Introduction
While basal cell carcinoma (BCC) is the most common malignancy found in humans, with over 2 million cases diagnosed each year in the United States, the disease remains localized in the great majority of cases. Locally advanced and metastatic disease is quite rare, with an incidence ranging from 0.18% to 3%. Complications of local disease include local tissue destruction, functional impairment, and cosmetic disfigurement. Metastatic disease causes additional complications, with the most frequently involved sites being the lymph nodes, bone, and lungs.

The incidence of basal cell carcinoma increases with age. While it is most frequently found in light-skinned individuals, all skin types are affected. The most common risk factor for BCC development is chronic UV exposure through sunlight, tanning booths, or UV light therapy.

The relationship between the timing and amount of ultraviolet radiation exposure has not been clearly established. Additional risk factors include history of exposure to ionizing radiation, arsenic exposure, and immunosuppression. Basal cell carcinoma may also develop in chronic scars, ulcers, or burns.

Several genodermatoses are associated with an increased risk of basal cell carcinoma. These include ocucutaneous albinism, xeroderma pigmentosum, epidermolysis bullosa, and basal cell nevus syndrome (BCNS). Rombo, Bazex-Dupré-Christol, Brooke-Spiegler, Schoedel-Schulz-Passarge, and Muir-Torre are other rare syndromes associated with BCC.

There are many risk factors contributing to the development of recurrent, locally advanced, or metastatic basal cell carcinoma. Anatomical locations with a higher risk of recurrence include the face, eyelid, nose, lip, ear, hands, and feet. Increased recurrence rates are further observed when poorly defined borders are present, in tumors larger than 2 cm in diameter, in perineural involvement, and in prior history of recurrent BCC. Patients who have had multiple lesions have a higher recurrence rate than those with single lesions. Tumors around the medial canthus, nose, and ear are more likely to become invasive compared to BCC of other sites.

The most likely lesions to metastasize include large tumors or those with more aggressive histological phenotypes (morphemic, infiltrating, basosquamous).

Several host factors are associated with an increased risk for recurrent disease. Patients who are diagnosed with BCC before the age of 40, are immunosuppressed, have a genetic syndrome, or have a history of aggressively behaving tumors are at higher risk. With regard to immunosuppression, this includes patients with a history of transplant, those with leukemia/lymphoma, and those on immunosuppressants for conditions such as rheumatoid arthritis.

As previously mentioned, radiation therapy, chronic scars, burns, or ulceration can make that particular area of the body more susceptible to recurrence of BCC.
Discussion

Perineural invasion is characterized by growth of tumor cells within any of the three layers of the nerve sheath. This is believed to be a result of reciprocal interactions between cancer cells and nerve elements. Perineural spread may be facilitated by neural secretion of glial-derived neurotrophic factor (GDNF), which phosphorylates the RET tyrosine kinase receptor, triggering downstream signaling pathways that stimulate proliferation and migration of cancer cells. High RET receptor expression has also been found in patients with pancreatic and prostate carcinomas, which are known to express perineural characteristics.

Perineural invasion may be categorized as either incidental invasion, which is asymptomatic, or clinical perineural invasion, which presents with cranial-nerve deficits such as paresthesia, pain, and numbness. Perineural spread from the head and neck tends to involve the trigeminal nerve, resulting in paresthesia. Facial nerve involvement results in palsy, as these nerves have a rich network of cutaneous endings.

Identifying risk factors for recurrent and advanced disease can aid the clinician in the appropriate management of patients with basal cell carcinoma. The location of this patient’s basal cell carcinoma, the ear, is a site known to be associated with more aggressive tumors. Studies suggest that there is a preference for tumor cells to grow in this area due to a larger degree of angiogenesis, making this an ideal environment for tumorigenesis and uncontrolled growth. This shows that there is a correlation between angiogenesis and increased aggressiveness, requiring more Mohs stages to achieve tumor-free margins.

Following the identification of perineural spread of basal cell carcinoma, the patient should undergo additional studies to further delineate the extent of disease. A complete skin examination should be performed, as patients often have additional cancer at other sites. Any suspicious lesion requires a biopsy for definitive diagnosis. A thorough history regarding paresthesias or palsy should be elicited, as the new onset or progression of paresthesias may be the only presenting sign of perineural spread. Gadolinium-enhanced MRI or MR neurography are the best imaging studies for the detection of perineural spread and are used to assess the extent of disease spread along the cranial nerves.

