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ORIGINAL ARTICLE

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Examining the relationship of immunotherapy and wound complications following flap reconstruction in patients with head and neck cancer

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Abstract

Background: Immunotherapy agents are used to treat advanced head and neck lesions. We aim to elucidate relationship between immunotherapy and surgical wound complications.

Methods: Retrospective multi-institutional case series evaluating patients undergoing ablative and flap reconstructive surgery and immunotherapy treatment. Main outcome: wound complications.

Results: Eight-two (62%) patients received preoperative therapy, 89 (67%) postoperative, and 33 (25%) in both settings. Forty-one (31%) patients had

recipient site complications, 12 (9%) had donor site. Nineteen (14%) had major recipient site complications, 22 (17%) had minor. There was no statistically significant difference in complications based on patient or tumor-specific variables. Preoperative therapy alone demonstrated increased major complications (odds ratio [OR] 3.7, $p = 0.04$), and trend to more donor site complications (OR 7.4, $p = 0.06$), however treatment in both preoperative and postoperative therapy was not.

Conclusions: Preoperative immunotherapy may be associated with increased wound complications. Controlled studies are necessary to delineate this association and potential risks of therapy.

KEYWORDS

free flap reconstruction, head and neck cancer, immunotherapy, wound complications

1 | INTRODUCTION

Although the history of immunotherapy dates back to antiquity, the field as we know it has experienced a boom in the 21st century. Within the past decade, agents such as ipilimumab (2011) and nivolumab (2014) received FDA approval for targeted immunotherapy of advanced melanoma, and in 2019 pembrolizumab was approved for the treatment of metastatic or locally advanced head and neck squamous cell carcinoma.[1] While today the use of immunotherapy is most commonly in the setting of clinical trials, it has growing indications within the field of head and neck cancer surgery.[2] Studies are ongoing to demonstrate its use as a standard. Wound healing complications have been described with use of bevacizumab, an anti-VEGF monoclonal antibody, which was first used for treatment of metastatic colon cancer[3,4]; however, there are few published studies which investigate impaired wound healing complications with targeted therapeutic agents used in the treatment of head and neck cancers, such as anti-PD1 therapy in squamous cell carcinoma.[5]

For head and neck cancers, oncologic ablative surgery is often paired with extensive reconstruction including pedicled and free tissue transfer in order to achieve acceptable functional and esthetic results. Here we seek to further elucidate if there is a relationship between delayed wound healing or other postoperative complications in patients with head and neck cancer treated with targeted immunotherapy either in a neoadjuvant or adjuvant setting who undergo oncologic resection and flap reconstruction.

2 | MATERIALS AND METHODS

This multi-institutional retrospective chart review was performed after Institutional Review Board approval at each individual institution, with data collected and stored at the study home base Louisiana State University School of Medicine – Otolaryngology, New Orleans, LA. Medical records of patients with head and neck cancer having undergone surgical ablation with a pedicled or free flap reconstruction and also having been treated with targeted immunotherapies in the preoperative or postoperative periods between 2016 and 2019 were included. Inclusion of patients with benign tumors was allowed as long as immunotherapy was dosed and surgical type fell in line with our criteria. Patients with follow-up less than 1 year, or management outside home institution without access to outcomes were excluded. Data points collected include demographic information (age, sex, comorbidities), tumor-specific information (diagnosis with tumor staging, history of prior chemoradiation, etc.), treatment-specific information (ablative and reconstruction type, pre/postoperative chemoradiation, and timing), and immunotherapy data (agent and timing) were collected. Outcomes variables were recipient and donor site complications, and subsequent treatments required. Wound complications were also categorized as major (invasive surgical procedure) or minor (local wound care, medical therapy such as antibiotics, or noninvasive surgical procedure). Patients with and without complications were included. Historical control complication rates were gathered from Pubmed literature search of studies that included similar patients that did not receive targeted immunotherapy. Recipient and/or donor site complication rates from studies with comparable ratings systems to our own were pooled and averaged for each presented rate.

