Aggressive Non-Melanomatous Skin Cancer of the Head and Neck
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	825 patients	To explore different characteristics of mixed type BCC.	483 (58.6%) of the lesions were on the face, 243 (29.5%) on scalp, 52 (6.3%) on ears, 20 (2.4%) on neck, 15 (1.8%) on trunk and 12 (1.4%) on extremities. Anatomic distribution of mixed type was as follows: 137 on face, (51.4%), 100 (37.3%) on scalp, 19 (7%) on ear, 6 (2.1%) on neck, 4 (1.5%) extremity and 1 (0.7%) on trunk, which the difference from nonmixed types was statistically significant (P=0.002). The mean diameter of the mixed types and nonmixed type BCCs were significantly different (2.7 +/- 2.1 cm vs 2.2 +/- 1.6 cm; P=0.01. The prevalence of necrosis in mixed type BCC was 2 times higher than nonmixed type BCCs (OR = 2.3, CI 95%, 1.3-3.9, P=0.001). The most frequent combined subtypes were nodular-infiltrative (P<0.001).	4
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.	Review/Other-Tx	5 cases	To review the pathological and clinical data and compare them with the reported characteristics of such lesions in the current literature on the subject.	The definition of aggressiveness in BCC consists of 3 criteria: 1. Initial size <1 cm; 2. More than 2 recurrences, despite adequate initial treatment; and 3. Extension to any extracutaneous tissue, at any time during the evolution of the disease. The association of at least 2 of these criteria seems to be predictive in terms of local aggressiveness, compared to the results in 20 'normal' BCCs. On the other hand, the histopathological factors which seem to be associated with aggressiveness of BCC, are incomplete excision of the primary tumor, adenoid types of differentiated BCC associated with little lymphocytic peritumoral dermal infiltrate, PNI and increased number of mitoses.	4
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.	Review/Other-Tx	N/A	To provide clinical practice guidelines on BCC and SCC.	No results stated in abstract.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	67 patients	A multivariate analysis of radical RT for T4 carcinoma of the skin of the head and neck.	67 patients with 68 stage T4 carcinomas of the skin of the head and neck were treated with radical RT. 33 lesions were previously untreated and 35 were recurrent. 29 lesions were SCC, 37 were BCCs, and 2 were basosquamous carcinomas. Minimum follow-up was 2 years. The 5-year local control, local control including surgical salvage, and cause-specific survival probabilities were 53%, 74%, and 75%, respectively. Local control rates with RT alone were poorer in patients with recurrent lesions (41% vs 67%, P=.07) or bone involvement (40% vs 62%, P=.08). Results were analyzed by multivariate methods using local control, local control with surgical salvage, and cause-specific survival as endpoints. The parameters analyzed were histology; size of primary lesion; previous treatment (previously untreated vs recurrent); involvement of bone, nerve, or cartilage; and skeletal muscle invasion. 3 important prognostic factors were identified, each predictive of poorer ultimate local control and cause-specific survival rates: (a) bone involvement (P<.01); (b) recurrent lesions (P<.01); and (c) nerve involvement (P<.02).	2
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.	Review/Other-Tx	N/A	To review skin carcinoma with PNI along with the treatment methods.	Skin carcinoma with PNI is relatively uncommon and has a worse prognosis compared with patients without evidence of this mode of spread. The optimal treatment is likely resection and postoperative RT for patients with apparently resectable disease. Those with incompletely resectable cancers are treated with definitive RT. Patients have a high risk of spread to regional nodes, and clinically negative nodes should be treated electively.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	347 patients	To assess the results of a randomized trial initiated in 1982 to compare surgery and RT in the treatment of primary BCC of the face measuring <4 cm.	The primary end point was the failure rate (persistent or recurrent disease) after 4 years of follow-up. The secondary end point was the cosmetic results assessed by the patient, the dermatologist and 3 persons not involved in the trial. In the course of the trial, 347 patients were treated. Of the 174 patients in the surgery group, 71% had local anesthesia and 91% frozen section examination. Of the 173 patients in the RT group, 55% were treated with interstitial brachytherapy, 33% with contactherapy and 12% with conventional RT. The 4-year actuarial failure rate (95% CI) was 0.7% (0.1%–3.9%) in the surgery group compared with 7.5% (4.2%–13.1%) in the RT group (log-rank P=0.003). The cosmetic results assessed by 4 of the 5 judges were significantly better after surgery than after RT. 87% of the surgery-treated patients and 69% of the radiation-treated patients considered the cosmetic result as good (P<0.01).	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	374 and 191 patients	To investigate the types of facial BCC in which MMS was more effective than SE.	Of the BCC included in the trial, 397 primary (198 MMS, 199 SE) and 201 recurrent (99, 102) tumors were actually treated. Of patients with primary carcinomas, 21 had both MMS and SE on different tumors. 9 with recurrent carcinomas had both treatments on different skin tumors. 66 primary and 13 recurrent carcinomas were lost to follow-up. Of the primary carcinomas, 5 (3%) recurred after SE compared with 3 (2%) after MMS during 30 months of follow-up. Of the recurrent carcinomas, 3 (3%) recurred after SE and none after MMS during 18 months of follow-up. 4 recurrent carcinomas randomly assigned to the SE group were treated with MMS. Although both differences favored MMS, they were not significant (primary, difference 1% [95% CI, -2.5% to 3.7%], P=0.724; recurrent, 3.2% [-2.0% to 5.0%], P=0.119). Total operative costs of MMS were higher than those of SE (primary 405.79 Euros vs 216.86 Euros, recurrent 489.06 Euros vs 323.49 Euros; both P<0.001).	1
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.	Observational-Tx	468 patients	To retrospectively review patterns of failure, cosmesis, and outcomes according to treatment modality of patients with histologically confirmed epithelial skin cancer.	The overall local tumor control rate was 89%; it was 93% for previously untreated lesions and 80% for recurrent lesions. Patients with BCC had a 92% overall control rate; patients with SCC 80%. Multivariate analysis showed that local failure was related to the daily dose fractionation. The maximal diameter of the lesion and pathologic tumor type were also significant (P=0.01). Treatment type, patient age, and treatment duration were not significant. Overall, 92% of the treated population with cosmesis data had excellent or good results. The overall complication rate was 5.8%, consisting primarily of soft-tissue necrosis.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	2,474 examinations of 1,149 irradiated fields	To answer the questions: How frequent are cosmetic changes after soft X-ray therapy? Do treatment parameters, tumor thickness, localization and size of the irradiated field have a major influence? Were patients irritated by the visual appearance of the irradiated field?	Hypopigmentation was found in 64.7% of examinations more than 90 days after therapy, teleangiectases in 43.1%, erythema in 24.8%, and hyperpigmentation in 16.8%. The frequency of hypopigmentation, teleangiectases and hyperpigmentation increased with time from X-ray exposure; more than 4 years after therapy hypopigmentation was diagnosed in 91.8% and teleangiectases in 82.2% of examinations. Total dose, the time-dose-fractionation factor, field size and dose per fraction were significantly related to the frequency of cosmetic changes. Incidence rates of cosmetic changes differed by <15% if different treatment conditions were compared: thicker vs thinner tumors, larger vs smaller fields, higher vs lower total doses, doses per fraction, and time-dose-fractionation factor. Frequencies of hypopigmentation, teleangiectases, erythema and hyperpigmentation differed by more than 15% between some localizations on the head. Women reported irritation by the visual appearance of the irradiated field in 12.6% of 1,116 interviews, and men in 4.4% of 1,284 interviews.	4
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.	Observational-Tx	560 men and 553 women	To evaluate the effectiveness of this schedule in terms of cure rate and late ulcerations.	The recurrence rate (5.1%) was related to tumor size and thickness and to the time-dose-fractionation factor. The frequency of ulcerations (6.3%) depended on field size, hardness of the x-rays, and in smaller fields (diameter up to 4 cm) on total dose, and time-dose-fractionation factor. Of all ulcerations, 82.5 % could be conservatively cured.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	182 patients	To determine the outcomes of patients with locally advanced BCC and SCC of the skin treated with RT.	4-year locoregional controls for BCC and SCC are 86% and 58%, respectively. The median time to recurrence of BCC and SCC are 40.5 months and 5.0 months, respectively. No deaths resulted from BCCs, but 65% (30/46) of all patients with locoregional recurrent SCCs died from the disease. Uncontrolled locoregional disease was the cause of death in 81% (30/37) of all patients who died of SCCs.	2
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.	Observational-Tx	40 previously untreated patients (Group 1) and 57 patients who had undergone surgery (Group 2)	To analyze outcomes after interstitial brachytherapy of facial periorificial skin carcinomas.	Median age was 71 years (range, 17–97 years). There were 29 T1, 8 T2, 1 T3, and 2 Tx tumors in Group 1. Tumors were <2 cm in Group 2. Local control was 92.5% in Group 1 and 88% in Group 2 (median follow-up, 55 months; range, 6–132 months). 5-year disease-free survival was better in Group 1 (91%; range, 75–97) than in Group 2 (80%; range, 62–90; P=0.23). Of the 34 patients whose results were reassessed, 8 presented with pruritus or epiphora; 1 Group 2 patient had an impaired eyelid aperture. Cosmetic results were better in Group 1 than in Group 2 with, respectively, 72% (8/11) vs 52% (12/23) good results and 28 (3/11) vs 43% (10/23) fair results.	2
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.	Observational-Tx	118 patients	To retrospectively reviewed outcomes in patients treated with RT for cutaneous head and neck carcinoma with PNI, with the aim of developing risk-adapted treatment guidelines.	The 5-year local control rates were 90% with pPNI and 57% with cPNI (P<.0001). The pPNI and cPNI groups also differed in relapse-free survival (76% vs 46%, P=.003), disease-specific survival (90% vs 76%, P=.002), and OS (69% vs 57%, P=.03). pPNI patients with BCC histology (n = 42) had better local control (97% vs 84%, P=.02) than pPNI SCC (n = 55).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	222 patients	To review the factors that influence outcome and patterns of relapse in patients with cutaneous SCC and BCC with PNI without clinical or radiologic features, treated with surgery and RT.	Patients with SCC did significantly worse than those with BCC (5-year relapse-free survival, 78% vs 91%; P<0.01). SCC with PNI at recurrence did significantly worse than *de novo* in terms of 5-year local failure (40% vs 19%; P<0.01) and regional relapse (29% vs 5%; P<0.01). Depth of invasion was also a significant factor. Of the PNI-specific factors for SCC, focal PNI did significantly better than more-extensive PNI, but involved nerve diameter or presence of PNI at the periphery of the tumor were not significant factors.	2
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.	Observational-Tx	122 patients	To compare the outcome of surgery against surgery plus RT in patients with metastatic cutaneous head and neck SCC to cervical nodes.	After surgery alone, 11 patients (55%) developed recurrence compared with 23 patients (23%) after surgery plus RT. On multivariate analysis, the following variables were significantly associated with disease-free survival: immunosuppression (P=.002), treatment modality (P<.001), extracapsular spread (P=.009), and pathological nodal stage (P=.04). Patients undergoing surgery plus RT had a significantly better 5-year disease-free survival (74% vs 34%; P=.001) and 5-year OS (66% vs 27%; P=.003) compared with surgery alone.	2
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.	Observational-Tx	168 patients	To determine whether there is a "low-risk" subset of patients with regional metastatic head and neck cutaneous SCC suitable for treatment with surgery alone and omission of adjuvant RT.	Disease-specific survival for the 33 patients treated with surgery alone was 97% at 5 years. In the subset of 19 patients without extracapsular nodal spread, there was 1 regional recurrence which was successfully salvaged yielding a 5-year disease-specific survival of 100%.	2

