American College of Radiology
ACR Appropriateness Criteria®

AGGRESSIVE NONMELANOMATOUS SKIN CANCER OF THE HEAD AND NECK

Expert Panel on Radiation Oncology–Head & Neck: Shlomo A. Koyfman, MD[1]; Jay S. Cooper, MD[2]; Jonathan J. Beitler, MD, MBA[3]; Paul M. Busse, MD, PhD[4]; Christopher U. Jones, MD[5]; Mark W. McDonald, MD[6]; Harry Quon, MD, MS[7]; John A. Ridge, MD, PhD[8]; Nabil F. Saba, MD[9]; Joseph K. Salama, MD[10]; Farzan Siddiqui, MD, PhD[11]; Richard V. Smith, MD[12]; Francis Worden, MD[13]; Min Yao, MD, PhD[14]; Sue S. Yom, MD, PhD.[15]

Summary of Literature Review

Introduction/Background

Although the overwhelming majority of nonmelanomatous and non-Merkel cell skin cancer (NMSC) of the head and neck, specifically basal cell carcinoma (BCC) and squamous cell carcinomas (SCC), is easily cured with surgical removal, superficial radiation therapy (RT), and/or ablation alone, there is a subset of these tumors—either due to neglect or unfavorable biological features—that exhibit aggressive clinical behavior. This subset also includes patients who present with locoregionally advanced disease and experience substantial rates of cancer recurrence and cancer-related morbidity and mortality. The incidence of these cancers is rising, most prominently among the immunosuppressed population. These patients commonly require multimodality therapy and frequently present therapeutic challenges as there is a paucity of high-quality clinical trials to guide clinical decision making. RT plays an important role in the management of these tumors, both in the postoperative and definitive settings.

Characterization of Aggressive Skin Cancer

Aggressive BCC are characterized by a number of high-risk features, including recurrent disease—especially in the setting of prior definitive therapy, infiltrative T4 disease, aggressive pathologic subtypes such as morpheaform, sclerosing, mixed infiltrative, and micronodular histologies, and those rare BCC that demonstrate perineural invasion (PNI) [1,2]. Although BCC arising in the mask areas of the face are also frequently categorized as high-risk, often necessitating advanced surgical or radiation techniques, in the absence of other high-risk features, outcomes are generally quite favorable [3]. Aggressive SCC is more common and is more likely to recur both locoregionally and distantly compared to BCC, and therefore has additional high-risk features that may call for treatment intensification. These include T4 disease, nodal metastases, extensive lymphovascular space or PNI, especially in the setting of neurological symptoms, rapidly growing tumors, satellitosis or in-transit metastases, spindle cell and/or poorly differentiated histology, tumors arising on the ear or non–hair-bearing lip, and deeply invasive tumors (eg, Clarks level IV/V and/or >2 mm depth) [3].

Recurrence rates vary considerably among cancers that demonstrate one or more of these features, and an additive effect is likely when multiple features are present. As an illustration, although a T2N0 SCC with focal PNI or 4 mm of depth may have a recurrence rate of 5%–10%, a patient with poorly differentiated T4 disease, those with nodal metastases, and/or those with extensive PNI have a >50% rate of recurrence if treated with single-modality therapy [4,5].

Indications for Radiotherapy

Definitive radiotherapy

Radiotherapy can be used for the definitive treatment of aggressive BCC and SCC. However, surgery is typically preferred for these lesions as it can be done more quickly, and there is some evidence that it may be associated

[1]Principal Author, Cleveland Clinic, Cleveland, Ohio. [2]Co-author, Maimonides Cancer Center, Brooklyn, New York. [3]Emory University School of Medicine, Atlanta, Georgia. [4]Massachusetts General Hospital, Boston, Massachusetts. [5]Radiologic Associates of Sacramento, Sacramento, California. [6]Indiana University School of Medicine, Indianapolis, Indiana. [7]Johns Hopkins University, Baltimore, Maryland. [8]Fox Chase Cancer Center, Philadelphia, Pennsylvania, American College of Surgeons. [9]Emory University, Atlanta, Georgia, American Society of Clinical Oncology. [10]Duke University, Durham, North Carolina. [11]Henry Ford Health System, Detroit, Michigan. [12]Montefiore Medical Center, Bronx, New York, American College of Surgeons. [13]University of Michigan, Ann Arbor, Michigan, American Society of Clinical Oncology. [14]University Hospitals Case Medical Center, Cleveland, Ohio. [15]Panel Chair, University of California San Francisco, San Francisco, California.

