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Skin cancer of the head and neck

Skin cancer of the head and neck with gross or microscopic perineural involvement: Patterns of failure ☆

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ABSTRACT

Objectives: Analyze patterns of failure of patients with head-and-neck cutaneous squamous cell carcinoma with perineural involvement: gross cranial nerve involvement (GCNI), microscopic focal perineural invasion (MFPNI), and microscopic extensive perineural invasion (MEPNI), managed with or without radiotherapy (RT).

Materials and methods: Retrospective review: 102 patients with GCNI, MFPNI and MEPNI, observed or treated with RT from 2000 through 2013. The pathology specimens were reviewed for the purpose of the study.

Results: 35 patients had GCNI, all irradiated definitely; 37% failed in-field, and two year disease free survival (DFS) rate was 56%. 19/30 patients (63%) with MEPNI without evidence of GCNI received adjuvant RT to the course of the nerves supplying the involved skin. Recurrence-free survival (RFS) in nerves (94% vs. 25%, $P = 0.01$) and DFS (73% vs. 40%, $P = 0.05$) were significantly higher in the irradiated MEPNI patients compared with the observed. 10/37 (27%) patients with MFPNI were irradiated adjuvantly. MFPNI had low rate of neural and overall failure, without significant benefit to irradiation over observation.

Conclusions: In patients with GCNI radiotherapy achieves a substantial chance of disease control. Radiotherapy to nerves at risk in MFPNI did not affect outcome, but in MEPNI it achieved less gross perineural recurrences and better DFS, compared with observation.

Perineural involvement (PNI) in head and neck cutaneous squamous cell carcinoma (HNCSCC) is a rare event, accounting for 3.7–6% of the HNCSCC cases [1,2], but its presence significantly affects local, local–regional and distant recurrence rates [1–7] and overall survival [8,9].

Branches of the trigeminal nerve (especially maxillary and mandibular nerves) and the facial nerve are almost exclusively involved [9], although direct involvement of orbital contents or cavernous sinus can lead to spread to cranial nerves III, IV and VI.

Microscopic PNI may be identified incidentally at skin cancer resection [10,11]. Gross PNI presents clinically with cranial nerve deficit (such as pain, numbness, facial musculature weakness etc.) [1,12], or diagnosed radiologically, most commonly by MRI [13–16].

Local surgery may provide cure for patients with skin cancer with microscopic PNI in the tumor specimen [10,11,17] and in selected cases of gross PNI [18]. Additional improvements in local control may be achieved by adjuvant radiotherapy with or without chemotherapy [1,4,5,10,19,20]. Mechanistically, radiation may not only directly affect cancer cell viability, but can also interrupt paracrine mechanisms underlying PNI and modulate the nerve microenvironment [21]. Patients with unresectable cancers involving nerves may be treated with definitive RT, resulting in 39% local control following conventional radiotherapy [5].

We have previously described predictable disease spread patterns along cranial nerves supplying the primary tumor sites in a limited number of patients with HNCSCC with radiological evidence of gross cranial nerve involvement [22]. In the present study we analyze the outcomes in a larger cohort of patients with

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HNCSCC with gross neural involvement treated with radiotherapy. We also analyze the outcomes of patients with microscopic PNI in the resection specimens who did not have evidence of gross nerve involvement, and whether radiotherapy to the nerves supplying the involved skin affects these outcomes.

Patients and methods

This is an IRB approved, institutional retrospective review of patients with histologically proven HNCSCC, with diagnosed microscopic PNI in the skin surgical specimen, or clinical cranial nerve dysfunction with or without MR evidence for gross perineural spread. 94 available pathological specimens of skin cancers were reviewed by the study's pathologist (JBM) for histological characterization of focal versus extensive perineural disease, involvement of large nerves with diameter >0.1 mm, and the presence of skip lesions (Fig. 1). Gross PNI is defined as perineural spread evidenced on by MRI imaging, with cranial nerve deficit or both. Microscopic focal PNI (MFPNI) was defined as involvement of 1–2 nerves in the resection specimen, and microscopic extensive PNI (MEPNI) was defined as >2 nerves involved. Skip lesions were defined as discontinuous foci of squamous cell carcinoma involving the perineural and/or intraneural space along the nerves in the pathologic specimen.

Radiation therapy

All patients with gross PNI were treated along the involved nerves, including the base of skull ganglions and elective uninvolved facial nerve and trigeminal nerve branches that were at risk because of the known anatomic connections between cranial nerves, such as between the 7th and branches of the 5th [22].

Nerves that innervated dermatomes involved with cancer were outlined as treatment targets in 29 (78%) of patients with microscopically extensive PNI and in 8 (22%) of patients with focal PNI. Usually base of skull nerve structures were spared in these cases. Cases with focal PNI receiving nerve RT included those with primary T4 disease (three cases), positive nerve margins (one case) or positive neck lymph nodes (four cases).

In patients treated with radiotherapy, the skin tumor bed was irradiated together with ipsilateral lymph nodes.