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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.	Review/Other-Tx	N/A	To discuss the role of RT in the treatment of cutaneous SCCs and BCCs of the head and neck.	The likelihood of cure with a good cosmetic outcome is high for patients with early-stage cancers treated with definitive RT. The probability of local control is higher for previously untreated cancers and is inversely related to tumor size. The likelihood of cure for patients with PNI is related to the presence of symptoms and to the radiographic extent of disease. It decreases as the tumor extends centrally towards the central nervous system. Patients with incidental PNI have a local control rate of 80% to 90% compared with about 50% to 55% for those with clinical PNI. The optimal treatment for patients with clinically positive nodes is surgery and postoperative RT. The likelihood of cure for those with positive parotid nodes is approximately 70% to 80%.	4
18. Warden KF, Parmar H, Trobe JD. Perineural spread of cancer along the three trigeminal divisions. *J Neuroophthalmol.* 2009;29(4):300-307.	Review/Other-Tx	N/A	To present single cases of perineural spread along each of the 3 divisions of the trigeminal nerve in which the perineural spread was initially overlooked.	Perineural spread of head and neck cancers is a well-documented phenomenon, but the diagnosis is often delayed due to lack of familiarity with clinical manifestations, anatomy of the head and neck, and imaging signs. Although perineural spread is often associated with a poor prognosis, earlier detection may improve outcome.	4
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.	Observational-Tx	33 patients	To more fully evaluate the efficacy and safety of vismodegib in patients with locally advanced or metastatic BCC.	In 33 patients with metastatic BCC, the independently assessed response rate was 30% (95% CI, 16 to 48; P=0.001). In 63 patients with locally advanced BCC, the independently assessed response rate was 43% (95% CI, 31 to 56; P<0.001), with complete responses in 13 patients (21%). The median duration of response was 7.6 months in both cohorts. Adverse events occurring in more than 30% of patients were muscle spasms, alopecia, dysgeusia (taste disturbance), weight loss, and fatigue. Serious adverse events were reported in 25% of patients; 7 deaths due to adverse events were noted.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	EORTC (334 patients); RTOG (414 patients)	To perform a comparative analysis of the selection criteria, clinical and pathologic risk factors, and treatment outcomes using data pooled from 2 trials.	Extracapsular extension and/or microscopically involved surgical margins were the only risk factors for which the impact of chemotherapy-enhanced radiation therapy was significant in both trials. There was also a trend in favor of chemotherapy-enhanced radiation therapy in the group of patients who had stage III-IV disease, PNI, vascular embolisms, and/or clinically enlarged level IV-V lymph nodes secondary to tumors arising in the oral cavity or oropharynx. Patients who had 2 or more histopathologically involved lymph nodes without extracapsular extension as their only risk factor did not seem to benefit from the addition of chemotherapy in this analysis.	4
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.	Review/Other-Tx	87 randomized trials	To evaluate the benefit of chemotherapy for each tumor location in terms of OS, event-free survival and absolute benefit and to investigate interactions between chemotherapy effect and patient or trial covariates by tumor site, and to provide comprehensive material for analysis, discussion and design of future clinical trials for each tumor site.	Individual patient data of 16,192 patients were analyzed, with a median follow-up of 5.6 years. The benefit of the addition is consistent in all tumor locations, with HRs between 0.87 and 0.88 (P-value of interaction=0.99). Chemotherapy benefit was higher for concomitant administration for all tumor locations, but the interaction test between chemotherapy timing and treatment effect was only significant for oropharyngeal (P<0.0001) and laryngeal tumors (P=0.05), and not for oral cavity (P=0.15) and hypopharyngeal tumors (P=0.30). The 5-year absolute benefits associated with the concomitant chemotherapy are 8.9%, 8.1%, 5.4% and 4% for oral cavity, oropharynx, larynx and hypopharynx tumors, respectively.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	22 patients	To determine the disease control rate and toxicity of treating patients with aggressive cutaneous SCC with neoadjuvant gefitinib.	23 patients were accrued and 22 patients were evaluable for response prior to definitive local treatment; complete responses were attained by 18.2% of patients and partial responses by 27.3%. Grades 2 to 3 toxicities were observed in 59.1% of patients experiencing class-specific effects during induction therapy. After induction, 11.8% underwent surgery alone, 17.6% had definitive radiation, 11.8% were treated with radiation and concurrent gefitinib, and 47% had surgery with postoperative radiation and concurrent gefitinib. Median follow-up for the censored observations was 32 months. 2-year overall, disease-specific, and progression-free survival rates were 72.1%, 72.1%, and 63.6%, respectively. No EGFR-activating mutations were identified in tumor samples available from 10 patients. No associations between EGFR correlative studies and patient outcomes were identified.	1
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.	Observational-Tx	15 patients	To assess the toxicity profile of erlotinib therapy combined with postoperative adjuvant RT in patients with advanced cutaneous SCC.	The majority of patients were male (87%) and presented with T4 disease (93%). The most common toxicity attributed to erlotinib was a grade 2-3 dermatologic reaction occurring in 100% of the patients, followed by mucositis (87%). Diarrhea occurred in 20% of the patients. The 2-year recurrence rate was 26.7%, and mean time to cancer recurrence was 10.5 months. 2-year OS was 65%, and disease-free survival was 60%.	1
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.	Review/Other-Tx	1 case	To present the case of a 92-year-old man with cutaneous SCC metastatic to the neck (7 cm) who was treated with primary cetuximab and has had a durable complete response for 7 months.	The patient had a complete response by 6 weeks. 7 months after discontinuing cetuximab, he continues to have a complete response.	4

