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ORIGINAL RESEARCH

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Definitive local therapy to head and neck squamous cell carcinoma with distant metastasis

Steven Borson MD[1] | Yongli Shuai PhD[1] | Barton F. Branstetter MD[2] | Marci Lee Nilsen PhD RN[3] | Marion A. Hughes MD[2] | Moon Fenton MD[1] | Mark Kubik MD[4] | Shaum Sridharan MD[4] | David A. Clump MD[5] | Heath D. Skinner MD, PhD[5] | Jonas T. Johnson MD[5] | Simion I. Chiosea MD[6] | James Ohr MD[4] | Umamaheswar Duvvuri MD, PhD[4] | Seungwon Kim MD[4] | Katie S. Traylor MD[2] | Robert Ferris MD, PhD[4] | Dan P. Zandberg MD[7]

[1]University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania, USA

[2]Department of Radiology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

[3]Department of Acute and Tertiary Care, School of Nursing, Pittsburgh, Pennsylvania, USA

[4]Department of Otolaryngology, UPMC, Pittsburgh, Pennsylvania, USA

[5]Department of Radiation Oncology, UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, USA

[6]Department of Pathology, UPMC, Pittsburgh, Pennsylvania, USA

[7]Department of Hematology/Oncology, UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, USA

Correspondence
Steven Borson, University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA.
Email: borsonsh@upmc.edu

Abstract

Objectives: Data on the efficacy of including definitive local therapy to the primary site for head and neck squamous cell carcinoma (HNSCC) patients with synchronous distant metastasis are lacking. In multiple different solid tumor types, there has been benefit when using systemic therapy followed by local consolidative therapy (stereotactic ablative radiotherapy or surgery) directed at metastases. We proposed to retrospectively evaluate patients at our institution that received definitive treatment to the primary.

Methods: Single institution retrospective study evaluating 40 patients with metastatic HNSCC treated with definitive surgery (55%) or chemoradiation (45%) to the primary site from 2000 to 2020. The major endpoints were overall survival (OS) and progression-free survival (PFS) for the total population and multiple sub-groups. Some variables were evaluated with multiple covariates Cox model.

Results: The median PFS was 8.6 months (95% CI, 6.4–11.6), and OS was 14.2 months (95% CI, 10.9–27.5). In 28% of patients that received induction therapy, there was a twofold increase in median overall survival to 27.5 months. In the 33% of patients that received anti-PD-1 mAb as part of their treatment course, the median OS was significantly increased to 41.7 months (95% CI, 8.7-NR) versus 12.1 months

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(95% CI, 8.4–14.4) with a 5-year OS of 39%. Multivariate analysis for OS showed significance for age at diagnosis, use of IO, and number of metastatic sites.

Conclusion: We observed impressive survival outcomes in metastatic HNSCC patients treated with definitive local therapy to the primary site in addition to induction and/or immunotherapy. Further study is warranted.

Level of Evidence: 3.

KEYWORDS

head and neck cancer, immunotherapy, oligometastatic

1 | INTRODUCTION

While the armamentarium of treatment options in head and neck squamous cell carcinoma (HNSCC) has grown in the last 15 years,[1] treatment for recurrent/metastatic HNSCC remains palliative with a significant need for better outcomes. The historical archetype treatment for these patients has been combination cytotoxic chemotherapy. However, over the last 5 years immunotherapy with anti-programmed cell death protein 1 (anti-PD-1) monoclonal antibodies pembrolizumab and nivolumab has become standard of care.[2,3] Initially approval was in the platinum failure setting, and now more recently KEYNOTE-048 showed a significant survival benefit to pembrolizumab monotherapy in programmed cell death ligand 1 (PD-L1) combined positive score greater than 1, and to platinum/5-fluorouracil plus pembrolizumab for the total population compared to the EXTREME regimen.[4] The results of KEYNOTE-048 have led to a new standard of care in the frontline setting.

While this represents great progress for systemic therapy there is still a need for continued improvement in outcomes, and an open question exists as to whether we can benefit patients with local therapies in addition to systemic therapy for those with distant metastasis. The oligometastatic hypothesis is that local therapy directed specifically to the metastases can prolong survival, and in some instances, cure patients. In multiple different solid tumor types, there has been significant benefit when utilizing systemic therapy followed by local consolidative therapy (i.e., stereotactic ablative radiotherapy [SABR] or surgery directed at metastases).[5,6] Randomized phase 2 studies have shown improvement in both progression-free survival (PFS) and overall survival (OS) in non-small cell lung cancer with this approach.[5] There are numerous single-institution studies showing benefit of SABR for oligometastatic lesions of various tumor types,[7] with some data specific for HNSCC[8–10] However, beyond just the treatment of metastatic disease, in HNSCC where morbidity and mortality are more often driven by local disease there is the additional question as to whether it is beneficial to treat the primary disease in the head and neck with definitive intent surgery or radiation in addition or in lieu of local therapy to metastasis in select patients.