with improved tumor control rates and cosmesis compared to RT alone. A prospective randomized study compared the use of the Mohs surgical technique to definitive RT in 347 patients with BCC of the face <4 cm. Local failure was <1% for patients treated with surgery compared to 7.5% for those treated with RT. Surgical patients also rated their cosmetic outcome as "good" or "better," more commonly (87% versus 69%). Although there was considerable variability in the method and techniques of RT administration (55% via interstitial brachytherapy, 45% with contact or orthovoltage therapy), which compromises the quality of the comparison between groups, this study remains the sole randomized study guiding medical decision making and suggests a benefit for surgery [6]. When performing surgery for these patients, Mohs micrographic surgery is typically favored for lesions of the head and neck based on a prospective randomized study that compared Mohs surgery to wide excision in 612 BCC lesions in a variety of anatomic locations [7]. The 2-year local control (LC) rate was comparable for primary lesions (98%) but superior for recurrent lesions (98% versus 92%). Mohs surgery was also associated with improved cosmesis and lower positive margin rates, especially for BCC with aggressive histologies or in the mask region of the face. Although there are no comparable studies in SCC, this treatment paradigm is often extrapolated to SCC, especially in the head and neck region.

Definitive RT for large or aggressive BCC or SCC is typically reserved for patients who are poor surgical candidates due to advanced age or comorbidities or in patients who strongly prefer nonoperative treatment (see Variant 1). In the definitive setting, doses of 60–70 Gy in 30–35 fractions or accelerated hypofractionated regimens with similar biologically effective tumor dosing is recommended (eg, 50–55 Gy in 20 fractions; 40–45 Gy in 10 fractions) to ensure adequate control (see Table 1). A large retrospective review of 531 lesions (BCC 389, SCC 142) treated with definitive RT over a 30-year period reported overall control rates of 94% and 89% in the primary setting and 86% and 68% in the recurrent setting for BCC and SCC, respectively [8]. In this report, hypofractionated regimens (>2 Gy/fraction) were associated with improved LC outcomes. This control advantage, however, may come at the price of impaired cosmesis. A large review of >1,000 patients from Germany treated with 4–5 Gy/fraction several days weekly to total doses of 50–60 Gy reported excellent LC of 95%, but 92% of patients experienced hypopigmentation, and 82% had telangiectasias, recapitulating this concern [9,10].

Although radiation monotherapy is often effective for larger tumors, inferior outcomes are seen for T4 tumors, especially those with bony involvement. In the Washington University cohort, for example, patients with T4 tumors had LC rates of 100% and 75% in the primary setting and 67% and 50% in the recurrent setting for BCC and SCC, respectively [8]. Similarly, University of Florida reported their LC with T4 BCC/SCC as 53% at 5 years and an even worse LC in patients who had recurrent disease, bone invasion, or nerve involvement [4]. This observation may support the use of intensified treatment approaches with multimodality therapy in these patients, most often consisting of primary surgery and adjuvant RT, with the goal of improving control rates. This is particularly acute in patients with T3/4 SCC and those with nodal metastases, where rates of locoregional recurrence with definitive RT alone range from 30% to 50%, and cancer-related mortality can be as high as 30%. Although suboptimal, outcomes for advanced primary BCC can be acceptable with definitive RT with 70%–90% control rates, and should be distinguished from the inferior control rates and higher rates of cancer-related mortality of advanced SCC [11].

Historically, superficial and orthovoltage techniques have been frequently used in definitive RT for small, and/or superficial skin cancers. Brachytherapy has also been used with excellent control rates for *de novo*, nonaggressive BCC and SCC of the head and neck, especially in cosmetically challenging areas [6]. Aggressive BCC and SCC of the skin, however, can be more infiltrative, and the modest penetration of these modalities into deeper tissues limits their use in these cases. Most often, these lesions will be managed surgically with or without adjuvant RT. However, when primary surgery is not used—either due to unresectable disease or a patient that is medically inoperable or refuses surgery—more deeply penetrating external RT is favored [12]. Electron beam therapy with custom bolus is an excellent choice for patients with targets that are not too thick (typically <4 cm) and encompass a fairly limited field size. For more complex situations that require nodal irradiation, and especially base of skull coverage, more conformal radiation, often using intensity-modulated radiotherapy (IMRT), is preferred to spare surrounding critical structures.

Postoperative radiotherapy

Postoperative RT is used sparingly for BCC and is reserved for patients with persistently positive margins or large infiltrative T4 tumors that extensively invade bone or soft tissue that would prove difficult to microscopically clear with surgery alone (see Variant 2). Even patients with clinically occult, pathologically identified PNI have

excellent long-term control rates with surgery alone. For those rare cases that do recur, salvage re-resection with or without adjuvant RT is a viable option with excellent results [13,14].