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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.	Observational-Tx	36 patients	To evaluate the efficacy and safety of cetuximab, a monoclonal antibody that inhibits the epidermal growth factor receptor, as a first-line monotherapy in patients with unresectable SCC of the skin.	Median age of the study population was 79 years. Disease control rate at 6 weeks was obtained in 25/36 patients (69%; 95% CI, 52% to 84%) of the intention-to-treat population. The best responses were 8 partial responses and 2 complete responses. There were no cetuximab-related deaths. There were 3 related serious adverse events: 2 grade 4 infusion reactions and 1 grade 3 interstitial pneumopathy. Grade 1 to 2 acne-like rash occurred in 78% of patients and was associated with prolonged PFS. One HRAS mutation was identified. Combined FcgammaRIIa-131H/H and/or FcgammaRIIIa-158V/V polymorphisms were not associated with the clinical outcomes.	2
26. Gordon Spratt EA, Carucci JA. Skin cancer in immunosuppressed patients. *Facial Plast Surg.* 2013;29(5):402-410.	Review/Other-Tx	N/A	To review skin cancer in immunosuppressed patients and its treatment modalities.	OTR suffer from an increased incidence and recurrence rate of nonmelanoma skin cancers. These cancers are often more aggressive than those in the general population, resulting in significant morbidity and mortality. Often times, routine treatment modalities are not adequate and the use of different management strategies is necessary. Treatment modalities, including SE, MMS, physically destructive modalities, topical therapy, and photodynamic therapy may be used. Combinations of these therapies may be used in rotation for treatment of extensive field disease. Chemoprophylaxis with oral retinoids and alteration of the immune suppression regimen may be indicated for specific cases. In addition, newly emerging therapies for SCC including cetuximab and capecitabine may offer heightened control in organ transplant patients with significant cutaneous disease.	4