Therefore, we conducted a retrospective analysis to evaluate the outcomes of HNSCC patients treated at our institution that presented with metastatic disease at initial diagnosis and received definitive therapy to the primary site as part of their treatment.

2 | MATERIALS AND METHODS

Approval was obtained for this retrospective review from the University of Pittsburgh Institutional Review Board. We conducted a single center retrospective study at University of Pittsburgh Medical Center (UPMC) to evaluate HNSCC patients with distant metastatic disease at initial diagnosis that were treated with definitive chemoradiation and/or surgery to all disease in the head and neck. Patients with primary tumors of the oral cavity, oropharynx, hypopharynx, and larynx were included in this analysis. We conducted an initial review of all patients seen at UPMC that were in the UPMC head and neck organ specific database, from the years of 2000 to May 2020 with metastatic HNSCC, including only those patients that received definitive therapy to the primary disease in the head and neck as part of their treatment.

We collected information regarding baseline demographics, treatment modalities, dates of treatment, and outcomes. The baseline characteristics that were collected included age, race, site of primary cancer, p16 status in oropharyngeal tumors, number of patients with single versus multiple distant metastases, and sites of metastases. For p16 analysis, immunohistochemical staining was performed with the p16 antibody (E6H4, pre-dilute, Ventana) according to manufacturer's recommendation. Diffuse and strong cytoplasmic and nuclear staining of >70% of tumor cells was considered positive. Treatment modalities were also collected, including surgery, definitive chemoradiation, induction therapy, immunotherapy, and local therapy to metastatic disease.

Overall survival (OS) was calculated from the "date of diagnosis" to the date of death. Progression free survival (PFS) was calculated from the "date of diagnosis" to the date of progression or death. For patients presumably still alive at the time of analysis, follow-up was censored as of the date of last contact. Kaplan–Meier method was used to estimate the survival distributions and Log-rank test was used to assess the difference. The relationship of survival outcome to patients' demographic, clinical and pathologic characteristics was further assessed by Cox proportional hazards regression. The univariate Cox regression was first used to assess the mortality rate in relation to the available explanatory variables in exploratory fashion. Based on this univariate analysis, the potential significant predictors were evaluated further in the multiple covariates Cox model via stepwise

TABLE 1 Baseline characteristics of the total population.

Total population	40
Age at diagnosis (median, range)	61, 35–88
Sex	
Male	31 (77.5%)
Female	9 (22.5%)
Race	
Caucasian	37 (92.5%)
African American	3 (7.5%)
Primary tumor location	
Oropharynx	21 (52.5%)
HPV positive	10/21 (47.6%)
Hypopharynx/larynx	16 (40%)
Oral cavity	3 (7.5%)
Tumor and nodal stage at diagnosis	
T1/T2	12 (30%)
T3/T4	27 (68%)
N0	4 (10%)
N1	4 (10%)
N2	30 (75%)
Diagnosis year	
Prior to 2015	21 (52.5%)
2015 or later	19 (47.5%)
Metastatic lesions	
One metastatic lesion	22 (55%)
One metastatic lesion in the lung	13 (33%)
Multiple metastatic lesions	18 (45%)
Solitary organ site	34 (85%)
Lung	22 (55%)
Bone	5 (12.5%)
Liver	3 (7.5%)
Other	4 (10%)
Multiple organs involved	6 (15%)
Treatment modalities	
Surgery to primary site	22 (55%)
Chemoradiation to primary site	18 (45%)
Induction chemotherapy	11 (27.5%)
Platinum/5FU/cetuximab	4 (36%)
Cisplatin/docetaxel/5FU	4 (36%)
Other[a]	3 (27%)
Immunotherapy (anti-PD-1 m-Ab)	11 (27.5%)
Local therapy for metastatic disease	18 (45%)
Surgery	1 (2.5%)
Radiation	15 (37.5%)
Both	2 (5%)

[a]Other includes platinum/paclitaxel/cetuximab (1), platinum/5FU/pembro (1), platinum/paclitaxel (1).

procedures. The corresponding relative mortality rates are summarized as hazard ratios (HR), with HR >1.0 corresponding to increased mortality. A significance level was set at .05 and all *p* values reported were two-sided. Statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Patient characteristics

One hundred and eighteen patients with HNSCC with metastatic disease at diagnosis were identified from 2000 to May 2020. Forty of those patients were treated with definitive chemoradiation and/or surgery to the primary site and thus were included in our analysis. Patient characteristics are shown in Table 1. Median age was 61 and patients were predominantly male. The primary sites included oropharynx in 52%, hypopharynx/larynx in 40%, and oral cavity in 8% of patients. Of those patients with oropharyngeal cancer, 10/21 (47.6%) were p16 positive, and 6/21(28.5%) had unknown HPV status. Sixty-eight percent of patients had T3/T4 primary and 75% had N2 disease. If these patients did not have M1 disease, 90% would have been characterized as locally advanced disease.

