INTRACRANIAL SKIP METASTASIS FROM PAROTID AND FACIAL SKIN TUMORS: MECHANISM, DIAGNOSIS, AND TREATMENT

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Perineural and endoneural tumor spread is a form of metastatic disease in which the primary tumors spread along neural pathways and gain access to noncontiguous regions. Although rare, this type of skip metastasis into the cranial cavity occurs from tumors of the parotid gland and facial skin. Recognition of this process, evaluation of the patient with proper diagnostic procedures, and its treatment are presented. (*J Natl Med Assoc.* 1993;85:369-374.)

Key words • head tumors • neck tumors • skip metastasis • brachytherapy

Intracranial metastases are important complications of systemic cancer, occurring in 30% of patients with cancer. They are a particular problem in melanoma, breast carcinoma, small-cell lung carcinomas, and non-Hodgkin's lymphoma because of the increasing ability to control the disease elsewhere in the body. In 50% of patients with intracranial metastases, the disease is found only in the central nervous system. In one large surgical series, the primary sites of origin were: the lung (40%), melanoma (11%), kidney (11%), colon (8%), soft-tissue sarcoma (8%), breast (6%), and other sites (15%).[1] Forty-nine percent of the patients had solitary intracranial metastases, and 11% had more than five lesions on computed tomography (CT) scan of the head.

Because intracranial metastases is a blood-borne disease, most lesions occur in distant arterial fields except for a preferential posterior fossa distribution for abdominal and pelvic primary tumors. Textbooks ordinarily give scant attention to the problem of spread along nerves. The first significant mention of neoplastic invasion of nerves was made by Cruveilheir[2] in 1842. In 1862, Neumann[3] reported a carcinoma of the lower lip that had extended into both mental nerves.

In 1905, Ernst[4] was one of the first to publicize the fact that carcinoma may spread via the perineural lymphatics. It was his opinion, however, that the nerve fibers themselves escaped invasion despite the permeation of the lymphatic channels of the endoneurium and perineurium. He recognized that the nerve trunk and its lymphatics might be a pathway for spread of carcinoma beyond the limits of its growth. In 1921, Shattock[5] reported a case of carcinoma of the tongue with invasion of the lymphatic channels of the lingual nerve. He believed that "There seems to be no reason why under such circumstances and the ease with which cells may be shifted, the proliferation might not extend to the central nervous system."

Perineural lymphatic extension from primary lesions of the breast was observed by Jentzen[6] and Askanazy.[7] These authors stated that cells of some carcinomas have a strong tendency to grow along nerve trunks and their sheaths and to produce carcinomatous foci in nerves at a distance from the primary tumor. Their term for this property was neurotropism, a term that possibly deserves wider acceptance with reference to tumors exhibiting this peculiar manner of spread.

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Quattlebaum[8] found that adenoid cystic carcinoma of the parotid gland tends to invade perineural lymphatics. The tendency for this tumor to involve nerves has became generally recognized. Dagnelie[9] described in detail a cylindroma of the palate that extended along the peripheral nerves to the central nervous system. Study of amputation specimens by Barber et al[10] disclosed spread in nerves in a significant number of extremities amputated for sarcoma. Mohs,[11] in discussing his chemosurgical technique for the treatment of skin cancer, also recognized that tumors of the skin may extend along nerves and may not be detected by the usual examinations.

Other authors[12-14] have remarked on the tendency of epithelial tumors to involve the regional nerves, and they regard the perineural and endoneural spaces as potential routes for distant spread of the disease. Ackerman and Del Regato[15] have urged that the usual channels be suspect in every tumor case.

This article presents two cases of head and neck cancer with intracranial extension along the cranial nerves (Figures 1 and 2) and discusses advances made in diagnosing and treating this disease entity.

CASE 1

A 39-year-old male underwent left superficial parotidectomy in 1982 for adenoid cystic carcinoma. The patient received postoperative irradiation to the tumor bed. A total dose of 5000 cGy was administered (3600 cGy with 15 MeV electron beam and 1400 cGy with 12 MeV electron beam). The patient remained asymptomatic until July 1985 when he developed progressive weakness over the left side of his face.

