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Samantha Tam
Henry Ford Health, stam2@hfhs.org

Mona Gajera

Xiaoning Luo

Bonnie S. Glisson

Renata Ferrarotto

See next page for additional authors

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Authors

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ORIGINAL ARTICLE

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Cytotoxic and targeted systemic therapy in patients with advanced cutaneous squamous cell carcinoma in the head and neck

Samantha Tam MD, MPH[1] | Mona Gajera BDS[2] | Xiaoning Luo MD, PhD[2] | Bonnie S. Glisson MD[3] | Renata Ferrarotto MD[3] | Faye M. Johnson MD, PhD[3,4] | Frank E. Mott MD[3] | Maura L. Gillison MD, PhD[3,4] | Charles Lu MD, SM[3] | Xiuning Le MD, PhD[3] | George R. Blumenschein MD[3] | Michael K. Wong MD, PhD[5] | David I. Rosenthal MD[6] | Priyadharsini Nagarajan MD, PhD[7] | Adel K. El-Naggar MD, PhD[7] | Michael R. Midgen MD[8] | Randal S. Weber MD[2] | Jeffrey N. Myers MD, PhD[2,4] | Neil D. Gross MD[2]

[1]Department of Otolaryngology – Head and Neck Surgery, Henry Ford Health System and Henry Ford Cancer Institute, Detroit, Michigan

[2]Division of Surgery, Department of Head and Neck Surgery, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

[3]Division of Cancer Medicine, Department of Thoracic Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

[4]The University of Texas Graduate School of Biomedical Sciences, Houston, Texas

[5]Division of Cancer Medicine, Department of Melanoma Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

[6]Division of Radiation Oncology, Department of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

[7]Division of Pathology/Lab Medicine, Department of Pathology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

[8]Division of Internal Medicine, Department of Dermatology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Correspondence
Neil D. Gross, Division of Surgery, Department of Head and Neck Surgery, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Suite 1445, Houston, TX 77030, USA.
Email: ngross@mdanderson.org

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Abstract

Background: The outcomes of patients treated with cytotoxic or targeted systemic therapy is not well defined for cutaneous squamous cell carcinoma of the head and neck (cSCCHN).

Methods: Patients with cSCCHN treated with cytotoxic or targeted systemic therapy were included. Patients were divided into two groups based on the presence of distant metastasis (M1 vs. M0) at presentation. A proportional hazards model was used to assess for independent predictors of overall survival.

Results: Of 129 patients with cSCCHN, 20 (16%) were M1 and 109 (84%) were M0. Independent predictors of improved survival were M0 status, treatment of locally advanced disease with radiotherapy, and lower Eastern Cooperative Oncology Group (ECOG) score.

Conclusions: Survival was worse in M1 patients treated with cytotoxic or targeted systemic therapy and poor baseline performance status but improved

in those receiving radiotherapy. These data can serve as historical controls for future systemic therapy trials, including immunotherapy.

KEYWORDS

chemotherapy, head and neck neoplasms, skin neoplasms, squamous cell carcinoma, systemic therapy

1 | INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most common nonmelanoma skin cancer, with an estimated lifetime risk of 7%–11%.[1] Despite being less common than basal cell carcinoma, cSCC accounts for 20% of skin cancer deaths. The incidence of cSCC is rising by approximately 10% each year because of an aging population and overall increased lifetime exposure to ultraviolet radiation.[2] The most common site of cSCC is the head and neck (cSCCHN),[3] where surgery is typically offered as first-line therapy.[4] Adjuvant radiation therapy is frequently applied to patients with cSCCHN with adverse pathologic features and/or advanced-stage disease.

The role of cytotoxic or targeted systemic therapy for cSCCHN remains poorly defined. Currently, no Food and Drug Administration (FDA)-approved systemic agents exist for cSCCHN in the neoadjuvant or adjuvant setting. Off-label use of chemotherapy has typically been reserved for patients with cSCCHN with high-risk features or metastatic disease. There are several reasons to consider including cytotoxic or targeted systemic therapy in the treatment of cSCCHN.[5] Chemotherapy may enhance radiosensitivity and eradication of micrometastatic disease. Previous randomized controlled trials have demonstrated improved survival with the addition of cytotoxic or targeted systemic therapy to postoperative adjuvant radiation therapy in patients surgically treated for head and neck mucosal squamous cell carcinoma with either positive margin or extranodal extension. Extrapolation of these results led to the occasional use of postoperative chemoradiation in the treatment of patients with cSCCHN.[6] However, a phase III trial from the Trans Tasman Radiation Oncology Group (TROG)[7] randomized patients with high-risk primary or nodal features to receive either adjuvant radiotherapy or radiotherapy with carboplatin.[8] While no benefit was found in terms of disease control or survival among 310 randomized patients, the addition of cytotoxic or targeted systemic therapy continues to be a consideration in the adjuvant setting in high-risk cSCCHN. This study aims to describe outcomes in patients with cSCCHN undergoing cytotoxic and targeted systemic therapy in the pre-immunotherapy era.