Immunocompetent patients with SCC who have T1–2 tumors that are resected with negative margins without evidence of perineural or lymphovascular space invasion and no evidence of lymph node metastases are well treated with surgery monotherapy (see Variant 3). For patients with evidence of any of these high-risk factors, adjuvant RT is typically recommended. Numerous retrospective series have demonstrated that patients with nodal metastases have high rates of recurrence and subsequently benefit from adjuvant RT. A study from Australia revealed improved 5-year disease-free survival (74% versus 34%; *P*=0.001) and 5-year overall survival (66% versus 27%; *P*=0.003) for patients treated with postoperative RT compared to surgery alone [15]. Similar to the mucosal head and neck cancer paradigm, an exception pertains to (immunocompetent) patients with a single involved parotid or cervical lymph node on a thorough neck dissection with parotidectomy without evidence of extracapsular spread, who can be treated with surgery monotherapy with low rates (<5%) of recurrence [16]. Patients with large T3 or T4 disease have a significant risk of local recurrence if treated with surgery alone. Occult lymph node metastases are also a concern in such settings, ranging from 29% to 50% for advanced T stage disease, and up to 30% in tumors that are deeply infiltrative (≥8 mm) and/or frankly invade into deep subcutaneous fat [11].

Another well-reported risk factor for recurrence and a common indication for adjuvant RT in resected cutaneous SCC is PNI. Overall, PNI is found in 5%–15% of these cancers [14]. The extent of PNI is relevant, as focal PNI has been associated with more favorable outcomes. In a series comprised predominantly of patients treated with resection and adjuvant RT, Lin et al [14] found that focal PNI was associated with improved relapse-free survival compared to extensive PNI (86% versus 74%; *P*=0.1). In addition to being associated with a 15%–25% risk of local recurrence, some studies suggest that the presence of PNI predicts for a higher likelihood of nodal metastases as well, ranging from 5% to 17% in varying studies, and serves as a rationale for elective nodal irradiation in these patients [14,17]. In the Australian series, patients with recurrent disease that demonstrate PNI at the time of recurrence are at significantly higher risk of recurrence both locally (40% versus 19%; P<0.01) and regionally (29% versus 5%; *P*=0.02), and strong consideration should be given to elective nodal irradiation in this setting [14]. Site of origin may influence this decision; for example, scalp lesions are less likely to have nodal metastases than nasal or cheek cancers. These data pertain to clinically occult, pathologically determined PNI. Patients with clinically evident PNI, either due to neurological symptoms such as numbness, pain, or facial weakness or radiographic evidence of nerve enhancement, have inferior outcomes with locoregional control rates of only 50% and cancer-related mortality as high as 40% [13,17]. Importantly, radiographic detection of PNI can be easily overlooked, and careful review with an expert neuroradiologist is crucial in cases where the index of suspicion is high [18].

When treating patients with PNI, targeting the course of the involved nerves back to the base of skull usually is desirable. Most commonly, branches of the trigeminal and facial nerves are involved. In the former case, when targeting the nerve branches back to their respective foramina in the skull base, including the gasserian ganglion found in Meckel cave and the cavernous sinus (when VI/II are involved) is recommended. For cranial nerve VII involvement, the nerve can be tracked back to the stylomastoid foramen. When targeting this region, care should be taken not to overly restrict dose to the ipsilateral cochlea to ensure adequate coverage of the geniculate ganglion. When nerves are radiographically involved at the skull base, consideration should be given to targeting the nerve root as it exits the brainstem (see Variant 4).

Systemic Therapies

A recent development in metastatic BCC has been the recent approval of the hedgehog pathway inhibitor, vismodegib, based on 30%–45% response rates in a phase II study of the drug in patients with advanced BCC [19]. It is indicated in patients who have recurrent or metastatic BCC and in patients who are not amenable to definitive resection or RT. This would also include patients with Gorlin syndrome who can develop hundreds of lesions and in whom RT is contraindicated given their inherent radiosensitivity. To date there are no data testing its efficacy in combination with surgery or RT, although clinical trials are underway exploring these potential applications.