For all statistical analyses, we used R.[6] For testing associations in the current study, odds ratios were calculated with logistic regression, not adjusted for any other factors, and p-values for categorical covariates with more

TABLE 1 Patient demographics and treatment profile

Variable	No. of patients (%)
Age	
62 years, SD 12	132
Sex	
Female	36 (27)
Male	96 (73)
Alcohol use	63 (48)
Tobacco use	
Former	55 (42)
Current	36 (27)
Never	41 (31)
Diabetes mellitus	26 (20)
Steroid use	8 (6)
Charlson Comorbidity Index	
2–4	72 (55)
5–7	50 (37)
8–11	10 (8)
Tumor variables	
Tumor subsite	
Oral cavity	73 (55)
Skin	20 (15)
Larynx	20 (15)
Oropharynx	10 (8)
Sinonasal	4 (3)
Skull base	2 (2)
Endocrine	1 (1)
Salivary (parotid)	1 (1)
Unknown primary	1 (1)
Histology	
Squamous cell carcinoma	116 (88)
Melanoma	9 (7)
Benign – osteoradionecrosis	2 (2)
Merkel cell carcinoma	1 (1)
Anaplastic thyroid	1 (1)
Basal cell carcinoma	1 (1)
Mucoepidermoid carcinoma	1 (1)
Meningioma	1 (1)
T classification	
1	7 (6)
2	16 (13)
3	27 (22)
4	73 (59)
N classification	
0	39 (31)
1	14 (11)
2	59 (47)
3	14 (11)
Disease status	
Primary	83 (63)
Recurrent	31 (23)
Persistent	18 (14)
Treatment variables	
Preoperative radiation	41 (31)
Preoperative chemotherapy[a]	29 (22)
Platinum	28 (21)
5-FU	3 (2)
Docetaxel	2 (2)
Preoperative immunotherapy	82 (62)
Pembrolivumab	59 (45)
Nivolumab	5 (4)
Cetuximab	5 (4)
Panitumulab	5 (4)
Cemiplimab	2 (2)
Ipilimumab	2 (2)
Avelumab	1 (1)
Lenvatinib	1 (1)
Sonidegib	1 (1)
Vismodegib	1 (1)
Clinical trial randomization[b]	10 (8)
Indication for preoperative immunotherapy	
Clinical trial/randomized controlled trial	60 (73)
Recurrent disease	14 (17)
Distant metastases	4 (5)
Neoadjuvant therapy	3 (4)
Dermal metastases	1 (1)
Free flap reconstruction	124 (94)
Anterolateral thigh	52 (42)
Radial forearm	37 (30)
Fibula	22 (18)
Latissimus	6 (5)
Rectus	5 (4)
Scapula	4 (3)
Ulnar artery perforator	2 (2)

(Continues)

(Continues)

TABLE 1 (Continued)

Variable	No. of patients (%)
Medial sural artery perforator	1 (1)
Local/regional flap	9 (7)
Postoperative radiation	90 (68)
Postoperative chemotherapy[a]	47 (36)
Platinum	44 (33)
Doxetaxel	3 (2)
5-FU	2 (2)
Doxorubicin	1 (1)
Postoperative immunotherapy[a]	89 (67)
Pembrolivumab	66 (50)
Nivolumab	8 (6)
Cetuximab	6 (5)
Panitumumab	6 (5)
Ipilimumab	2 (2)
Talimogene laherparepvec	1 (1)
Avelumab	1 (1)
Trametinib	1 (1)
Cemiplimab	1 (1)
Everolimus	1 (1)
Dabrafenib	1 (1)
Sorafenib	1 (1)
Dabrafenib	1 (1)
Indication for postoperative immunotherapy	
Clinical trial/randomized controlled trial	23 (26)
Recurrent disease	21 (24)
Unresectable disease	14 (16)
High risk features on path	13 (15)
Persistent disease	7 (8)
Distant metastases	6 (7)
Patient choice	2 (2)

[a]Some patients received more than one treatment (i.e., drug, flap).
[b]Due to randomization, treatment group or placebo unknown.

than two levels were calculated with chi-square tests. All tests were conducted at a nominal significance level of 0.05. Tests of this kind included four different outcomes with 13 covariates, for a total of 52 significance tests. When comparing results in the current study against historical complication rates, we assumed the historical rates to be correct and tested for deviations from these rates. We used chi-square tests for these comparisons, at a nominal significance level of 0.05.

3 | RESULTS

One hundred thirty-two patients were included across all head and neck subsites. Mean age was 62 years (SD 12 years). Oral cavity was the most common subsite ($n = 73$, 55%) and squamous cell carcinoma the most common histology ($n = 116$, 88%). Eighty-one percent patients were advanced stage (T3-4) and 61% were treated as new primary cancers. Table 1 details patient demographic information and treatment data.