On physical examination in February 1986, left facial nerve paralysis was evident. A $3 \times 3 \times 2$ cm nodule was palpable anterior to the left mastoid. A needle biopsy of this nodule was consistent with adenoid cystic carcinoma. The patient underwent intratemporal and extratemporal facial nerve decompression, total parotidectomy, and resection of the facial nerve and the premastoid tumor in mid-February. The surgical specimen showed perineural invasion of the facial nerve (Figure 3).

In March 1987, the tumor recurred anterior to the left mastoid. The tumor measured $2 \times 2 \times 1.5$ cm. A single high activity (10 mCi) I-125 seed was implanted into the center of the tumor. The tumor received 80 Gy over the average life of the radionuclide (87 days) at a dose rate of 4 cGy/hour. By July 1987, the tumor had resolved completely.

In October 1989, the patient presented with headaches, dizziness, nausea, vomiting, difficulty in swallowing with occasional aspiration, and hoarseness of voice. On physical examination, the 1st through 6th cranial nerves were intact. There was obvious 7th cranial nerve (facial) paralysis on the left side, and hearing also was diminished on the left side. The gag reflex on the left side was decreased with uvular deviation to the left. On mirror examination, the left vocal cord was paralyzed. There was also weakness of the left sternocleidomastoid and trapezius. The 12th cranial nerve was intact. The dizzy spells occurred infrequently, lasted for several minutes, and were associated with loss of balance and nausea. The spells appeared to be vestibular in origin. The findings of the neurological examinations were consistent with the dysfunction of the left 8th, 9th, 10th, and 11th cranial nerves pathognomonic of left cerebellopontine angle tumors. Computed tomography scans of the head revealed a contrast-enhanced mass in the left cerebellopontine angle (Figure 4).

In early November 1989, a needle biopsy revealed adenoid cystic carcinoma. A 5.2 mCi I-125 seed was stereotactically implanted into the tumor. The tumor received 200 Gy over the average life of the radionuclide (87 days) at a dose rate of 10 cGy/hour (Figure 5). Following the I-125 seed implant, the patient's headaches, dizziness, and swallowing problems slowly resolved. A gold weight was implanted into the left upper eyelid to facilitate closure. Teflon was injected into the left true vocal cord for rigidity. The patient was closely monitored. Repeat CT of the head with contrast 16 months following the I-125 seed implant showed complete resolution of the tumor (Figure 6). To date, the patient is alive and remains asymptomatic.

CASE 2

A 49-year-old male underwent Mohs' skin surgery for squamous cell carcinoma of the skin overlying his left parotid gland in 1986. The patient remained asymptomatic until October 1988 when he presented with paresthesia involving the left lower face. Clinical examination failed to reveal any local or regional recurrence of skin cancer. Computed tompgraphy and magnetic resonance imaging (MRI) scans of the head and neck also were negative for intra- and extracranial pathology.

By January 1989, the patient had developed left facial nerve paralysis. A diagnosis of local tumor recurrence involving the left facial nerve was made, and in late February, the patient underwent left parotidectomy along with the facial nerve up to the stylomastoid

foramen, left mastoidectomy, and left suprahyoid neck node dissection. The surgical specimen showed well-differentiated squamous cell carcinoma involving the skin and the superficial parts of the parotid gland with intraneural and perineural invasion of the buccal and oral branches of the facial nerve (Figure 7). However, no tumor was seen in the facial nerve at the level of the stylomastoid foramen. The lymph nodes were negative for tumor.

Because of the frank perineural involvement of the buccal and oral branches of the facial nerve in the surgical specimen and clinical involvement of the mandibular branch of the trigeminal nerve from sensory loss over the left lower face, perineural intracranial extension was anticipated, and the patient received postoperative irradiation to the tumor bed and skull base. A dose of 6440 cGy was given from mid-May to mid-June. The first 5440 cGy was delivered through a wedged pair using a 10-MV photon beam at 160 cGy per fraction twice a day, 5 days per week (hyperfractionation). The remaining 1000 cGy was delivered through a direct port using a 15-MeV electron beam at 100 cGy per fraction twice a day 5 days per week. The left temporal lobe received the entire prescribed dose as well. During the irradiation treatments, a 7-day break was given due to mucositis. The patient was examined at regular intervals.