Other signs of perineural invasion include enhancement with or without enlargement of the nerve, mass in the cavernous sinus or Meckel cave. Denervation of a group of muscles innervated by the affected cranial nerve is an indirect sign of perineural spread. Plain radiographs and CT scan are used to visualize expansion of neural foramina and canals such as the inferior alveolar canal, infraorbital foramen, foramen rotundum or facial (Fallopian) canal. PET scan can also be used to visualize possible extension through the bone and foramina. In cases where the tumor has spread to regional lymph nodes, visualization can be seen on MRI.

There is no universally accepted protocol for the treatment of basal cell carcinoma with perineural invasion. Treatment is mostly individualized, depending on the patient’s co-morbidities, anatomical location of the lesion, previous treatment history, patient preference, and other factors. Adequate surgical removal based on histologic findings is the primary treatment used with adjunctive radiotherapy. Surgical treatment methods include Mohs surgery, standard surgical excision, curettage alone, and curettage and electrodesiccation. Non-surgical methods include topical chemotherapy, radiation therapy, and photodynamic therapy. The five-year recurrence rates for recurrent basal cell carcinoma are significantly higher than with primary BCC. They are estimated as follows: 5.6% with Mohs surgery, 17.4% with surgical excision of the tumor, 40% with curettage and electrodessication, and 13% with radiation therapy.

Hedgehog pathway inhibitors, including vismodegib, may have a potential role in the treatment of advanced or metastatic cases of basal cell carcinoma when surgery is contraindicated or deferred by the patient. A recent study of 499 patients with advanced or metastatic disease who were ineligible for surgical treatment found that 302 of 453 patients with locally advanced basal cell carcinoma had an overall response to daily treatment with vismodegib. Of the 302 patients, 153 had a complete response, and 149 patients had a partial response. In addition, 11 of 29 patients with metastatic basal cell carcinoma had an overall response (two complete responses, nine partial responses). The long-term efficacy and tolerability of hedgehog pathway inhibitors is still being investigated.

In non-melanoma skin carcinomas, radiation can be used as primary treatment or as adjuvant therapy. Radiation works by inducing death of cancer cells present along the invading nerve and can interrupt paracrine interactions between cancer cells and nerves, in particular the GDNF-RET axis. There are three different radiation methods used: orthovoltage superficial X-rays, megavoltage electron-beam therapy, and Brachytherapy. Radiotherapy can be low-energy, which treats superficial lesions, or high-energy, which can spare the skin and penetrate to deep-seated lesions.

Patients with focal, incidental perineural invasion with negative margins, such as BCC that is not adjacent to a major cranial nerve, are likely to...
be cured with surgery alone. However, those with multifocal perineural spread should be considered for postoperative radiotherapy, especially patients with recurrent cancers, those who are immunocompromised due to solid organ transplant and/or chronic lymphocytic leukemia, and those with tumors in locations close to cranial nerves V and VII. Since patients with extensive microscopic BCC with perineural invasion have a high risk for recurrence, they should be considered for radiotherapy as well. Radiotherapy can be effective in treating microscopic deposits of cancer cells that remain after surgical removal of the tumor mass. It may also be used for tumor destruction in places that are difficult to reach by surgical excision.

Not all patients with tumors characterized by perineural invasion are able to receive adjuvant radiotherapy. Some patients are unable to tolerate the side effects, such as redness and irritation of the area treated. Recurrent lesions that are close to a site previously treated by irradiation cannot be treated with radiotherapy due to risk of necrosis. Radiotherapy can cause orbital and central nervous system damage as well as bone exposure, fistula formation, and wound infection. Patients with connective tissue diseases and those with genetic conditions that predispose them to skin cancer, such as xeroderma pigmentosum, are more susceptible to radiation and therefore should not receive radiation treatment.

Conclusion
Perineural invasion of basal cell carcinoma is a poor prognostic indicator, associated with higher rates of morbidity and mortality. Management of advanced disease such as this can be challenging. This case study demonstrates a rare circumstance in which a basal cell carcinoma located on a high-risk site recurred twice in a patient with no known personal risk factors.

References