3-1-2022

Influence of Treatment Package Time on outcomes in High-Risk Oral Cavity Carcinoma in patients receiving Adjuvant Radiation and Concurrent Systemic Therapy: A Multi-Institutional Oral Cavity Collaborative study

Ahmed I. Ghanem
Henry Ford Health, AGHANEM1@hfhs.org

Neil M. Woody

Matthew A. Schymick
Henry Ford Health, mschymi1@hfhs.org

Nikhil P. Joshi

Jessica L. Geiger

See next page for additional authors

Recommended Citation

Ghanen AI, Woody NM, Schymick MA, Joshi NP, Geiger JL, Jillian Tsai C, Dunlap NE, Liu HY, Burkey BB, Lamarre ED, Ku JA, Scharpf J, Caudell JJ, S VP, Lee NY, Adelstein DJ, Koyfman SA, and Siddiqui F. Influence of Treatment Package Time on outcomes in High-Risk Oral Cavity Carcinoma in patients receiving Adjuvant Radiation and Concurrent Systemic Therapy: A Multi-Institutional Oral Cavity Collaborative study. Oral Oncol 2022; 126:105781.

Authors

Ahmed I. Ghanem, Neil M. Woody, Matthew A. Schymick, Nikhil P. Joshi, Jessica L. Geiger, Chiaojung Jillian Tsai, Neal E. Dunlap, Howard Y. Liu, Brian B. Burkey, Eric D. Lamarre, Jamie A. Ku, Joseph Scharpf, Jimmy J. Caudell, Sandro V. Porceddu, Nancy Y. Lee, David J. Adelstein, Shlomo A. Koyfman, and Farzan Siddiqui

Oral Oncology 126 (2022) 105781

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Influence of Treatment Package Time on outcomes in High-Risk Oral Cavity Carcinoma in patients receiving Adjuvant Radiation and Concurrent Systemic Therapy: A Multi-Institutional Oral Cavity Collaborative study☆

Ahmed I Ghanem [a,b,*], Neil M Woody [c], Mathew A Schymick [a], Nikhil P Joshi [c], Jessica L Geiger [d], Chiaojung Jillian Tsai [e], Neal E Dunlap [f], Howard Y Liu [g], Brian B Burkey [h], Eric D Lamarre [h], Jamie A Ku [h], Joseph Scharpf [h], Jimmy J Caudell [i], Sandro V Porceddu [g], Nancy Y Lee [e], David J Adelstein [d], Shlomo A Koyfman [c], Farzan Siddiqui [a]

[a] Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, USA
[b] Clinical Oncology Department, Faculty of Medicine, University of Alexandria, Alexandria, Egypt
[c] Department of Radiation Oncology, Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH, USA
[d] Department of Hematology and Medical Oncology, Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH, USA
[e] Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
[f] Department of Radiation Oncology, University of Louisville, School of Medicine Hospital, Louisville, KY, USA
[g] Department of Head and Neck Oncology, Princess Alexandra Hospital/University of Queensland, Brisbane, Australia
[h] Section of Head and Neck Surgery and Oncology Head and Neck Institute, Cleveland Clinic Foundation, Cleveland, OH, USA
[i] Department of Radiation Oncology, H Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA

ARTICLE INFO

Keywords:
Oral cavity cancer
Squamous cell carcinoma
High-risk patients
Radiation therapy
Concomitant chemotherapy
Treatment package time
Survival

ABSTRACT

Objectives: To explore the influence of treatment package time(TPT) in high-risk oral cavity squamous cell carcinoma(OCSCC) receiving adjuvant radiotherapy with concurrent chemotherapy(CRT).

Materials and Methods: We queried our multi-institutional OCSCC collaborative database for cases diagnosed between 2005 and 2015 who underwent surgery followed by adjuvant CRT. All patients had high-risk features: extranodal extension(ENE) and/or positive surgical margin(PM). TPT was days between surgery to last radiotherapy fraction. Kaplan-Meier curves, log-rank p-values and multivariate analysis(MVA) were used to investigate the impact of TPT on overall(OS), disease-free(DFS), locoregional failure-free(LRFS) and distant metastases-free(DMFS) survival.

