JAMA Dermatology | Original Investigation

Association of Disease Recurrence With Survival Outcomes in Patients With Cutaneous Squamous Cell Carcinoma of the Head and Neck Treated With Multimodality Therapy

Lillian Sun, BS; Re-I Chin, MD; Brian Gastman, MD; Wade Thorstad, MD; Sue S. Yom, MD, PhD; Chandana A. Reddy, MS; Brian Nussenbaum, MD; Steven J. Wang, MD; Thomas Knackstedt, MD; Allison T. Vidimos, MD; Shlomo A. Koyfman, MD; Bindu V. Manyam, MD

IMPORTANCE It has previously been demonstrated that immunosuppressed patients with cutaneous squamous cell cancer of the head and neck (cSCC-HN) treated with surgery and postoperative radiotherapy have significantly inferior disease-related outcomes compared with immunocompetent patients, but data on outcomes after disease recurrence are limited.

OBJECTIVES To report survival outcomes in patients with cSCC-HN after disease recurrence after surgery and postoperative radiotherapy and to investigate the association of immune status with disease-related outcomes.

DESIGN, SETTING, AND PARTICIPANTS A multi-institutional study of 205 patients treated at the Cleveland Clinic, Washington University in St Louis, and the University of California, San Francisco, in which patients who underwent surgical resection and postoperative radiotherapy for primary or recurrent stage I to IV (nonmetastatic) cSCC-HN between January 1, 1995, and December 31, 2014, were identified. Patients with any disease recurrence, defined as local, regional, and/or distant failure, were included. Patients were categorized as immunosuppressed if they received a diagnosis of chronic hematologic malignant neoplasm or HIV or AIDS, or were treated with immunosuppressive therapy for organ transplantation 6 months or more before diagnosis. Statistical analysis was conducted from January 1, 1995, to December 31, 2015.

MAIN OUTCOMES AND MEASURES Overall survival calculated using the Kaplan-Meier method and compared using the log-rank test.

RESULTS Of the 205 patients in the original cohort, 72 patients (63 men and 9 women; median age, 71 years [range, 43-91 years]) developed disease recurrence after surgery and postoperative radiotherapy. Forty patients (55.6%) were immunosuppressed, and 32 patients (44.4%) were immunocompetent. Locoregional recurrence was the most common first pattern of failure for both groups (31 immunosuppressed patients [77.5%]; 21 immunocompetent patients [65.6%]). After any recurrence, 1-year overall survival was 43.2% (95% CI, 30.9%-55.4%), and median survival was 8.4 months. For patients for whom information on salvage treatment was available (n = 45), those not amenable to surgical salvage had significantly poorer median cumulative incidence of survival compared with those who were amenable to surgical salvage (4.7 months; 95% CI, 3.7-7.0 months vs 26.1 months; 95% CI, 6.6 months to not reached; $P = .01$), regardless of their immune status.

CONCLUSIONS AND RELEVANCE Results of this study suggest that patients with cSCC-HN who experience disease recurrence after definitive treatment with surgery and postoperative radiotherapy have poor survival, irrespective of immune status. Survival rates are low for patients with recurrent disease that is not amenable to surgical salvage. The low rate of successful salvage underscores the importance of intensifying upfront treatment to prevent recurrence.

JAMA Dermatol. 2019;155(4):442-447. doi:10.1001/jamadermatol.2018.5453
Published online February 27, 2019.

Author Affiliations: Department of Radiation Oncology, Cleveland Clinic, Cleveland, Ohio (Sun, Reddy, Koyfman, Manyam); Department of Radiation Oncology, Washington University in St Louis, St Louis, Missouri (Chin, Thorstad); Department of Plastic Surgery, Cleveland Clinic, Cleveland, Ohio (Gastman); Department of Radiation Oncology, University of California, San Francisco (Yom); Department of Otolaryngology, Washington University in St Louis, St Louis, Missouri (Nussenbaum); Department of Otolaryngology, University of Arizona, Tucson (Wang); Department of Dermatology, Cleveland Clinic, Cleveland, Ohio (Knackstedt, Vidimos).