Radiotherapy was delivered with IMRT in 58 patients (91%), four patients (6%) received three dimensional radiotherapy and additional 2 patients with MFPNI (3%) were treated adjuvantly with electron beam radiotherapy). Radiation was typically delivered five times a week (except for three cases that were managed with accelerated hyperfractionation) over a median course of 6.5 weeks (range 3–7). Median dose to gross disease was 66 Gy (range 40–72 Gy), and 60 Gy to the course of nerves and structures that were judged at risk (range 39–60 Gy). Chemotherapy was used concomitantly with radiotherapy in 24 cases: 18 patients (75%) with gross PNI, and 6 patients (25%) with MEPNI.

Statistical analysis

Recurrence free survival RFS was used to define specific recurrence outcomes, namely RFS in nerves, RFS in the skin tumor bed, RFS in lymph nodes and distant metastases RFS (Table 2), whereas DFS refers to overall recurrences both local–regional and distant. SCC that occurred elsewhere on skin and was not related to the originally treated skin cancer was not included in the definition of the DFS. Patients who died of any reason unrelated to their skin cancer were censored for RFS and DFS purposes, while any death from the treated cancer was accounted as an event for RFS and DFS. Patients without known recurrence were censored at the last date on which they were assessed for recurrence. Disease free survival was defined as the time after therapy that the patient survives without persistent or recurrent cancer. Kaplan–Meier method was used to estimate overall survival (OS), disease free survival (DFS), and specifically perineural recurrence free survival

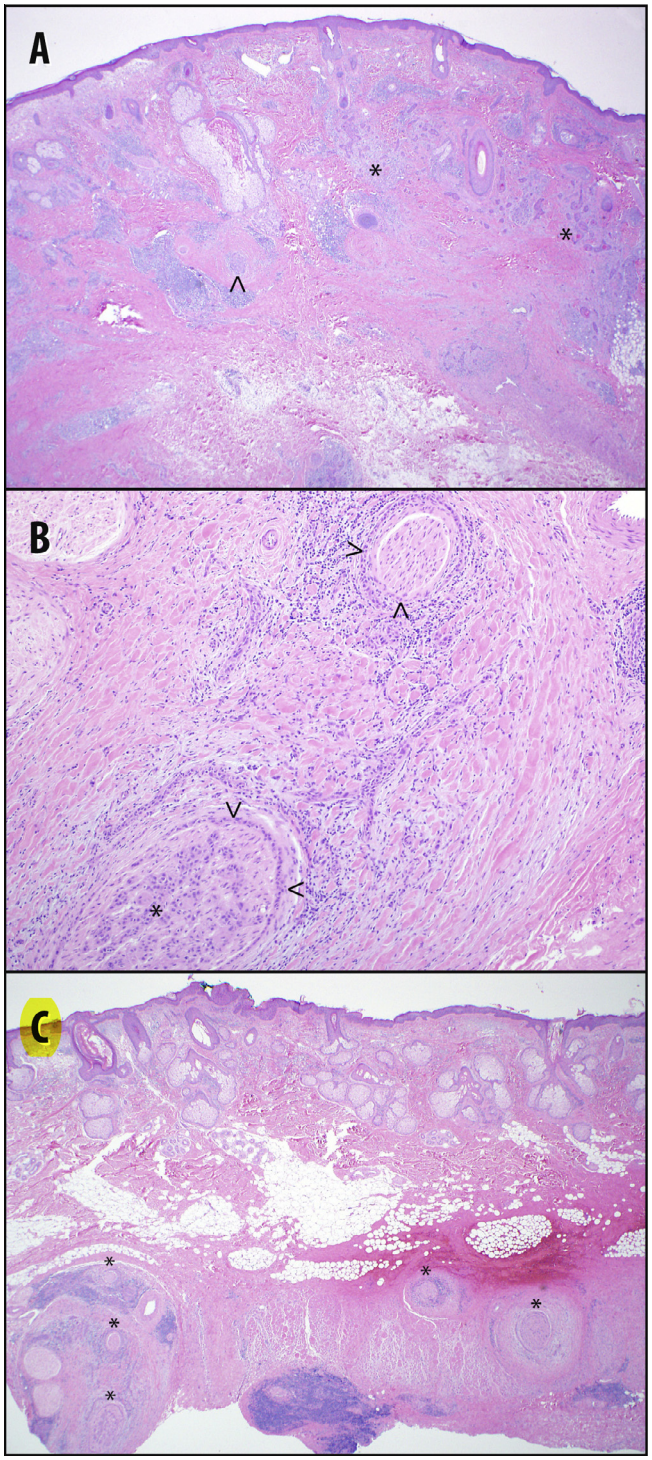

Fig. 1. Illustration of representative histologic slides of A: Microscopic focal perineural invasion (Hematoxylin and eosin, 20× magnification). The primary squamous cell carcinoma (asterisks) is centered in the dermis with a single focus of perineural invasion (arrowhead) in the deeper dermis; B Microscopic extensive perineural invasion with numerous small nerves involved by squamous cell carcinoma (asterisks) in muscle and aponeurosis layers of the scalp (Hematoxylin and eosin, 20× magnification); C Microscopic extensive perineural invasion with squamous cell carcinoma involving the perineurium (arrowheads) and intraneural space (asterisks) (Hematoxylin and eosin, 100× magnification).