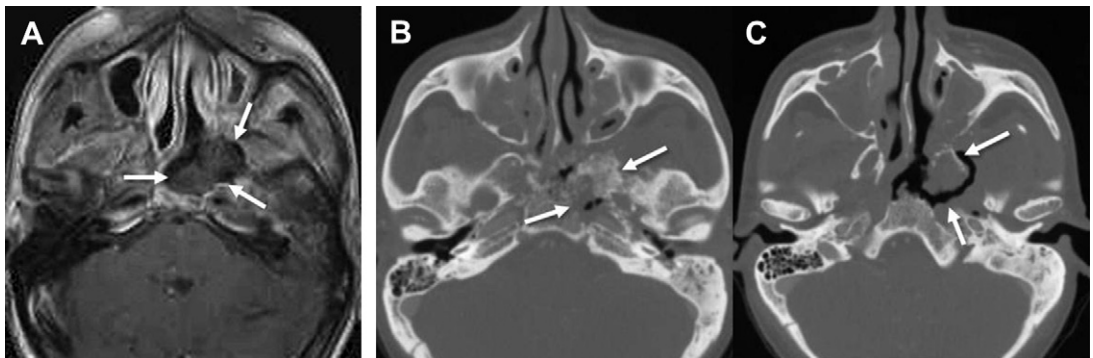

Fig. 10. Skull base osteoradionecrosis complicating treatment of a 40-year-old man treated 9 years ago with radiation for NPC. He was subsequently treated with radiation 6 years ago for local recurrence. Patient now presents with severe headaches, blurry vision, diplopia, and malodor. (*A*) Axial, fat-saturated, postcontrast, T1-weighted MR images show no solid enhancement to indicate local recurrence but an unusual appearance in the skull base with a rounded area of nonenhancement (*arrows*). (*B, C*) Axial contrast-enhanced CT images show the clivus and sphenoid left greater wing (*arrows*) to have ill-defined heterogeneous texture with air extending up to the skull base. PET showed no uptake, and operative biopsy showed necrotic amorphous material with degenerative changes.