Corresponding Author: Bindu V. Manyam, MD, Department of Radiation Oncology, Cleveland Clinic, 9500 Euclid Ave, CA-5, Cleveland, OH 44195 (manyamb@ccf.org).

Cutaneous squamous cell carcinoma (cSCC) has a favorable prognosis, with rates of locoregional recurrence and distant metastasis less than 5%. However, there is a subset of patients with adverse pathologic features and a more aggressive clinical course, with substantially higher rates of locoregional recurrence (13%-41%) and distant metastasis (7%-16%) after surgical resection.[1-4] Postoperative radiotherapy (RT) has been used to optimize locoregional control in these patients who are at higher risk for recurrence.[5-9]

Despite intensified bimodality therapy, the presence of features such as deep invasion, perineural invasion, poor differentiation, positive margins, node-positive disease, and extracapsular extension have been identified in the literature as factors associated with inferior outcomes.[1-4] A previous report of a multi-institutional experience of patients with aggressive cSCC of the head and neck (cSCC-HN) treated with surgery and postoperative RT demonstrated that patients who are chronically immunosuppressed have dramatically lower 2-year locoregional recurrence-free survival (47.3% vs 86.1%; $P < .001$) and progression-free survival (38.7% vs 71.6%; $P = .002$) compared with patients who are immunocompetent.[10] Building on these data, the present study further examines the subset of patients with disease recurrence after surgery and postoperative RT to identify survival rates after recurrence and determine the association of immune status with this outcome. We hypothesized that survival outcomes after disease recurrence would be inferior in immunosuppressed patients, similar to their initial disease-related outcomes.

Key Points

Question What are expected survival outcomes for patients with cutaneous squamous cell carcinoma of the head and neck who demonstrate locoregional and/or distant disease recurrence after surgery and postoperative radiotherapy?

Findings In this multi-institutional cohort study, 1-year overall survival was 43.2% and median survival was 8.4 months after disease recurrence; median survival did not differ significantly between immunosuppressed and immunocompetent patients (8.0 vs 12.9 months). In patients who were not amenable to surgical salvage, significantly poorer median survival was observed compared with patients who underwent surgical salvage (4.7 vs 26.1 months), regardless of their immune status.

Meanings Patients with cutaneous squamous cell carcinoma of the head and neck who experience disease recurrence after definitive treatment with surgery and postoperative radiotherapy have poor survival, irrespective of immune status; the low rate of successful surgical salvage underscores the importance of intensifying upfront treatment to prevent recurrence.

Methods

This study included patients who underwent surgical resection and postoperative RT for primary or recurrent cSCC-HN between January 1, 1995, and December 31, 2014, at the Cleveland Clinic (Cleveland, Ohio), Washington University in St Louis (St Louis, Missouri), and the University of California San Francisco. All patients included in this study were age 18 years or older and had a histologic diagnosis of cSCC-HN. Patients with upfront distant metastatic disease, squamous cell carcinoma (SCC) in situ alone, cSCC of the trunk or extremities, SCC of unknown primary site, palliative doses of RT, or inadequate medical records were excluded. From this larger initial cohort, patients who developed locoregional or distant recurrence after surgery and postoperative RT were selected for inclusion in the current study. All patients were restaged according to the American Joint Committee on Cancer, 7th edition, staging system.[10] Surgical resection was by wide local excision or Mohs micrographic surgery, and was at the discretion of the treating surgeon. This study was approved by the institutional review boards of the Cleveland Clinic, Washington University in St Louis, and the University of California San Francisco. Patient consent for this study was waived by the institutional review board of each respective institution as the data were deidentified.

The patients were categorized as immunosuppressed if they received a diagnosis of chronic hematologic malignant neoplasm or HIV or AIDS, or were treated with immunosuppressive therapy for organ transplantation 6 months or more prior to diagnosis. Organ transplant recipients included those who received kidney, heart, lung, liver, pancreas, or bone marrow transplant. Immunosuppressive agents included prednisone, cyclosporine, azathioprine sodium, sirolimus, tacrolimus, and mycophenolate mofetil.

