Postoperative Imaging and Surveillance in Large Nerve Perineural Spread

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Abstract

Keywords

- magnetic resonance imaging
- perineural spread
- tumor recurrence
- head and neck malignancy
- imaging surveillance

We present a review of the imaging surveillance following treatment for large nerve perineural spread in the skull base. The expected appearance and possible complications following surgery and radiotherapy are discussed. Imaging examples of the possible sites of disease recurrence are also presented.

Introduction

Imaging forms a crucial component of surveillance following treatment for perineural spread of malignancy. There is limited research regarding the imaging follow-up for these patients; however, magnetic resonance imaging (MRI) is considered the most appropriate modality in patients with a suspicion for perineural spread.^{1,2} Early MRI detection of locoregional recurrence may allow salvage surgery, but in patients treated with chemoradiotherapy as their primary treatment modality, imaging is also used to assess response. The other purpose of surveillance imaging is to keep the patient informed of their prognosis. Even in the absence of further surgical options in the case of a recurrence, patients will generally elect to continue with imaging surveillance to remain informed.

Once a nerve has been resected, the clinician can no longer rely on symptoms related to that nerve as a sign of disease progression. Having a free flap in place also limits clinical assessment of the deep surgical bed. If the disease process spreads to involve another nerve, there may be new symptoms, but otherwise there is minimal clinical information to guide monitoring for recurrence. Thus, the dependence on progress imaging with an appropriate baseline increases.

A multidisciplinary team approach is also important, as the radiologist needs to have a good understanding of the procedure performed, the margins achieved, type of reconstruction used as well as the radiation fields. All this information is vital in interpreting the posttreatment imaging. Studies have shown that the accuracy of interpretation of imaging in the head and neck is improved when performed at a dedicated tertiary referral center.³

In this article, the imaging protocols that we use in surveillance following surgery and postoperative radiotherapy (XRT) for perineural spread in the skull base will be discussed. The spectrum of expected findings following treatment as well as the appearance of treatment complications is also described. The imaging appearance of disease recurrence, both peripherally and centrally, is also reviewed.

Imaging Protocols

Following treatment, we use the same MRI protocols as in the preoperative setting. That is, axial and coronal T1, coronal T2 fat-suppressed, postgadolinium fat-suppressed 2D T1 (slice thickness 2 mm with 0.4–1 mm spacing, on a matrix of 240 × 320 pixels with a small field of view) and a 3D isotropic T1 sequence postcontrast sequence. Occasionally,

extrasequences, such as diffusion-weighted or perfusion imaging, are added.

At our institution, positron emission tomography-computed tomography (PET-CT) or PET-MRI may be used to help with problem solving or if there is concern regarding distant or nodal disease. CT is used when the patient is unable to have an MRI or if there is a question regarding osteoradionecrosis (ORN) or bony involvement. Often, a combination of imaging modalities as well as follow-up imaging is required due to the complexities of the postoperative appearance, and difficulties in distinguishing treatment-related change and recurrence.

An MRI is generally performed at 3 months following treatment completion to have a baseline study for future comparison. Depending on the level of concern for recurrence (surgical margins, zonal classification of disease at surgery), MRI scans are performed at 6 months intervals for 3 years posttreatment and then continued annually until year 5. In a study by Warren et al,⁴ 95% of recurrences occurred within 5 years of surgery, and therefore follow-up beyond this point, is clinically directed.

Expected Appearance Following Surgery and Radiotherapy

During the first few months following radiotherapy, there are several expected changes evident within the soft tissues. These include generalized thickening of the skin, edema within the subcutaneous fat and soft tissues (►Fig. 1), thickening of the platysma muscle, increased enhancement of salivary glands, and reticular stranding within the fat spaces within the neck.^{5,6} Over time these become less pronounced and there may be progressive atrophy of structures, such as the salivary glands and lymphatic tissue (►Fig. 2). The skull base and vertebral bodies may also demonstrate fatty marrow replacement.

Fig. 1 Axial T1 image demonstrates that early postradiotherapy changes include edema within the soft tissues and reticular stranding within the subcutaneous fat on the right (arrows).

Fig. 2 Coronal T2 fs image demonstrating atrophy of the left submandibular gland (arrow), a late effect following radiotherapy.

There are multiple reconstructive options following surgery that may be used. These include free flaps or locoregional flaps with an intact vascular pedicle. The flap may contain a combination of skin, fat, fascia, muscle, and sometimes bone. It is important to have an understanding of the type of flap used as occasionally the vascular pedicle may be mistaken for a mass within the surgical bed.