Results: We identified 187 cases: median age 58 (range, 24–87 years), males 66%, and ever smokers 69%. ENE and PM were detected in 85% and 32%, and oral tongue and floor of the mouth constituted 49% and 18%, respectively. Median radiotherapy and cisplatin doses received were 66 Gy and 200 mg/m2. Overall, median TPT was 98 (range, 63–162 days). OS was worse for TPT > 90-days (n = 134) than TPT ≤ 90 (n = 53) at two-(65% vs. 71%) and five-years (45% vs. 62%); $p = 0.05$, with similar results for DFS. No influence on LRFS or DMFS was noted. More lymph nodes(LN) dissected($P = 0.039$), T3-4 disease($P = 0.017$), and unplanned reoperations($P = 0.037$) occurred with TPT > 90-days. On MVA, TPT in 10-day increments was independently detrimental for OS (Hazard Ratio: 1.14; 95 %Confidence Interval [1–1.28]; $P = 0.043$), perineural invasion, age and positive LN ($p < 0.05$ for all).

☆ The results of this study were presented in part at the 61st Annual Meeting of the American Society for Radiation Oncology (ASTRO), held in Chicago, IL, from September 15 to 18, 2019 (Abstract ID 2924).

* Corresponding author at: Department of Radiation Oncology, Henry Ford Cancer Institute, 2800 West Grand Blvd., Detroit, MI 48202, USA. Tel.: +1 313 9163488.

E-mail addresses: aghanem1@hfhs.org (A. I Ghanem), woodyn@ccf.org (N.M. Woody), mschymi1@hfhs.org (M.A. Schymick), joshin@ccf.org (N.P. Joshi), geigerj@ccf.org (J.L. Geiger), tsaic@mskcc.org (C. Jillian Tsai), neal.dunlap@louisville.edu (N.E. Dunlap), howard.liu@health.qld.gov.au (H.Y. Liu), burkeyb1@ccf.org (B.B. Burkey), lamarre@ccf.org (E.D. Lamarre), kuj@ccf.org (J.A. Ku), scharpj@ccf.org (J. Scharpf), jimmy.caudell@moffitt.org (J.J. Caudell), sandro.porceddu@health.qld.gov.au (S. V Porceddu), leen2@mskcc.org (N.Y. Lee), adelstd@ccf.org (D.J. Adelstein), koyfmas@ccf.org (S.A. Koyfman), fsiddiq2@hfhs.org (F. Siddiqui).

https://doi.org/10.1016/j.oraloncology.2022.105781
Received 9 November 2021; Received in revised form 25 January 2022; Accepted 14 February 2022
Available online 17 February 2022

Conclusion: In one of the largest multi-institutional cohorts, TPT > 90-days predicted worse OS for high-risk OCSCC receiving adjuvant CRT. All efforts are needed to optimize perioperative care and baseline conditions for favorable outcomes.

Introduction

Oral cavity cancers constitute a significant challenge, with around 2% of all new cancer cases and 1.8% of total deaths in 2020 worldwide [1]. In the United States, 35 540 new cases and 6980 deaths are expected in 2021 [2]. The standard of care for oral cavity squamous cell carcinoma (OCSCC) involves definitive surgical resection followed by adjuvant radiation therapy (RT) with/without concomitant chemotherapy (CRT) according to patient, surgical and tumor characteristics [3].

According to the combined analysis of two major randomized trials by Radiation Therapy Oncology Group (RTOG 9501) [4], and European Organization for Research and Treatment of Cancer (EORTC 22931) [5], the benefit of the addition of concurrent chemotherapy was predominantly seen in those with positive surgical margins (PM) or extranodal extension (ENE) or both. OCSCC formed approximately 26% of both trials' population [6]. Improved outcomes were maintained at ten years' follow up of the combined analysis [7].

In patients undergoing surgical staging and receiving post-operative RT alone, the detrimental impact of prolonging the treatment duration has been reported. Treatment duration parameters includes interval from surgery to RT commencement, overall RT duration (first to last day of RT course) and treatment package time (TPT) which encompasses the time from surgical resection till the last RT fraction. The National Comprehensive Cancer Network (NCCN) endorsed the recommendation to start adjuvant RT within six weeks interval surgery [3]. This guideline was based primarily upon a *meta*-analysis of six important trials that included 851 patients. The authors noted an odds ratio of 2.89 for local recurrence in patients starting RT beyond six weeks of surgery [8]. Nevertheless, a National Cancer Database (NCDB) study revealed that 55.7% of the included subjects failed to start adjuvant RT within the preferred six weeks window, and OCSCC constituted a more significant proportion of them than other subsites [9]. Another study in patients with locally advanced head and neck cancer noted a 61% non-compliance with the 42-day surgery to RT start cut-off. However, this delay did not have a prognostic impact on the OCSCC patient subgroup analysis [10].