Fifty-five percent of patients had one metastatic lesion with a median size of 1.6 cm. Fifty-nine percent of these patients had their lesion in the lung. The remainder had more than one metastatic lesion, with the median number of distant lesions being 6. The most common sites of metastatic lesions were lung, bone, and liver, with 85% having all metastatic disease confined to one organ. Forty percent of patients underwent biopsy to confirm metastatic disease, including 46% of patients that had one lesion in the lung. Twenty-two (55%) of patients underwent surgical resection while the remaining underwent definitive chemoradiation to the primary site. Immunotherapy treatment was with anti-PD-1 mAb therapy.

3.2 | Outcomes

Univariate survival analysis of PFS and OS are shown in Table 2. For the entire population of 40 patients, the median PFS was 8.6 months (95% CI, 6.4–11.6 months) and the median OS was 14.2 months (95% CI, 10.9–27.5 months), Figure 1A,B. Progression was distant in 79% of patients. There was no significant difference in PFS or OS for those patients with one lesion versus multiple or one organ system versus multiple organ systems involved. Among those with lesions in one organ system there was no significant difference in outcomes by location (lung vs. liver vs. bone). Younger age was significantly associated with increased OS but not PFS. There was no significant difference in outcomes by HPV status, gender, or year of diagnosis.

No difference in outcomes were seen between modality used for definitive local therapy to the primary site (surgery

TABLE 2 Univariate analysis of progression free survival and overall survival.

	Median PFS[a] (95% CI)	*p* value	Median OS[a] (95% CI)	*p* value
Total population	8.6 (6.4–11.6)		14.2 (10.9–27.5)	
Definitive local therapy		.8857		.6708
Surgery	8.3 (5.7–12.7)		14.5 (8.4–42.7)	
Chemoradiation	8.7 (6.3–13.7)		14.1 (7.4–21.2)	
Induction vs. not		.7836		.0689
Induction	8.6 (2.0–13.7)		27.5 (5.9–NR[b])	
No Induction	8.3 (5.7–11.6)		13.7 (8.7–14.5)	
Immunotherapy vs. not		.0706		.0126
Immunotherapy	11.3 (6.4–22.5)		41.7 (8.7-NR)	
No Immunotherapy	8.2 (5.7–9.2)		12.1 (8.4–14.4)	
Local therapy to mets		.4735		.4233
Local therapy	8.2 (6.3–13.7)		14.2 (7.4–58.9)	
No local therapy	8.7 (5.1–12.7)		14.1 (10.9–28.5)	
Single vs. multiple met lesions		.2593		.1787
Single	9.7 (7.1–12.7)		15.7 (13.7–42.7)	
Multiple	6.4 (2.7–13.7)		8.4 (4.4–21.2)	
Single vs. multiple organ systems		.2652		.0852
Single	8.7 (6.8–11.6)		14.4 (11.0–29.8)	
Multiple	5.7 (1.2–15.9)		6.9 (1.7–41.7)	
Single organ system		.9169		.709
Lung	9.2 (6.4–13.7)		17.9 (10.9–42.7)	
Liver	8.7 (NA[c])		13.9 (13.7–14.1)	
Bone	7.1 (2.7–34.4)		8.4 (3.8–58.9)	
Primary tumor origin		.0083		.5713
Oropharynx	9.2 (6.8–15.9)		13.7 (8.7–21.2)	
Hypopharynx/larynx	8.3 (5.7–12.7)		14.5 (7.4–60.6)	
Oral cavity	5.3 (2.3–5.7)		29.8 (3.5–30.3)	
HPV status		.4047		.9294
p16+ oropharynx tumor	13.1 (2.0–22.5)		15.7 (5.9–NR)	
Others	8.3 (5.7–11.3)		14.2 (10.9–29.8)	

[a]All numeric values for PFS and OS are in months.
[b]NR = not reached.
[c]NA = due to small number of patients CI was not able to be derived.

vs. chemoradiation). Eighteen (45%) patients received some form of local therapy (surgery or SABR) for metastatic disease. Fourteen of those 18 patients (77.7%) received local therapy to all known metastatic lesions, while four (22.2%) received local therapy to only some of the metastatic lesions. Comparison of PFS and OS between those that did or did not receive local therapy to metastatic lesions was nearly identical, with a median PFS of 8.2 months (95% CI, 6.3–13.7) versus 8.7 months (95% CI, 5.2–12.7) ($p = .4735$) and median OS of 14.2 (95% CI, 7.4–58.9) versus 14.1 months (95% CI, 10.9–27.5), respectively, $p = .4233$.