In the high-risk cutaneous SCC, there are no randomized studies confirming the added utility of concurrent systemic chemotherapy in conjunction with RT either in the definitive or adjuvant settings. Some clinicians have extrapolated from randomized trials conducted in the mucosal head and neck cancer setting, in which cisplatin-

based chemoradiotherapy has demonstrated superior results for locally advanced patients treated nonoperatively, as well as for select high-risk patients requiring postoperative intensification. [20,21]. More recently, there is growing interest in the use of epidermal growth factor receptor (EGFR) inhibitors in this disease either as monotherapy in advanced disease, or in combination with surgery or RT. A recent prospective phase II study investigated the use of the oral tyrosine kinase inhibitor gefitinib as an induction strategy followed by local surgery, RT, or both in patients with locally advanced disease. Of 22 assessable patients, 18% had a complete response, and an additional 27% had a partial response with a promising 2-year progression-free survival of 64% [22]. A different phase I study specifically investigated the addition of the oral tyrosine kinase inhibitor erlotinib concurrently with conventional RT for T4 lesions. The regimen proved safe with a 2-year progression-free survival of 60% [23]. Cetuximab is a monoclonal antibody-based EGFR inhibitor that produced response rates of 30% and disease stabilization rates of 70% when used as monotherapy in a French phase II study of patients with unresectable/metastatic SCC of the skin [24,25]. Given their substantial activity, these therapies are frequently employed as a concurrent treatment in patients with unresectable, locally advanced cutaneous SCC of the head and neck undergoing definitive RT. However, randomized studies have not yet established a definitive role for these agents in cutaneous SCC of the head and neck, and these approaches remain investigational (see Variant 5, and Variant 6 and Variant 7).

Considerations in the Immunosuppressed Patient

NMSC is emerging as an increasingly common and dangerous problem for patients who are chronically immunosuppressed. The incidence of BCC and SCC can be 10 fold and 60–250 fold higher, respectively, than the general population in patients who have undergone solid organ transplantation, were exposed to extensive chemotherapy, or received longstanding corticosteroid therapy, and affects >20% of all such patients [26]. SCC in particular has a higher likelihood of forming in higher risk sun-exposed areas such as the scalp, lip, and ears [27,28].

Immunosuppressed patients more often develop SCC rather than BCC, and they do so at younger ages and with more frequent multifocality, PNI, and deeper infiltration than immunocompetent patients [29,30]. Once they develop a skin cancer, >75% develop additional lesions within the next 5 years, at times within months of each other [31]. SCC can even account for 5%–10% of the mortality in these patients [32]. BCC tends to behave fairly similarly independent of immune status. As such, an immunosuppressed patient status is a prominent risk factor for both BCC and SCC, more so for the latter, and often manifests with a more aggressive clinical phenotype. This has significant implications for potentially requiring intensified, multimodality therapy.

Few studies have directly compared outcomes between immunosuppressed and immunocompetent patients with high-risk BCC and SCC. Although adjuvant RT is typically recommended in either case in the presence of high-risk features, it is unclear if disease control rates as well as tolerability of RT differ between these patient cohorts. Manyam et al recently reported a retrospective comparison of 38 immunocompetent and 21 immunosuppressed patients treated for cutaneous SCC of the head and neck with resection and adjuvant RT. Most had nodal metastases (63%), 50% had PNI, and 15% were T3/4. Actuarial locoregional control (48% versus 73%; P=0.01) and disease-free survival (44% versus 62%; P=0.03) at 2 years were significantly inferior in the immunosuppressed population [33]. Others have also found immunosuppressed status to portend inferior prognosis in the locally advanced setting [34]. This raises an important unanswered question: Are immunosuppressed patients intrinsically more resistant to traditional adjuvant therapies, or can intensification of therapy with earlier and perhaps dose-escalated RT and/or concurrent systemic therapies improve outcomes (see Variant 8)? This question merits future prospective study.

The pattern of spread may also vary in immunosuppressed patients. Discontinuous spread or satellitosis is not uncommon in these patients, and tumors can recur further away from the clinically evident primary tumor site. This may very well be manifestations of field cancerization with separate primary tumors but may have implications for the extent of surrounding tissue that requires targeting in the adjuvant setting, especially in the setting of extensive PNI or lymphovascular space involvement [35].

Another important consideration in transplant patients relates to their immunosuppression regimens. Calcineurin inhibitors are frequently used to prevent graft rejection in these patients but have been shown to have promitogenic properties. Sirolimus (also known as rapamycin), however, is an mTOR inhibitor with antineoplastic properties and may be preferable in these patients, especially those who have already developed aggressive skin cancers. In a phase III randomized study comparing the use of a calcineurin inhibitor (often FK-

506, tacrolimus) with sirolimus in patients with organ transplants, the latter drug was associated with a significant reduction in the incidence of new SCC (relative risk 0.56; 22% versus 39%; *P*=0.02). Although there were more frequent side effects in the sirolimus group, there was no evidence of higher rates of graft loss [36]. Although a more recently published randomized trial from the Netherlands failed to reproduce these results, it did demonstrate decreased tumor burden with sirolimus-based regimens with moderate increased morbidity [37]. Oral capecitabine, as well as oral retinoids, has also been used with some success as a chemopreventant in these patients [38] (see Variant 8). In addition to deciding on the use of adjuvant RT in these high-risk patients, radiation oncologists should consider discussing the risks and benefits of modulation of patients' immunosuppressive regimens with the transplant physicians.