Other studies demonstrated detrimental effects for unplanned treatment breaks during radiation therapy, which extended overall RT duration [11–13]. This impact became deleterious when restricted to higher risk cases receiving > 60 Gy [13]. On the other hand, a prospective trial failed to show improved locoregional control with accelerated fractionation for high-risk candidates, except for those who started RT more than six weeks after surgery [14].

Therefore, the concept of TPT, which includes both the previous time components, emerged. A multitude of studies depicted a robust influence for TPT on survival endpoints, and accordingly, they proposed a range of 77–100 days to represent the ideal TPT [14,15–17]. Tribius et al. and Rosenthal et al. utilized recursive partitioning analysis (RPA) and determined the optimal TPT to be 87 and 85 days, respectively [18,19]. Contrarily, other studies refuted the significance of TPT favoring other time components [11,12].

Nonetheless, these studies had some limitations: the utilization of old RT modalities, the inclusion of non-OCSCC cases, and, more importantly, lack or under-representation of patients that received adjuvant CRT. Therefore, in a multi-institutional setting, we investigated the impact of TPT on survival endpoints for a homogenous population of surgically resected high-risk OCSCC, who received adjuvant CRT using contemporary techniques and modern doses.

Materials and Methods

Data source and patient selection

We queried our multi-institutional OCSCC collaborative database, which includes a total of 1282 patients from six different academic institutions, to identify non-metastatic high-risk patients managed by surgical staging followed by adjuvant CRT between January 31st, 2005 and January 31st, 2015. Approvals were obtained from each of the six participating institutional review boards before populating the database.

Covariates (Study Variables)

Data collection included demographics, pathological features and treatment details (surgery, radiation therapy and chemotherapy) in addition to follow up, recurrence patterns and survival status at last follow-up. High-risk patients are defined as having a positive final surgical margin (PM), ENE or both. ENE encompassed any evidence for extracapsular extension of positive lymph nodes (LN) in the final surgical pathology report, with no data on the exact extent or any other details not reported consistently in participating institutions along the study timeline. Accordingly, we excluded all low/intermediate-risk cases lacking any of these features, those treated outside the study date range, and those who did not receive adequate RT (total dose < 50 Gy) and/or concomitant chemotherapy. We also excluded patients where the TPT was>180 days or dates of therapy were not exactly determined.

Outcome assessment

TPT was calculated for all included cases as days elapsing between the date of surgery and the date of last RT fraction. This included components of time from surgery to initiation of RT and overall RT duration (first-last RT fraction), that were also calculated. Consequently, we stratified TPT in 10 days increments (10D-INC). In order to investigate the optimal TPT cutoff value, Kaplan-Meier curves were plotted, and log-rank tests were used to compare survival endpoints across different cutoff points (90, 100, and 110 days) and in 10D-INCs of TPT.

Endpoints included overall survival (OS) which was calculated from the date of surgery to the date of death from any cause), disease free survival (DFS) which was calculated from the date of surgery to the date of death or first recurrence, locoregional failure free survival (LRFS) which was calculated from the date of surgery to the date of first regional/nodal recurrence and distant metastases free survival (DMFS) which was calculated from the date of surgery to the date of first distant recurrence.

Statistical analysis

Patient, pathological and treatment characteristics were compared between TPT groups using Chi-square and Fisher's Exact tests for categorical (expressed in frequencies and percentages) and Wilcoxon test for continuous variables (expressed in median and range). A multivariate analysis (MVA) Cox regression model was developed to identify independent predictors for survival endpoints. All tests were two-sided and P-values of 0.05 or less were considered statistically significant. All statistical analyses were performed using SPSS Statistics V24, IBM Armonk NJ or R 3.4 (R Foundation Vienna, Austria).