The red marrow of the irradiated skull base becomes replaced with yellow (fatty) marrow and so appears hyperintense on T1-weighted images. If skull base invasion was present before chemoradiation, the treated tumor here tends to become scar tissue. This scar tissue is of variable signal intensity on MR imaging but tends to be hypointense on T1-weighted images, hyperintense on T2-weighted images, and may continue to enhance (see Fig. 9). Any increase in bulk of abnormal signal in the skull base on MR imaging after baseline imaging may represent recurrent disease. Osteoradionecrosis with or without osteomyelitis can be extremely difficult to differentiate from recurrent tumor, although frank bone destruction without a soft-tissue mass is most
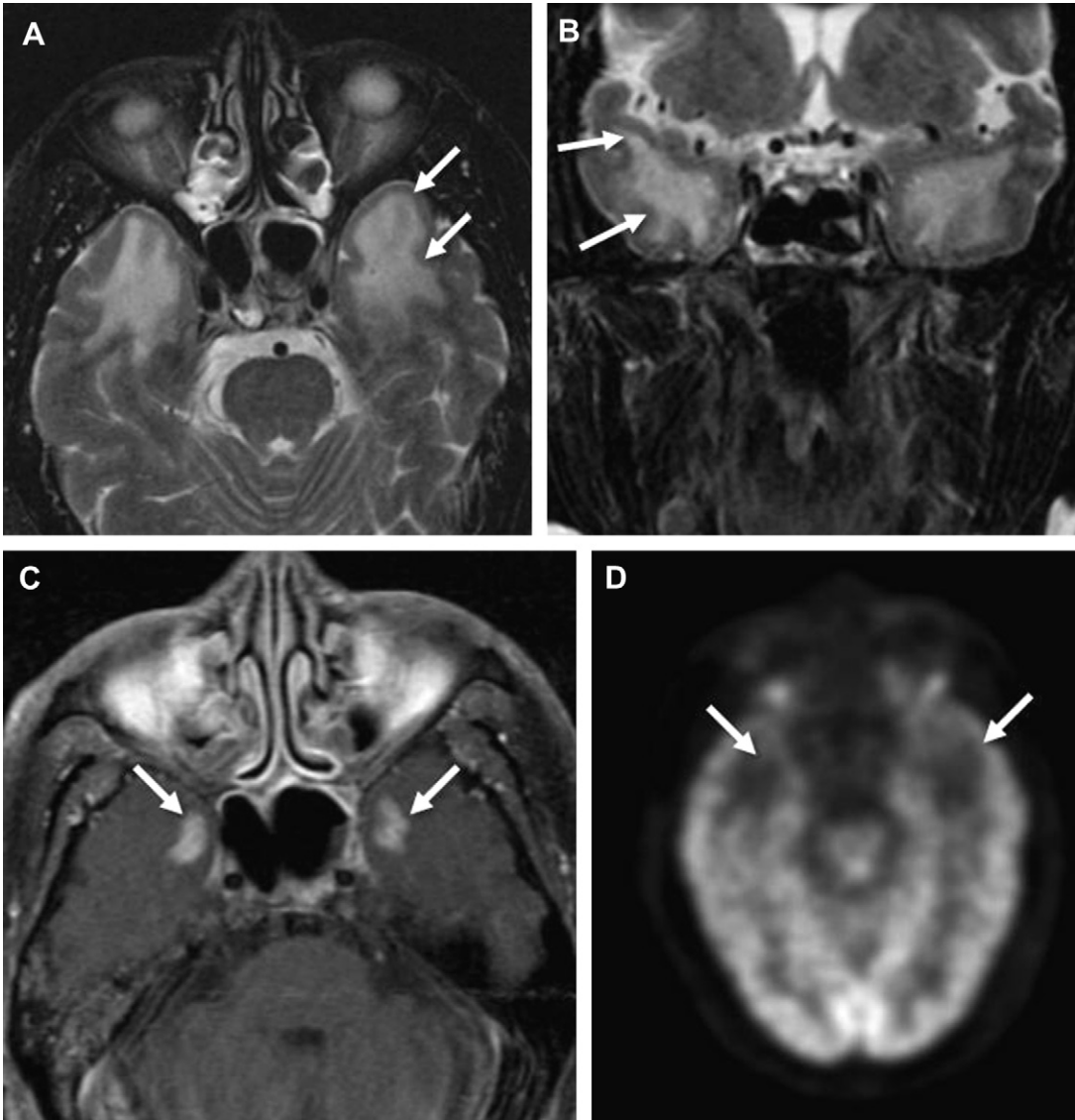

Fig. 11. Unusual case of bilateral temporal lobe necrosis in a 59-year-old man with T3N1 NPC treated with external beam radiation 8 years before and lost to follow-up. The patient returns for follow-up for nasopharyngeal wall pain from ulceration but is otherwise asymptomatic. Axial (A) and coronal (B) fat-saturated T2-weighted MR images demonstrate hyperintensity of the white matter of both temporal lobes (arrows). Both lobes appear expanded indicating edema rather than gliosis. Axial, fat-saturated, postcontrast, T1-weighted MR image (C) reveals focal enhancement of the medial aspects of the temporal lobes (arrows). The characteristic location with history is key for this diagnosis, although bilateral necrosis is very unusual. Axial FDG-PET image (D) demonstrates relative reduced uptake in both temporal lobes (arrows) as is typically seen with necrosis.

suggestive of osteoradionecrosis (**Fig. 10**).[32] CT classically shows bony cortical disruption with loss of marrow trabeculations. When a bulky soft tissue mass is seen in conjunction with bone destruction, a biopsy should be performed to exclude tumor recurrence.[33,34]

