Definitive Radiotherapy for Skin and Adenoid Cystic Carcinoma with Perineural Invasion

William M. Mendenhall¹ Roi Dagan¹ Curtis M. Bryant¹ Robert J. Amdur¹

¹Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, Florida, United States

Address for correspondence William M. Mendenhall, MD, 2000 SW Archer Road, PO Box 100385, Gainesville, FL 32610-0385, United States (e-mail: mendwm@shands.ufl.edu).

J Neurol Surg B 2016;77:169–172.

Abstract

Adenoid cystic carcinomas (ACC) and, to a lesser extent, cutaneous squamous cell carcinomas and basal cell carcinomas may exhibit perineural invasion (PNI). A subset of patients have tumors with extensive PNI tracking to the skull base that are incompletely resectable and are treated with definitive radiotherapy (RT). RT may be administered with intensity-modulated RT or proton RT. Patients with ACC may also be considered for neutron RT, although the number of available neutron facilities is limited. A substantial proportion of patients with incompletely resectable ACCs and cutaneous carcinomas may be cured with definitive RT. Proton RT provides a more conformal dose distribution compared with other modalities and is likely associated with a lower risk of complications.

Keywords

- head and neck
- outcomes
- radiotherapy
- radiation therapy
- skin cancer

Introduction

The likelihood of perineural invasion (PNI) by cancer depends on the histology, location, and extent of the lesion. Head and neck cancers that exhibit PNI include adenoid cystic carcinomas (ACC) and, to a lesser extent, cutaneous squamous (SCC) and basal cell (BCC) carcinomas.^{1,2} Resection specimens and biopsy samples of mucosal primary squamous carcinomas of the oral cavity, oropharynx, hypopharynx, and larynx are also frequently found to involve the perineurium of small nerves, but these infrequently progress along major cranial nerves. The cranial nerves that are involved depend on the location of the tumor. Although PNI usually spreads centrally to the skull base and central nervous system (CNS), it may also extend peripherally away from the skull base. As the PNI progresses, it may be visualized radiographically on magnetic resonance imaging. It is unusual to detect PNI radiographically in the absence of symptoms.

Adenoid Cystic Carcinoma

ACCs arise in either the major or minor salivary glands and frequently are found to have PNI on pathology without associated symptoms (incidental PNI).¹ As the tumor progresses, the patient may develop one or more cranial neuropathies or radiographic evidence of perineural tumor.

The optimal treatment for ACC is surgery, usually followed by postoperative radiotherapy (RT).¹ However, as the PNI progresses centrally to the skull base, a subset of patients has ACCs that are not amenable to a gross total resection with acceptable morbidity. Because it is unlikely that such patients benefit from a subtotal resection, these patients are treated with definitive RT.

Definitive RT may be accomplished with photons employing intensity-modulated RT (IMRT) to create a conformal dose distribution. Patients with tumors extending to the central skull base may benefit from proton beam RT to create an even more conformal dose distribution to adequately irradiate the tumor while reducing the dose to the eyes, optic nerves, and CNS compared with what can be achieved with IMRT.³

The majority of patients present with a clinically negative neck and, depending on the primary site and the estimated risk of subclinical regional disease, patients may benefit from elective neck irradiation (ENI). An additional factor to consider is whether the addition of ENI significantly increases treatment toxicity. If not, our bias is to employ ENI even if the risk of subclinical regional disease is in the range of 10%.

The dose fractionation schedules that may be employed to treat the primary site include: standard fractionation, 70 Gy/35 fractions/7 weeks; hyperfractionation, 74.4 Gy/62 twice-daily fractions (Fx) over 6.5 weeks; and the Danish Head and Neck Cancer Group (DAHNC), 70 Gy/35 Fx/30 treatment

days/6 weeks.⁴ The latter schedule was employed in Denmark to treat head and neck SCCs and, by treating twice daily once a week during the last 5 weeks of RT, compresses the overall treatment time from 7 to 6 weeks. The goal of accelerated fractionation is to improve tumor control probability, by overcoming tumor cell repopulation, while hyperfractionation may be advantageous to reduce the risk of damaging the visual apparatus depending on the tumor location.^{5,6}

While it may be tempting to add adjuvant chemotherapy in these patients to radiosensitize the tumor, there are no data to support doing so.

Balamucki et al¹ reported on 120 patients treated at the University of Florida between 1966 and 2008; 74 patients (62%) were treated with surgery and adjuvant RT and 46 patients (38%) were treated with RT alone. Patients treated with RT alone usually had incompletely resectable tumors due to PNI to the skull base. Incidental and clinical PNI were present in 41 (34%) and 35 patients (29%), respectively. Median follow-up was 8.6 years; median follow-up on survivors was 11.6 years. The 10-year outcomes after RT alone were: local control, 36%; distant metastasis-free survival, 76%; cause-specific free survival, 46%; and overall survival, 37%. In contrast, the 10-year outcomes after surgery and adjuvant RT were: local control, 84%; distant metastasis-free survival, 62%; cause-specific survival, 71%; and overall survival, 57%.