Myocutaneous flaps have a variable signal intensity and enhancement in the initial postoperative setting and will change in appearances over time (►Fig. 3). Initially, the flap will be bulky with increased T2 signal and enhancement within the muscular component. Over time there are denervation and fatty infiltration of the muscle that becomes reduced in volume (►Fig. 4).^{5,7}

One of the challenges of imaging in the postoperative setting is distinguishing fibrosis and vascularized granulation tissue from residual or recurrent disease. On all imaging modalities there is an overlap of the appearances of these entities⁸ and ultimately repeat imaging or biopsy may be required. Fibrosis and granulation tissue may demonstrate variable enhancement but generally shows lower T2 signal than tumor (►Fig. 5).⁶ It can also demonstrate concave margins, as opposed to recurrence, which may be more convex and mass-like. Stability or reduction in size over time is also reassuring.

Other sequences, such as dynamic contrast enhanced sequences or diffusion-weighted sequences, have been suggested to help differentiate tumor from fibrosis.^{6,9,10} The mean ADC (apparent diffusion coefficient) value for recurrent tumor is lower than the value in areas of posttreatment fibrosis.¹¹ This is related to the cellularity of tumor in comparison with the edema seen in areas of posttreatment change. Similarly, perfusion MRI may have a role in assessing for tumor recurrence, but there is limited research validating this technique and it is not used routinely in our practice.

Another postsurgical phenomenon that we commonly see following surgery for perineural spread is a nodule of

Fig. 3 Free-flap repair following right lateral temporal bone resection and infratemporal fossa clearance. Coronal T2 fs (A) image 3 months after surgery shows residual fluid deep to the flap with generalized stranding within the fat on the axial T1 image (B).

enhancement at the site of nerve resection. We have termed this finding a “stump neuroma.” Traumatic neuromas are well described in other locations in the body and are nonneoplastic lesions created by disorganized proliferation of nerves at the site of surgery.¹²

At initial surveillance imaging in patients with clear pathological margins, there is often a focal nodule of enhancement that occurs at the point of nerve resection. For example, patients who have zone 1 disease of the infraorbital nerve usually undergo resection of the nerve at the foramen rotundum. In these cases, we may see a nodule of enhancement within the foramen where the nerve was cut (→Fig. 6). At our institution we have observed this in 40% of cases who underwent curative intent surgery over a 12-year period.¹³ Stability of the nodule of enhancement over time is reassuring and consistent with a stump neuroma. In patients with a positive margin at surgery, the

concern is for residual disease and therefore close surveillance is required. Postoperative radiotherapy is imperative in these cases to treat the microscopic residual disease. Any increase in size of the nodule suggests progressive central tumor spread.

Complications Posttreatment

Early postsurgical complications include infection, hematoma, seroma, and flap necrosis.⁶ Because of the difficulties in interpretation of imaging in this early phase as well as the ease of availability, CT is generally preferred over MRI (→Fig. 7).

Flap necrosis and failure is evident clinically and rarely requires assessment with imaging. Flap reconstructions will have variable signal characteristics and enhancement, and therefore interpretation of viability of the flap on imaging is limited.⁷

Fig. 4 Axial T1 image (A) 2 years after right orbital exenteration demonstrates a flap that has reduced in volume when compared with the initial postoperative MRI (B). There is also fatty infiltration within the muscular component.

Fig. 5 T1, T2 fs, and T1 fs postcontrast sequences in two cases of previous parotidectomy and temporal bone resection for SCC with perineural invasion. The first case (A–C) demonstrates postoperative fibrosis and the second (D–F) is of tumor recurrence in the surgical bed. Both fibrosis (A) and recurrence (D) may be intermediate signal intensity on T1, but fibrosis (B) tends to have lower T2 signal than tumor (E) and will often have more concave margins. It also does not enhance (C) as much as tumor, which can demonstrate necrosis and peripheral enhancement (F).

Infection is also clinically evident, with features such as raised inflammatory markers, fever and overt sepsis. Wound infections don't require further imaging unless there is a suspicion of a deep collection or abscess. CT with contrast is

generally adequate to define this. In the initial postoperative phase, there may be small fluid collections around the flap. These do not demonstrate peripheral enhancement, as opposed to an abscess that will enhance at the margins (►Fig. 8).

Fig. 6 Coronal T1 fs postcontrast image demonstrates a nodule of enhancement within the right foramen rotundum at the site of surgical resection of V2 (arrow). This was stable over multiple scans, consistent with a stump neuroma.

A resolving hematoma or organizing fluid collection can also show peripheral enhancement, and fluid aspiration may be needed to confirm or exclude the presence of infection.

