Sensitivity of lip squamous cell carcinoma to delays in postoperative adjuvant radiation therapy

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Abstract

Introduction: Time to adjuvant radiation (TTR) within 6 weeks is a quality benchmark in head and neck cancer and delays are broadly associated with inferior outcomes. However, this time cutoff has not been validated in lip squamous cell carcinoma (SCC), which may be less aggressive than SCCs of other head and neck mucosal sites. To evaluate the role of TTR in lip SCC, we examine its association with overall survival (OS) in a cohort of patients from the National Cancer Database (NCDB).
Methods: Retrospective analysis of patients diagnosed with SCC of the lip between 2004 and 2020 who were treated with definitive surgery and adjuvant radiation. Patients were identified using ICD-O site and histology codes for squamous cell carcinoma of the lip. Clinicopathologic measures were compared between groups using Chi-Square tests. Survival was determined using the Kaplan-Meier method and hazard ratios (HR) were calculated from univariate and multivariate Cox proportional hazard regressions.
Results: 998 patients with lip SCC were identified for inclusion, of whom 72% (n=714) experienced delays in adjuvant radiation (TTR > 6 weeks). Most patients in both TTR groups were White males aged 60 or older. A larger proportion of patients experiencing TTR delays had T3/4 disease ($p = 0.01$) or nodal metastasis ($p < 0.001$). Delayed TTR was not associated with significantly worse OS (HR: 1.20, 95% CI: 0.96-1.49, $p = 0.11$); this remained the case in a subgroup analysis of patients with advanced (T3/4) primaries or nodal metastasis. On multivariate analysis, age, Asian race, T classification, N classification, positive surgical margins, and Charlson Comorbidity Index were associated with worse OS; however, TTR of >6 weeks was not (aHR: 0.94, 95% CI: 0.70-1.3, p = 0.66).
Conclusions: Delays in PORT were not associated with worse survival in lip SCC. This finding contrasts with studies in heterogeneous HNSCC patient populations or patients with cancers in other oral cavity sites, highlighting potential variability in treatment sensitivity across HNSCC subtypes.

Background and Objectives

Adjuvant radiation after surgery improves survival in patients with head and neck squamous cell carcinoma (HNSCC) and is standard for those with **high-risk features**[1-2]. **Timing of postoperative radiation therapy** (PORT) is a modifiable quality-of-care factor. **NCCN** and **CoC** guidelines recommend initiation within **6 weeks**[3], but studies on **delays in time to radiation** (TTR) show **conflicting evidence**[4-7]. Differences in sensitivity to timeliness may reflect **variable tumor biology and clinical behavior** across subsites. **Lip squamous cell carcinoma** (lip SCC) is a unique entity: less aggressive than other oral cavity cancers and **clinically intermediate between mucosal and cutaneous SCC**[8]. Adjuvant radiation is used for advanced or complicated lip SCC, but **no prior studies have evaluated whether TTR delays impact outcomes in this subsite**. We aim to investigate the impact of delays on overall survival in patients with lip SCC to generate subsite-specific evience and guide individualized clinical decision-making.

Methods

Data source and cohort

•National Cancer Database (NCDB). Retrospective cohort of patients with lip SCC (ICD-O-3 codes C000–C009; histology codes 8070–8078).

Outcome and variables

•Primary outcome: overall survival (OS).

•Covariates: demographics, tumor grade, T/N stage, surgical margins, comorbidity index.

Statistics

•Clinicopathologic characteristics - Chi-Square test. Survival estimated using Kaplan-Meier method with log-rank test. Hazard was determined using uni- and multivariable regression analyses. $P < 0.05$, two-sided.

Results

Patients who do not meet guideline-concordant care are more likely to exhibit advanced disease

