The Sensitivity and Specificity of High-Resolution Imaging in Evaluating Perineural Spread of Adenoid Cystic Carcinoma to the Skull Base

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Objective: To evaluate the sensitivity and specificity of computed tomography (CT) and magnetic resonance imaging (MRI) in detecting perineural spread (PNS) of adenoid cystic carcinoma of the head and neck to the skull base.

Design: Adenoid cystic carcinoma of the head and neck frequently exhibits PNS across the skull base. Failure to detect PNS before treatment can have significant negative consequences on the planning and outcome of therapy. High-resolution CT, MRI, or both are used to evaluate the presence of PNS; however, their accuracy in detecting perineural involvement has not yet been determined.

Patients: Twenty-six consecutive patients with adenoid cystic carcinoma, who were treated with cranial base resection, were included in this study. The surgical resection specimens of all patients were thoroughly examined by 1 pathologist for the presence of PNS along cranial nerves or their named branches. A total of 38 nerves were examined, and PNS was defined as the presence of tumor in the perineural or endoneural space. The results of the preoperative imaging studies (CT and/or MRI) were then reviewed retrospectively by 1 head and neck radiologist, who was unaware of the pathology report. Radiological evidence of PNS was considered to be present on CT, MRI, or both if nerves showed evidence of thickening (regardless of enhancement), contrast enhancement (regardless of size), or widening of their bony foramina or canals.

Results: Histopathologic evidence of PNS was present in 25 (66%) of 38 named nerves. The sensitivity and specificity of CT in detecting PNS were 88% and 89%, respectively. Magnetic resonance imaging had a higher sensitivity (100%) and specificity (85%).

Conclusions: Perineural spread across the skull base is a frequent occurrence in patients with adenoid cystic carcinoma of the head and neck. Magnetic resonance imaging has a higher sensitivity and specificity than CT in detecting PNS along the base of the skull.

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Invasion of the Skull Base by Head and Neck Cancer Frequently Necessitates Combined Extracranial and Intracranial Approaches to Achieve Safe and Complete Oncologic Resection. Perineural spread (PNS) is common in head and neck malignancy, especially adenoid cystic carcinoma (ACC). Perineural spread is a precursor of cranial nerve infiltration, skull base invasion, and cavernous sinus involvement. These findings have a profound negative effect on survival and may drastically change the therapeutic plan, including the surgical approach and adjuvant therapy. Patients with cancer of the nasal cavity, paranasal sinuses, nasopharynx, orbit, and parotid gland commonly have PNS along branches of cranial nerves I through VII. This provides a route of invasion of the cranial base along the cribiform plate, optic canal, superior and inferior orbital fissures, foramina ovale and rotundum, the vidian canal, and the stylomastoid foramen. Tumors extending to the parapharyngeal space, carotid sheath, and infratemporal fossa may have PNS along the lower cranial nerves (IX-XII). This provides a route of invasion of the skull base along the jugular foramen and hypoglossal canal. Cranial base invasion usually heralds intracranial extension of tumor. Although the dura is an effective barrier that delays, to a certain extent, brain invasion, dural involvement has a major negative effect on the survival of patients with skull base cancer. Eventually, brain in-
volvement does occur, especially with recurrent or incompletely resected tumors, which has a grave effect on prognosis. Failure to detect PNS before surgical resection may result in poor planning of the surgical approach and inability to obtain tumor-free margins. Although postoperative radiation, chemotherapy, or both have been advocated in the treatment of patients with positive margins, the outcome of such patients is still poor.6,7 Detecting PNS is, therefore, critical before initiating therapy of head and neck and skull base tumors.

Although PNS may present with sensory or motor deficits, it is often asymptomatic. High-resolution imaging is, therefore, of paramount importance in such cases to detect perineural involvement. The criteria of nerve involvement on computed tomography (CT) rely on bony changes in the foramina, fissures, or canals where nerves normally traverse the skull base. These changes include bone erosion, sclerotic margins, and widening of the normal diameter of these cranial base channels (Figure 1A). However, these findings are late indicators of PNS.1 Presumably, PNS can be detected earlier on magnetic resonance imaging (MRI), because of better soft tissue delineation. The capability of MRI to detect the different signal intensity of tumor, fat, nerve, cerebrospinal fluid, meninges, and brain is thought to allow for better assessment of PNS. The criteria of nerve involvement on MRI include replacement of normal perineural fat with tumor, enhancement with gadolinium (regardless of size), and increased size of the nerve in question (regardless of enhancement) (Figure 1B).1 Although commonly used, the accuracy of these criteria in detecting PNS has not been validated by comparing them with histologic findings. The objective of this study is to determine the sensitivity and specificity of CT and MRI in detecting PNS of ACC of the head and neck to the skull base.