Table 1. Select Examples of Curative RT Regimens
60–70 Gy in 30–35 fractions
50–55 Gy in 17–20 fractions
40–44 Gy in 10 fractions
40 Gy in 5 fractions (twice weekly)
30 Gy in 3 fractions (once weekly)
20–25 Gy in 1 fraction
NOTE: Longer fractionation schedules are preferred when target volumes are in close proximity to neural, optic, and other radiosensitive organs at risk.

Summary of Recommendations

- BCC is highly radiosensitive and is amenable to definitive radiotherapy, especially for those lesions that would entail morbid resection, or in the elderly or infirm.
- In the adjuvant setting, radiotherapy is indicated for recurrent basal cell cancer with persistently positive margins or in large infiltrative tumors that extensively invade bone or soft tissue that would prove difficult to microscopically clear with surgery alone.
- Cutaneous squamous cell cancer that is resected with negative margins and does not display high-risk features can be safely observed postoperatively.
- Resected SCC that demonstrate perineural invasion, especially multifocal, should be considered for adjuvant radiotherapy. A full discussion with the patient of the potential benefits and risks should be documented. In cases of extensive perineural invasion or invasion of named nerves, the nerve should be targeted with radiotherapy back to the skull base.
- Patients with periparotid nodal disease ideally should be managed by surgical resection with neck dissection (and often parotidectomy) followed by adjuvant radiotherapy.
- Concurrent cisplatin-based chemotherapy can be considered, by extrapolation of practices from head and neck mucosal SCC, in patients with high-risk pathologic features (eg, margin positivity or extracapsular extension) or in the unresectable, locally advanced setting.
- Immunosuppressed patients may experience unusually aggressive clinical tumor behavior and warrant multidisciplinary evaluation.
- Intensified adjuvant therapies, such as radiotherapy for intermediate-risk patients and incorporating systemic therapies concurrently with radiotherapy, may benefit certain classes of patients.
- Management of immunosuppressed patients should include multidisciplinary discussion of long-term plans for immunosuppression and surveillance measures.

Summary of Evidence

Of the 38 references cited in the *ACR Appropriateness Criteria® Aggressive Nonmelanomatous Skin Cancer of the Head and Neck* document, all of them are categorized as therapeutic references including 6 well-designed studies and 12 good quality studies. There are 20 references that may not be useful as primary evidence.

The 38 references cited in the *ACR Appropriateness Criteria® Aggressive Nonmelanomatous Skin Cancer of the Head and Neck* document were published between 1993–2014.

While there are references that report on studies with design limitations, 18 well-designed or good quality studies provide good evidence.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