Results

Patient, pathological and treatment characteristics:

We were able to identify a final cohort of 187 cases for high-risk OCSCC cases managed with surgery followed by adequate doses of adjuvant CRT between 2005 and 2015 who fit our inclusion criteria as depicted in Figure.1. The median age was 58 years (range, 24–87 years), males constituted 65.8%, ever smokers were 68.8% with median pack-years of 30 (range, 1–110 pack-years), and 15.4% had a history of heavy alcohol use. The most common subsite was oral tongue (48.6%; n = 91) followed by the floor of mouth (17.6%; n = 33). Per the American Joint Committee on Cancer (AJCC) 8th version, pathological stage IVB was prevalent (71.4%), followed by stage IVA (24.3%) [20]. ENE and PM were detected in 68.4% (n = 128) and 16% (n = 30) respectively; whereas 15.5% (n = 29) had both.

Surgical staging involved bilateral LN dissection in 35.8%, while the remainder underwent unilateral LN dissection. The median dissected LNs were 37 (range 9–199) per case with a median positive LN of 2 (range 0–43). Intensity-modulated RT (IMRT) was utilized by 85.8%, and the rest received conventional three-dimensional RT. Median RT dose delivered was 66 Gy (50–72 Gy). Cisplatin was used by 75.9% of the study cohort (median dose: 200 mg/m2 (80–300 mg/m2)), whereas 24.1% received carboplatin or cetuximab according to the decision of the institutional multidisciplinary tumor board. This decision was owing to renal disease, hearing problems, or other comorbidities that precluded cisplatin administration.

TPT groups and survival outcomes

For the entire cohort, the median TPT was 98 days (63–162 days) split among time to start RT of 51 days (29–109 days) and overall RT duration of 45 days (33–97 days). Using 10D-INC around median TPT, only 53 patients (28%) had TPT $\leq$ 90 days, 57% had TPT $\leq$ 100, and 79% $\leq$ 110 days. After a median follow up of 30 months (2.8–145.6 months), each 10D-INC in TPT was associated with worse OS (Hazard Ratio [HR]:1.18 [95% Confidence Interval [CI]:1.06–1.33]; $P = 0.003$) and DFS (HR:1.15 [95% CI:1.03–1.28]; $P = 0.011$), on log-rank test. Only TPT > 90 vs. TPT $\leq$ 90 was associated with worse two- and five-years' OS (64.7% vs. 70.5% & 45% vs. 62% respectively; $P = 0.05$) (Figure 2A) as well as worse DFS at two (50.9% vs. 61.9%) and five-years (45% vs. 62%); $P = 0.049$ (Figure 2B); with a median follow up time of 26.7 (4.7–145.6 months) vs 40.1 (2.8–113.8 months) for both, respectively. No significant differences were noted for the 100- and 110-days' time-points. Moreover, there was no significant interaction between 10D-INC TPT and both LRFS (HR:1.07 [95% CI:0.91–1.24]; P = 0.397) and DMFS (HR:0.95 [95% CI:0.78–1.15]; P = 0.60). At two- and five-years LRFS was (71% vs. 76.6% & 65.5% vs. 67.7%); while DMFS was (79.8% vs. 74.6% & 73.7% vs. 71.9%) for TPT > 90 vs. TPT $\leq$ 90; P > 0.05 for all (Figure 2C & 2D).

After we dichotomized our study cohort at TPT 90 days' time point (cutoff for OS difference), baseline demographic, and clinicopathological details were well-balanced between the two resultant groups as portrayed in Table 1. However, T3-4 tumors were more frequent for TPT > 90 days ($P = 0.017$). Both components of TPT (time to RT start and overall RT duration) were more extended with TPT > 90 days ($P < 0.001$ for both).

Multivariate analysis for predictors of survival outcomes

On MVA for OS, 10-D INC (HR:1.14(95% CI:1–1.28); $P = 0.043$) remained detrimental after adjusting for lymphovascular invasion (LVI) and AJCC stage. Perineural invasion (PNI) ($P = 0.002$), number of positive LN ($P = 0.001$), and 10-year increment of age ($P = 0.007$) were also independently prognostic for OS. The same factors were also predictive for DFS except for the 10D-INC of TPT, which was rendered only marginal (HR:1.1 [95% CI:0.98–1.23]; $P = 0.096$) as shown in Table 2. For DMFS, PNI was independently prognostic ($P = 0.004$), and LVSI was marginal ($P = 0.078$) in an exploratory model. There was no significant MVA model for LRFS

Surgical quality metrics analysis

In an attempt to explore the independent impact of TPT on OS rather than other tumor specific outcomes (LRFS & DMFS) we retrieved available surgical quality metrics data for our cohort (Table 3). Patients with TPT > 90 days underwent bilateral LN dissection more frequently ($P = 0.05$), with a significantly higher median number of retrieved LN (38 vs. 35; $P = 0.039$); and had more unplanned reoperations within 14 days (12.8% vs. 2.1%; $P = 0.037$) as well.