One hundred twenty-four (94%) patients underwent free flap reconstruction after ablative resection. Forty-one (31%) patients had preoperative radiotherapy. Eighty-two (62%) patients received preoperative targeted therapy, with pembrolizumab being the most common preoperative agent ($n = 59$, 45%). Ten patients were treated in a blinded clinical trial with a treatment: placebo ratio of 4:1. The most common indication for receiving preoperative immunotherapy was clinical trial participation (73%). The average time of discontinuation of drug prior to surgery was 19.5 days.

Eighty-nine (67%) received postoperative targeted therapy with pembrolizumab being the most common postoperative agent ($n = 66$, 50%). The most common indication for receiving postoperative immunotherapy was clinical trial participation (26%). Average time of initiation of drug after surgery was 173 days. Thirty-three (25%) patients received immunotherapy both preoperatively and postoperatively.

3.1 | Wound complications

Table 2 details the recipient and donor wound complications. Forty-one (31%) patients had recipient site complications, 12 (9%) had donor site complications. Nineteen (14%) had major complications requiring invasive surgery for treatment (all in the recipient site), 22 (17%) had minor complications requiring local or medical therapy.

3.2 | Outcome comparisons

Table 3 details analyses comparing treatment variables to primary outcomes. There were no statistically significant differences in wound complication profile based on patient-specific variables (Charlson comorbidity status, tobacco/alcohol use, history of diabetes, and steroids) or tumor-specific variables (stage, prior chemotherapy). Preoperative radiation history was associated with worse donor site complications (odds ratio [OR] 5.5, $p = 0.01$) but not recipient site complications. Those treated for

TABLE 2 Wound complication profile

Variable	No. of patients (%)
Recipient site wound complication[a]	41 (31)
Wound dehiscence	14 (11)
Fistula	13 (10)
Hematoma/Seroma	6 (5)
Infection/cellulitis	5 (4)
Major flap complication	4 (3)
Donor site wound complications[a]	12 (9)
Hematoma/Seroma	6 (5)
Wound dehiscence	5 (4)
Delayed wound healing	3 (2)
Wound treatment	49 (37)
Local wound care	21 (16)
Minor surgical procedure	9 (7)
Major surgical procedure	6 (5)
Antibiotics	5 (4)
Overall wound complication class	
None	91 (69)
Minor	22 (17)
Major	19 (14)

[a]Some patients had more than one complication.

recurrent disease were more likely to experience recipient site complications as compared to those treated for persistent disease ($p = 0.05$, OR 5). Those patients treated with preoperative immunotherapy for both recurrent disease and distant metastases experienced worse donor site complications than those receiving no therapy (OR 31, $p = 0.003$ and OR 50, $p = 0.006$, respectively). Immunotherapy treatment in both the preoperative and postoperative settings was not associated with an increase in wound complications. Patients receiving preoperative immunotherapy demonstrated increased likelihood of major complications (OR 3.7, $p = 0.04$), trend to more donor site complications (OR 7, $p = 0.06$), and increased need for treatment of wound complications (OR 2.9, $p = 0.008$).

3.3 | Historical control comparison

Tables 4 and 5 detail our patient sample (treatment group) comparison to historical controls. When compared to historical controls based on tumor subsite and reconstructive type, complication rates of the treatment group were not statistically different. However, in looking at only those receiving preoperative immunotherapy, there was a statistically significant difference between patients treated with drug and the historical controls based on subsite ($p = 0.001$). Directionality was unable to be determined as individual variables did not meet statistical significance, except for the skin/scalp subsite that demonstrated a statistically significant increase in recipient site complications ($p = 0.005$).

4 | DISCUSSION

Targeted immunotherapy has demonstrated efficacy in the treatment of unresectable and metastatic head and neck squamous cell carcinoma. The Checkmate 141 study reported longer overall survival in patients receiving nivolumab for platinum-refractory recurrent and metastatic head and neck squamous cell carcinoma.[7] Further studies have indicated improved efficacy in patients selected by tumor PD-L1 expression.[8] More recently in the setting of clinical trials, immunotherapy has been used in the neoadjuvant setting prior to surgical resection, and data are limited regarding the safety of these treatments with regards to wound healing and surgery-related outcomes. Data are particularly sparse regarding the outcomes of complex reconstructive procedures with microvascular free flaps, specifically when performed in the salvage setting after ongoing immunotherapy.