During the earlier years of the study, electron beam and 3-D conformal RT techniques were used, and in more recent years of the study, intensity-modulated RT was used. Treatment volumes included the tumor bed in all patients; ipsilateral lymphatics were included if they were involved or thought to be at risk of microscopic disease. Nerve roots were targeted to the skull base in cases of extensive perineural invasion. Concurrent chemotherapy was administered for select patients, most commonly in the setting of positive margins and/or extracapsular extension.

Follow-up included postoperative treatment imaging with computed tomography or positron emission tomography 3 months after RT and continued multidisciplinary care. Locoregional recurrence was defined as recurrence at the primary site, resection margin, or regional lymph nodes. Distant failure included failure outside of the head and neck, most often in the lungs and other viscera. A subset of 45 patients had sufficient clinical information after failure to determine whether salvage surgery was performed.

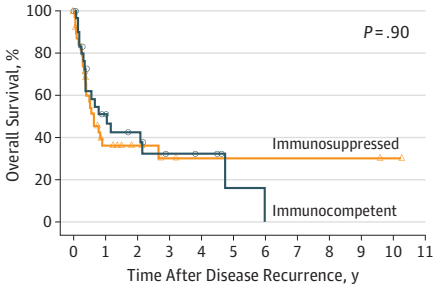
Statistical analysis was conducted from January 1, 1995, to December 31, 2015. Overall survival was calculated using the Kaplan-Meier method from the date of local, regional, or distant recurrence, whichever occurred first, and compared using the log-rank test. All P values were from 2-tailed tests and results were deemed statistically significant at $P \leq .05$. Statistical analysis was performed using SAS, version 9.4, software (SAS Institute Inc).

Table. Baseline Demographics, Tumor Characteristics, and Patterns of First Failure

Variable	Patients, No. (%)	
	Immunocompetent (n = 32)	Immunosuppressed (n = 40)
Age, median (range), y	73 (43-89)	68 (46-91)
Male sex	26 (81.3)	37 (92.5)
KPS score, median (range)	80 (60-90)	80 (50-90)
Type of immunosuppression		
Organ transplant recipient	NA	21 (52.5)
Hematologic malignant neoplasm	NA	16 (40.0)
HIV	NA	3 (7.5)
pT stage		
Tx	8 (25.0)	3 (7.5)
T1/T2	11 (34.4)	28 (70.0)
T3/T4	13 (40.6)	9 (22.5)
pN stage		
N0	16 (50.0)	27 (67.5)
N1	1 (3.1)	3 (7.5)
N2	12 (37.5)	10 (25.0)
N3	3 (9.4)	0
Time to first recurrence after postoperative RT, median (range), mo	10.1 (1.4-57.4)	9.1 (1.0-77.4)
Type of first recurrence		
Both	4 (12.5)	5 (12.5)
Locoregional	21 (65.6)	31 (77.5)
Distant	7 (21.9)	4 (10.0)

Abbreviations: KPS, Karnofsky Performance Status; NA, not applicable; RT, radiotherapy.

Figure 1. Overall Survival After Disease Recurrence After Definitive Surgery and Postoperative Radiotherapy by Immune Status



No. at risk

Immunocompetent patients	32	13	9	5	4	1	1	0	0	0	0	0
Immunosuppressed patients	40	11	7	4	2	2	2	2	2	2	1	0

The median survival time was 12.9 months for immunocompetent patients and 8.0 months for immunosuppressed patients.

Results

The original multi-institutional cohort comprised 205 patients with cSCC-HN.[10] The present analysis includes 72 patients from this original cohort who demonstrated any local, regional, and/or distant recurrence after surgery and postoperative RT for cSCC-HN. Baseline demographics, tumor characteristics, and patterns of first failure are included in the **Table**. There were 40 patients (55.6%) who were immunosuppressed and 32 patients (44.4%) who were immunocompetent. The median time to any disease recurrence after completion of postoperative RT was 10.1 months (range, 1.4-57.4 months) for immunocompetent patients and 9.1 months (range, 1.0-77.4 months) for immunosuppressed patients; locoregional recurrence was the most common first pattern of failure for both groups (immunosuppressed, 31 [77.5%]; and immunocompetent, 21 [65.6%]).