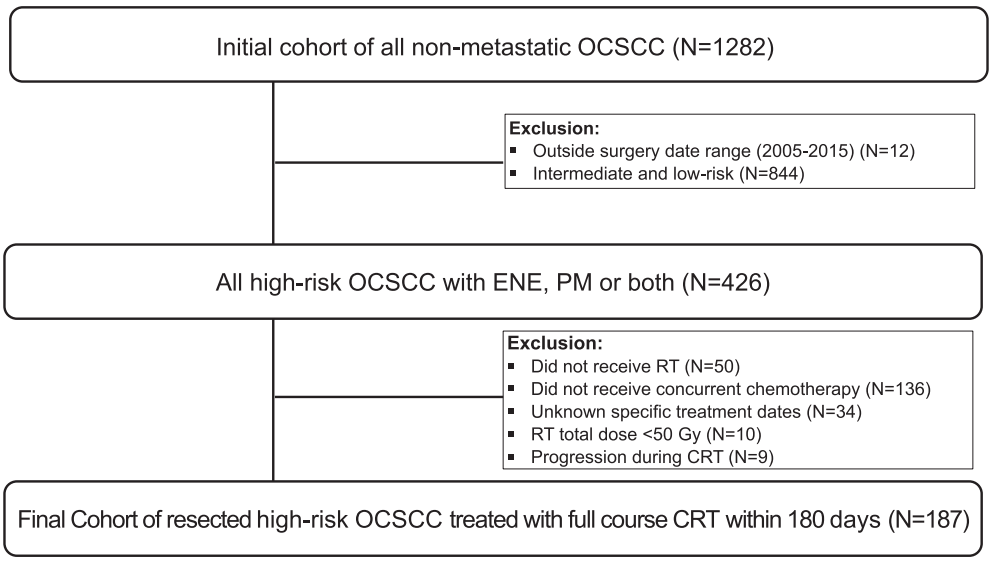

Figure 1. CONSORT flow chart of inclusion and exclusion criteria reaching the final study cohort of high-risk oral cavity squamous cell carcinoma treated with surgery followed by adequate radiotherapy with concomitant systemic therapy within 180 days (n = 187) OCSCC, oral cavity squamous cell carcinoma; ENE, extranodal extension; PM, positive surgical margin; RT, radiation therapy; CRT, chemoradiotherapy.