Cerebrospinal fluid (CSF) leak is an uncommon occurrence following skull base surgery for perineural spread. It may occur in the setting of a craniotomy or orbital exenteration, and is generally the result of opening Meckel cave when resecting the Gasserian Ganglion. This may be evident at surgery and is repaired at the time of operation. Alternatively, the leak may become apparent in the postoperative period. Imaging may demonstrate a fluid collection adjacent to the

Fig. 7 Day 1 postoperative CT following an orbital exenteration and right pterional craniotomy demonstrates a small right middle cranial fossa subdural hematoma. This resolved without surgical intervention.

craniotomy site or within the orbit (**Fig. 9**). Persistent pneumocephalus also raises suspicion for CSF leak.¹⁴

ORN can affect any part of the bone within the radiation field but is most common in the mandible.¹⁵ The greatest risk for development is within the first 12 months following radiotherapy. Radiologic features include cortical erosion, bony sequestration, pathologic fracture and marrow infiltration. Occasionally there may be gas within the bone and fistula formation. Clinically, necrotic bone may be on view. ORN is rare in the skull base and temporal bone but demonstrates similar radiologic changes.

Radiation necrosis is a rare complication of radiotherapy that typically occurs within 3 years, although it has been reported to occur as late as 10 years posttreatment. The risk increases with the radiation dose given as well as the type of radiation and technique used.¹⁶ Given the proximity of the cranial nerves and skull base to the parenchyma, it may be encountered in the setting of treatment for perineural spread (PNS). On imaging, this will present as a focal area of abnormal T2 high signal with central necrosis and peripheral enhancement, predominantly involving white matter (**Fig. 10**). There may also be foci of hemorrhage or susceptibility artifact within the involved regions.¹⁷ Review of the radiation fields is helpful to confirm that the area of abnormality lies within the planned target volume, and therefore is consistent with radiation necrosis rather than a primary brain neoplasm or metastasis.

Tumor Recurrence

In patients with perineural spread, tumor recurrence can occur locally, within the radiation field, or locally out of the field. Within the radiation field the recurrence may occur centrally or peripherally. Centrally, there may be proximal tumor spread along the cranial nerves toward the brainstem or direct invasion into the neuroparenchyma. Peripheral recurrence occurs within the distal nerve and soft tissues.

Tumor recurrence often occurs at the margins of the flap (**Fig. 11**), within the surgical bed (**Fig. 12**) or at elsewhere within the skin. In the early posttreatment stage, it is difficult to distinguish posttreatment fibrosis from tumor and in some cases the only option is to rescans the patient at a short interval (3 months). Imaging guided-biopsy can also be offered although fine-needle aspiration (FNA) has limitations following radiotherapy and often a core biopsy will be required.

The most common imaging finding in patients with local tumor recurrence is a solid or cystic mass¹⁸ generally within the surgical bed. The signal intensity of recurrent tumor is variable on T2 but tends to be isointense to muscle on T1. Enhancement of the tumor is typical. On diffusion-weighted imaging, tumor typically has lower ADC values than scar tissue.

With our treatment regimen of aggressive surgery and postoperative radiotherapy (XRT), we have found that most patients have peripheral failure, that is, failure at the skin and soft tissues supplied by the nerve. Because of this, we consciously examine the subcutaneous tissues adjacent to the flap and the region adjacent to the original primary tumor and resection to assess for early recurrence.

Fig. 8 A 60-year-old man with zone 2 perineural spread of cutaneous SCC involving V2, V3, and auriculotemporal nerve, treated with right hemimandibulectomy, parotidectomy, lateral temporal bone resection, and infratemporal fossa clearance. At day 10 postsurgery he developed a collection deep to the flap. This is seen on ultrasound (**A**) as a heterogenous hypoechoic collection superficial to the flap. On CT (**B**), the collection demonstrates a thin rim of enhancement (arrow), suspicious for developing infection.

Some patients will have multifocal cutaneous disease, which means that they may have multiple nerves involved. In the posttreatment setting, close attention should be paid to all of the commonly involved nerves as well as the contralateral side. In these cases, detection of involvement of the contralateral side is difficult in the absence of a “normal” side for comparison (►**Fig. 13**). There is also the potential for spread of perineural tumor across the midline peripherally because of crossover anastomoses that occur between cutaneous branches of the nerves.¹⁹

Central failure occurs when there is ongoing perineural spread along the involved nerve toward the brainstem. In this case, there is enhancement and thickening of the

involved nerve that progresses on follow-up imaging (►**Fig. 14**). In patients with positive surgical margins or zone 2 disease, there is an increased likelihood of central progression.