After any recurrence, 1-year overall survival was 43.2% (95% CI, 30.9%-55.4%) and median survival was 8.4 months for the entire cohort. Median survival did not significantly differ between the immunosuppressed and immunocompetent groups (8.0 months; 95% CI, 4.8-32.3 months vs 12.9 months; 95% CI, 4.7-57.2 months; $P = .90$) (**Figure 1**). There were 3 patients (2 immunosuppressed and 1 immunocompetent) who survived beyond 5 years after recurrence.

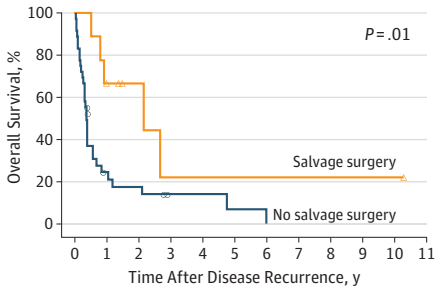
Of the 72 patients included in the study, 27 patients from 1 of the 3 institutions did not have data regarding salvage therapies available for analysis. Of the 45 patients for whom data on salvage treatment were available, 9 patients were amenable to salvage surgery owing to limited extent of disease and good performance status, with 4 of these patients also undergoing postoperative re-irradiation. Of the 9 patients who were able to undergo salvage surgery, 7 underwent surgical salvage for local-only recurrence and 2 for nodal-only recurrence. There were 36 patients who were not considered amenable to salvage surgery, owing to disease extent or performance status; they received treatment with palliative RT (n = 21), palliative chemotherapy (n = 4), or cetuximab (n = 2), or were transferred to hospice care with no further therapy (n = 9).

Patients who were not amenable to surgical salvage had significantly poorer median cumulative incidence of survival compared with those who were amenable to surgical salvage (4.7 months; 95% CI, 3.7-7.0 months vs 26.1 months; 95% CI, 6.6 months to not reached; $P = .01$) (**Figure 2**). Survival was not was not significantly different between immunosuppressed and immunocompetent patients with unsalvageable disease (3.9 months; 95% CI, 1.3-5.0 months vs 5.0 months; 95% CI, 2.6-14.4 months; $P = .09$) (**Figure 3**). Patients who underwent salvage surgery alone (n = 5) had a median survival of 32.3 months (95% CI, 9.8-32.3 months), and patients who underwent salvage surgery and postoperative re-irradiation (n = 4) had a median survival of 26.1 months (95% CI, 6.6 to not reached).

Discussion

Outcomes for recurrent cSCC-HN after surgery and postoperative RT are not well studied, to our knowledge. This study demonstrates that survival in this population is poor. Although we hypothesized that immunosuppressed status would be a significant contributor to outcomes in these patients, similar to findings in the upfront treatment setting,[10] the current

Figure 2. Overall Survival by Disease Recurrence Among Patients Treated With Salvage Surgery vs No Salvage Surgery

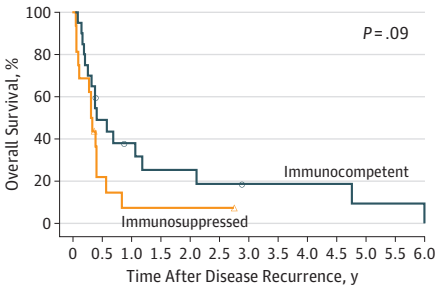


No. at risk

Patients who underwent salvage surgery	9	6	3	1	1	1	1	1	1	1	1
Patients who did not undergo salvage surgery	36	7	5	2	2	1	1	0			

The median survival time was 26.1 months for patients who underwent salvage surgery and 4.7 months for patients who did not undergo salvage surgery.

