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[Cetuximab-Based vs Carboplatin-Based Chemoradiotherapy for Patients with Head and Neck Cancer](#)

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From the **JAMA Otolaryngol Head Neck Surg**. November 2022.

Objectives: To compare survival with cetuximab-based and carboplatin-based CRT in locally advanced head and neck squamous cell carcinoma (HNSCC).

Design, setting, and participants This cohort study included US veterans who received a diagnosis of HNSCC between January 2006 and December 2020 and were treated with systemic therapy and radiation. Data cutoff was March 1, 2022, and data analysis was conducted from April-May 2022.

Methods: Overall survival by systemic therapy was estimated using Kaplan-Meier methods. We used propensity score and inverse probability weighting to achieve covariate balance between cetuximab-treated and carboplatin-treated patients and used Cox regression to estimate cause-specific hazard ratios of death associated with carboplatin vs cetuximab. We also performed subgroup analyses of patients with oropharynx vs nonoropharynx primary sites.

Results: A total of 8290 patients (median [IQR] age, 63 [58-68] years; 8201 men [98.9%]; 1225 [15.8%] Black or African American and 6424 [82.6%] White individuals) with nonmetastatic HNSCC were treated with CRT with cisplatin (5566 [67%]), carboplatin (1231 [15%]), or cetuximab (1493 [18%]). Compared with cisplatin-treated patients, patients treated with carboplatin and cetuximab were older with worse performance status scores and higher comorbidity burden. Median (IQR) overall survival was 74.4 (22.3-162.2) months in patients treated with cisplatin radiotherapy (RT), 43.4 (15.3-123.8) months in patients treated with carboplatin RT, and 31.1 (12.4-87.8) months in patients treated with cetuximab RT. After propensity score and inverse probability weighting, carboplatin was associated with improved overall survival compared with cetuximab (cause-specific hazard ratio, 0.85; 95% CI, 0.78-0.93; $P = .001$). This difference was prominent in the oropharynx subgroup.

Conclusion: In this cohort study of a US veteran population with HNSCC undergoing treatment with CRT, almost a third of patients were ineligible to receive treatment with cisplatin and received cetuximab-based or carboplatin-based radio sensitization. After propensity score matching, carboplatin-based systemic therapy was associated with 15% improvement in overall survival compared with cetuximab, suggesting that carboplatin may be the preferred radiosensitizer, particularly in oropharynx cancers.

Summary Statements:

- Retrospective cohort study from the Veterans Health Administration of patients with head and neck squamous cell carcinoma undergoing definitive chemoradiation between

2006 and 2020, including 1231 patients receiving carboplatin-based regimens and 1493 patients receiving cetuximab based regimens.

- Propensity score matching and Cox regression were used to account for covariates and estimate cause-specific hazard ratios for overall survival.
- Inverse probability weighted cause-specific hazard ratio of death for carboplatin-based regimens relative to cetuximab was 0.85 (CI 0.78-0.93) and in a subgroup including only patients with oropharynx cancer was 0.82 (CI 0.72-0.94)

Strengths

- Large study including multiple centers.
- Propensity score matching allowed for adjusted comparison between groups accounting for relevant covariates.

Weaknesses

- Retrospective design precluded analysis of treatment toxicities.
- Given lack of survival differences between groups in the no oropharynx sub-analysis, further differentiation between subsites other than oropharynx would have enhanced study findings.

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[Sinonasal Squamous Cell Carcinoma Survival Outcomes Following Induction Chemotherapy vs Standard of Care Therapy](#)

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From the *Otolaryngol Head Neck Surg.* November 2022.

Objectives: To compare oncologic outcomes in sinonasal squamous cell carcinoma (SNSCC) treated with standard of care (SOC) definitive therapy, consisting of surgery or chemoradiotherapy, vs induction therapy followed by definitive therapy.

Methods: The medical records of patients with biopsy-proven SNSCC treated between 2000 and 2020 were reviewed for demographics, tumor characteristics, staging, treatment details, and oncologic outcomes. Patients were matched 1-to-1 by age, sex, and cancer stage according to treatment received. Time-to-event analyses were conducted.

Results: The analysis included 26 patients with locally advanced SNSCC who received either induction therapy (n = 13) or SOC (n = 13). Baseline demographics, Charlson Comorbidity Index, and median follow-up time were well balanced. Weekly cetuximab, carboplatin, and paclitaxel were the most common induction regimen utilized. Tolerance and safety to induction were excellent. Objective responses were observed in 11 of 13 patients receiving induction. No difference in disease-free survival was found between the induction and SOC groups at 1 or 3 years. However, when compared with SOC, induction therapy resulted in significant

improvement in overall survival at 2 years (100% vs 65.3%, $P = .043$) and 3 years (100% vs 48.4%, $P = .016$) following completion of definitive therapy. Two patients in the SOC group developed metastatic disease, as compared with none in the induction group.