References

1. Ghanadan A, Abbasi A, Rabet M, Abdollahi P, Abbasi M. Characteristics of Mixed Type Basal Cell Carcinoma in Comparison to Other BCC Subtypes. *Indian J Dermatol.* 2014;59(1):56-59.
2. Vico P, Fourez T, Nemec E, Andry G, Deraemaecker R. Aggressive basal cell carcinoma of head and neck areas. *Eur J Surg Oncol.* 1995;21(5):490-497.
3. NCCN Clinical Practice Guidelines in Oncology. Basal Cell and Squamous Cell Skin Cancers. Version 2.2014. 2014; Available at: http://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf. Accessed March 26, 2014.
4. Lee WR, Mendenhall WM, Parsons JT, Million RR. Radical radiotherapy for T4 carcinoma of the skin of the head and neck: a multivariate analysis. *Head Neck.* 1993;15(4):320-324.
5. Mendenhall WM, Amdur RJ, Hinerman RW, et al. Skin cancer of the head and neck with perineural invasion. *Am J Clin Oncol.* 2007;30(1):93-96.
6. Avril MF, Auperin A, Margulis A, et al. Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study. *Br J Cancer.* 1997;76(1):100-106.
7. Smeets NW, Krekels GA, Ostertag JU, et al. Surgical excision vs Mohs' micrographic surgery for basal-cell carcinoma of the face: randomised controlled trial. *Lancet.* 2004;364(9447):1766-1772.
8. Locke J, Karimpour S, Young G, Lockett MA, Perez CA. Radiotherapy for epithelial skin cancer. *Int J Radiat Oncol Biol Phys.* 2001;51(3):748-755.
9. Rupprecht R, Lippold A, Auras C, et al. Late side-effects with cosmetic relevance following soft X-ray therapy of cutaneous neoplasias. *J Eur Acad Dermatol Venereol.* 2007;21(2):178-185.
10. Schulte KW, Lippold A, Auras C, et al. Soft x-ray therapy for cutaneous basal cell and squamous cell carcinomas. *J Am Acad Dermatol.* 2005;53(6):993-1001.
11. Kwan W, Wilson D, Moravan V. Radiotherapy for locally advanced basal cell and squamous cell carcinomas of the skin. *Int J Radiat Oncol Biol Phys.* 2004;60(2):406-411.
12. Rio E, Bardet E, Ferron C, et al. Interstitial brachytherapy of periorificial skin carcinomas of the face: a retrospective study of 97 cases. *Int J Radiat Oncol Biol Phys.* 2005;63(3):753-757.
13. Jackson JE, Dickie GJ, Wiltshire KL, et al. Radiotherapy for perineural invasion in cutaneous head and neck carcinomas: toward a risk-adapted treatment approach. *Head Neck.* 2009;31(5):604-610.
14. Lin C, Tripcony L, Keller J, et al. Perineural infiltration of cutaneous squamous cell carcinoma and basal cell carcinoma without clinical features. *Int J Radiat Oncol Biol Phys.* 2012;82(1):334-340.
15. Wang JT, Palme CE, Morgan GJ, Gebski V, Wang AY, Veness MJ. Predictors of outcome in patients with metastatic cutaneous head and neck squamous cell carcinoma involving cervical lymph nodes: Improved survival with the addition of adjuvant radiotherapy. *Head Neck.* 2012;34(11):1524-1528.
16. Ebrahimi A, Clark JR, Lorincz BB, Milross CG, Veness MJ. Metastatic head and neck cutaneous squamous cell carcinoma: defining a low-risk patient. *Head Neck.* 2012;34(3):365-370.
17. Mendenhall WM, Amdur RJ, Hinerman RW, Cognetta AB, Mendenhall NP. Radiotherapy for cutaneous squamous and basal cell carcinomas of the head and neck. *Laryngoscope.* 2009;119(10):1994-1999.
18. Warden KF, Parmar H, Trobe JD. Perineural spread of cancer along the three trigeminal divisions. *J Neuroophthalmol.* 2009;29(4):300-307.
19. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med.* 2012;366(23):2171-2179.
20. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck.* 2005;27(10):843-850.
21. Blanchard P, Baujat B, Holostenco V, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. *Radiother Oncol.* 2011;100(1):33-40.
22. Lewis CM, Glisson BS, Feng L, et al. A phase II study of gefitinib for aggressive cutaneous squamous cell carcinoma of the head and neck. *Clin Cancer Res.* 2012;18(5):1435-1446.