Figure 3. Overall Survival After Disease Recurrence for Patients Not Eligible for Salvage Surgery by Immune Status



No. at risk

Immunocompetent patients	20	9	6	4	4	3	2	2	2	1	1
Immunosuppressed patients	16	3	1	1	1	1	0				

The median survival time was 5.0 months for immunocompetent patients and 3.9 months for immunosuppressed patients.

study suggests that this is not the case. Once cancer recurs in patients with high-risk cSCC-HN after surgery and postoperative RT, outcomes are suboptimal, independent of immune status. Similar to outcomes among patients in the upfront setting with unresectable disease, survival was poor in patients with recurrent cSCC-HN who were not amenable to surgical salvage. An exception to this observation seems to include the small number of patients who were amenable to salvage surgery and demonstrated dramatically improved survival as a result. Most of our patients already underwent comprehensive surgery and RT, so the ability to undergo salvage surgery may have selected patients who had either less extensive initial treatment or more limited recurrence with correspondingly more favorable outcomes.

There are several important implications to these findings. First, the low rates of successful salvage treatment underscore the importance of intensifying upfront treatment to prevent recurrence. In addition to surgery and RT, systemic therapy should be considered. There is no level I evidence that supports the use of concurrent systemic therapy in the upfront management of high-risk cSCC-HN. For decades, oncologists have extrapolated from the experience with mucosal head and neck cancer in which concurrent cisplatin-based chemotherapy is a standard of care in resected high-risk disease with evidence of positive margins and/or extracapsular extension.[11] Therefore, given its efficacy for mucosal SCC, concurrent cisplatin has been used by some for cSCC. This speculation was formally tested in the Trans Tasman Radiation Oncology Group 05.01 POST trial.[12] This trial included patients with extracapsular extension, intraparotid nodal disease, more than 2 cervical lymph nodes, lymph nodes larger than 3 cm, T3and T4 primary tumor, or in-transit metastases, randomized to receive postoperative RT (60-66 Gy) or concurrent postoperative RT with 6 cycles of weekly carboplatin. There was no significant difference in 2-year locoregional failure-free survival (88% vs 89%; $P = .59$), 2-year disease-free survival (67% vs 73%; $P = .43$), and 2-year overall survival (76% vs 79%; $P = .84$) for postoperative RT and postoperative RT with concurrent chemotherapy. Although this study failed to show a benefit to the addition of cytotoxic chemotherapy to RT in the initial management of high-risk disease, some have pointed out that the outcomes in the control arm were better than expected and that carboplatin may have been a poor choice compared with cisplatin, as there are data to suggest that single-agent carboplatin may have inferior outcomes compared with cisplatin in the setting of mucosal head and neck SCC.[13]

A second important lesson from this study is that systemic therapies used for the recurrent and metastatic setting have limited efficacy. For patients with metastatic and/or recurrent cSCC, older studies demonstrated modest efficacy with cytotoxic chemotherapy and/or retinoic acid regimens, with response rates in the range of 30% to 35%.[14,15] More recently, targeted agents inhibiting the epidermal growth factor receptor have been studied and shown activity as well. An initial phase 2 study using gefitinib, an oral tyrosine kinase inhibitor, observed a response rate of 15% and a radiographic disease control rate of 45% in patients with incurable disease.[16] A more recent phase 2 study tested the anti-epidermal growth factor receptor antibody cetuximab as monotherapy in the setting of unresectable and metastatic disease.[13-15] The primary end point of the trial, radiographic disease control rate at 6 weeks, was 69%. In addition, they determined an overall response rate of 30%, with a complete response rate of 6%.[13-15] Although all of these systemic therapy options have some activity, their efficacy is limited, which helps explain the poor survival that we observed in our study.

A new class of agents is now being tested in cSCC and has shown promising early results. Immune checkpoint inhibitors are a burgeoning class of immunotherapy drugs that have demonstrated activity in many cancers and have shown some of the highest response rates in other cutaneous cancers, including melanoma and Merkel cell carcinoma.[17-20] The most active agents in this class inhibit the programmed cell death protein 1 or programmed death-ligand 1 (PD-L1).[17,21,22] Initial results of a phase 1 trial of a PD-L1 inhibitor, cemiplimab, in patients with recurrent and/or metastatic cSCC were recently reported and showed an overall response rate of 46.2% and a disease control rate of 69.2% with a median follow-up of 6.9