**METHODS**

**PATIENT CHARACTERISTICS**

Twenty-six consecutive patients with ACC of the head and neck, who were treated with cranial base resection, were included in this study. The site of origin of these tumors included the parotid gland, paranasal sinuses, and nasopharynx. All patients were examined and treated by a multidisciplinary cranial base team, including a neurosurgeon, a head and neck surgeon, and a neuroradiologist (J.W.). All patients underwent surgical excision of the primary tumor via a combined intracranial and extracranial approach.

**HISTOPATHOLOGIC EXAMINATION FOR PNS**

The surgical resection specimens of all patients were thoroughly examined by 1 pathologist for the presence of PNS along cranial nerves or their named branches. The specimens were paraffin embedded, serially sectioned along the entire length of the resected nerve, and stained with hematoxylin-eosin. A total of 38 nerves were examined, and PNS was defined as the presence of tumor in the perineural or intraneural space (Figure 2).

**IMAGING**

All patients underwent preoperative high-resolution imaging: CT, MRI, or both. Computed tomography was done with and without contrast, using soft tissue and bone algorithms, to obtain axial and either direct or reformatted coronal views. Magnetic resonance imaging was performed using head and neck coils to obtain T1-weighted images with and without gadolinium (fat suppressed) and T2-weighted images in the axial, coronal, and sagittal planes. The preoperative imaging study results (CT and/or MRI) were then reviewed retrospectively for evidence of PNS by 1 head and neck radiologist (J.W.) who...
was unaware of the pathology report. The criteria of PNS on CT included nerve thickening or bone erosion, sclerotic margins, and widening of the normal diameter of the foramina, fissures, or canals where nerves normally traverse the skull base (Figure 1A). The criteria of PNS on MRI included replacement of normal perineural fat with tumor, enhancement with gadolinium (regardless of size), and increased size of the nerve in question (regardless of enhancement) (Figure 1B).

DEFINITIONS OF IMAGING RESULTS

The following definitions were used for specificity and sensitivity analysis: true positive, positive imaging results and positive pathological results; false positive, positive imaging results and negative pathological results; false negative, negative imaging results and positive pathological results; and true negative, negative imaging results and negative pathological results.

Sensitivity was defined as the ability of imaging to detect the presence of nerve involvement, and was calculated as follows: Sensitivity = \( \frac{\text{True Positive}}{\text{True Positive} + \text{False Negative}} \times 100 \).

Specificity was defined as the ability of imaging to detect the absence of nerve involvement, and was calculated as follows: Specificity = \( \frac{\text{True Negative}}{\text{True Negative} + \text{False Positive}} \times 100 \).

RESULTS

Perineural spread was detected by histopathologic examination in 25 (66%) of 38 nerve specimens. Preoperative high-resolution CT and/or MRI studies were evaluated for the presence of PNS for all 38 nerves (22 combined CT and MRI studies, 11 CT studies only, and 5 MRI studies only). The results of CT scans in the detection of PNS in 33 nerves were as follows: true positive, 21; true negative, 8; false negative, 3; and false positive, 1. The results of MRI in the detection of PNS in 27 nerves were as follows: true positive, 14; true negative, 11; and false positive, 2. There were no false-negative results for MRI. The sensitivity and specificity of CT in determining PNS were 88% and 89%, respectively. The sensitivity and specificity of MRI were 100% and 85%, respectively.

COMMENT

Adenoid cystic carcinoma has a peculiar tendency to spread along nerves. The reported incidence of PNS in patients with ACC is widely variable and ranges from 20% to 80%. The identification of PNS during histopathologic examination of ACC specimens depends largely on the diligence of the examining pathologist, which explains, at least in part, the wide range of the reported incidence of PNS in ACC. The pathogenesis of perineural involvement is poorly understood and was initially thought to be due to spread of tumor through perineural lymphatics. According to this theory, spread occurs by emboli along the perineural lymphatics and, therefore, skip metastasis can occur with no direct continuity with the main tumor mass. If this mechanism were true, the achievement of negative surgical margins via en bloc resection of ACC would be not only impossible to guarantee but also meaningless. However, this notion of perineural lymphatic emboli was dispelled by well-executed studies that showed that neural spread occurs by direct invasion of malignant cells through the path of least resistance, in the perineural space, endoneural space, or both (Figure 2). This theory assumes microscopic continuity of perineural tumor with the primary tumor and provides the rationale for striving to achieve negative surgical margins of nerves involved by ACC.