Eleven patients (28%) received induction chemotherapy. Induction chemotherapy was defined as any systemic therapy given prior to definitive local treatment to the primary disease in the head and neck. Induction therapy was platinum based with regimens shown in Table 1. The response rate to induction by RECIST 1.1 was 91% with one additional patient having stable disease. While PFS was similar (Supplemental Figure S1), those that received induction chemotherapy had a twofold increase in median OS (27.5 months (95% CI, 5.9-not reached) compared to 13.7 months (95% CI, 8.7–14.5), $p = .0689$), Figure 2. Eleven (28%) received immunotherapy with anti-PD-1monoclonal antibody during their treatment course. One patient received anti-PD-1 as part of induction and the other 10 patients received anti-PD-1 after progression with the indication being platinum failure. There was no significant difference in the PFS of those that received anti-PD-1 as part of their treatment course compared to those that did not (Figure 3A). There was a significant increase in OS in those patients that received anti-PD-1 as part of their treatment course with a median OS of 41.7 months (95% CI, 8.7-not reached)

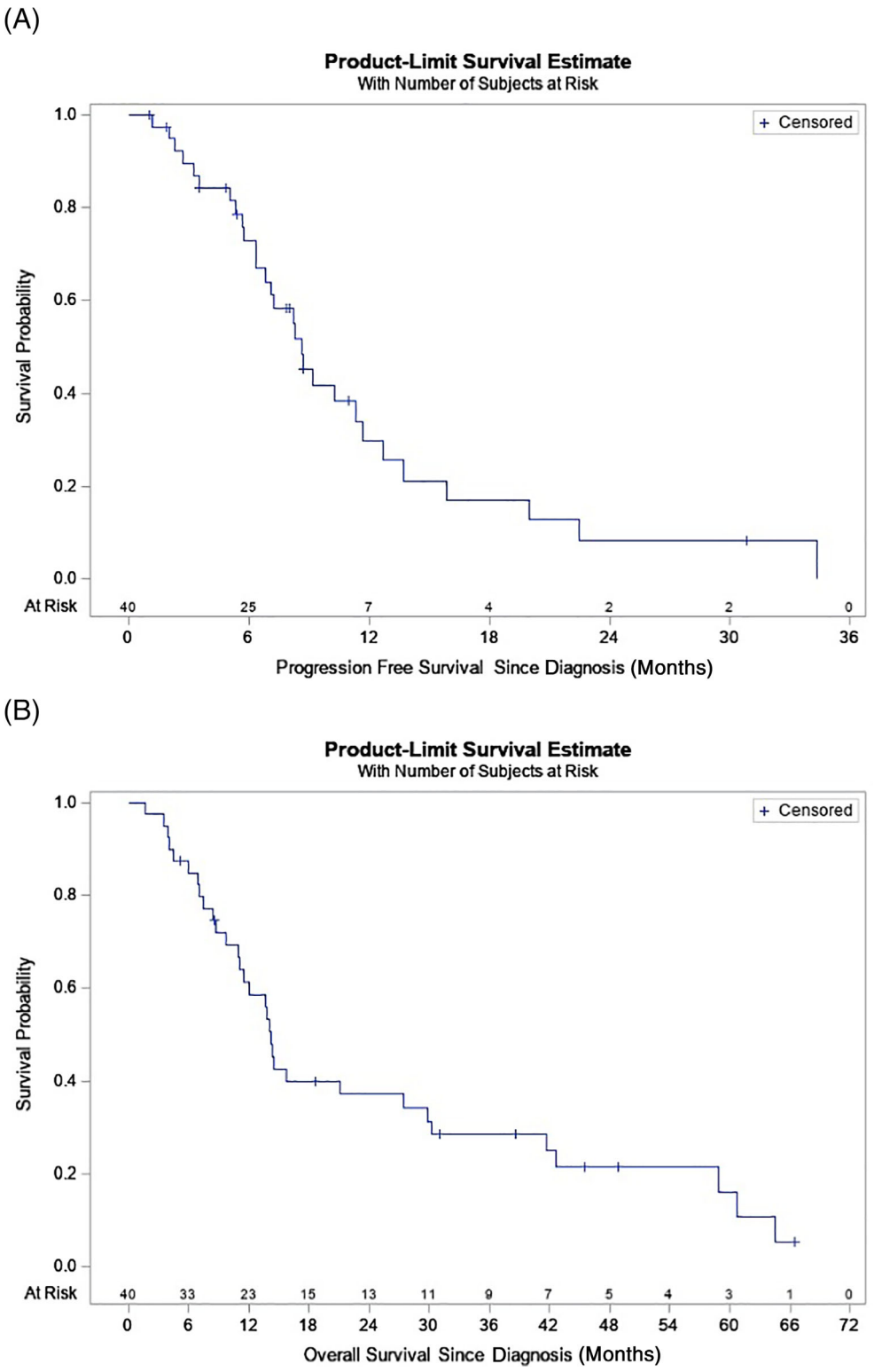

FIGURE 1 Survival outcomes for the total population. (A) Progression free survival. (B) Overall survival.