By April 1990, the numbness over the left lower face progressed upward and involved the left lower eyelid. Repeat MRI with and without contrast showed tumor involving the left cavernous sinus (Figures 8, 9, and 10). By August 1990, as various therapeutic options were being considered including proton beam therapy, the left facial numbness extended upward to the supraorbital region. The patient also started experiencing difficulty in opening his mouth. Because of the MRI evidence of tumor involvement of the left cavernous sinus and the progression of signs and symptoms, the patient was referred for further management. Because of the proximity of the lesion to the internal carotid artery (Figures 8, 9, and 10), a biopsy was not taken. A single 5.3 mCi I-125 seed was implanted into the tumor stereotactically under local anesthesia. The tumor received 120 Gy over the average life of the radionuclide (87 days) at a dose rate of 6 cGy/hour (Figure 11). The patient was closely monitored with clinical and MRI examinations.

In November 1990, follow-up MRIs showed resolution of the tumor. However, a contrast-enhanced mass appeared in the middle of the left temporal lobe (Figure 12). Repeat MRI in February 1991 showed progression of this lesion involving the entire anterior pole of the left temporal lobe (Figure 13). A stereotactic needle biopsy of this lesion revealed gliosis and necrosis consistent with radiation changes but no tumor was present. The patient was experiencing symptoms of increased intracranial pressure from increasing edema around the necrosis. Debridement was done in April 1991, and no tumor was present in the specimen. The radiation necrosis in the temporal lobe was probably caused by the hyperfractionated external irradiation. To date, the patient is alive and remains asymptomatic.

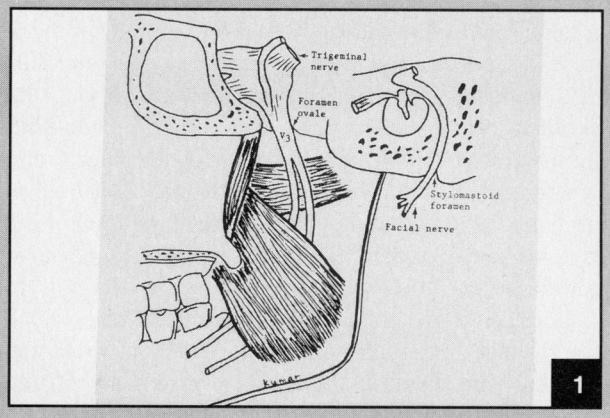
DISCUSSION

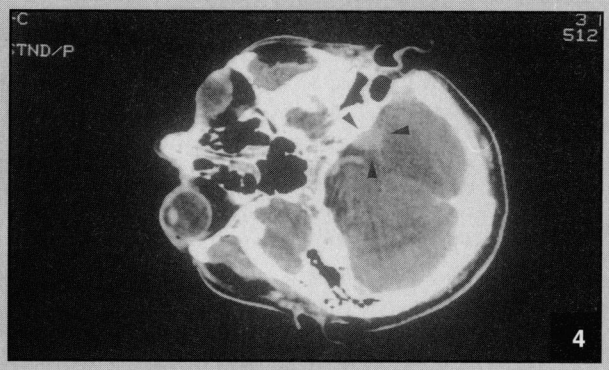
Tumors of the parotid gland and the facial skin can spread along the neural pathways and metastasize to noncontiguous regions such as the cranial fossa. Perineural and endoneural tumor extension along the mandibular division of the trigeminal nerve passing through the foramen ovale gains access into the middle cranial fossa and can involve the cavernous sinus (Figures 1, 2, and 8). The presenting signs and symptoms will therefore be related to the involvement of the 3rd, 4th, 1st, and 2nd branches of the 5th and 6th cranial nerves as they run their course through the cavernous sinus.

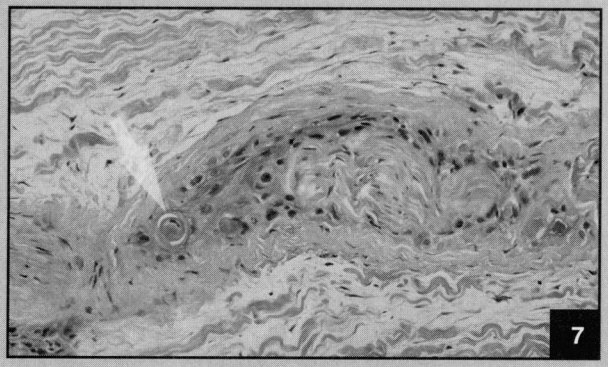
Perineural tumor extension along the facial nerve passing through the stylomastoid foramen, facial canal, and internal acoustic meatus gains access into the posterior cranial fossa and grows in the cerebellopontine angle (Figures 1, 2, and 4). The presenting signs and symptoms therefore will be related to the involvement of the 7th and 8th cranial nerves, which pass through the internal acoustic meatus, and the 9th, 10th, and 11th cranial nerves, which pass through the jugular foramen. Patients also will experience occipital headaches and cerebellar dysfunction depending on the size of the lesion.