Outcomes for patients with malignant melanoma undergoing surgery during ongoing immunotherapy provide some insight on safety. Multiple series have indicated improved overall survival when complete resection of persistent or oligoprogressive lesions is accomplished, although these studies do not report on perioperative and wound outcomes.[9-11] Sun and colleagues report 29 patients who underwent surgery for melanoma after neoadjuvant immunotherapy regimens, achieving a low rate of complications with four minor wound infections and one hematoma requiring intervention.[12] The procedures ranged from lymphadenectomy alone, to radical resections with or without skin graft reconstructions, but none included microvascular reconstruction. Additional data have found only minor perioperative complications related to immunotherapy usage in both melanoma and other histopathologies.[13] Similar results on treatment-related adverse events affecting surgical safety with neoadjuvant nivolumab for Merkel cell carcinoma are reported.[14] Although these studies indicate the feasibility, utility, and relative safety of surgery in patients receiving immunotherapy, wound outcomes in those undergoing complex reconstructive efforts are not well reported.

The effects of targeted immunotherapy on the inflammatory cascade are well studied. There is evidence that

TABLE 3 Primary outcome to treatment variable comparison

Variable	Estimate	SE	*p* value	Odds ratio
Recipient site complications				
Tobacco use			0.59	
Never				
Former	0.67	0.45	0.13	2.0
Current	−0.42	0.55	0.45	0.66
Diabetes mellitus	−0.25	0.49	0.61	0.78
Steroid use	−16.9	1399	0.99	<0.001
Charlson Comorbidity Index	0.10	0.10	0.35	1.1
Tumor subsite			0.48	
Disease status			0.09	
Recurrent				
Persistent	−1.6	0.84	**0.05**	0.20
Primary	−0.27	0.44	0.54	0.76
Preoperative radiation	0.20	0.40	0.61	1.2
Preoperative targeted therapy	0.50	0.40	0.21	1.6
Indication preoperative targeted therapy			0.46	
Postoperative radiation	−0.47	0.40	0.23	0.63
Postoperative targeted therapy	0.06	0.40	0.89	1.1
Indication postoperative targeted therapy			0.80	
When was targeted therapy given			0.07	
Preoperative				
Postoperative	−0.49	0.48	0.31	0.61
Both	0.61	0.49	0.21	1.8
Randomized	1.3	0.98	0.20	3.7
Donor site complications				
Tobacco use			0.21	
Never				
Former	0.30	0.66	0.65	1.3
Current	−1.3	1.1	0.24	0.27
Diabetes mellitus	0.34	0.71	0.63	1.4
Steroid use	0.38	1.1	0.73	1.5
Charlson Comorbidity Index	0.27	0.16	0.08	1.3
Tumor subsite			0.81	
Disease status			0.06	
Recurrent				
Persistent	−0.65	0.88	0.45	0.52
Primary	−1.6	0.69	**0.02**	0.20
Preoperative radiation	1.7	0.65	**0.01**	5.5
Preoperative targeted therapy	2.0	1.1	0.06	7.4
Indication preoperative targeted therapy			**0.0005**	
Recurrent disease	3.4	1.2	**0.003**	31.3
Distant metastases	3.9	1.4	**0.006**	50.0

TABLE 3 (Continued)

Variable	Estimate	SE	*p* value	Odds ratio
Postoperative radiation	−2.1	0.70	**0.003**	0.12
Postoperative targeted therapy	−0.81	0.61	0.19	0.44
Indication postoperative targeted therapy			0.54	
When was targeted therapy given			0.23	
Preoperative				
Postoperative	−1.5	0.85	0.08	0.22
Both	−0.60	0.75	0.422	0.55
Randomized	0.35	1.2	0.77	1.4
Required treatment for wound complications				
Tobacco use			0.59	
Never				
Former	0.44	0.43	0.31	1.55
Current	0.20	0.48	0.68	1.22
Diabetes mellitus	0.27	0.45	0.54	1.31
Steroid use	−1.5	1.1	0.17	0.22
Charlson Comorbidity Index	−0.04	0.11	0.70	0.96
Tumor subsite			0.49	
Disease status			0.35	
Recurrent				
Persistent	−0.79	0.68	0.24	0.45
Primary	0.04	0.43	0.92	1.04
Preoperative radiation	−0.19	0.39	0.64	0.83
Preoperative targeted therapy	1.07	0.41	**0.008**	2.9
Indication preoperative targeted therapy			0.11	
Postoperative radiation	−0.21	0.38	0.59	0.81
Postoperative targeted therapy	−0.44	0.38	0.24	0.64
Indication postoperative targeted therapy			**0.03**	
When was targeted therapy given			**0.06**	
Preoperative				
Postoperative	−0.72	0.45	0.11	0.49
Both	0.41	0.47	0.39	3.0
Randomized	0.81	0.97	0.40	0.54
Complication class – major versus minor/none				
Tobacco use			**0.03**	
Never				
Former	1.1	0.61	0.08	3.0
Current	−0.61	0.90	0.50	0.54
Diabetes mellitus	0.45	0.57	0.44	1.6
Steroid use	−15.9	1399	0.99	<0.001
Charlson Comorbidity Index	0.03	0.14	0.84	1.0
Tumor subsite			0.96	