Conclusion: Induction therapy was safe and effective. When compared with SOC, induction therapy improved 3-year overall survival.

Summary Statements:

- Sinonasal squamous cell carcinoma (SNSCC) is a rare malignancy of the head and neck and standard of care (SOC) treatment is either surgery or chemoradiation, but morbidity remains high, and 5-year overall survival has remained stagnant at 30%. Induction chemotherapy (IC) has been utilized as an organ-preservation strategy and prior retrospective studies have demonstrated potentially improved survival with IC. Currently there are no results from randomized controlled trials in this space.
- A 1:1 matched analysis based on age, sex, race and TNM staging of SNSCC of 26 patients (13 SOC and 13 IC) treated from 2000-2020 was performed with the main outcome measures of disease-free survival, overall survival, and response to IC. Coexisting comorbidities were accounted for with the Charlson Comorbidity Index (CCI).
- Most patients had a partial response to IC (10/13). When comparing SOC to IC, there was no difference in disease-specific survival at 1, 2, and 3 years but overall survival was significantly better for IC at 2 and 3 years. Other comorbidities did not impact outcomes between SOC and IC.

Strengths

- This study bolsters the evidence supporting IC for SNSCC with one of the largest cohorts of IC patients reported in the literature. The induction regimen was well tolerated. IC can be considered an option with potentially improved overall survival in patients who desire organ preservation (i.e. avoiding an orbital exenteration) or patients where obtaining a R0 resection with negative margins is of concern.

Weaknesses

- It is challenging to draw definitive conclusions from an under powered study with a small number of patients treated over 20 years with heterogenous treatment modalities within both the SOC and IC groups. There is unavoidable selection bias in which patients were deemed surgical candidates and those deemed appropriate for IC. Finally, normalizing the groups by comparing 10-year mortality based on the CCI is relatively crude. As always, a randomized, controlled trial is necessary to determine the population of patients who would benefit from IC.

Incidence and impact of skip metastasis in the neck in early oral cancer: Reality or a myth?

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From *Oral Oncology* March 2022.

Background: The objective of this study was to explore the incidence, identify factors predicting its presence, and determine survival outcomes to possibly decide “adequacy” of neck dissection for this select group.

Methods: This study was a single center, they performed a univariate analysis using chi-square test. A review of audit records (clinical and pathologic) was undertaken to identify early stage (cT1/T2 cN0) oral squamous carcinoma patients operated between January 2016 and December 2020. Skip metastasis was defined as presence of nodal metastases distant from the primary tumor and at a lower level without metastases at levels above this.

Results: Occult metastasis rate was 17.9 % among 761 patients, with 47.1 % travelling to level I. Skip metastasis at level III was seen in 1.2 % and level IV was 0.3 %. Presence of PNI predicted the presence of skip metastasis at level III ($p = 0.041$, OR-0.241, 95 % CI 0.062–0.942) and no significant factors were identified for level IV. The 5- year disease-free survival was significantly reduced with isolated level IV metastasis (50 % vs 79.6 %, $p = 0.017$). Isolated occult metastasis at level Ia was in 0.3 %, all from tongue cancers. Their presence did not impact the 5- year overall survival (100 % vs 90.7 %, $p = 0.628$) and disease-specific survival (100 % vs 92.5 %, $p = 0.675$).

Conclusion: The negligible incidence of skip metastasis to level IV in a clinically node negative neck suggests that clearance up to level III might be adequate in a large majority of patients.

Strengths

- Among the strengths of the study, the large number of patients included in the analysis stands out, which increases the statistical validity of the results. In addition, a multivariate analysis was used to determine the relationship between jumping metastasis and other clinical variables, allowing potential confounding factors to be controlled for.
- Multivariate analysis allowed us to determine that the depth of tumor invasion and the presence of regional lymph node metastases were significant risk factors for jump neck metastasis. These results are important for surgeons, as they allow them to identify patients at the highest risk of skipping metastases and plan appropriate treatment.
- Another strength of the study was that the patients were followed up long-term, which made it possible to determine the survival rate and the recurrence of the cancer. This increases the validity of the results and allows evaluation of the effectiveness of the treatment.



Weaknesses

- Based on retrospective data, which may limit the precision of the results. Furthermore, the study was limited to patients treated at a single hospital, which may limit the generalizability of the results to other clinical settings. It could also be possible that this extremely low incidence of skip metastasis detected could have been erroneously reported due to sampling errors.

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