Trismus is seen in up to 35% of patients treated with traditional radiation therapy and is thought to be caused by sclerosis in the pterygoid muscles and temporomandibular joint.[32,35] MR imaging is recommended for patients with prior treated NPC and new trismus to look for evidence of perineural tumor or a recurrent mass and distinguish this from radiation-induced muscle inflammation. In some patients, extensive abnormal T2 signal and muscle atrophy is evident on MR imaging, and evidence of a clear field effect should differentiate radiation myopathy from denervation of the masticator muscles from perineural tumor involving the third division of the trigeminal nerve.[31]

One of the most serious side effects from traditional EBRT is temporal lobe necrosis, which
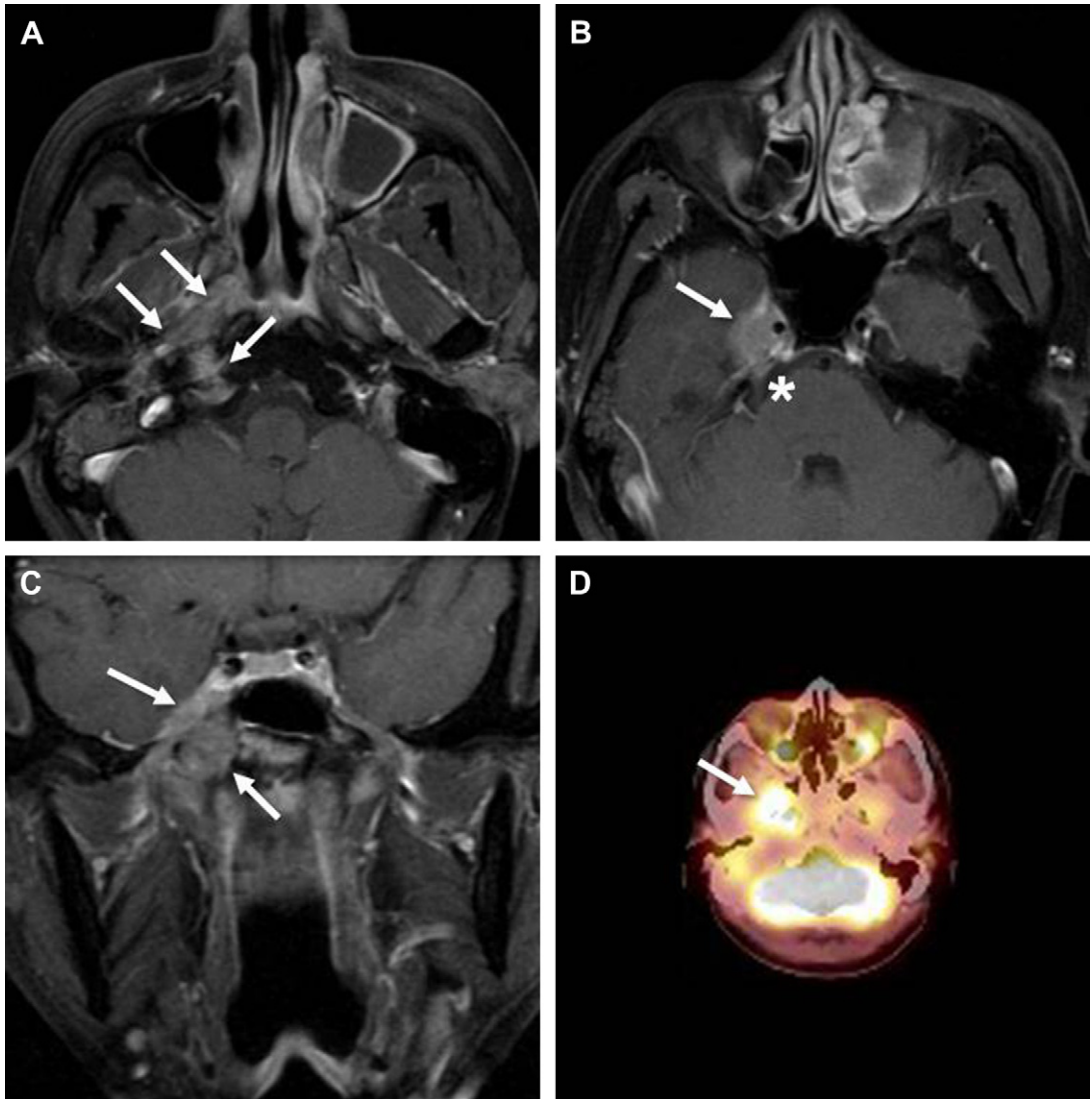