Although PNS is characteristic of ACC, this neurotropic tendency for spread has been reported in a variety of other tumors, such as squamous cell carcinoma, malignant melanoma, lymphoma, basal cell carcinoma, adenocarcinoma, mucoepidermoid tumor, rhabdomyosarcoma, chondrosarcoma, malignant mixed tumor, and esthesioneuroblastoma. Recently, several studies have shown that neural cell adhesion molecules may have a role in the pathogenesis of PNS of malignant tumors, including ACC and squamous cell carcinoma.

Perineural spread can occur in an axial and a circumferential pattern along the involved nerve, and further spread can occur in an antegrade or retrograde fashion. The maxillary, mandibular, and vidian nerves are the most frequently involved and allow PNS of sinonasal ACC through the foramina rotundum and ovale and the vidian canal. This probably reflects the more frequent occurrence of ACC in the palate and sinonasal region. Perineural spread of ACC along these nerves provides an avenue for skull base invasion. Eventually, tumor cells may reach the trigeminal (gasserian) ganglion, pterygopalatine ganglion, or cavernous sinus (Figure 3). These neural pathways may act as “relay stations” and provide access for further PNS in a centripetal (toward the brain) or a centrifugal (peripheral) fashion.

Perineural involvement is more frequent in advanced, recurrent, and high-grade tumors. The presence of PNS in patients with cancer of the head and neck is associated with a poor prognosis. Whether this is because of an inherently aggressive behavior of tumors with neurotropic tendency or because of the difficulty of obtaining tumor-free margins of resection in these patients is still unclear. There is little doubt, however,
leagues evaluated the accuracy of CT in determining imaging criteria to define PNS, Mukherji and colleagues in the same patient population. Using the same specificity of CT and MRI in detecting PNS to the skull base in the same patient population. Concurrently compared the sensitivity and the specificity of these imaging modalities in the same patient population. In their criteria, they included “proximity” of a nerve to an area of abnormal tumor enhancement. This may explain the high false-positive rate and related low specificity in their study. This addition might enhance sensitivity (ie, the ability of MRI to detect the presence of PNS). In our study, however, we found similar (100%) sensitivity, but without the loss of specificity (ie, the ability of MRI to detect the absence of PNS).

The high sensitivity and specificity of MRI in detecting PNS reported in our study may also be related to the routine application of the fat suppression technique. Although PNS is best shown as nerve enhancement or thickening on T1-weighted contrast images, determining PNS may not always be possible in these images because of the high signal intensity of fat, which is abundant in the parapharyngeal space and skull base. In these circumstances, the fat suppression technique is highly beneficial. However, 1 limitation of our study is that not all patients underwent CT and MRI, which precludes direct comparison of the sensitivity and specificity of these imaging modalities in the same patient population.

In conclusion, preoperative identification of PNS had a drastic effect on planning the surgical approach. For example, in several patients in this series, demonstration of PNS to the skull base by imaging led to the addition of an intracranial approach to the planned extracranial resection. This also has a significant effect on counseling patients regarding not only the extent of resection but also the expected loss of nerve function should the nerves in question be resected. The results of this study indicate that MRI is more sensitive and specific in detecting PNS of ACC across the skull base. In fact, in some patients, CT scans failed to detect PNS that was discovered only by MRI and confirmed histopathologically. If these patients had not been evaluated by MRI, a craniotomy would not have been planned and the tumor would have been incompletely resected. Most patients with cancer of the head and neck are usually evaluated with a CT scan for staging the disease. In patients with malignancy (especially ACC) of the sinonasal tract, nasopharynx, parotid, parapharyngeal space, and infratemporal fossa, we recommend the addition of MRI to better evaluate the presence and extent of PNS across the cranial base.

In conclusion, PNS across the skull base is common in patients with malignant tumors, especially ACC, of the head and neck and is associated with poor prognosis. Detection of PNS to the cranial base is critical in planning the proper surgical approach so that complete resection may be achieved. Using the imaging criteria defined in this study, MRI is more sensitive and specific than CT in detecting PNS and should be considered in patients with cancer of the head and neck at risk of PNS.

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Author Contributions: Drs Hanna, Vural, Prokopakis, Snyderman, and Weissman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hanna, Vural, and Prokopakis. Acquisition of data: Hanna and Carrau. Analysis and interpretation of data: Hanna, Vural, Snyderman, and Weissman. Drafting of the manuscript: Hanna and Prokopakis. Critical revision of the manuscript for important intellectual content: Hanna, Vural, Carrau, Snyderman, and Weissman. Administrative, technical, and material support: Hanna, Vural, and Prokopakis. Study supervision: Hanna and Snyderman.

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REFERENCES