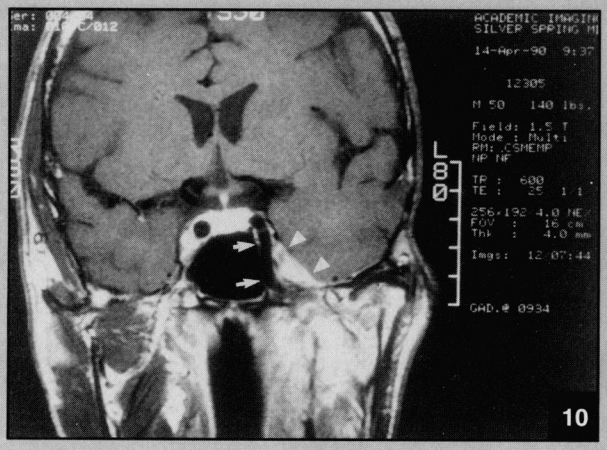
When patients with a prior history of head and neck malignancies develop the signs and symptoms of cranial nerve palsies, it is important to recognize the possibility of neurotropism and carry out appropriate diagnostic procedures. The availability of CT and MRI have greatly improved the ability to diagnose this problem. Although CT is accurate in detecting lesions in the cerebellopontine angle (Figure 4) and the cavernous sinus, it cannot detect small lesions in the trigeminal cisterna or slight destruction of the bony basal foramina or the actual involvement of the nerve itself. Magnetic resonance imaging has shown superior contrast resolution and will more accurately depict tumor soft tissue margins. The characteristics of

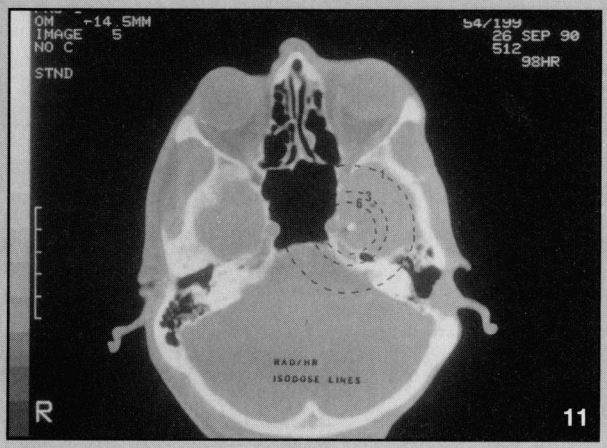
Figure 1. The tumors in the distribution of mandibular branch (V_3) of the trigeminal nerve and facial nerve can spread along the perineural and endoneural lymphatics of these nerves and enter the middle cranial fossa through the foramen ovale and posterior cranial fossa through the stylomastoid foramen, respectively. **Figure 2.** The relationship of the foramen ovale to the cavernous sinus and the internal acoustic meatus to the jugular foramen are shown. **Figure 3.** *Case 1.* Surgical specimen showing adenoid cystic carcinoma involving a nerve (arrow) (hematoxylin-eosin stain, magnification ×128). **Figure 4.** *Case 1.* Pre-implant CT scan of the head showing contrast-enhanced mass in the left cerebellopontine angle (black arrowheads). **Figure 5.** *Case 1.* Postimplant CT scan of the head showing single high-activity I-125 seed (white dot) superimposed by rad/hour (cGy/hour) isodose lines. **Figure 6.** *Case 1.* CT scan of the head with contrast 16 months after the implant showing complete resolution of the tumor. Note the decayed I-125 seed in place (black arrow). **Figure 7.** *Case 2.* Surgical specimen showing squamous cell carcinoma involving a nerve (arrow) (hematoxylin-eosin stain, magnification ×128). **Figure 8.** *Case 2.* Axial MRI of the head through the cavernous sinus with contrast. Note the hyperintense lesion in the left cavernous sinus (white arrowheads) lateral to the left internal carotid artery (white arrow). **Figure 9.** *Case 2.* Coronal MRI through the cavernous sinus of the head without contrast. Note the isointense lesion in the left cavernous sinus (white arrowheads) lateral to the left internal carotid artery (white arrows). **Figure 10.** *Case 2.* MRI with contrast showing hyperintense lesion in the left cavernous sinus (white arrowheads) lateral to the left internal carotid artery (white arrows). **Figure 11.** *Case 2.* Postimplant CT scan of the head showing a single high-activity I-125 seed (white dot) superimposed by rad/hour (cGy/hour) isodose lines. **Figure 12.** *Case 2.* MRI of the head with contrast 2 months after the implant showing resolution of the hyperintense lesion in the left cavernous sinus (white arrow). The I-125 seed is in place (black arrow). A new hyperintense lesion (black arrowheads) appeared in the left temporal lobe. **Figure 13.** *Case 2.* MRI of the head with contrast 5 months after the implant showing extensive changes in the left temporal lobe (black arrowheads). The left internal carotid artery (white arrow) is seen medial to the decayed I-125 seed (black arrow).

