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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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From the *Head and Neck*. May 2021

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.

Summary statements

- Use of immunotherapeutic agents are becoming more popular in the setting of locally advanced and metastatic head and neck SCC.
- Wound healing issues have been previously noted with the use of other immunotherapeutic agents, but few in the context of microvascular reconstruction.
- This paper aims to understand the wound healing and/or post-operative ramifications of the use of immunotherapeutics in the adjuvant or neoadjuvant setting in those undergoing resections with reconstruction.

Strengths

- This paper includes 132 patients which is the largest collection of patients analyzed in this setting and some interesting data points have emerged as a result:
 - Preoperative therapy demonstrated an increase in major complications (OR 3.7, $p=0.04$) and increased need for treatment of wound complications (OR 2.9,

$p=0.008$); this was thought to be due to the short timeframe between the delivery of this treatment and surgery (mean of 19 days).

- However, immunotherapy in the combined pre- and post-operative settings was not associated with an increase in wound complications and apart from the longer mean time in the postoperative setting (173 days), the reasons for this are unclear.

Weaknesses

- While the paper examines mostly SCC (88%), it does also pool other entities including melanoma and osteoradionecrosis. It would be better if it focused solely on one histopathological entity, and this will no doubt be easier as experience with immunotherapy grows.
- Again, the paper examines mostly advanced stage disease (59%), however it does also examine early-stage disease (19%). Furthermore, there were varying protocols for the use of immunotherapy.
- Ultimately subsequent papers will have to narrow their focus in all respects, to understand if there are truly potential risks of therapy, however this paper does lay some decent groundwork.

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[Neck Dissections Based on Sentinel Lymph Node Navigation Versus Elective Neck Dissections in Early Oral Cancers: A Randomized, Multicenter, and Noninferiority Trial](#)

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From *Journal of Oncology*. June 2021

Purpose: This study aimed to compare patients with early oral cavity squamous cell carcinoma (OCSCC) (tumor category [T] 1-2, node-negative, and no distant metastasis) treated with traditional elective neck dissection (ND) with those managed by sentinel lymph node biopsy (SLNB) using survival and neck function and complications as end points.

Methods: Sixteen institutions in Japan participated in the study (trial registration number: UMIN000006510). Patients of age ≥ 18 years with histologically confirmed, previously untreated OCSCC (Union for International Cancer Control TNM Classification of Malignant Tumors 7th edition T1-2, node-negative no distant metastasis), with ≥ 4 mm (T1) depth of invasion, were randomly assigned to undergo standard selective ND (ND group; $n = 137$) or SLNB-navigated ND (SLNB group; $n = 134$). The primary end point was the 3-year overall survival rate, with a 12%



noninferiority margin; secondary end points included postoperative neck functionality and complications and 3-year disease-free survival. Sentinel lymph nodes underwent intraoperative multislice frozen section analyses for the diagnosis. Patients with positive sentinel lymph nodes underwent either one-stage or second-look ND.

Results: Pathologic metastasis-positive nodes were observed in 24.8% (34 of 137) and 33.6% (46 of 134) of patients in the ND and SLNB groups, respectively ($P = .190$). The 3-year overall survival in the SLNB group (87.9%; lower limit of one-sided 95% CI, 82.4) was noninferior to that in the ND group (86.6%; lower limit 95% CI, 80.9; P for noninferiority $< .001$). The 3-year disease-free survival rate was 78.7% (lower limit 95% CI, 72.1) and 81.3% (75.0) in the SLNB and ND groups, respectively (P for noninferiority $< .001$). The scores of neck functionality in the SLNB group were significantly better than those in the ND group.

Conclusion: SLNB-navigated ND may replace elective ND without a survival disadvantage and reduce postoperative neck disability in patients with early-stage OCSCC.

Strengths

- Randomized phase III study with balanced arms for relevant factors, adequately powered for non-inferiority detection with appropriate description of SLNB technique
- Resulted in avoidance of neck dissection in 60% of the SLNB arm with no difference in OS or DFS and improvement in neck functionality scores.

Limitations

- Use of AJCC 7th staging which does not include depth of invasion (DOI) as part of the T staging and therefore part of balancing of the groups. DOI has been shown to affect risk of LN mets
- The Non-inferiority margin was set at 12% which was a bit high. A lower margin may have been more accurate but would have resulted in many more patients needing to be accrued

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