23. Heath CH, Deep NL, Nabell L, et al. Phase 1 study of erlotinib plus radiation therapy in patients with advanced cutaneous squamous cell carcinoma. *Int J Radiat Oncol Biol Phys.* 2013;85(5):1275-1281.
24. Kim S, Eleff M, Nicolaou N. Cetuximab as primary treatment for cutaneous squamous cell carcinoma to the neck. *Head Neck.* 2011;33(2):286-288.
25. Maubec E, Petrow P, Scheer-Senyarich I, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. *J Clin Oncol.* 2011;29(25):3419-3426.
26. Gordon Spratt EA, Carucci JA. Skin cancer in immunosuppressed patients. *Facial Plast Surg.* 2013;29(5):402-410.
27. Leisenring W, Friedman DL, Flowers ME, Schwartz JL, Deeg HJ. Nonmelanoma skin and mucosal cancers after hematopoietic cell transplantation. *J Clin Oncol.* 2006;24(7):1119-1126.
28. Moloney FJ, Comber H, O'Lorcain P, O'Kelly P, Conlon PJ, Murphy GM. A population-based study of skin cancer incidence and prevalence in renal transplant recipients. *Br J Dermatol.* 2006;154(3):498-504.
29. Lott DG, Manz R, Koch C, Lorenz RR. Aggressive behavior of nonmelanotic skin cancers in solid organ transplant recipients. *Transplantation.* 2010;90(6):683-687.
30. Smith KJ, Hamza S, Skelton H. Histologic features in primary cutaneous squamous cell carcinomas in immunocompromised patients focusing on organ transplant patients. *Dermatol Surg.* 2004;30(4 Pt 2):634-641.
31. Wisgerhof HC, Edelbroek JR, de Fijter JW, et al. Subsequent squamous- and basal-cell carcinomas in kidney-transplant recipients after the first skin cancer: cumulative incidence and risk factors. *Transplantation.* 2010;89(10):1231-1238.
32. Buell JF, Hanaway MJ, Thomas M, Alloway RR, Woodle ES. Skin cancer following transplantation: the Israel Penn International Transplant Tumor Registry experience. *Transplant Proc.* 2005;37(2):962-963.
33. Manyam B, Saxton JP, Reddy CA, et al. Inferior Outcomes in Immunosuppressed Patients with High Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck Treated with Surgery and Radiation Therapy Paper presented at: 2014 Multidisciplinary Head and Neck Cancer Symposium; Scottsdale, Arizona.
34. Oddone N, Morgan GJ, Palme CE, et al. Metastatic cutaneous squamous cell carcinoma of the head and neck: the Immunosuppression, Treatment, Extranodal spread, and Margin status (ITEM) prognostic score to predict outcome and the need to improve survival. *Cancer.* 2009;115(9):1883-1891.
35. Lang PG, Jr., Braun MA, Kwatra R. Aggressive squamous carcinomas of the scalp. *Dermatol Surg.* 2006;32(9):1163-1170.
36. Euvrard S, Morelon E, Rostaing L, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. *N Engl J Med.* 2012;367(4):329-339.
37. Hoogendijk-van den Akker JM, Harden PN, Hoitsma AJ, et al. Two-year randomized controlled prospective trial converting treatment of stable renal transplant recipients with cutaneous invasive squamous cell carcinomas to sirolimus. *J Clin Oncol.* 2013;31(10):1317-1323.
38. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part II. Management of skin cancer in solid organ transplant recipients. *J Am Acad Dermatol.* 2011;65(2):263-279; quiz 280.

Clinical Condition: **Aggressive Nonmelanomatous Skin Cancer of the Head and Neck**

Variant 1: **77-year-old woman with mild congestive heart failure and insulin-dependent diabetes presents with a long neglected 8-cm T4N0M0, stage IV nodular BCC of the left temple, involving the forehead and encroaching upon the lateral canthus. CT reveals underlying bony involvement of the facial bones and no evidence of orbital invasion. The wound is oozing and intermittently bleeding, but she is without pain. Her vision remains intact, and she refuses surgical resection. Karnofsky performance score (KPS) 70.**

Treatment	Rating	Comments
Conventionally fractionated curative intent RT (eg, 60–70 Gy in 30–35 fractions)	8	See Table 1 above for commonly used regimens. Assume that some portion of the eye, lachrymal gland, and/or brain needs to be included in the treatment portal.
Palliative intent RT	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. See Table 1 above for commonly used regimens. Assume that some portion of the eye, lachrymal gland, and/or brain needs to be included in the treatment portal.
Hypofractionated curative intent RT (eg, 40 Gy in 5 fractions)	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. See Table 1 above for commonly used regimens. Assume that some portion of the eye, lachrymal gland, and/or brain needs to be included in the treatment portal.
Best supportive care/hospice	4	
Systemic vismodegib monotherapy	4	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Aggressive Nonmelanomatous Skin Cancer of the Head and Neck**

Variant 2: **57-year-old otherwise healthy woman presents with a neglected 10-cm T4N0M0, stage IV nodular BCC of the posterior and vertex of the scalp, with calvarial involvement on MRI, no frank brain invasion. She undergoes a radical soft-tissue and calvarial resection with titanium mesh closure and anterolateral thigh free-flap reconstruction. She has pathologic evidence of perineural invasion, though margins and dural biopsy are negative. She is healing well at 5 weeks after the operation. KPS 90.**

Treatment	Rating	Comments
Adjuvant Recommendations		
Conventionally fractionated curative intent RT	8	See Table 1 above for commonly used regimens.
Hypofractionated curative intent RT	5	See Table 1 above for commonly used regimens. This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. Assume that some portion of the brain needs to be included in the treatment portal.
Observation	3	
Vismodegib	1	
RT + vismodegib	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 3: **46-year-old man presents with an asymptomatic 3-cm moderately differentiated SCC of the right cheek. Contrast-enhanced MRI of the neck reveals the primary lesion without any nodal metastases or cranial nerve abnormalities. He undergoes resection and reconstruction with widely negative margins. No perineural or angiolymphatic invasion is noted. He has healed well postoperatively. KPS 90.**