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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.	Review/Other-Tx	4,810 patients	To evaluate the incidence of and risk factors for BCC and SCC in survivors of hematopoietic cell transplantation.	Among allogeneic hematopoietic cell transplantation recipients, 237 developed at least 1 skin or mucosal cancer (BCC, n = 158; SCC, n = 95). 20-year cumulative incidences of BCC and SCC were 6.5% and 3.4%, respectively. Total-body irradiation was a significant risk factor for BCC (P=.003), most strongly among patients younger than 18 years old at hematopoietic cell transplantation (P=.02, interaction). Light-skinned patients had an increased risk of BCC (P=.01). Acute graft-versus-host disease increased the risk of SCC (P=.02), whereas chronic graft-versus-host disease increased the risk of both BCC (P=.01) and SCC (P<.001).	4
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.	Review/Other-Tx	N/A	To determine the incidence of all cancers following renal transplantation and to make a detailed examination of trends and patterns associated with postrenal transplant skin cancers.	There was a steady increase in risk for older renal transplant recipients (age 50+ years) from year 2 post-transplant, whereas the increased risk in younger renal transplant recipients (age <50 years) occurred later but much more significantly, reaching 200 times the risk for an age-matched nontransplanted population by year 6 post-transplant. The number of nonmelanoma skin cancers registered in renal transplant recipients accounted for 1% of all nonmelanoma skin cancers registered nationally over the study period. The standardized incidence rates for invasive nonmelanoma skin cancer (33-fold increase) and in situ carcinoma of the skin (65-fold increase) were significantly increased (P<0.05). The risk for invasive SCC was increased 82-fold compared with the nontransplanted population. Male renal transplant recipients were at particular risk of invasive SCC at sun-exposed sites such as the scalp and the external ear. Risk of malignant melanoma and Kaposi sarcoma were also increased relative to the nontransplanted population.	4