compared to 12.1 months (95% CI, 8.4–14.4), $p = .0126$ (Figure 3B). One patient received anti-PD-1 as part of induction with Cis/5FU and had a PFS of 22.8 months and OS of 69.3 months. For the 10 patients that received anti-PD-1 for platinum failure after progression the median PFS and OS after initiation of anti-PD-1 was 7.4 and 30.1 months, respectively. Eight out of the 10 patients that received anti-PD-1 for platinum failure did so because of distant only progression.

A multivariate analysis was conducted for PFS and OS. Treatment with immunotherapy was independently associated with improved OS (HR 3.123 [No IO vs. IO] [95% CI, 1.198–8.137], $p = .02$), as was age and one metastatic lesion versus multiple, while treatment with

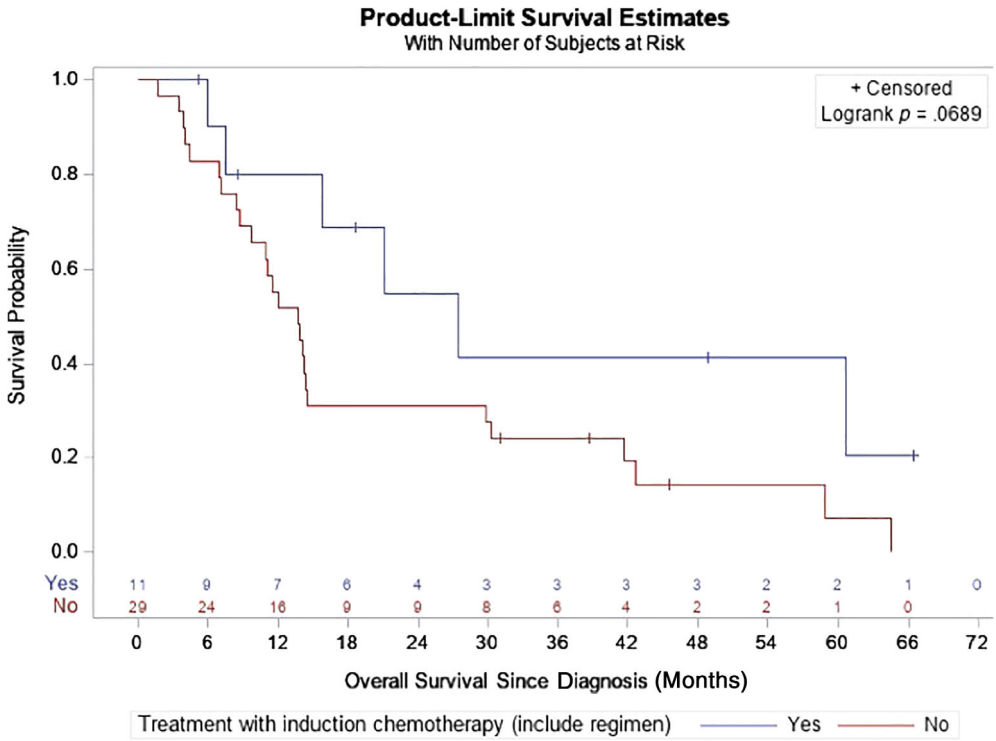

FIGURE 2 Overall survival for patients treated with induction therapy.

induction did not meet statistical significance (Table 3). Primary site was the only variable significantly associated with PFS in multivariate analysis (Supplemental Table S1).

4 | DISCUSSION

We retrospectively analyzed the efficacy of definitive local therapy to the head and neck given as part of treatment of non-nasopharyngeal HNSCC patients with distant metastasis at diagnosis. Our analysis showed a median PFS and OS for the entire cohort of 8.6 and 14.2 months, respectively. Treatment with immunotherapy with anti-PD-1 mAb as part of the treatment course was independently associated with improved OS with these patients having an impressive median OS of 41 months. To our knowledge, this is the first analysis that has evaluated the efficacy of treatment for patients with synchronous metastatic disease that included definitive local therapy to the primary site when immunotherapy was given during the treatment course.