Fig. 12. Patient with local recurrence with intracranial extension. Axial (*A, B*) and coronal (*C*) fat-saturated, post-contrast, T1-weighted MR images in a 39-year-old man treated 6 years before with chemoradiation for T3N1 disease. The patient returns with facial pain, which is caused by an infiltrating mass in the right skull base that extends through foramen ovale to Meckel cave (*arrows*). Subtle perineural tumor is also seen along the cisternal segment of the trigeminal nerve (*asterisk*). Axial fused PET-CT (*D*) in the same patient reveals intense uptake at the right skull base corresponding to this local recurrence (*arrow*). This area can be difficult to evaluate on PET because of the intense, normal FDG uptake by the brain.

peaks at approximately 12 to 15 months after treatment but can occur after more than 5 years. It is seen in up to 40% of patients treated with EBRT for NPC but seems to be markedly decreased with the use of targeted IMRT.[33] Temporal lobe necrosis appears as white matter edema with T2 and fluid-attenuated inversion recovery hyperintensity and variable focal enhancement in the anteromedial temporal lobe. It typically follows a waxing and waning time course; if the edema or symptoms are severe, then it is typically treated with steroids. Temporal lobe necrosis is well described but is infrequently mistaken for metastatic brain disease. Brain metastases from NPC are uncommon and the characteristic location of this abnormality coupled with the absence of other brain lesions is key for the correct imaging diagnosis (Fig. 11).

In those long-term survivors of NPC, for which there are expected to be many, the possibility of a radiation-induced neoplasm must also be considered when reviewing follow-up examinations. Radiation-induced sarcomas of the deep face and sinuses have been reported 5 to 10 years after completion of treatment and generally have a poor prognosis.[36] Squamous cell carcinoma, particularly of the external auditory canal, may also be a late complication of traditional EBRT radiation for NPC, seen 10 to 15 years after treatment.[33]

Most NPC recurrences occur within the first 2 years after treatment and can be manifest as local or systemic; 10% to 20% of patients with local or systemic recurrence may be curable with additional treatment.[7] Any enlarging posttreatment soft tissue mass or any new deep face or intracranial enhancement is concerning for recurrent disease (Fig. 12). At the authors' institution, those patients with a suspicious MR scan typically also undergo PET-CT. Additionally, for those patients with a suspicious clinical examination, both PET-CT and MR imaging are performed to restage patients before confirmatory biopsy. MR imaging has excellent sensitivity for the detection of small recurrences and can even detect primary lesions that are endoscopically not evident.[37] Current literature shows that MR imaging trends toward higher accuracy than PET-CT in detecting local residual and/or recurrent disease. However, the combined use of MR imaging and PET-CT is more accurate for tumor restaging than either modality independently.[38]

FUTURE DIRECTIONS AND ADVANCED IMAGING

Diffusion-weighted imaging has been performed to look at primary nasopharyngeal tumors; however, it is limited by extensive artifact at the skull base. Overlapping apparent diffusion coefficient values do not permit differentiation of NPC from other tumors, such as lymphoma.[39] Diffusion may yet prove to be useful for the detection of early local recurrence and differentiation from posttreatment changes.

Early MR spectroscopic data suggest that both primary and metastatic NPC (>1 cm^3) have abnormally elevated choline (creatine ratios compared with normal muscles).[40] MR spectroscopy shows potential as an additive tool for detecting residual disease after treatment and for differentiating recurrent tumor from treated disease. This may also have a future application for predicting tumoral behavior and monitoring treatment or, with technical advances that minimize the sample volume, it may be possible to detect small nodal metastases.

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