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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.	Observational-Tx	7,021 patients	To determine the aggressiveness of nonmelanotic skin cancers in a large transplant population compared with an immunocompetent control population with similar cancers.	Three hundred seven patients had SCC (OTR: 153, control: 154), and 246 patients had BCC (OTR: 123, control: 123). SCC in OTR was significantly more likely to have an increased number of primary tumors; deep tissue spread, perineural and lymphatic invasion, recurrence, and need for radiation or chemotherapy. BCC in OTR was not associated with more aggressive disease when compared with controls with BCC.	2
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.	Review/Other-Tx	518 immunocompetent individuals	To determine whether any histologic features were characteristic or more common in cutaneous SCC of OTR.	The findings confirmed the association of ultraviolet radiation exposure with development of cutaneous SCCs in OTR. The increased depth of the primary cutaneous SCCs in OTR is surprising because these patients are followed closely for skin cancer compared with immunocompetent patients. The other morphologic features that were significantly more common in OTR may theoretically reflect not only the type of iatrogenic immunosuppression in these patients, but also other procarcinogenic effects of their medications.	4
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.	Review/Other-Tx	1,906 patients	To estimate the cumulative incidence of subsequent SCC and BCC and to analyze potential risk factors.	A total of 239 (13%) of 1,906 kidney-transplant recipients developed skin cancer of whom 222 were diagnosed in our hospital. Altogether 167 (75%) of these 222 patients developed multiple skin cancers. The cumulative incidence of a second skin cancer increased from 32%, 1 year, to 59%, 3 years, and 72%, 5 years after the first skin cancer. Kidney-transplant recipients who started with SCC mainly developed SCC and recipients who started with BCC mainly developed BCC as second skin cancer. Immunosuppression with azathioprine in combination with prednisone was associated with a significantly increased risk of subsequent SCCs but not with subsequent BCCs.	4

