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Title page

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

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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 pre-operative therapy, 89 (67%) post-operative, 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. Pre-operative therapy alone demonstrated increased major complications (OR 3.7, p=0.04), and trend to more donor site complications (OR 7.4, p=0.06), however treatment in both pre- and post-operative therapy was not.

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

Introduction

Though 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 post-operative 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.

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, Louisiana. Medical records of head and neck cancer patients having undergone surgical ablation with a pedicled or free flap reconstruction and also having been treated with targeted immunotherapies in the pre-or post-operative periods between 2016-2019 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, gender, comorbidities), tumor specific information (diagnosis with tumor staging, history of prior chemoradiation, etc), treatment specific information (ablative and reconstruction type, pre/post operative 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 non-invasive 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 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 4 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.

Results

One hundred thirty-two (132) patients were included across all head and neck subsites. Mean age was 62 years (standard deviation, 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 (81%) 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 pre-operative radiotherapy. Eighty-two (62%) patients received pre-operative targeted therapy, with pembrolizumab being the most common pre-operative 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 pre-operative immunotherapy was clinical trial participation (73%). The average time of discontinuation of drug prior to surgery was 19.5 days.

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

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.

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). Pre-operative 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 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 pre-operative 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 pre- and post-

operative settings was not associated with an increase in wound complications. Patients receiving pre-operative 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).

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 pre-operative 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.

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 is 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 peri-operative 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]. Though 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 immunotherapy agents against PD-1 can relieve postoperative T-cell dysfunction and can mitigate the immunosuppressive effects of the peri-operative 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 reported in the post-operative 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 pre-operative 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 towards but does not reach statistical significance ($p = 0.06$). In particular, those treated in the pre-operative 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). Further, those that received pre-operative 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 pre-operative administration alone to combined pre- and post-operative treatment, was not significantly related to adverse wound

healing outcomes. In addition, the use of post-operative immunotherapy alone did not affect either donor or recipient site healing. These findings suggest that pre-operative immunotherapy exposure may be a detriment to wound healing. It is important to point out that the mean time for pre-operative treatment cessation prior to surgery was 19 days versus a mean time to initiation of treatment in the post-operative 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 pre-operative setting alone compared to those treated in both settings. Further our comparisons to the historical controls corroborate our theory that pre-operative immunotherapy may affect wound healing. Study patients who received pre-operative 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 post-operative 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 one 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 pre-operative radiotherapy. Our data is 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 pre-operative 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.

Conclusion

Though 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 pre-operative setting portends to wound complications at the recipient and donor surgical sites. This data suggests 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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Tables

Table 1. Patient demographics and treatment profile.

Variable	No. of patients	%
Age 62yrs SD 12	132	
Gender		
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		
Pre-operative radiation	41	31
Pre-operative chemotherapy[1]	29	22
Platinum	28	21
5-FU	3	2
Docetaxel	2	2
Pre-operative 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[2]	10	8
Indication for Pre-operative 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

Medial sural artery perforator	1	1
Local/regional flap	9	7
Post-operative radiation	90	68
Post-operative chemotherapy[1]	47	36
Platinum	44	33
Doxetaxel	3	2
5-FU	2	2
Doxorubicin	1	1
Post-operative immunotherapy[1]	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 Post-operative 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

[1]Some patients received more than one treatment (ie drug, flap)
[2]Due to randomization, treatment group or placebo unknown

Table 2. Wound complication profile.

Variable	No. of patients	%
Recipient site wound complication[1]	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[1]	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

[1]Some patients had more than one complication

Table 3. Primary outcome to treatment variable comparison

Variable	Estimate	Standard error	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
Pre-Operative Radiation	0.20	0.40	0.61	1.2
Pre-Operative Targeted therapy	0.50	0.40	0.21	1.6
Indication Pre-Operative Targeted therapy			0.46	
Post-operative radiation	-0.47	0.40	0.23	0.63
Post-Operative Targeted therapy	0.06	0.40	0.89	1.1
Indication Post-Operative Targeted therapy			0.80	
When was targeted therapy given			0.07	
Pre-operative				
Post-operative	-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
Pre-Operative Radiation	1.7	0.65	**0.01**	5.5
Pre-Operative Targeted therapy	2.0	1.1	0.06	7.4

Indication Pre-Operative Targeted therapy			**0.0005**	
Recurrent disease	3.4	1.2	**0.003**	31.3
Distant metastases	3.9	1.4	**0.006**	50.0
Post-operative radiation	-2.1	0.70	**0.003**	0.12
Post-Operative Targeted therapy	-0.81	0.61	0.19	0.44
Indication Post-Operative Targeted therapy			0.54	
When was targeted therapy given			0.23	
Pre-operative				
Post-operative	-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
Pre-Operative Radiation	-0.19	0.39	0.64	0.83
Pre-Operative Targeted therapy	1.07	0.41	**0.008**	2.9
Indication Pre-Operative Targeted therapy			0.11	
Post-operative radiation	-0.21	0.38	0.59	0.81
Post-Operative Targeted therapy	-0.44	0.38	0.24	0.64
Indication Post-Operative Targeted therapy			**0.03**	
When was targeted therapy given			**0.06**	
Pre-operative				
Post-operative	-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	
Disease Status			0.03	
Recurrent				
Persistent	-17.3	1537	0.99	<0.001
Primary	-0.55	0.53	0.30	0.58
Pre-Operative Radiation	-0.27	0.56	0.63	0.76
Pre-Operative Targeted therapy	1.3	0.66	**0.048**	3.7
Indication Pre-Operative Targeted therapy			0.27	
Post-operative radiation	0.01	0.53	0.98	1.0
Post-Operative Targeted therapy	-0.74	0.50	0.14	0.48
Indication Post-Operative Targeted therapy			0.79	
When was targeted therapy given			0.09	
Pre-operative				
Post-operative	-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

Table 4. Recipient site complications versus historical control group by subsite – subgroup for pre-operative 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	
Pre-operative 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	

Table 5. Donor site complications versus historical control by flap type - subgroup for pre-operative 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[37]	4	0	2	
Fibula[38-39]	27	27	22	
Anterolateral thigh[40-42]	10	5.8	52	
Latissimus[43-45]	30	33	6	
Rectus[46]	3.7	20	5	
Scapula[47,48]	25	0	4	
Pre-operative 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	