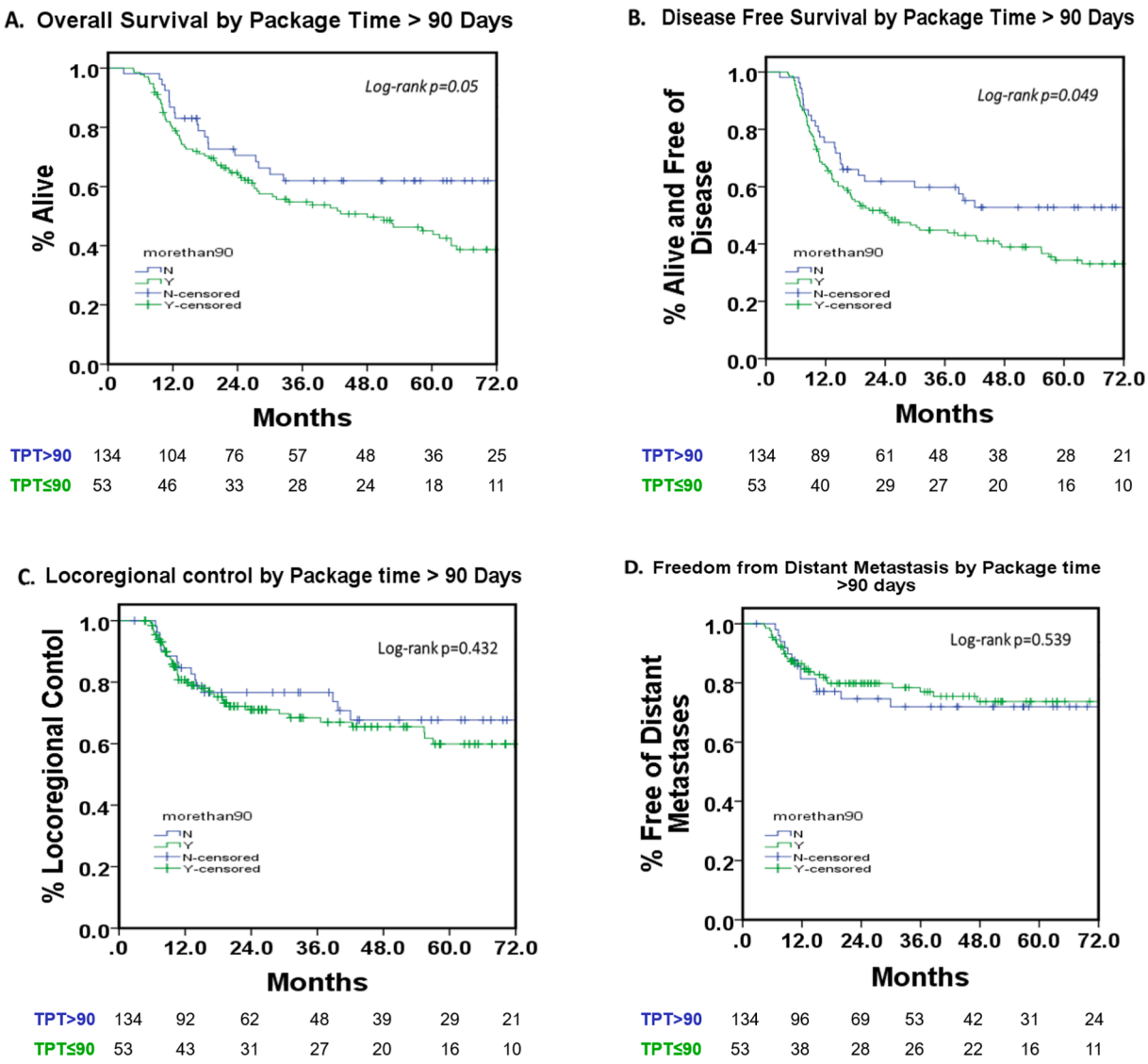

Figure 2. Kaplan-Meier estimates of survival endpoints for the study cohort (n = 187) dichotomized by treatment package time > 90 days (n = 134) vs. ≤ 90 days (n = 53) with Log-rank test results: overall survival (A), disease free survival (B), locoregional recurrence free survival (C), and distant-metastasis free survival (D).

Discussion

It is recommended to start RT within the shortest possible time after surgery based on an individual evaluation of each patient's recovery and healing which is usually within around 4–6 weeks (28–42 days) . An uninterrupted course of adjuvant head and neck RT should take 40–45 days for a dose of 60–66 Gy. This results in an ideal TPT of 68–87 days. Our study demonstrated a detrimental impact on overall survival for each 10 day increase of the TPT in a homogenous group of high-risk OCSCC managed by adjuvant CRT following definitive surgery in a multi-institutional database. This deleterious effect was maintained after adjusting for other confounding factors, albeit no interaction was detected for locoregional and distant failure. Other classical factors remained significant.

Tam et al. investigated a similar cohort treated exclusively with adjuvant CRT and, like the current study, depicted an independent effect of TPT as a continuous variable on OS with a threshold value of 97 days beyond which survival worsens. Similar to our study, the median TPT was around 100 days, and it was even longer for OCSCC subjects. Unlike our analysis, they did not exclude patients without high-risk features who received adjuvant CRT and did not perform a sub-analysis for OCSCC [21]. Another study, with the same median TPT, that has undergone a subset analysis for OCSCC confirmed a dismal impact on OS for TPT > 14 weeks (98 days) that was more pronounced in advanced stages, which parallels our findings, even though only 52% received CRT [22]. Nonetheless, being NCDB analyses, both studies could not investigate effect of TPT on tumor-specific outcomes (LRFS & DMFS) in contrast to this study [21,22].