months.[23] The median progression-free survival and overall survival were not reached at the data cutoff date, and perhaps most compelling was the observation that some responses were quite durable, lasting more than 1 year in some patients. This study led to the US Food and Drug Administration approval of this agent as the first and only systemic therapy specifically for locally advanced cSCC not amenable to surgical resection and for metastatic cSCC. These agents may be adopted as the standard of care for these patients with limited options otherwise. In addition to the setting of recurrent and metastatic disease, the significant activity of checkpoint inhibitors in this disease provides a strong rationale to incorporating them in the upfront curative setting in patients with high-risk disease. An ongoing phase 2 study, NCT 03057613, is evaluating the addition of pembrolizumab to postoperative RT for patients with high-risk cSCC-HN. This study includes patients who have undergone a gross total resection with T4 or node-positive disease, or T2 or T3N0 disease with 1 of the following additional features: recurrent disease, perineural invasion, lymphovascular space invasion, poor differentiation, positive margins, or in-transit metastases.[24] Further data regarding these agents may help improve outcomes for these patients. Use of immunotherapy is likely to be limited among patients who are substantially immunocompromised. Specifically, the use of immunotherapy should be avoided for patients who have undergone solid-organ transplant given the risk of organ rejection, whereas its use can still be considered for patients with chronic lymphocytic leukemia.

Limitations

Limitations of our study include its retrospective design and small sample size. Furthermore, as the data come from tertiary referral centers, a referral bias may have contributed to more patients with advanced disease that is not amenable to further definitive therapy, reflecting poorer outcomes. Another source of selection bias is that we included only patients who were candidates for definitive surgery and postoperative RT in the upfront setting, excluding patients who received palliative RT, potentially skewing the survival outcomes to be better than that reflected in this entire patient population. In addition, the absence of patient data after failure from 1 of the participating centers reduced the numbers of patients who could be used for this analysis. With burgeoning data for immunotherapy in immunocompetent patients with advanced disease, the salvage strategies used in this study may not reflect current practice patterns, and outcomes with immunotherapy may be better than what we have described.

Future directions of this work, with a larger data set, could include an analysis of the most common patterns of failure and their associated risk factors to drive the nature of treatment intensification upfront, whether it be more extensive primary surgery, nodal dissection, RT volumes, or addition of systemic therapy. Furthermore, it would be prudent to expand the study to include more centers to increase the power of this study. Despite the limitations discussed, our study provides an important baseline for clinical outcomes after post-RT recurrence and can help inform clinical trial design in this population. Most important, it underscores the need for more effective regimens in this space and the need for additional clinical trials.

Conclusions

Patients with cSCC-HN who experience disease recurrence after definitive treatment with surgery and postoperative RT have poor survival, irrespective of immune status. Further clinical trials evaluating the role of concurrent chemotherapy, targeted agents, and immunotherapy are warranted.

ARTICLE INFORMATION

Accepted for Publication: December 3, 2018.

Published Online: February 27, 2019. doi:10.1001/jamadermatol.2018.5453

Author Contributions: Drs Koyfman and Manyam had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Gastman, Knackstedt, Vidimos, Koyfman, Manyam.
Acquisition, analysis, or interpretation of data: Sun, Chin, Thorstad, Yom, Reddy, Nussenbaum, Wang, Koyfman, Manyam.
Drafting of the manuscript: Sun, Knackstedt, Koyfman, Manyam.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Reddy, Manyam.
Administrative, technical, or material support: Thorstad, Yom, Knackstedt, Vidimos, Koyfman.
Supervision: Gastman, Thorstad, Yom, Vidimos, Koyfman, Manyam.

Conflict of Interest Disclosures: Dr Yom reported receiving clinical trial support from Genentech, Merck, and Bristol-Myers Squibb. Dr Koyfman reported receiving clinical trial support from Merck. No other disclosures were reported.

Meeting Presentation: This article was presented at the 2018 Multidisciplinary Head and Neck Cancers Symposium; February 16, 2018; Scottsdale, Arizona.