Douglas et al⁷ reported on 151 patients treated with neutron RT at the University of Washington between 1985 and 1997 for previously unirradiated nonmetastatic locally advanced and/or recurrent ACCs that were unresectable or had gross residual disease after surgery. The 5-year outcomes were: local-regional control, 57%; cause-specific survival, 77%; and overall survival, 72%. Multivariate analysis of local-regional control revealed that skull base invasion ($p < 0.01$) and treatment with RT alone ($p = 0.03$) adversely impacted this endpoint. Local-regional control was 43% after neutron RT alone and 71% after subtotal resection and neutron RT ($p = 0.03$).

Pommier et al³ reported on 23 patients treated with proton-beam RT at Massachusetts General Hospital between 1991 and 2002 with ACC involving the skull base. Biopsy alone was performed in 48% and 39% had a subtotal resection; only 13% of patients had a gross total resection. The median RT dose was 75.9 Gy. Median follow-up for living patients was 64 months. The 5-year outcomes were: local control, 93%; distant metastasis-free survival, 62%; and overall survival, 77%. One patient experienced a grade 4 retinopathy; there were no grade 5 visual complications.

Cutaneous Squamous and Basal Cell Carcinomas

Depending on location and extent, patients with cutaneous SCCs and BCCs of the head and neck are treated with surgery or definitive RT.^{8,9} PNI is found in approximately 2% of patients with BCCs and 3% of those with SCCs.^{2,10,11} Patients with PNI are optimally treated with surgery and postoperative RT. However, a subset of patients has clinical PNI with skull base invasion that is incompletely resectable; these patients are treated with definitive RT. An example of such a patient is depicted in **Fig. 1**.

Patients with PNI tend to be male and to have lesions that are recurrent, involve the midface, and/or are poorly differentiated. The cranial nerves most commonly involved are the infraorbital nerve (V2) and the facial nerve (VII). PNI may extend from the facial nerve to the trigeminal nerve via the auriculotemporal nerve and vice versa.

Patients are treated with IMRT using the same dose-fractionation schedules previously outlined for ACCs. Depending on the location and extent, proton RT is often advantageous to improve the probability of tumor control or reduce the risk of late complications, particularly to the eyes and optic nerves.^{5,8}

Patients with SCC and PNI, whether incidental or clinical, have a 15 to 20% risk of subclinical regional disease when the neck is clinically N0 and receive ENI in conjunction with RT with the primary site. The risk of subclinical regional disease with BCC is negligible and the N0 regional lymphatics are not irradiated. The risk of subclinical regional disease in the occasional patient with metatypical BCC and PNI is unclear and we tend to treat them as we would a patient with SCC.

While it is tempting to extrapolate data pertaining to mucosal head and neck SCC to cutaneous SCC/BCC and add concomitant cisplatin to definitive RT, there are no data to support the use of adjuvant chemotherapy in this setting.

Balamucki et al² reported on 216 patients treated with RT alone or combined with surgery for cutaneous SCC and BCC of the head and neck with incidental (107 patients) or clinical (109 patients) PNI at the University of Florida between 1965 and 2007. All patients were treated with high-energy photons and/or electrons; no patient received proton RT. Median follow-up was 4 years; median follow-up for living patients was 6.6 years. Clinical PNI was present in 109 patients. Histologies were SCC, 88 patients; BCC, 13 patients; and metatypical BCC, 8 patients. A total of 49 patients (45%) were treated with definitive RT alone (36 patients) or combined with adjuvant chemotherapy (13 patients). The 5-year local control after definitive RT alone or combined with adjuvant chemotherapy was 54%. The 5-year outcomes after definitive RT alone versus RT combined with adjuvant chemotherapy were: local control, 42 and 62%; local-regional control, 41 and 62%; cause-specific survival, 63 and 76%; and overall survival, 57 and 57%, respectively.

Of the 109 patients with clinical PNI, 39 (36%) experienced 54 grade 3 or higher complications due to RT and/or surgery. Complications included soft tissue necrosis, 3 patients; fistula, 5 patients; wound infection, 6 patients; dehiscence, 1 patient; blindness, 12 patients (ipsilateral, 9 patients; contralateral, 1 patient; bilateral, 2 patients); and other, 9 patients. Those who developed ipsilateral blindness usually received high-dose RT to the eye and loss of ipsilateral vision was anticipated. Although bilateral blindness is never anticipated, at times it was necessary to give high-dose RT to the optic nerves and/or chiasm to adequately irradiate the cancer.