This primary question driving this analysis was whether the addition of definitive local therapy to the primary site is better than systemic therapy alone. The patients included in our study spanned from 2003 to 2019, and while anti-PD-1 monoclonal antibody therapy was FDA approved only starting in 2016, the most appropriate historical control comparison is to the current frontline regimen of pembrolizumab +/− platinum and 5-fluorouracil based on the results of KEYNOTE 048.[4] The median PFS, which reflects only 1 anti-PD-1 treated patient, who received anti-PD-1 as part of induction, was higher in our population compared to Pembrolizumab monotherapy or combined with chemotherapy in KEYNOTE 048 (8.6 months vs. 2.3 months vs. 4.9 months, respectively), with comparable OS. Patients that did receive immunotherapy later in their treatment course in our cohort had a significantly higher median OS at 41 months, an OS over three times higher than chemotherapy plus pembrolizumab (median 13 months) or pembrolizumab monotherapy (median 11.5 months) in KEYNOTE 048. The aforementioned numeric comparisons are to the total population in KEYNOTE 048, as PD-L1 status of our patient population is unknown, but relative comparisons remain the same when considering the efficacy in PD-L1 expressing patients from KEYNOTE 048. Remarkably 39% of immunotherapy treated patients were still alive at 5 years and beyond in our cohort. Importantly, 10 out of 11 patients that received anti-PD-1 received it for platinum failure after initial progression of disease on their therapy that included the local definitive treatment. Notably, the median PFS and OS of anti-PD-1 mAb therapy in these patients were 7.4 and 30 months, respectively. Therefore, the patients in our cohort that received definitive local therapy as part of initial therapy then progressed and received anti-PD-1 had a greater than threefold increase in PFS and fourfold increase in OS with anti-PD-1 as compared to the reported efficacy of anti-PD-1 in the platinum failure setting from phase III trials.[2,3] This prolonged survival from anti-PD-1 mAb treatment may have been partially driven by local therapies lowering the overall burden of disease, including locoregional disease, with 80% of these patients receiving anti-PD-1 mAb therapy for distant only progression, as lower tumor volume has been associated with increased efficacy with anti-PD-1 mAb therapy.[11]

Patients that received induction therapy had an increase in median OS by 13.8 months compared to those that did not (27.5 vs. 13.7 months, respectively). This may be from early systemic therapy to control metastatic disease and subsequent biological selection