Treatment	Rating	Comments
Adjuvant Recommendations		
Observation	8	
Adjuvant RT to tumor bed alone	2	
Adjuvant RT to tumor bed and V2 nerve pathway	2	
Adjuvant RT to tumor bed, V2 nerve pathway, and ipsilateral facial and cervical lymphatics	2	
Adjuvant systemic therapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Aggressive Nonmelanomatous Skin Cancer of the Head and Neck**

Variant 4: **46-year-old man presents with an asymptomatic 3-cm moderately differentiated SCC of the right cheek. Contrast-enhanced MRI of the neck reveals the primary lesion without any nodal or cranial nerve abnormalities. He undergoes resection and reconstruction with widely negative margins. Multifocal perineural invasion is noted pathologically. He has healed well postoperatively. KPS 90.**

Treatment	Rating	Comments
Adjuvant Recommendations		
Adjuvant RT to tumor bed and V2 nerve pathway	8	
Adjuvant RT to tumor bed, V2 nerve pathway, and ipsilateral facial and cervical lymphatics	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Observation	3	
Adjuvant RT to tumor bed alone	3	
Adjuvant systemic therapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 5: **58-year-old healthy man with a history of a poorly differentiated 3-cm SCC of the right preauricular region, status post Mohs surgery with negative margin on the second stage of resection with no perineural invasion, presents 6 months later with a right-sided parotid mass. PET/CT reveals a hypermetabolic 3-cm intraparotid mass without any other areas of hypermetabolism. Fine-needle aspiration is positive for SCC.**

Treatment	Rating	Comments
Initial Management		
Parotidectomy and neck dissection	8	
Curative intent RT	4	
Curative intent RT with concurrent systemic therapy	4	
Induction chemotherapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 6: **Patient described in variant 5 elects for a nerve sparing parotidectomy and an ipsilateral neck dissection. Lymphatic metastases are found in 2 intraparotid and 2 level II lymph nodes, with extranodal extension. He is 4 weeks postop, recovering well. KPS 90.**

Treatment	Rating	Comments
Adjuvant Therapy		
RT alone	7	
RT + concurrent cisplatin	7	
RT + concurrent EGFR inhibitor	5	
Systemic therapy alone	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Aggressive Nonmelanomatous Skin Cancer of the Head and Neck**

Variant 7: **68-year-old healthy woman with a history of a 2.5-cm moderately differentiated SCC of the right cheek, status post Mohs surgery with negative margins on the third stage of resection and focal perineural involvement, is treated with postoperative radiation to the tumor bed. 9 months later, she presents with pain and numbness in the V2 distribution and diplopia. MRI of brain/neck reveals an enhancing mass in the right base of skull involving the foramen rotundum, Meckel cave, and cavernous sinus, 8 mm from the right optic nerve. The brainstem is uninvolved. No primary site or lymphadenopathy disease is noted. Biopsy is consistent with recurrent SCC. KPS 80.**

Treatment	Rating	Comments
Treatment Recommendation		
Curative intent RT alone	7	
Curative intent RT + cisplatin	7	
Curative intent RT + EGFR inhibitor	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Systemic therapy alone +/- delayed RT dependent on response	4	
RT Approach		
70 Gy in 35 fractions	8	
74.4 Gy in 62 fractions (1.2 Gy BID)	7	
60 Gy in 30 fractions	5	
40 Gy in 5 fractions using SBRT	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
50 Gy in 20 fractions	4	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Aggressive Nonmelanomatous Skin Cancer of the Head and Neck**

Variant 8: **54-year-old man with a history of a liver transplant and a previous 2.5-cm upper lip SCC, status post resection with negative margins 9 months ago presents with biopsy-proven recurrence in his right level IB lymph node. He is currently maintained on FK-506 (tacrolimus) and prednisone 5 mg daily. He undergoes bilateral neck dissections and is found to have 7/54 involved lymph nodes (right level Ib, 2, 4; left level 2) without evidence of extracapsular extension. He recovers well from surgery. KPS 90.**

Treatment	Rating	Comments
Adjuvant Recommendations		
RT alone	8	
RT + concurrent cisplatin	5	
RT + concurrent EGFR inhibitor	5	
Systemic therapy alone	1	
RT Targets		
Bilateral cervical nodes levels 1–5 + facial lymphatics	7	
Bilateral cervical nodes levels 1–5	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Bilateral cervical nodes levels 1–5 + facial lymphatics + upper lip primary site	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Immunosuppressive Therapy		
Inform transplant physicians and review possibility for safe reduction of immunosuppression	9	
Continue present immunosuppressive regimen independent of cancer therapy	4	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		