2 | METHODS

This is a retrospective cohort study of patients with cSCCHN treated with cytotoxic and targeted systemic therapy at the University of Texas M. D. Anderson Cancer Center (MDACC) from January 1, 1995 to September 30, 2015. Institutional research board approval was obtained and a waiver of informed consent was granted due to the retrospective nature of data collection. Patients with pathologically confirmed cSCCHN, 18 years or older were eligible for inclusion if they received cytotoxic or targeted systemic therapy. Patients were excluded if (1) they had concurrent diagnosis of another malignancy, (2) follow-up was less than 1 month after presentation, and (3) received immunotherapy. Demographic, clinical, and pathologic data were collected. Tumors were staged according to the 7th edition of the American Joint Committee on Cancer staging manual.[9] Chronic immunosuppression was defined as patients having solid organ transplantation, stem cell transplantation, hematologic malignancy (e.g., lymphoma or leukemia), autoimmune disease requiring immunosuppressive therapy, insulin-dependent diabetes mellitus, human immunodeficiency virus or acquired immunodeficiency syndrome, or hematoproliferative disorder. Persistent/recurrent disease was defined as previously treated disease with disease at presentation with the same pathology and the same local site or regional/distant metastasis without another known primary site of disease. Details of cytotoxic or targeted systemic therapy included the agent(s) given and response to therapy. Response to therapy was determined based on radiographic report or review of the patient record. Formal assessment using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria was not available due to the retrospective nature of the study. All the data obtained from chart review were maintained in Research Electronic Data Capture (REDCap), a secure, web-based database application.

Patients were divided into two groups based on M (distant metastasis) classification as (1) M0, when distant metastasis was not identified during presentation or initial workup (time from initial presentation to initiation of treatment) and (2) M1, when distant metastasis was present at time of initial presentation. Distant metastatic disease did not include patients who were seen only with regional metastases to the neck. Primary outcome

TABLE 1 Baseline characteristics of patient cohort undergoing systemic therapy for cutaneous squamous cell carcinoma of the head and neck by M classification ($N = 129$)

Characteristic	M_0 $N = 109$, No. of patients (%)	M_1 $N = 20$, No. of patients (%)	*p*-value
Age (years, median, range)[a]	66 (39–90)	69 (38–82)	0.900
Sex			
Female	17 (16)	3 (15)	0.625
Male	92 (84)	17 (85)	
Race			
White	97 (89)	19 (95)	0.345
Black	3 (3)	0 (0)	
Hispanic	8 (7)	0 (0)	
Other	1 (1)	1 (5)	
History of skin cancer			
Yes	97 (89)	20 (100)	0.213
No	12 (11)	0 (0)	
Recurrent or persistent disease			
Yes	82 (75)	18 (90)	0.242
No	27 (25)	2 (10)	
Chronic immunosuppression			
Yes	25 (23)	2 (10)	0.191
No	84 (77)	18 (90)	
T classification			
T0	6 (6)	2 (10)	<0.001
T1	1 (2)	1 (5)	
T2	7 (6)	0 (0)	
T3	36 (33)	1 (5)	
T4	35 (32)	1 (5)	
TX	24 (22)	15 (75)	
N classification			
N0	56 (55)	3 (15)	<0.001
N1	11 (9)	3 (15)	
N2	30 (28)	5 (25)	
N3	5 (2)	0 (0)	
NX	7 (6)	9 (45)	
Overall AJCC stage			
I	0 (0)	0 (0)	0.011
II	2 (2)	0 (0)	
III	31 (26)	0 (0)	
IV	60 (68)	20 (100)	
Unknown	16 (14)	0 (0)	
ECOG performance status			
0	17 (16)	4 (20)	0.807
1	58 (53)	11 (55)	
2	16 (15)	4 (20)	
3	3 (3)	0 (0)	

(Continues)

TABLE 1 (Continued)

Characteristic	M_0 $N = 109$, No. of patients (%)	M_1 $N = 20$, No. of patients (%)	*p*-value
Unknown	15 (14)	1 (5)	
Prior treatment			
None	14 (13)	0 (0)	0.160
Surgery only	37 (37)	6 (30)	
Surgery and radiotherapy/systemic therapy	54 (50)	14 (70)	
Radiotherapy only	2 (2)	0 (0)	
Radiotherapy and systemic therapy	2 (2)	0 (0)	
Clinical site[b]			
Scalp/forehead	14 (12)	1 (5)	0.001
Periorbital	5 (5)	0 (0)	
Cheek	37 (34)	2 (10)	
Nasal	4 (4)	0 (0)	
Ear	17 (16)	0 (0)	
Lip	2 (2)	0 (0)	
Neck	21 (19)	9 (45)	
Other	9 (8)	8 (40)	
Median follow-up (months, range)[a]	22 (1–157)	6 (2–66)	0.128

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]Median (range).
[b]Total greater than 100% due to lesions involving multiple sites.

measures were overall survival (OS), which was the time from initial presentation to MDACC to death from any cause or loss to follow-up, and disease-specific survival (DSS), which was the time from initial presentation to MDACC to death from disease or loss to follow-up.

Continuous variables were compared using the Student *t* test and categorical variables were compared using the chi-square test or the Fisher exact test as appropriate. Survival probabilities were calculated using the Kaplan–Meier method and were compared with the log-rank test. Univariate and multivariable Cox proportional hazard models for OS and DSS were used to explore predictors of survival. The Hosmer–Lemeshow purposeful selection method was employed for covariate selection for use in the multivariable model.[10] The most parsimonious model adequately representing the data was utilized as the final model. All tests were 2-tailed and alpha was set to a *p*-value of 0.05 for significance. All statistical analyses were completed using STATA 14.2 (Statcorp, College Station, TX).

