



High Risk Nonmelanoma Skin Cancers of the Head and Neck

Roger Ove*

Department of Radiation Oncology, Case Western University, USA

Editorial

Skin cancer is the most common malignancy in the world, and occurs very commonly in the head and neck. Squamous and basal cell carcinomas are by far the most common, and while both can be locally advanced, the former has the capacity to impact survival. Such locally advanced squamous cell carcinomas of the head and neck do not readily fit existing clinical trials, and are generally treated with a combination of surgery, radiotherapy, and sometimes chemotherapy. It is something of a paradox that in a field (head and neck malignancies) where the majority of recommendations have a foundation in clinical trials, the most common malignancy of the head and neck has almost no clinical trial support, with the majority of recommendations based on retrospective data. The reason for this disparity is that, fortunately, the majority of nonmelanomatous skin cancers are early stage superficial cases, readily treated with surgery or radiotherapy. Locally advanced cases are much rarer, but remain a serious clinical problem that can lead to substantial morbidity, in part due to the potential for such cases to invade the cranial nerves and base of skull.

Locally advanced squamous cell carcinoma of the skin is comprised of those that are stage T2 or higher, node positive, exhibit bone or cartilage invasion, or present with extensive perineural invasion or clinical nerve involvement. Perineural invasion (PNI) occurs in roughly 10% of squamous cell cases, and can be either focal or extensive. The presence of clinically symptomatic nerve invasion carries a worse prognosis. There is some evidence indicating that the presence of perineural invasion also increases the risk of lymph node metastases. Published experience from the University of Florida indicates that the presence of clinically evident perineural invasion, either symptomatic or seen on imaging, leads to a worse prognosis, with 50% local failure and 40% disease specific mortality [1-4].

A recent publication from the University of Michigan substantiates these findings, reporting on their institutional experience over a 14 year period [5]. This series describes the outcomes of 102 patients, all presenting with squamous cell carcinoma of the skin of the head and neck, with either gross or microscopic PNI. The majority were treated surgically, with some variation in the radiation treatment volumes and technique over that 14 year period. This series confirmed the dismal outcomes for patients with gross PNI, with 64% recurrence in the nerves at 2 years after being treated with surgery and postoperative radiotherapy. All patients with such gross PNI received postoperative radiotherapy. These researchers also found that a patient with microscopically extensive PNI has a very high recurrence rate in the nerves with clinical progression of disease if they received no postoperative radiotherapy. Radiotherapy to the involved and associated nerves and ganglia improved DFS (in nerves) from 25% to 94%. For those with focal PNI the recurrence rate was relatively low and the benefit of radiotherapy was not as significant. For those with extensive microscopic PNI, postoperative radiotherapy conferred a substantial benefit both in terms of recurrence free survival in the nerves and disease-free survival, and this would be expected to translate to a survival benefit, given the prognosis of patients with such base of skull failures. It should be noted that there is no universally accepted definition of extensive PNI. In the Michigan series it was defined as having more than two nerves involved in the surgical specimen. Some researchers have suggested that involvement of nerves greater than 0.1mm in diameter confers a worse prognosis. An interesting finding in the Michigan series is that for patients presenting with clinically involved nerves, failure were seen in other cranial nerves. This was attributed to crossover between cranial nerves, typically 5 and 7. Another explanation would be that the peripheral skin cancers with PNI could infiltrate along any nerves that innervate the region involved. The recommendations from Michigan were to cover the base of skull and nerve ganglia to at least 60 Gray as tolerated by the brainstem and other critical structures, and the entire involved dermatome should be irradiated.

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*Correspondence:

Roger Ove, Department of Radiation Oncology, Case Western University, University Hospitals Seidman Cancer Center, Lorain, Ohio, USA, Tel: (252) 721-5392;

E-mail: pr_ove@yahoo.com

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Another recent publication on the topic, from the University of Florida, documents their experience over a 28 year span, describing the outcome of locally squamous skin cancer patients that received elective nodal radiation [6]. In 1985 it became the practice of that institution to offer such extended field radiotherapy for high risk cases. These were primarily surgical patients that received postoperative therapy. Patients whose elective nodal radiotherapy required little modification of the primary site fields were not included. This somewhat weakens the conclusions of the paper, as the outcome of the excluded patients is not documented, or how limited the fields actually were. The majority of patients in this series had a gross PNI (13%) or microscopic PNI (78%) on pathological evaluation. Only 71 patients were evaluated over a 28 year span, indicating how difficult it would be to perform a clinical trial for this population at any single institution. The University of Florida found a very low neck failure rate of only 4% in patients that received elective nodal irradiation in this setting. Similarly, in the University of Michigan series, radiated patients also received elective neck radiotherapy and a low neck failure rate was documented. In contrast, a British Columbia series of locally advanced cases treated definitively with radiotherapy documented a high neck failure rate for the higher T-stage cases, in the absence of such elective neck irradiation [7]. Together these series illustrate the importance of recognizing extensive PNI in locally advanced cases, and the importance of adjuvant radiotherapy covering the appropriate base of skull and dermatome innervations, as well as the regional nodal basins.

In the British Columbia series as well as others, local failure or base of skull failure with squamous cell carcinoma was the predominant cause of death. Aggressive management of such high risk cases is warranted. MD Anderson reported on their experience with aggressive multimodality management of such cases, usually incorporating base of skull surgery followed by adjuvant therapy, and such an approach had a substantial impact on this pattern of failure [8].

Clinical trials are lacking in this area, in large part because of the relative rarity of these high risk cases. Although concurrent postoperative chemoradiation is not substantiated by any clinical trial

data, currently both NCCN and ACR recommend extrapolating from head and neck mucosal postoperative chemoradiation trials to justify the addition of chemotherapy to the regimen for high risk cases. A clinical trial was recently completed by the Trans-Tasman Radiation Oncology Group (TROG), offering postoperative radiotherapy (60-66Gy) with concurrent carboplatin. Results are pending. This group is to be commended on completing this important trial, and further clinical research in this area is indicated.

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