	Total Patients (n = 998)	PORT ≤ 6 weeks (n = 284)	PORT > 6 weeks (n = 714)	*P* value*
Age				0.11
<50	140 (14.0%)	49 (17.3%)	91 (12.7%)	
50-50	243 (24.3%)	57 (20.1%)	186 (26.1%)	
60-69	278 (27.9%)	82 (28.9%)	196 (27.5%)	
≥70	337 (33.8%)	96 (33.8%)	241 (33.8%)	
Gender				0.24
Male	768 (77.0%)	211 (74.3%)	557 (78%)	
Female	230 (23.0%)	73 (25.7%)	157 (22%)	
Race				0.08
White	850 (85.2%)	251 (88.4%)	599 (83.9%)	
Black	26 (2.6%)	7 (2.5%)	19 (2.7%)	
Hispanic	88 (8.8%)	20 (7%)	68 (9.5%)	
Asian	16 (1.6%)	0 (0%)	16 (2.2%)	
T Stage				**0.01**
T1-2	455 (45.6%)	146 (51.4%)	309 (43.3%)	
T3-4	217 (21.7%)	48 (16.9%)	169 (23.7%)	
N Stage				**>0.001**
N0	423 (42.4%)	141 (49.6%)	282 (39.5%)	
N+	253 (25.4%)	52 (18.3%)	201 (28.2%)	
Surgical Margins				0.68
Negative	793 (79.5%)	222 (78.2%)	571 (80%)	
Positive	163 (16.3%)	52 (18.3%)	111 (15.5%)	

Table 1.
Baseline demographic, clinicopathologic, and treatment characteristics of patients with lip squamous cell carcinoma. Selected variables from the NCDB cohort are displayed.

Failure to initiate adjuvant radiotherapy within 6 weeks does not result in diminished survival even after adjusting for relevant clinicopathologic variables

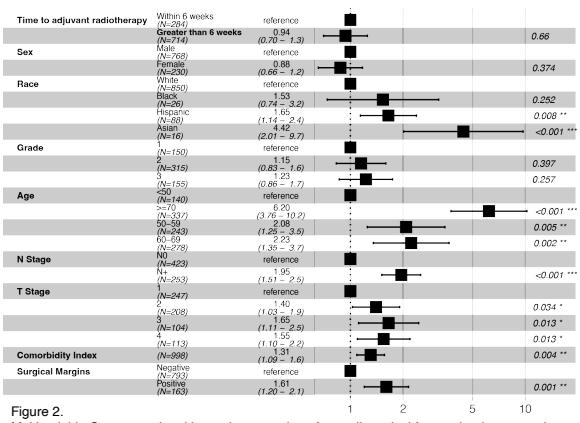

Figure 2.
Multivariable Cox proportional hazards regression of overall survival forest plot demonstrating adjusted hazard ratios (aHR) with 95% confidence intervals for clinicopathologic and treatment variables in lip SCC patients receiving surgery and adjuvant radiation (N=998). Independent predictors of worse overall survival included advanced T stage, positive nodal status, higher comorbidity index, positive surgical margins, and Hispanic/Asian race. Time to PORT >6 weeks was not associated with inferior survival.

Greater than 6 week delays in adjuvant radiotherapy are not associated with decreased overall survival

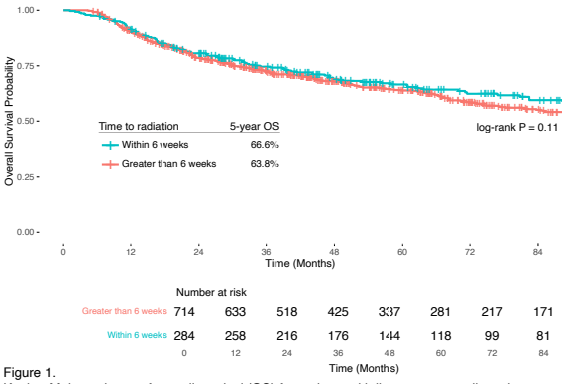

Figure 1.
Kaplan-Meier estimate of overall survival (OS) for patients with lip squamous cell carcinoma who received postoperative radiation therapy, stratified by time to radiation. Numbers at risk are shown at 12-month intervals.

Discussion and Conclusions

In this **NCDB cohort of lip SCC**, **TTR delays >6 weeks were not associated with worse overall survival**, contrasting broader HNSCC literature. Our findings indicate that modest **TTR delays** may have **less impact** on survival in lip SCC than **established prognostic factors such as tumor stage, node-positivity, and margin status**, which were also associated with poorer outcomesin this cohort. These findings may reflect smaller average tumor volumes, higher rates of resectability, and relatively earlier detection in lip SCCs broadly[8]. Going forward, analysis of subsite-specific outcomes as a whole may provide a framework for refining guideline recommendations and developing subsite-specific treatment benchmarks.

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