3 | RESULTS

3.1 | Baseline group characteristics

Of 738 patient with cSCCHN records reviewed, 129 patients met inclusion criteria. All 607 excluded patients were due to receiving cytotoxic or targeted systemic therapy not being indicated or having incomplete follow-up data. Two patients were excluded due to a concurrent diagnosis of malignant melanoma and Merkel cell carcinoma. One-hundred and nine patients (84%) had M0 disease and 20 (16%) had M1 disease (Table 1). Tumor (T) and nodal (N) classifications as well as overall staging differed between the two groups. Patients seen with distant metastases (DM) were more likely to have primary disease originating on the skin of the neck compared to other head and neck subsites. In the M0 group, 25 (23%) had chronic immunosuppression, compared to 2 (10%) in the M1 group. Median follow-up for patients with M0 classification was 22 months (range = 1–157) and 6 months (range = 2–66) for M1 patients ($p = 0.109$). Follow-up in the M1 patients was limited due to the 70% (14/20) mortality rate.

Patient treatment characteristics are summarized in Table 2. Forty-four (40%) of M0 patients and 12 (60%) of M1 patients received systemic therapy alone. Patients with M1 disease were less likely to undergo surgery ($p = 0.013$). In M0 patients undergoing surgery, 6/26 (23%) patients underwent induction chemotherapy followed by surgery alone. The remaining 20/26 patients (77%) underwent postoperative radiotherapy following surgery. Forty percent of patients (8/20) underwent induction chemotherapy followed by surgery and

TABLE 2 Treatment characteristics of patients undergoing cytotoxic or targeted systemic therapy for cutaneous squamous cell carcinoma of the head and neck by M classification ($N = 129$)

Treatment type	M_0 $N = 109$, No. of patients (%)	M_1 $N = 20$, No. of patients (%)	*p*-value
Surgery			
Ind + Sx	6 (6)	0 (0)	0.013
Ind + Sx + PORT	8 (7)	0 (0)	
Sx + POCRT	11 (10)	0 (0)	
Ind + Sx + POCRT	1 (1)	0 (0)	
Radiotherapy			
CRT	24 (22)	2 (25)	
Ind + RT	10 (9)	5 (63)	
Ind + CRT	4 (4)	0 (0)	
Unknown sequence radiation and systemic therapy	1 (1)	1 (13)	
Systemic therapy alone	44 (40)	12 (60)	
Type of systemic therapy			
Cisplatin based	28 (26)	2 (10)	0.482
Carboplatin based	33 (30)	7 (35)	
EGFR inhibitor only	40 (37)	8 (40)	
Other	8 (7)	3 (15)	

Abbreviations: CRT, concurrent systemic and radiation therapy; EGFR, epithelial growth factor receptor; Ind, induction systemic therapy; PORT, postoperative radiation therapy; POCRT, postoperative systemic and radiation therapy; RT, radiotherapy; Sx, surgery.

postoperative radiotherapy. Eleven patients (55%) underwent surgery followed by postoperative concurrent chemoradiotherapy. One patient (5%) underwent induction chemotherapy, surgery, followed by concurrent chemoradiotherapy.

In patients with M0 disease, 39 patients (36%) underwent radiotherapy without surgery. The most common treatment regimen was concurrent chemoradiation ($N = 24/39$, 62%), then induction systemic therapy followed by radiotherapy alone ($N = 10/39$, 26%). Four patients (10%) underwent induction systemic therapy followed by concurrent chemoradiation. One patient (3%) underwent treatment at an outside institution and the type of systemic therapy was unknown.

In patients with M1 disease, only eight patients underwent radiotherapy treatment for locoregional disease ($N = 8/20$, 40%). In these patients, the most common treatment regimen was induction systemic therapy followed by radiation therapy ($N = 5/8$, 63%).

3.2 | Cytotoxic or targeted systemic therapy

Cytotoxic or targeted systemic treatment regimens were divided into four major groups based on the primary agent in each regimen: cisplatin-based, carboplatin-based, epithelial growth factor receptor (EGFR) inhibitor-based, and other (Table 2, detailed data in Table S1, Supporting Information). In those receiving cisplatin-based therapy, 22/30 patients (73%) received cisplatin only, 7 (23%) cisplatin and taxane, and 1 (3%) cisplatin, taxane, and systemic 5-fluorouracil. In those receiving carboplatin-based therapy, 7/40 (18%) received carboplatin alone, and 33 (82%) carboplatin and taxane. All those receiving EGFR inhibitor-based therapy received this as a single agent. Other regimens included targeted therapies (i.e., bevacizumab ($n = 3$), dasatinib ($n = 1$), methotrexate ($n = 1$), oxaliplatin ($n = 1$), and other specific agents under a clinical trial ($n = 5$)). No differences were demonstrated in treatment regimens according to M classification ($p = 0.482$).

In the 30 patients undergoing cisplatin-based therapy, 19 patients (63%) had a partial response, and 9 (29%) had stable disease. One patient (3.2%) had a complete response following therapy and one patient (3.2%) was lost to follow-up prior to assessment of treatment response. In those treated with carboplatin-based therapy, 21 (53%) had a partial response, and 19 (47%) had stable disease. In patients treated with EGFR inhibitor-based therapy, 17 (35%) had partial response and 27 (56%) had stable disease. Of all 129 patients, two patients (1.6%) did not have their response to therapy assessed due to lost to follow-up prior to completion of the treatment course, and two patients (1.6%) died due to disease prior to treatment completion. No patients receiving carboplatin-based or EGFR inhibitor-based therapy had complete response. Response rates were not different between treatment regimens ($p = 0.100$).