(Continues)

TABLE 3 (Continued)

Variable	Estimate	SE	*p* value	Odds ratio
Disease status			0.03	
Recurrent				
Persistent	−17.3	1537	0.99	<0.001
Primary	−0.55	0.53	0.30	0.58
Preoperative radiation	−0.27	0.56	0.63	0.76
Preoperative targeted therapy	1.3	0.66	**0.048**	3.7
Indication preoperative targeted therapy			0.27	
Postoperative radiation	0.01	0.53	0.98	1.0
Postoperative targeted therapy	−0.74	0.50	0.14	0.48
Indication postoperative targeted therapy			0.79	
When was targeted therapy given			0.09	
Preoperative				
Postoperative	−1.6	0.70	**0.03**	0.20
Both	−0.30	0.59	0.61	0.74
Randomized	−0.15	1.2	0.90	0.86

Note: The significant values ($p > .05$) are marked in bold.

TABLE 4 Recipient site complications versus historical control group by subsite – subgroup for preoperative targeted therapy alone

Subsite	Historical control complication rate (%)	Treatment group complication rate (%)	Treatment group, no. of patients	*p* value
Full treatment group				0.17
Skin/scalp[23,24]	8.5	20	20	
Sinonasal/maxilla[25]	24	25	4	
Oral cavity[26-28]	23	33	73	
Oropharynx[29]	21	30	10	
Larynx[30]	31	40	20	
Skull base[31-33]	18	0	2	
Preoperative targeted therapy				0.001
Skin/scalp	8.5	44	9	0.005
Sinonasal/maxilla	24	0	2	
Oral cavity	23	33	51	
Oropharynx	21	20	5	
Larynx	31	47	15	

immunotherapy agents against PD-1 can relieve postoperative T-cell dysfunction and can mitigate the immunosuppressive effects of the perioperative state.[15] The prevention of the iatrogenic immunosuppression and potential tumor progression is considered a potential window of opportunity for the use of targeted immunotherapy. As such, there is a trend toward the study of neoadjuvant immunotherapy given the purported benefits of reduction of the extent of surgery, reduction in intensity of adjuvant therapy, and reduction of the risk of distant metastatic disease.[16] Previous phase II studies of targeted systemic therapies such as trametinib have indicated the wound-related and surgical safety, with no wound issues related to the study drug.[17] In this report a single free flap failure was ascribed to technical and geometric issues related to the surgery rather than the neoadjuvant regimen. More recent studies of patients undergoing oral cancer resection within days of a neoadjuvant nivolumab regimen have been reported.[18] Here, 28 patients went on to surgery with one patient death

TABLE 5 Donor site complications versus historical control by flap type – subgroup for preoperative targeted therapy alone

Flap type	Historical control complication rate (%)	Treatment group complication rate (%)	Treatment group, no. of patients	*p* value
Full treatment group				0.36
Radial forearm[34-36]	8.3	2.7	37	
Ulnar artery perforator[35]	4	0	2	
Fibula[27,37]	27	27	22	
Anterolateral thigh[27,31,38]	10	5.8	52	
Latissimus[39-41]	30	33	6	
Rectus[42]	3.7	20	5	
Scapula[43,44]	25	0	4	
Preoperative targeted therapy				0.36
Radial forearm	8.3	4.5	22	
Fibula	27	33	15	
Anterolateral thigh	10	9.4	32	
Latissimus	30	50	4	
Rectus	3.7	20	5	
Scapula	25	0	4	

reported in the postoperative phase with reported free flap failure and stroke. The authors suggest this was unrelated to the study treatment, and no other wound or surgical issues are reported.