REFERENCES

1. 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. doi:10.1097/TP.0b013e3181ec7228

2. Lewis KG, Weinstock MA. Nonmelanoma skin cancer mortality (1988-2000): the Rhode Island Follow-Back Study. *Arch Dermatol*. 2004;140(7):837-842. doi:10.1001/archderm.140.7.837

3. Zavos G, Karidis NP, Tsourouflis G, et al. Nonmelanoma skin cancer after renal transplantation: a single-center experience in 1736 transplantations. *Int J Dermatol*. 2011;50(12):1496-1500. doi:10.1111/j.1365-4632.2011.04939.x

4. Brantsch KD, Meisner C, Schönfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. *Lancet Oncol*. 2008;9(8):713-720. doi:10.1016/S1470-2045(08)70178-5

5. Koyfman SA, Cooper JS, Beitler JJ, et al. ACR Appropriateness Criteria aggressive nonmelanomatous skin cancer of the head and neck. *Head Neck*. 2016;38(2):175-182. doi:10.1002/hed.24171

6. 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. doi:10.1002/hed.21965

7. Slodzinski MK, Blaustein MP. Physiological effects of Na+/Ca2+ exchanger knockdown by antisense oligodeoxynucleotides in arterial myocytes. *Am J Physiol*. 1998;275(1, pt 1):C251-C259. doi:10.1152/ajpcell.1998.275.1.C251

8. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: squamous cell skin cancer. https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed January 22, 2019.

9. Manyam BV, Gastman B, Zhang AY, 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. *J Am Acad Dermatol*. 2015;73(2):221-227. doi:10.1016/j.jaad.2015.04.037

10. Manyam BV, Garsa AA, Chin RI, et al. A multi-institutional comparison of outcomes of immunosuppressed and immunocompetent patients treated with surgery and radiation therapy for cutaneous squamous cell carcinoma of the head and neck. *Cancer*. 2017;123(11):2054-2060. doi:10.1002/cncr.30601

11. 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. doi:10.1002/hed.20279

12. Porceddu SV, Bressel M, Poulsen MG, et al. Postoperative concurrent chemoradiotherapy versus postoperative radiotherapy in high-risk cutaneous squamous cell carcinoma of the head and neck: the randomized phase III TROG 05.01 trial. *J Clin Oncol*. 2018;36(13):1275-1283. doi:10.1200/JCO.2017.77.0941

13. 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. doi:10.1200/JCO.2010.34.1735

14. Shin DM, Glisson BS, Khuri FR, et al. Phase II and biologic study of interferon alfa, retinoic acid, and cisplatin in advanced squamous skin cancer. *J Clin Oncol*. 2002;20(2):364-370. doi:10.1200/JCO.2002.20.2.364

15. Sadek H, Azli N, Wendling JL, et al. Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin. *Cancer*. 1990;66(8):1692-1696. doi:10.1002/1097-0142(19901015)66:8<1692::AID-CNCR2820660807>3.0.CO;2-Y

16. William WN Jr, Feng L, Ferrarotto R, et al. Gefitinib for patients with incurable cutaneous squamous cell carcinoma: a single-arm phase II clinical trial. *J Am Acad Dermatol*. 2017;77(6):1110-1113. doi:10.1016/j.jaad.2017.07.048

17. Robert C, Schachter J, Long GV, et al; KEYNOTE-006 investigators. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372(26):2521-2532. doi:10.1056/NEJMoa1503093

18. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2017;377(14):1345-1356. doi:10.1056/NEJMoa1709684

19. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. *N Engl J Med*. 2016;374(26):2542-2552. doi:10.1056/NEJMoa1603702

20. Weber J, Mandala M, Del Vecchio M, et al; CheckMate 238 Collaborators. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med*. 2017;377(19):1824-1835. doi:10.1056/NEJMoa1709030

21. Boussiotis VA. Molecular and biochemical aspects of the PD-1 checkpoint pathway. *N Engl J Med*. 2016;375(18):1767-1778. doi:10.1056/NEJMra1514296

22. Chan TA, Wolchok JD, Snyder A. Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med*. 2015;373(20):1984. doi:10.1056/NEJMc1508163

23. Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med*. 2018;379(4):341-351. doi:10.1056/NEJMoa1805131

24. Tremont-Lukats IW, Ratilal BO, Armstrong T, Gilbert MR. Antiepileptic drugs for preventing seizures in people with brain tumors. *Cochrane Database Syst Rev*. 2008;(2):CD004424.