In the 44 patients with M0 disease receiving systemic therapy alone, 15 patients (35%) had a partial response, 27 (63%) had no response (stable or progressive disease), and 1 (2%) had an unknown response. In 12 with M1 disease receiving systemic therapy alone, two patients (17%) had partial response, nine (75%) had no response (stable or progressive disease), and one (8%) had an unknown response. There was no difference between patients with M0 or M1 disease in terms of disease response.

3.3 | Survival outcomes

OS was 46.8% (95% confidence interval [CI] = 36.5–55.4) at 24 months for M0 patients and 25.5% (95% CI = 7.2–49.1) for M1 patients. There was only one patient with M1 disease who was alive past 5 years, treated with induction carboplatin, paclitaxel, and cetuximab and radiation to a lung nodule, resulting in partial response with stable disease for 66 months. Median OS was 22 months in those with M0 classification compared to 13 months in M1 classification (log rank p-value = 0.0357). DSS for patients with M0 disease was 57.9% (95% CI = 46.9–67.4) at 24 months and 38.2% (95% CI = 15.0–61.4) for patients with M1 disease. Using the log rank test, DSS was statistically significantly better in patients with M0 disease compared to M1 disease ($p = 0.016$).

In patients with M0 disease undergoing systemic therapy only, 24 month OS and DSS were 30.4% (95% CI = 17.1–44.8) and 37.4% (95% CI = 22.4–52.4), respectively, compared to 58.0% (95% CI = 43.9–69.7) and 71.8% (95% CI = 57.3–82.1) in those undergoing systemic therapy with surgery and/or radiotherapy ($p < 0.001$ and $p < 0.001$, respectively; Figure 1(A), (C)). OS and DSS was poor in those with M1 disease, and median OS and DSS was 13 months in those undergoing systemic therapy with radiotherapy compared to 7 months in those undergoing systemic therapy only ($p = 0.044$ and $p = 0.125$, respectively; Figure 1(B), (D)). Patients undergoing concurrent chemoradiotherapy or sequential systemic therapy followed by radiotherapy had better OS and DSS in patients with M0 disease compared to those undergoing chemotherapy only ($p < 0.001$ and $p = 0.002$, respectively; Figure 2). No differences were found in OS or DSS when comparing different systemic treatment regimens for M0 patients (Figure 3). Among M1 patients, those treated with cisplatin-based regimens had a longer median OS compared to those on other regimens ($p = 0.031$).

3.4 | Predictors of survival

Univariate analysis (Table 3) demonstrated that patients with recurrent or persistent disease (hazard ratio