Balamucki et al¹⁰ reported on 65 patients with cutaneous skin cancers (SCC, 59 patients; BCC, 4 patients; metatypical BCC, 2 patients) and clinical PNI who were treated at the University of Florida between 1965 and 2009 with RT alone (32 patients) or combined with surgery (33 patients). Adjuvant chemotherapy

Fig. 1 A 70-year-old white male patient with recurrent cutaneous squamous cell carcinoma of the temporal scalp after Moh's resection with incidental PNI. (A) Perineural recurrence at the primary site involving the dermis and subcutaneous tissues (maroon). (B) Retrograde perineural spread is seen along the branches of left V1 (yellow) extending back to the root of left CN V (blue). Antegrade spread of tumor is seen along V2 (aqua) and V3 (green). Changes from denervation are noted within the left temporalis muscle (arrows). CN, cranial nerve; PNI, perineural invasion.

was employed in 19 patients. The median RT dose was 72.6 Gy (range, 50.4–79.2 Gy). Median follow-up overall and for living patients was 5.4 and 11.6 years, respectively. Radiographic extent of the PNI was assessed on pretreatment magnetic resonance imaging and/or computed tomography in all patients and defined as none, 11 patients; minimal or moderate peripheral, 18 patients; and central and/or macroscopic, 36 patients.¹⁰ The 5-year local control rates were: imaging negative, 81%; minimal or moderate peripheral disease, 60%; and central and/or macroscopic disease, 47% ($p = 0.2321$). The 5-year cause-specific survival rates were: imaging negative, 100%; minimal or moderate peripheral disease, 58%; and central and/or macroscopic disease, 65% ($p = 0.0815$). The 5-year overall survival rates were: imaging negative, 82%; minimal or moderate peripheral disease, 50%; and central and/or macroscopic disease, 52% ($p = 0.2637$).

Conclusion

Patients with incompletely resectable cutaneous SCC/BCC and ACC and clinical PNI are optimally treated with definitive RT. Patients are treated with IMRT or, depending on the location and extent of the cancer, proton RT.

References

- Balamucki CJ, Amdur RJ, Werning JW, et al. Adenoid cystic carcinoma of the head and neck. *Am J Otolaryngol* 2012;33(5): 510–518
- Balamucki CJ, Mancuso AA, Amdur RJ, et al. Skin carcinoma of the head and neck with perineural invasion. *Am J Otolaryngol* 2012; 33(4):447–454
- Pommier P, Liebsch NJ, Deschler DG, et al. Proton beam radiation therapy for skull base adenoid cystic carcinoma. *Arch Otolaryngol Head Neck Surg* 2006;132(11):1242–1249
- Mendenhall WM, Riggs CE, Vaysberg M, Amdur RJ, Werning JW. Altered fractionation and adjuvant chemotherapy for head and neck squamous cell carcinoma. *Head Neck* 2010;32(7): 939–945
- Bhandare N, Monroe AT, Morris CG, Bhatti MT, Mendenhall WM. Does altered fractionation influence the risk of radiation-induced optic neuropathy? *Int J Radiat Oncol Biol Phys* 2005;62(4): 1070–1077
- Monroe AT, Bhandare N, Morris CG, Mendenhall WM. Preventing radiation retinopathy with hyperfractionation. *Int J Radiat Oncol Biol Phys* 2005;61(3):856–864
- Douglas JG, Laramore GE, Austin-Seymour M, Koh W, Stelzer K, Griffin TW. Treatment of locally advanced adenoid cystic carcinoma of the head and neck with neutron radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;46(3):551–557
- Mendenhall WM, Amdur RJ, Hinerman RW, Cогnetta AB, Mendenhall NP. Radiotherapy for cutaneous squamous and basal cell

- carcinomas of the head and neck. *Laryngoscope* 2009;119(10):1994–1999
- 9 Kropp L, Balamucki CJ, Morris CG, et al. Mohs resection and postoperative radiotherapy for head and neck cancers with incidental perineural invasion. *Am J Otolaryngol* 2013;34(5):373–377
- 10 Balamucki CJ, DeJesus R, Galloway TJ, et al. Impact of radiographic findings on for prognosis skin cancer with perineural invasion. *Am J Clin Oncol* 2015;38(3):248–251
- 11 Mendenhall WM, Ferlito A, Takes RP, et al. Cutaneous head and neck basal and squamous cell carcinomas with perineural invasion. *Oral Oncol* 2012;48(10):918–922