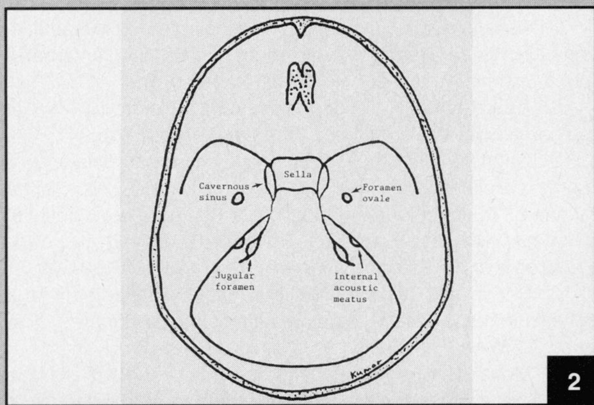








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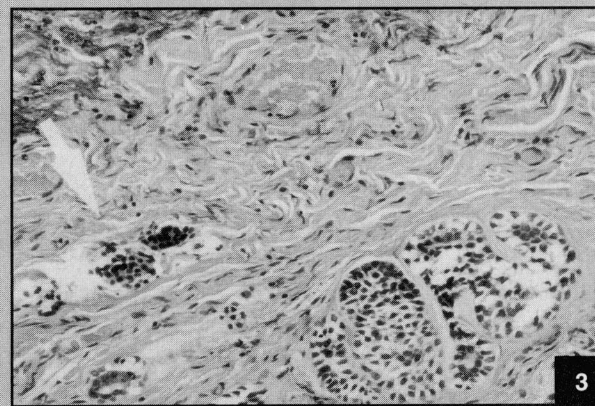