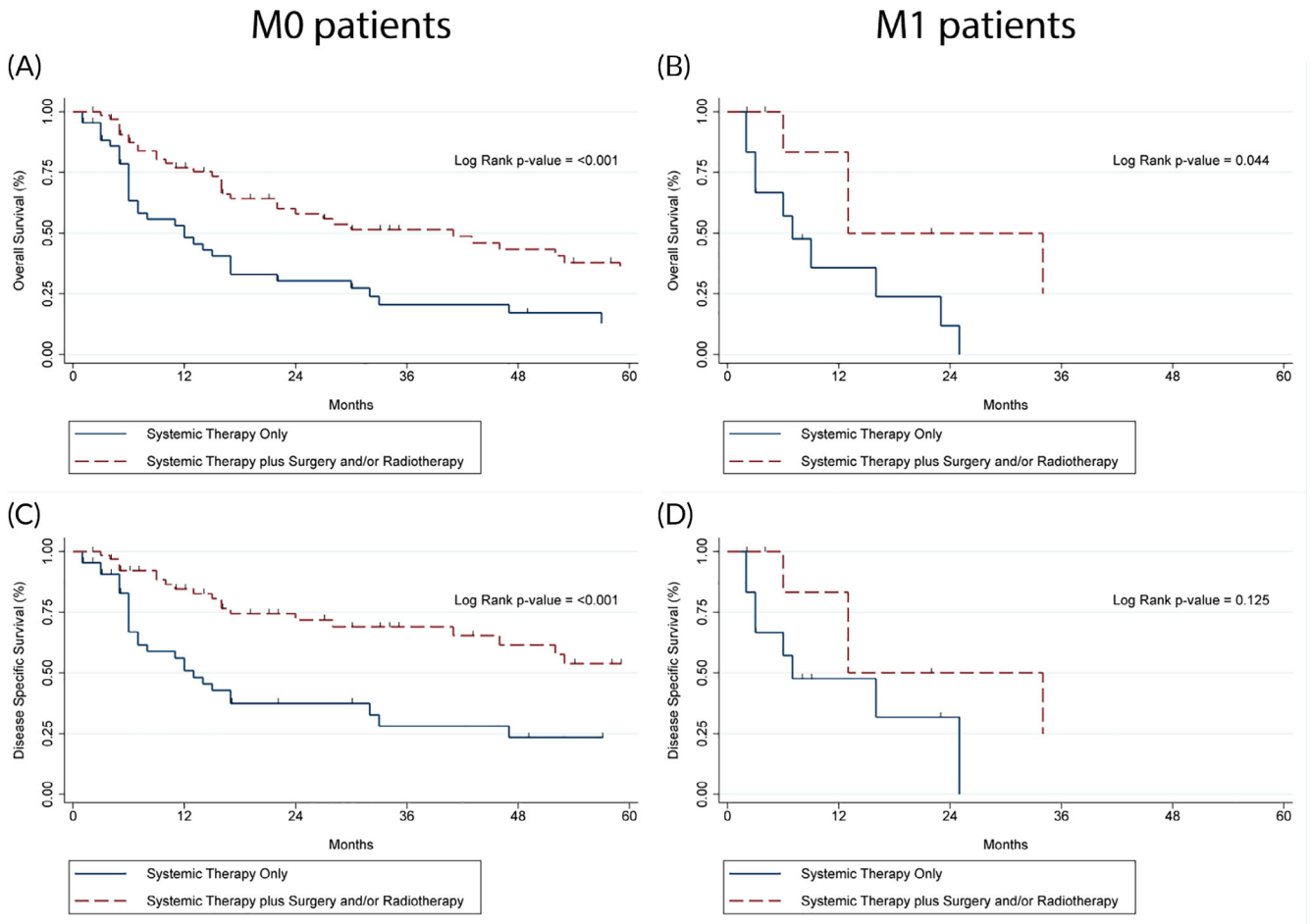

FIGURE 1 Kaplan–Meier survival plots of overall (A) and disease-specific (C) survivals in M0 patients and overall (B) and disease-specific (D) survival in M1 patients comparing receipt of cytotoxic or targeted systemic therapy alone versus cytotoxic or targeted systemic therapy and surgery and/or radiotherapy [Color figure can be viewed at wileyonlinelibrary.com]

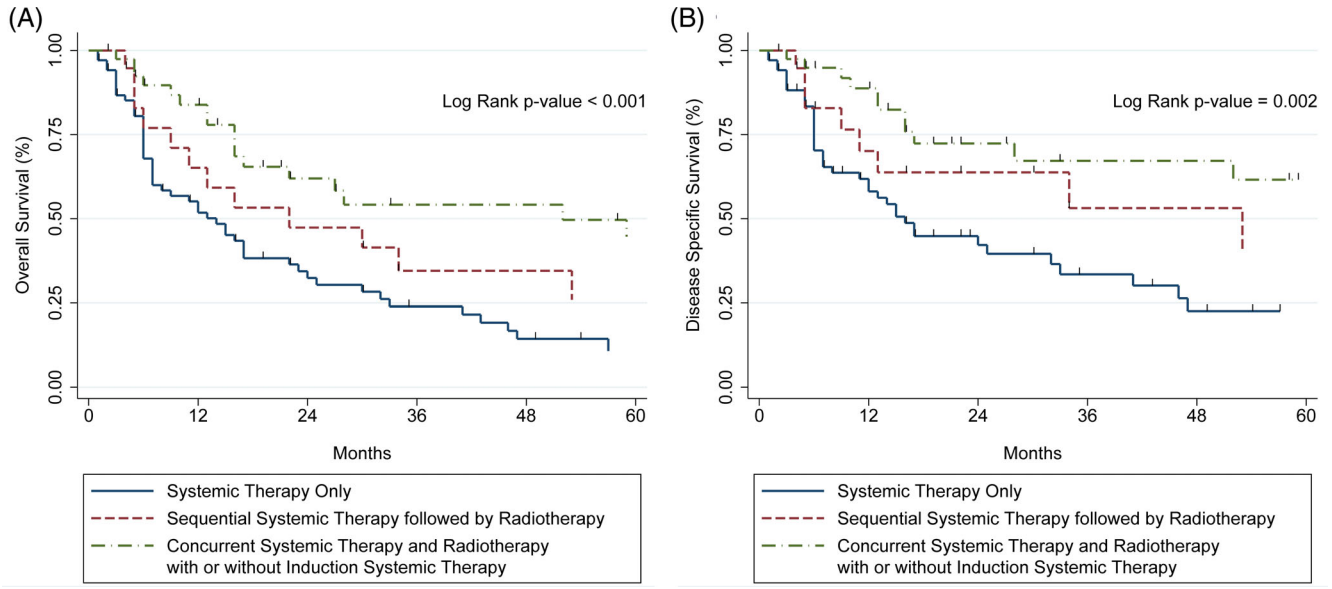

FIGURE 2 Kaplan–Meier survival plots of overall (A) and disease-specific (B) survivals in patients receiving cytotoxic or targeted systemic therapy with or without radiotherapy according to timing of systemic therapy [Color figure can be viewed at wileyonlinelibrary.com]