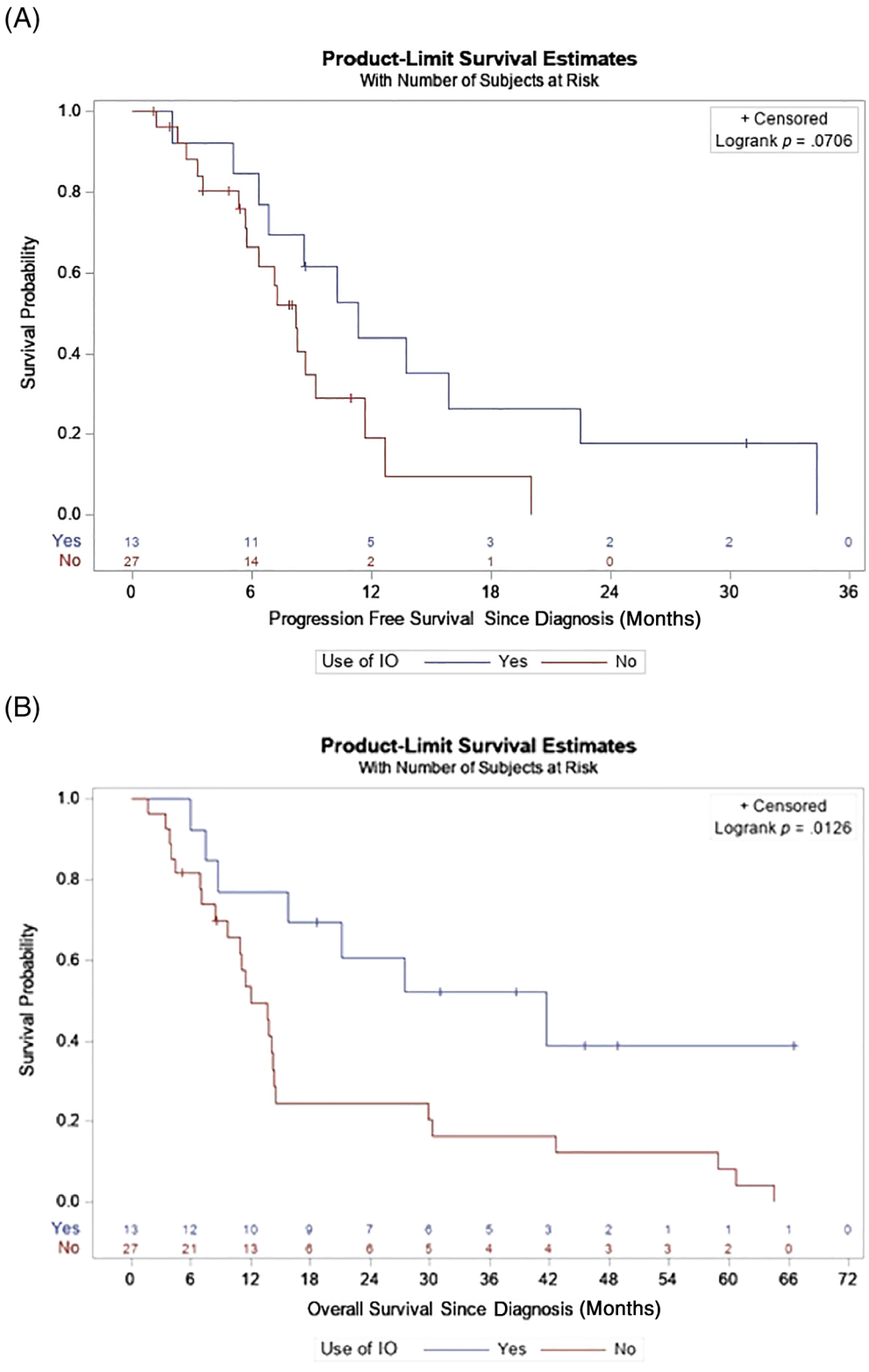

FIGURE 3 Survival outcomes for patients treatment with immunotherapy. (A) Progression free survival. (B) Overall survival.

TABLE 3 Multivariate analysis of overall survival.

Variable	Description	Hazard ratio	95% Wald confidence limits		*p*-Value
Age at diagnosis	Age	1.062	1.022	1.104	.0021
Treatment with immunotherapy (IO)	No IO vs. IO treatment	5.198	1.697	15.92	.0039
Number of metastatic lesions	More than one vs. one	3.912	1.597	9.583	.0028
Treatment with induction therapy	No induction vs. induction treatment	0.867	0.298	2.522	.7932

before transition to definitive local therapy. For example, definitive local therapy with chemoradiation therapy was independently associated with improved OS in nasopharyngeal carcinoma patients that achieved response or stable disease with induction.[11] As expected by the years examined in our study, the majority of immunotherapy treated patients received anti-PD-1 monoclonal antibody after progressing however in the patient that received it as part of induction therapy the median PFS and OS was 22.8 and 69.3 months, respectively. This highlights the therapeutic potential when anti-PD-1 monoclonal antibody therapy is given as part of initial induction therapy in these patients. Interestingly though, no improvement in outcomes were seen for patients that received therapy (radiation or surgery) to metastatic lesions, even though the majority (78%) of these patients had all of the metastatic lesions treated. This suggests that the improved outcomes in our cohort were more likely driven by definitive local treatment of the head and neck disease rather than to metastatic lesions. Analysis of HNSCC patients from other retrospective analysis have shown a significant OS benefit with the addition of definitive local therapy compared to systemic therapy alone in patients with synchronous metastatic disease.[12–14] Notably a national cancer database analysis showed that definitive local therapy to the primary site (>60 Gray of radiation) was significantly better than lower intensity local therapy (<60 Gray of radiation therapy), the latter having similar survival to systemic therapy alone, and this was independent of the number of distant metastasis. Greater benefit was seen in those patients that received early definitive therapy (within the first 6 months).[13] While improved outcomes with metastatectomy or SABR for oligometastatic disease in HNSCC have been observed,[15–17] these patients have mostly had metachronous metastasis and the contribution of concurrent local therapy to the disease in the head and neck has not been studied previously. Our data suggests that there may not be additional benefit to treating distant disease when the primary site is treated definitively, however further studies are needed to confirm this.

We acknowledge the limitations of our retrospective analysis at a single institution, including potential for selection bias. Our sample size of 40 limits our comparisons as well as our multivariate analysis and likely explains some of the lack of significant difference despite sizable improvement in PFS/OS for some of the categories examined. Another limitation is that patients included spanned 17 years, however we highlight that the majority of patients included were diagnosed in 2011–2019, and there was no difference in outcomes by diagnosis year. We acknowledge that 55% of our patients had only one metastatic lesion which may limit applicability of this approach to all patients with synchronous metastasis. There is a need to better understand the disease characteristics that would best predict who would benefit from this approach, especially given the morbidity associated with definitive treatment to the primary tumor. Additionally, 32% (13/40) of our patients had only one lung lesion with only 46% of these patients undergoing a biopsy, and three patients undergoing radiation or surgery to the one lung lesion. Seven out of these 13 patients were HPV negative of which three underwent biopsy consistent with SCC. While the lesions were pathologically and/or clinically favored to be metastatic disease, we cannot rule out a second primary NSCLC in all of these cases, that could have affected prognosis. That being said the median OS of the total population was still only 14.2 months.