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	2,018 patients	To analyze a large series of skin cancers in solid OTR to determine their biologic behavior.	Transplant recipients from the United States with skin malignancies were identified (n = 2,018) and assigned to 1 of 3 groups: SCC, BCC, or combined malignancies (BCC/SCC). SCC to BCC ratio was found to be 1.9 to 1. The ratio of extrarenal to renal allograft recipients was identical for all 3 groups (3:1). The median interval from transplant to skin cancer diagnosis was greater than 4 years in each group and longest in those with isolated SCC lesions. In the SCC group, there was a 9% incidence of nodal or secondary site involvement affecting the cervix, perineum, or lung. The highest recurrence rate was demonstrated in the combined malignancy group. Cancer-specific deaths were significantly higher in the SCC (8%) and BCC/SCC (6.8%) groups compared to the BCC (3.6%) group.	4

Aggressive Non-Melanomatous Skin Cancer of the Head and Neck
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	59 patients	To compare disease outcomes and treatment toxicity in immunocompetent and immunosuppressed patients with high risk SCC head and neck treated with surgery and postoperative RT.	In this study of 59 patients, 38 (64%) were immunocompetent and 21 (36%) were immunosuppressed. There were no significant baseline differences between the 2 groups. The cohort was predominantly male (88%) with a median age of 72, median KPS of 90, and median follow-up of 17.7 months. Recurrent tumors (63%), N+ disease (61%), and stage IV disease (61%) were most common. Lymphovascular space invasion (29% vs 11%; P=0.077), nodal extracapsular extension (61% vs 33%), and poorly differentiated tumors (62% vs 21%; P=0.009) were more frequently observed in immunosuppressed. Locoregional recurrence was significantly higher in immunosuppressed compared to immunocompetent (48% vs 24%; P=0.01). 2 year LRFS (73% vs 48%; P=0.01) and disease-free survival (62% vs 45%; P=0.04) were significantly higher in immunocompetent compared to immunosuppressed, while rates of distant metastases (13% vs 19%; P=0.339) and OS (43 vs 15 months; P=0.266) were comparable. Univariate analysis and multi-variant analysis demonstrated that immunosuppressed status (HR 3.12; P=0.014) and nodal extracapsular extension (HR 3.80; P=0.048) were significantly associated with increased risk for locoregional recurrence. Immunosuppressed patients experienced increased rates of grade ≥3 (11% vs 29%; P=0.077) and grade 2 (53% vs 62%; P=0.492) acute RT toxicity.	2