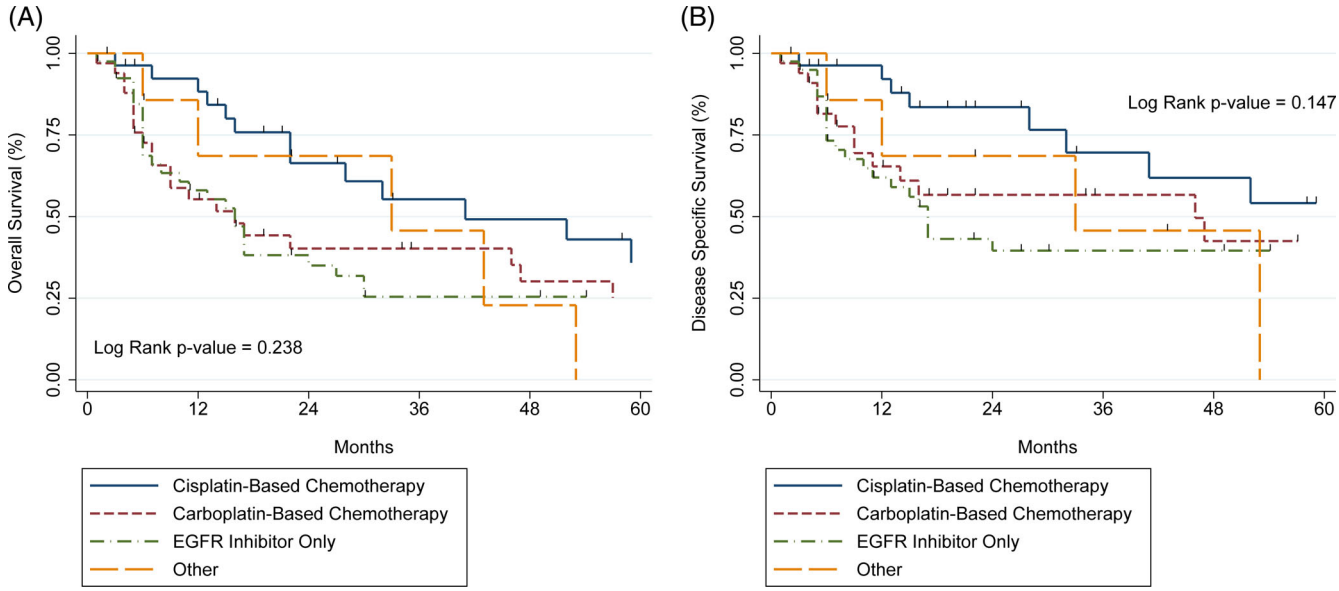

FIGURE 3 Kaplan–Meier survival plots of overall (A) and disease-specific (B) survivals in M0 patients according to cytotoxic or targeted systemic therapy treatment regimen [Color figure can be viewed at wileyonlinelibrary.com]

[HR] = 2.20, 95% CI = 1.17–4.15), treatment with EGFR inhibitor only (HR = 2.07, 95% CI = 1.14–3.74), or poor Eastern Cooperative Oncology Group (ECOG) performance score (2: HR = 3.82, 95% CI = 1.79–8.16; 3: HR = 6.94, 95% CI = 1.89–25.56) had worse OS. Treatment with surgery (HR = 0.58, 95% CI = 0.23–0.68) and any radiotherapy (HR = 0.40, 95% CI = 0.26–0.61) resulted in better OS. Multivariable analysis was then performed, adjusting for age, M classification, treatment with radiotherapy, chemotherapy regimen, and ECOG performance score. M classification ($HR_{adjusted}$ = 2.40, 95% CI = 1.24–4.66), treatment with any radiotherapy ($HR_{adjusted}$ = 0.31, 95% CI = 0.19–0.51), and ECOG performance status (2: $HR_{adjusted}$ = 4.61, 95% CI = 2.02–10.49; 3: $HR_{adjusted}$ = 13.73, 95% CI = 3.81–49.4; unknown: $HR_{adjusted}$ = 2.70, 95% CI = 1.16–6.32) were independent predictors of OS.

For DSS, univariate analysis demonstrated patients with recurrent or persistent disease (HR = 2.87, 95%

TABLE 3 Univariate and multivariable Cox proportional hazards model for overall and disease-specific survivals

	Overall survival				Disease-specific survival			
	Univariate		Multivariable		Univariate		Multivariable	
Characteristic	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age[a]	1.00	0.98–1.06	1.01	0.98–1.03	1.00	0.97–1.02	1.00	0.97–1.02
Recurrent/persistent disease								
No	Ref							
Yes	2.20	1.17–4.15			3.13	1.26–7.81		
T classification								
T0/T1/T2/TX	Ref				Ref			
T3/T4	1.37	0.88–2.13			1.41	0.83–2.41		
N classification								
N0	Ref				Ref			
N+	1.04	0.68–1.61			1.12	0.67–1.87		
M classification								
0	Ref							
1	1.82	1.04–3.20	2.05	1.11–3.79	2.13	1.16–3.90	2.04	1.03–4.06
Chronic immune suppression								
Yes	Ref							
No	0.58	0.32–1.05			0.42	0.23–0.77	0.61	0.30–1.23
Surgery								
No	Ref							
Yes	0.40	0.23–0.68			0.27	0.13–0.56	0.44	0.18–1.06
Radiotherapy								
No	Ref							
Yes	0.40	0.26–0.61	0.34	0.21–0.56	0.32	0.19–0.55	0.32	0.17–0.62
Chemotherapy regimen								
Cisplatin based	Ref							
Carboplatin based	1.43	0.76–2.69	1.04	0.53–2.04	2.03	0.88–4.72	1.53	0.62–3.82
EGFR inhibitor only	2.07	1.14–3.74	1.58	0.82–3.05	3.00	1.36–6.64	2.31	0.93–5.72
Other	2.16	0.92–5.08	1.26	0.49–3.22	3.49	1.26–9.67	1.53	0.46–5.10
ECOG performance status								
0	Ref							
1	1.28	0.67–2.45	1.37	0.71–2.67	0.46	0.64–3.36	1.64	0.69–3.91
2	3.82	1.79–8.16	4.14	1.83–9.37	4.44	1.74–11.36	4.76	1.72–12.98
3	6.94	1.89–25.56	11.00	2.68–45.18	6.71	1.34–33.44	6.99	1.21–40.43
Unknown	1.55	0.70–3.45	2.85	1.20–6.80	2.35	0.89–6.17	4.90	1.64–14.62
Clinical site								
Scalp/forehead	Ref							
Periorbital	1.20	0.37–3.82			1.13	0.30–4.29		
Cheek/face	0.50	0.23–1.08			0.44	0.18–1.07		
Nose	0.77	0.21–2.81			0.34	0.04–2.73		
Ear	1.65	0.71–3.86			1.27	0.48–3.42		
Lip[b]	N/A				N/A			