Our study reports the wound outcomes at both the reconstructed recipient site as well as the flap donor site. Our data did indicate worse recipient site complications in the setting of recurrent disease, compared to persistent or primary tumors. Overall, those who receive preoperative immunotherapy were found to have overall worse outcomes in multiple parameters. They were more likely to develop major complications requiring invasive surgical treatment (OR 3.7, $p = 0.048$) and were more likely to have donor site complications (OR 7.4), a finding which trends toward but does not reach statistical significance ($p = 0.06$). In particular, those treated in the preoperative setting for indications of recurrent disease or distant metastases were more likely to develop donor site complications than those who receive no treatment (OR 31, $p = 0.003$ and 50, $p = 0.006$, respectively). Furthermore, those that received preoperative immunotherapy were more likely to require any type of treatment for complications (OR 2.9, $p = 0.008$).

We found that total drug exposure, that is, comparing preoperative administration alone to combined preoperative and postoperative treatment, was not significantly related to adverse wound healing outcomes. In addition, the use of postoperative immunotherapy alone did not affect either donor or recipient site healing. These findings suggest that preoperative immunotherapy exposure may be a detriment to wound healing. It is important to point out that the mean time for preoperative treatment cessation prior to surgery was 19 days versus a mean time to initiation of treatment in the postoperative setting was 173 days. Typically healing should have occurred by this period, raising the possibility that the lessened wound complications may be due to time of administration versus actual drug therapy. However, we must acknowledge the clear increase in complications of those treated in the preoperative setting alone compared to those treated in both settings. Furthermore, our comparisons to the historical controls corroborate our theory that preoperative immunotherapy may affect wound healing. Study patients who received preoperative immunotherapy fared worse than the historical controls (never treated with immunotherapy) with regards to recipient site wound complications, specifically for cutaneous and scalp reconstruction ($p = 0.005$), whereas there was no significant difference in the overall study cohort compared to the historical controls. The apparent minimal impact of postoperative immunotherapy may be due to withholding drug administration until total or near-total wound healing has taken place.

Many patients who receive immunotherapy have undergone prior radiotherapy either in the definitive or adjuvant settings. The relationship between these combined modalities and the effect on tissues is not well known. In a small series of patients with head and neck cancer, Hwang and colleagues report two patients with mandible osteonecrosis, occurring after 14 and 41 doses

of checkpoint inhibitor therapy.[5] Both instances occurred within radiation fields provided for tumors outside of the oral cavity. Another patient developed frontal bone and anterior skull base necrosis after prior chemoradiotherapy and 25 doses of checkpoint inhibitor therapy for maxillary sinus cancer. Studies of melanoma patients have indicated an increased risk of developing brain radionecrosis in those receiving whole-brain or stereotactic cerebral radiation within 1 year of initiating check-point inhibitor therapy, although this finding may be confounded by prolonged survival in these patients leading to an increased incidence of cerebral radionecrosis.[19]

Although not definitive, these above reports suggest a pattern of wound issues within previously radiated fields. This was not corroborated in our study as there was no increase in recipient site wound issues in patients who have been exposed to preoperative radiotherapy. Our data are in keeping with multiple large studies which do not find increased infection or wound complications after head and neck reconstruction in the radiated field.[20-22] This is likely due to contemporary surgical techniques designed to address the changes in tissue quality after radiotherapy. However, we did find that patients who have had preoperative radiotherapy had a higher rate of donor site complications (OR 5.5, $p = 0.01$). This cannot be due to tissue changes created by the radiation itself, of course, but may be related to a decline in functional status and increased frailty after prior cancer treatments. Such conclusions may be better delineated in future prospective studies.

There are a number of inherent weaknesses of our study. As a retrospective study without a true matched case–control group of patients untreated by immunotherapy to compare to our treatment cohort, a causal relationship between targeted therapy and complications cannot be inferred. As the use of immunotherapy in the head and neck population is recent, less recent studies examining wound complications in this population served as our surrogate. Future studies will include a case matched control group for robust comparison. Also, there is potential bias in that patients receiving immunotherapy may potentially represent a more advanced patient cohort with more risk of complications compared to controls that did not receive therapy. Given our findings, further prospective matched case–control studies are warranted.

5 | CONCLUSION

Although our wound complication rates in these complex ablative and reconstructive cases is largely in line with prior studies in those not treated with immunotherapy, our findings do suggest that timing of drug administration in the preoperative setting portends to wound complications at the recipient and donor surgical sites. These data suggest a thoughtful review of optimal timing and timeframe of drug cessation prior to surgery is imperative. As targeted immunotherapy becomes more a part of the head and neck cancer treatment standard, controlled prospective studies are warranted to assess acute and long-term consequences of therapy in surgical patients.

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DATA AVAILABILITY STATEMENT

Author elects to not share data

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