Aggressive Non-Melanomatous Skin Cancer of the Head and Neck
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	250 patients	To propose a prognostic score model using a prospective study of patients with regional metastatic cutaneous SCC of the head and neck.	At a median follow-up of 54 months (range, 1.3–212 months) 70/250 patients (28%) developed recurrent disease: Most were regional recurrences (51/70 patients; 73%) in the treated lymph node basin. After regional recurrence, a majority (73%) died of disease. The following 4 variables were associated significantly with survival: immunosuppression (HR, 3.13; 95% CI, 1.39–7.05), treatment (HR, 0.32; 95% CI, 0.16–0.66), extranodal spread (HR, 9.92; 95% CI, 1.28–77.09), and margin status (HR, 1.85; 95% CI, 1.85–3.369); and those 4 variables (immunosuppression, treatment, extranodal spread, and margin status) were used to calculate the ITEM score. The 5-year risk of dying from disease for patients with high-risk (>3.0), moderate-risk (>2.6–3.0), and low-risk (≤2.6) ITEM scores were 56%, 24%, and 6%, respectively. 56/250 patients (22%) died from another cause.	1
35. Lang PG, Jr., Braun MA, Kwatra R. Aggressive squamous carcinomas of the scalp. *Dermatol Surg*. 2006;32(9):1163-1170.	Review/Other-Tx	11 patients	To describe a series of 11 cases of extraordinarily aggressive SCCs of the scalp.	5/11 patients have succumbed to their disease. Of note is that the patients all had significant long-standing alopecia or thinning of their hair with marked actinic damage. Initial biopsies of the tumors revealed them to be either moderate or well-differentiated. 4/11 patients developed satellite lesions and experienced recurrences despite obtaining clear margins with Mohs micrographic surgery.	4

Aggressive Non-Melanomatous Skin Cancer of the Head and Neck
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	120 patients	To assess, in a large cohort, the efficacy of sirolimus for the secondary prevention of skin cancers in kidney-transplant recipients receiving calcineurin inhibitors.	Survival free of cutaneous SCC was significantly longer in the sirolimus group than in the calcineurin-inhibitor group. Overall, new SCC developed in 14 patients (22%) in the sirolimus group (6 after withdrawal of sirolimus) and in 22 (39%) in the calcineurin-inhibitor group (median time until onset, 15 vs 7 months; P=0.02), with a relative risk in the sirolimus group of 0.56 (95% CI, 0.32 to 0.98). There were 60 serious adverse events in the sirolimus group, as compared with 14 such events in the calcineurin-inhibitor group (average, 0.938 vs 0.250). There were twice as many serious adverse events in patients who had been converted to sirolimus with rapid protocols as in those with progressive protocols. In the sirolimus group, 23% of patients discontinued the drug because of adverse events. Graft function remained stable in the two study groups.	1
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.	Experimental-Tx	155 patients	To investigate whether conversion to sirolimus-based immunosuppression from standard immunosuppression could diminish the recurrence rate of these skin cancers.	After 2 years of follow-up, the risk reduction of new SCCs in the multivariable analysis was not significant, with a HR of 0.76 (95% CI, 0.48 to 1.2; P=.255), compared with a non-sirolimus-based regimen. After the first year, there was a significant 50% risk reduction, with an HR of 0.50 (95% CI, 0.28 to 0.90; P=.021) for all patients together and an HR of 0.11 (95% CI, 0.01 to 0.94; P=.044) for patients with only 1 previous SCC. The tumor burden of SCC was reduced during the 2-year follow-up period in those receiving sirolimus (0.82 v 1.38 per year; HR, 0.51; 95% CI, 0.32 to 0.82; P=.006) if adjusted for the number of previous SCCs and age. 29 patients stopped taking sirolimus because of various adverse events.	1

Aggressive Non-Melanomatous Skin Cancer of the Head and Neck
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	N/A	To discuss the management of skin cancer and advances in therapy.	The management of skin cancer in solid OTR is a challenge to both the dermatologist and transplant physician. Part II of this continuing medical education review offers an approach to the management of this increasing problem. The importance of specialty dermatology clinics providing access to transplant patients, frequent skin cancer screening, patient education, and multidisciplinary care is discussed. The management of low risk SCC with topical therapies, photodynamic therapy, systemic retinoids, and capecitabine is reviewed. Revision of immunosuppression in the management of high-risk patients is discussed in association with the potential role of sentinel lymph node biopsy for aggressive disease. Finally, management of in-transit and metastatic SCC is reviewed, with a discussion of the role of more recent innovative therapies, including epidermal growth factor receptor inhibitors in advanced SCC in solid OTRs.	4

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:

  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

BCC = Basal cell carcinoma

CI= Confidence interval

HR = Hazard ratio

MMS = Mohs' micrographic surgery

OR = Odds ratio

OS = Overall survival

OTR = Organ transplant recipients

PNI = Perineural invasion

RT = Radiotherapy

SCC = Squamous cell carcinoma

SE = Surgical excision