5 | CONCLUSION

In summary, our analysis suggests the therapeutic potential of definitive treatment to the primary disease in the head and neck for select non-nasopharyngeal HNSCC patients with synchronous distant metastasis, when anti-PD-1 mAb therapy is also given as part of the treatment course. Further studies are needed including prospectively testing this approach with immunotherapy initiated earlier as part of induction systemic therapy, in an effort to improve outcomes for this subset of HNSCC patients.

CONFLICTS OF INTEREST

Dr. Robert L. Ferris, MD, PhD: Aduro Biotech, Inc: Consulting; AstraZeneca/MedImmune: Clinical Trial, Research Funding; Bristol-Myers Squibb: Advisory Board, Clinical Trial, Research Funding; EMD Serono: Advisory Board; MacroGenics, Inc.: Advisory Board; Merck: Advisory Board, Clinical Trial; Novasenta: Consulting, Stock, Research Funding; Numab Therapeutics AG: Advisory Board; Pfizer: Advisory Board; Tesaro: Research Funding. **Dr. Dan Zandberg, MD:** Research support (institutional) for role as principal investigator for clinical trials with Merck, Bristol Myers-Squibb, AstraZeneca, Aduro, ISA Therapeutics, Astelles, Glaxo Smith-Kline, and Regeneron. All other authors have no conflicts to disclose.

ORCID

Steven Borson https://orcid.org/0000-0002-7690-4087
Marci Lee Nilsen https://orcid.org/0000-0002-5888-668X
Mark Kubik https://orcid.org/0000-0002-8646-9920
Jonas T. Johnson https://orcid.org/0000-0002-2376-4594

REFERENCES

1. Szturz P, Vermoken JB. Management of recurrent and metastatic oral cavity cancer: raising the bar a step higher. *Oral Oncol*. 2020;101:104492.
2. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2016;375(19):1856-1867.
3. Cohen EEW, Soulières D, Le Tourneau C, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet*. 2019;393(10167):156-167.
4. Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet*. 2019;394(10212):1915-1928.
5. Gomez DR, Tang C, Zhang J, et al. Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol*. 2019;37(18):1558-1565.

6. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet*. 2019;393(10185):2051-2058.
7. Sutera P, Clump DA, Kalash R, et al. Initial results of a multicenter phase 2 trial of stereotactic ablative radiation therapy for oligometastatic cancer. *Int J Radiat Oncol Biol Phys*. 2019;103(1):116-122.
8. Pasalic D, Betancourt-Cuellar SL, Taku N, et al. Outcomes and toxicities following stereotactic ablative radiotherapy for pulmonary metastases in patients with primary head and neck cancer. *Head Neck*. 2020;42(8):1939-1953.
9. Bates JE, De Leo AN, Morris CG, Amdur RJ, Dagan R. Oligometastatic squamous cell carcinoma of the head and neck treated with stereotactic body ablative radiotherapy: single-institution outcomes. *Head Neck*. 2019;41(7):2309-2314.
10. Schulz D, Wirth M, Piontek G, et al. Improved overall survival in head and neck cancer patients after specific therapy of distant metastases. *Eur Arch Otorhinolaryngol*. 2018;275(5):1239-1247.
11. Joseph RW, Elassaiss-Schaap J, Kefford R, et al. Baseline tumor size is an independent prognostic factor for overall survival in patients with melanoma treated with pembrolizumab. *Clin Cancer Res*. 2018;24(20):4960-4967.
12. Zeng L, Tian YM, Huang Y, et al. Retrospective analysis of 234 nasopharyngeal carcinoma patients with distant metastasis at initial diagnosis: therapeutic approaches and prognostic factors. *PLoS One*. 2014;9(9):e108070.
13. Zumsteg ZS, Luu M, Yoshida EJ, et al. Combined high-intensity local treatment and systemic therapy in metastatic head and neck squamous cell carcinoma: an analysis of the National Cancer Data Base. *Cancer*. 2017;123(23):4583-4593.
14. Vengaloor Thomas T, Packianathan S, Bhanat E, et al. Oligometastatic head and neck cancer: comprehensive review. *Head Neck*. 2020;42(8):2194-2201.
15. Mazer TM, Robbins KT, McMurtrey MJ, Byers RM. Resection of pulmonary metastases from squamous carcinoma of the head and neck. *Am J Surg*. 1988;156(4):238-242.
16. Oki T, Hishida T, Yoshida J, et al. Survival and prognostic factors after pulmonary metastasectomy of head and neck cancer: what are the clinically informative prognostic indicators? *Eur J Cardiothorac Surg*. 2019;55(5):942-947.
17. Dohopolski MJ, Horne Z, Clump D, Burton SA, Heron DE. Stereotactic body radiation therapy for pulmonary oligometastases arising from non-lung primaries in patients without extrapulmonary disease. *Cureus*. 2018;10(2):e2167.

SUPPORTING INFORMATION

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