Central failure may also include subarachnoid or meningeal spread of tumor or direct invasion of the neuroparenchyma. When the dura has been opened during surgery to access the gasserian ganglion, there is the potential to seed tumor into the subdural and subarachnoid space. ►**Fig. 15** demonstrates subarachnoid spread of tumor that occurred approximately 2 years after left orbital exenteration and resection of the trigeminal nerve branches to the ganglion for zone 2 disease.

Fig. 9 CT of the head with contrast demonstrates significant pneumocephalus and a fluid collection with the orbit in a patient 10 days after orbital exenteration for perineural spread of V1 on the right. This was treated conservatively with a lumbar drain with spontaneous resolution of the leak.

Fig. 10 Radiation necrosis of the left temporal lobe that developed 2.5 years after left lateral temporal bone resection and XRT for perineural spread involving the facial and auriculotemporal nerves. There is extensive FLAIR high signal within the white matter of the left temporal lobe (A) with multiple foci of ring enhancement conforming to the radiation fields (B).

Fig. 11 Large free-flap repair in a 49-year-old man who underwent right lateral temporal bone resection and infratemporal fossa clearance for extensive cutaneous SCC involving both V3 and VII. The field of view on the axial T1 image (A) almost misses the nodular recurrence at the posterior margin of the flap. This is more easily seen on the postcontrast T1 sequence (B).

Regional nodal disease occurs in approximately 10% (9–16%) of patients with perineural spread^{4,20,21} and, likewise, nodal recurrence following treatment is also low. As such, our MRI protocol for surveillance includes a single coronal STIR (short tau inversion recovery) sequence of the neck to assess for nodal disease. If clinical assessment of the neck is concerning for nodal involvement, a CT or PET may also be performed to assess for this (►Fig. 16). Ultrasound-guided biopsy may also be indicated to assess for nodal disease.

Conclusion/Summary

Perineural spread is associated with high mortality rates and recurrence is common following treatment. The clinical assessment is often limited due to the changes in sensation and function that occur following nerve resection. Radiologic appearances are also difficult to interpret with an overlap of features between recurrent tumor and posttreatment change. Other findings such as denervation change can also occur in the setting of nerve resection.

Fig. 12 A 45-year-old man with recurrence in the surgical bed following right parotidectomy and lateral temporal bone resection for SCC with perineural spread. There is a nodule of enhancement deep to the free flap, adjacent to the right mandibular condyle (arrow) on this axial postcontrast T1 fat-suppressed image. Multiple foci of susceptibility artifact within this region (asterisk) represent surgical clips (A). On the coronal T2 with fat suppression (B), the nodule is hyperintense as opposed to fibrosis, which is often lower signal on T2.

Fig. 13 A 56-year-old man with perineural tumor spread in V1 on the left that developed 2 years after orbital exenteration for zone 2 disease of V1 on the right. Coronal postcontrast T1 fs image illustrates the postsurgical change on the right and a thickened and enhancing frontal branch of V1 on the left (arrow).

The radiologist needs to have a high index of suspicion for recurrence when reading posttreatment scans but also be aware of the normal posttreatment appearances. It is important to have a close working relationship with clinicians to have a good understanding of the surgery performed and radiation fields to assist in interpretation.

Fig. 14 Axial T1 fs postcontrast image of a 63-year-old man who developed central progression into the preganglionic segment of the left trigeminal nerve. He originally underwent a left orbital exenteration for zone 2 disease of V1, which had positive margins at surgery.

Key Points

- Distinguishing posttreatment change from tumor recurrence is challenging and will often require follow-up imaging.
- Knowledge of the surgery performed, pathologic margins achieved, and the radiation fields are important in interpreting imaging studies after treatment.
- A stump neuroma is a nodule of enhancement that occurs at the point of nerve resection that remains stable on follow-up imaging.

Fig. 15 Axial (A) and coronal (B) postcontrast T1 images demonstrate subarachnoid spread of tumor that occurred approximately 2 years after left orbital exenteration and resection of the trigeminal nerve branches to the ganglion for zone 2 disease involving both the facial and maxillary nerves.

Fig. 16 PET-CT in a patient with extensive nodal metastases within the neck, left axilla, and superior mediastinum 1 year after treatment for cutaneous SCC with involvement of V2. The nodal disease was felt to be secondary to a large recurrence in the surgical bed, rather than related to the perineural spread of tumor.

- Close attention should be paid to the margins of the flap and the surgical bed, as these are common locations for recurrence.
- Contralateral tumor spread may be difficult to identify after treatment as there is no normal side for comparison

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