TABLE 3 (Continued)

	Overall survival				Disease-specific survival			
	Univariate		Multivariable		Univariate		Multivariable	
Characteristic	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Neck	1.53	0.72–3.26			1.32	0.56–3.13		
Other	1.22	0.54–2.77			1.43	0.58–3.49		

Abbreviations: CI, confidence interval; ECOG, European Cooperative Oncology Group; HR, hazard ratio.

[a]Per unit change.

[b]Unable to determine due to small size of subgroup.

CI = 1.25–6.56), M1 classification (HR = 2.05, 95% CI = 1.11–3.79), and ECOG performance status (2: HR = 4.14, 95% CI = 1.83–9.37; 3: 11.00, 95% CI = 2.68–45.18) were negative prognostic factors. Absence of chronic immunosuppression (HR = 0.42, 95% CI = 0.23–0.77), treatment with surgery (HR = 0.27, 95% CI = 0.13–0.56), and treatment with radiotherapy (HR = 0.32, 95% CI = 0.19–0.55) were protective against disease-specific death. By multivariable analysis adjusted for age (as a continuous variable), M classification ($HR_{adjusted}$ = 2.04, 95% CI = 1.03–4.06), treatment with radiotherapy ($HR_{adjusted}$ = 0.32, 95% CI = 0.19–0.55), and ECOG performance status (2: $HR_{adjusted}$ = 4.76, 95% CI = 1.72–12.98; 3: $HR_{adjusted}$ = 6.99, 95% CI = 1.21–40.43; unknown: $HR_{adjusted}$ = 4.90, 95% CI = 1.64–14.62) were independent predictors of DSS, similar to OS.

4 | DISCUSSION

Treatment for early stage cSCCHN is relatively straightforward often cure can be achieved with single modality of surgery or radiotherapy. However, in those with advanced disease, treatment is more challenging. Despite multimodality therapy with surgery and radiation therapy, the risk of recurrence remains high. Cytotoxic or targeted systemic therapy has been used off-label in cSCCHN, but a standard of care regimen is yet to be defined. The role of chemotherapy in the adjuvant setting with postoperative radiotherapy for cSCCHN has recently been called into question given the negative findings from a Phase III TROG randomized trial comparing radiation alone to radiation with carboplatin after surgery.[7] Despite these findings, clinical practice remains variable in treating patients with cSCCHN demonstrating high-risk features. Understanding current practices and outcomes is essential to the rational incorporation of future therapies. This is particularly important in light of emerging data on the effectiveness of immunotherapy for cSCCHN.[11] Currently, cemiplimab has demonstrated promise in a phase 1 and 2 trials in patients with locally advanced and metastatic cSCC and has been approved by the FDA for patients who are not candidates for curative surgery or radiotherapy.[11,12]

In this study, we describe a large cohort of highly selected patients with cSCCHN undergoing cytotoxic or targeted systemic therapy. As expected, patients with M1 disease had a worse prognosis, with a 24-month OS of 25.5% and with most patients dying due to their disease. OS in patients with locally advanced disease with no distant metastasis was also poor (24-month OS = 46.8%). Indeed, patients with advanced cSCCHN frequently have several comorbid conditions given the advanced age of this patient population. Thus, these data reflect the conventional clinical setting, including patients who may not qualify for inclusion in clinical trials.

No difference in prognosis was observed between the different cytotoxic or targeted systemic treatment regimens in this study after multivariable adjustment. Due to the retrospective nature of our study, regimen selection was likely determined based on multiple factors, including age, comorbidities, performance status, availability of therapeutic agents, and physician preference. Thus, the differences observed on univariate analysis might reflect patient selection rather than true efficacy of different treatment regimens. Overall, patients were most often treated with either carboplatin- or EGFR inhibitor-based regimens. In those with distant metastatic disease, neoadjuvant systemic regimens were more common, in contrast to concurrent regimens in those with only locoregionally advanced disease. For cSCCHN, clinical trials have largely been limited to one arm studies with small sample sizes as no standard regimen has been determined in this patient population.[13-15] In fact, most therapeutic regimens have been extrapolated based on their effectiveness in head and neck mucosal squamous cell carcinoma with varying success.[5] As such, the potential role of EGFR inhibitors has been heavily investigated.[16,17] This study demonstrates general cytotoxic and targeted systemic treatment patterns at a tertiary head and neck cancer specialty practice.