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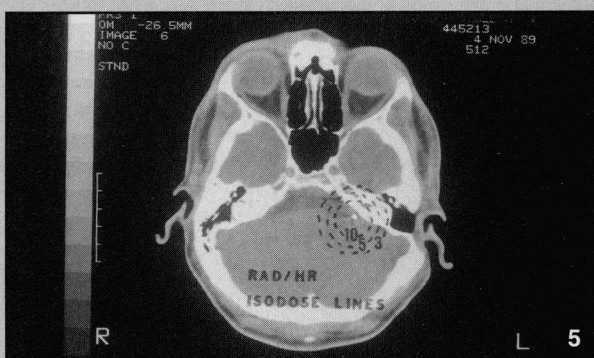
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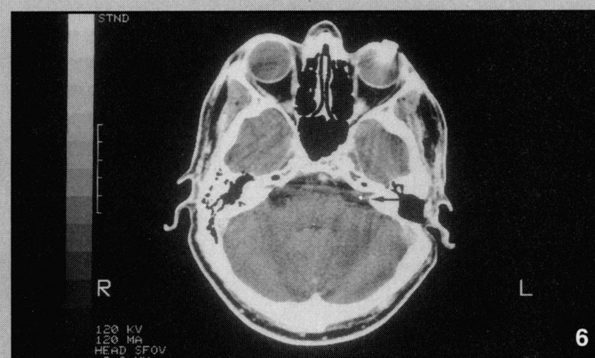
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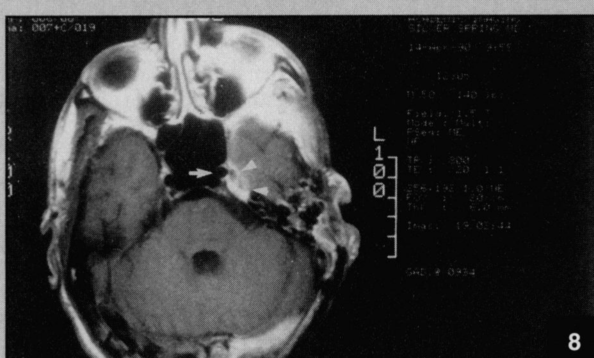
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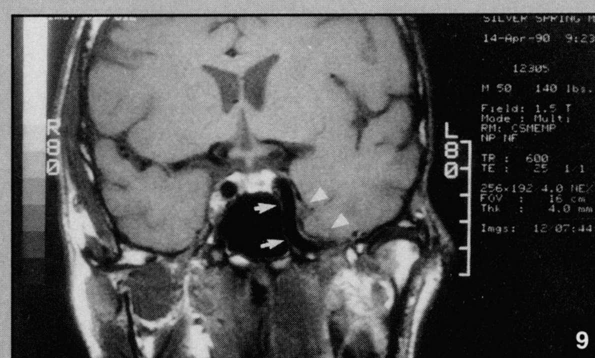
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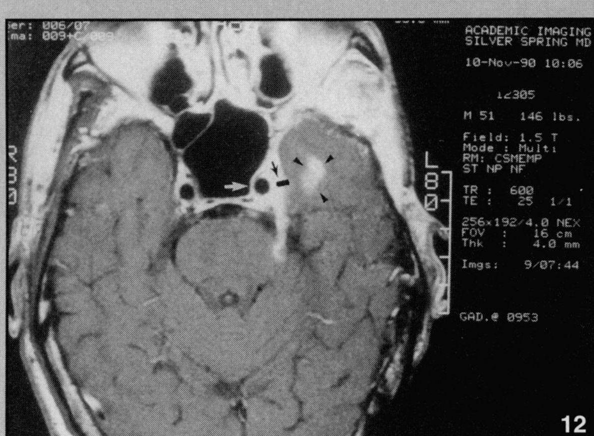
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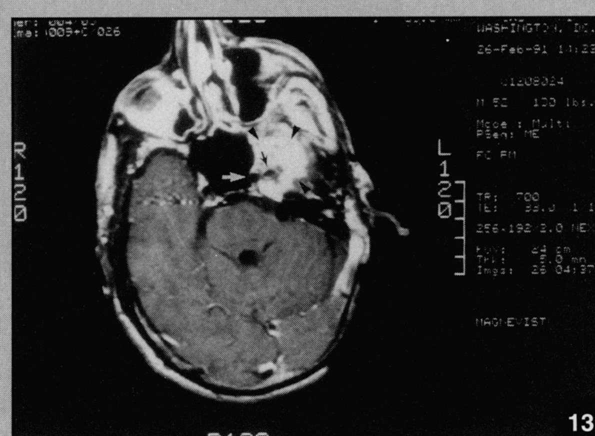
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perineural tumor spread include smooth isointense thickening of V_3 and mild concentric enlargement of the foramen ovale. Replacement of the normal hypointensity of the trigeminal cisterna by an isointense mass with lateral bulging of the cavernous sinus and dural membranes indicate ganglionic and cavernous sinus involvement[16] (Figures 9 and 10).

Because most of these patients routinely receive postoperative conventional external beam irradiation at the time of initial treatment, they are precluded from retreatment with additional external beam irradiation. Over the last 8 years, we have successfully treated both primary and recurrent skull base tumors with interstitial irradiation by permanently implanting one or more high activity I-125 seeds.[17-21] The physical characteristics of this isotope (low photon energy of 32 keV and long half-life of 62 days) make it ideal for interstitial irradiation in previously irradiated areas as well as in critical locations such as the skull base. Tumor doses as high as 400 Gy can be given without any deleterious effects on the surrounding normal structures.[22-24]

CONCLUSION

Perineural and endoneural skip metastasis from head and neck tumors can grow in the skull base region. Initially, patients might only have signs and symptoms of cranial nerve palsies without any radiographic findings. Magnetic resonance imaging, especially coronal sections, help in diagnosing early involvement of the V_3. High activity I-125 stereotactic brachytherapy is a safe and effective method of treating these lesions, which usually are located in previously irradiated areas.

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