On univariate analysis, treatment with surgery and/or radiotherapy resulted in improved OS, even in patients with M1 disease. Thus, locoregional treatment should be considered in patients that are able to tolerate this treatment, even in the presence of distant metastases. On multivariable analysis, we found that M classification, treatment with radiotherapy, and ECOG performance status were independent predictors of OS and DSS. The presence of distant metastatic disease and poor baseline ECOG performance status are known predictors of mortality. Radiotherapy has been demonstrated to be effective in locoregionally advanced cSCCHN, especially those with high-risk features.[5] However, since this study was retrospective and patients were not randomized to receipt of radiotherapy, the selection of patients for radiotherapy was based on tumor characteristics, comorbidity, performance status, and predicted prognosis.

Limitations of this study must be considered in the interpretation of the results. The patient list for this study was generated from the institutional tumor registry and likely underestimates the total number of patients with cSCCHN treated at MDACC during the study period due to misclassification of the disease site. This study aimed to describe the variability of treatment approaches in patients undergoing cytotoxic or targeted systemic therapy with cSCCHN. Because of the variability in clinical approaches to these patients, there exists significant heterogeneity in the sample. While attempts were made to statistically control for this variability, some variables were unavailable in the chart and could not be adjusted for (e.g., curative- vs. palliative-intent treatment). Thus, this study should be taken as a descriptive snapshot in the pre-immunotherapy era rather than prescriptive for best treatment practices. The design of our study was retrospective and relied on the accuracy of the medical records with the possibility of the important data not being available or accessible. For example, RECIST criteria could not be applied to assess treatment response as objective measurement of tumors was not consistently available. As well, we were unable to use date of diagnosis as the start point of survival analyses as most diagnoses were made prior to presentation and availability of outside records was incomplete. Treatment regimen depended on decisions made based on patient and tumor characteristics, as well. Thus, the risk of selection bias is inherent. Although we attempted to adjust for these factors using multivariable analysis, not all nuances that influence treatment choice could be adequately accounted for in our models. Additionally, this study was completed at a tertiary cancer center, where high-risk patients are referred frequently, therefore potentially limiting the external validity of our findings.

Despite these limitations, this cohort of highly selective patients with cSCCHN provides essential data on the performance of cytotoxic or targeted systemic therapies in this high-risk population. We hope our experience can help guide cytotoxic or targeted systemic treatment recommendations in advanced cSCCHN and serve as a historical reference as immunotherapy becomes more integrated into treatment regimens. Novel therapies are being applied to cSCCHN with the promise of improving our understanding of the molecular mechanisms of the disease.[18] Considering the exclusion of nonmelanoma skin cancers in U.S. national cancer registries, these data can serve as a valuable resource on the subset of patients with advanced cSCCHN. Moving forward, we hope these data can provide an essential comparator of effectiveness for novel therapies in the treatment of cSCCHN.

5 | CONCLUSION

In conclusion, OS and DSS in patients with cSCCHN requiring cytotoxic systemic therapy is poor. Survival was worse in patients with DM at presentation and poor baseline performance status in spite of cytotoxic or targeted systemic therapy, but the additional receipt of radiotherapy was associated with improved disease outcome. Further investigations are needed to discover novel combination strategies of conventional, molecularly targeted, and immunotherapeutic agents. These data can serve as a historical control for future trials using systemic therapies, including immunotherapy, in advanced cSCCHN.

CONFLICT OF INTEREST

Renata Ferrarotto received personal fees from Regeneron-Sanofi, Ayala Pharma, Klus Pharma, Medscape, Cellestia Biotech; receiving grants from ASCO Career Development Award, Oropharynx Program Stiefel/clinical trials, and M. D. Anderson Khalifa Award. Funds to institution from AstraZeneca, Merck, Genentech, Ayala Pharma and Pfizer. Faye M. Johnson received research funding from PIQUR Therapeutics and Trovagene. Maura L. Gillison is a consultant and receiving personal fees from Bristol-Myers Squibb (BMS), Genocea Biosciences, EMD Serono, Bayer Healthcare Pharmaceuticals, New Link Genetics Corporation, Roche, Aspyrian Therapeutics, TRM Oncology, Merck, Amgen, Astra Zeneca, Celgene; receiving grants from Cancer Prevention & Research Institute of Texas, UT Stars Award,

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AUTHOR CONTRIBUTIONS

Samantha Tam: Conceptualization; data analysis and curation; methodology; manuscript writing – original draft, review and editing. **Mona Gajera**: Data acquisition; manuscript writing – original draft. **Xiaoning Luo**: Data acquisition, manuscript writing – review and editing. **Bonnie S. Glisson and Renata Ferrarotto**: Data interpretation; manuscript writing – review and editing. **Faye M. Johnson, Frank E. Mott, Maura L. Gillison, Charles Lu, Xiuning Le, George R. Blumenschein, Michael K. Wong, David I. Rosenthal, Priyadharsini Nagarajan, Adel K. El-Naggar, Michael R. Midgen, Randal S. Weber, and Jeffrey N. Myers**: Data interpretation; manuscript writing – review and editing. **Neil D. Gross**: Conceptualization; data curation and interpretation; manuscript writing – review and editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Renata Ferrarotto https://orcid.org/0000-0002-3561-215X
Randal S. Weber https://orcid.org/0000-0002-1980-7248
Neil D. Gross https://orcid.org/0000-0002-9427-0743

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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