Regarding influence of TPT on RFS, a single institutional study in which all subjects received CRT showed results like this study, although OCSCC was only 40% of the cases. TPT cutoff level of 100 days which was independently prognostic with OS, failed to predict recurrence-free survival despite being significant in the univariate log-rank test [23]. Similarly, Tribius et al. reported a non-significant association with LRFS at TPT 100 days (classic cutoff) and also at 87 days (RPA derived) on MVA, with a positive influence on OS. Nevertheless, OCSCC formed only 28% of the cohort, and CRT was utilized by only 43% with no sub-analyses for both [18]. Contrarily, in the final report (20-years follow up) for a prospective trial for OCSCC, TPT < 85 days was independently prognostic for better LRFS as well as OS, whereas RT dose-escalation failed to attain this benefit. However, in this study, none of the high-risk patients had received concurrent chemotherapy [19]. Also, a single institution study addressing only OCSCC, demonstrated an independent effect on RFS (HR 2.94 [95% CI:1.20–7.18]) with TPT > 11

Table 1
Baseline demographics, clinicopathological characteristics and treatment details for the study cohort (n = 187) dichotomised by TPT: ≤90 days (n = 53; 28%) vs. > 90 days (n = 134; 72%).

Characteristic	TPT ≤ 90 daysN = 53; 28%	TPT > 90 daysN = 134; 72%	P-value
	N (%)	N (%)	
Median age in years (range)	54 (24–84)	59 (27–87)	0.965
Race			0.964
Caucasian	43 (81.1%)	108 (80.6%)	
African American and others	10 (18.9%)	26 (19.4%)	
Male	53 (67.9%)	134 (64.9%)	0.696
Smoking status			0.998
Current smokers	19 (38%)	46 (38.3%)	
Prior smokers	14 (28%)	33 (27.5%)	
Never smoker	17 (34%)	41 (34.2%)	
Median Smoking index (pack-years) (range)	25 (2–90)	59 (1–110)	0.827
Heavy alcohol use	14 (31.1%)	29 (27.8%)	0.230
Median charlson comorbidity Index (range)	0 (0–8)	1 (0–7)	0.343
Oral cavity subsite			0.167
Oral tongue	24 (45.3%)	67 (50%)	
Floor of mouth	10 (18.9%)	23 (17.2%)	
Alveolus and retromolar trigone	9 (17%)	27 (20.1%)	
Other	10 (18.8%)	17 (12.7%)	
PET-CT performed for staging	24 (52.2%)	49 (52.9%)	0.568
Histologic grade			0.981
Grade 1–2	37 (69.9%)	94 (70.1%)	
Grade 3	16 (30.2%)	40 (29.9%)	
pT stage (AJCC 8th)			0.017
T1-2	20 (42.6%)	27 (23.5%)	
T3-4	27 (57.4%)	88 (76.5%)	
pN stage (AJCC 8th)			0.481
N0-1	6 (11.3%)	14 (10.4%)	
N2	13 (24.5%)	23 (17.2%)	
N3	34 (64.2%)	97 (72.4%)	
Median positive LN (range)	2 (0–14)	3 (0–43)	0.071
High-risk features			
ENE	46 (90.2%)	110 (82.7%)	0.206
Positive final surgical margin	13 (24.5%)	46 (34.6%)	0.177
Perineural invasion	28 (52.8%)	87 (65.9%)	0.100
Lympho-vascular invasion	22 (43.1%)	54 (40.9%)	0.915
Median time to start RT (days) (range)	41 (29–51)	56 (30–109)	<0.001
Median overall RT duration (days) (range)	43 (33–52)	46 (33–97)	0.001
Median RT dose delivered (Gy) (range)	64 (52–71)	66 (50–70)	0.727
Median total cisplatin dose (mg/m2) (range)	200 (100–300)	200 (80–300)	0.788

Abbreviations: TPT, treatment package time; PET-CT, positron emission tomography-computed tomography; pT, pathological Tumor stage; AJCC 8th, American Joint Committee on Cancer 8th edition; pN, pathological Nodal stage; LN, lymph node; ENE, extranodal extension; RT, radiation therapy; Gy, gray

weeks, with only 49.2% receiving CRT [24].

One of the salient features of this study is that we focused only on high-risk cases with PM and/or ENE, which resulted in a predominance of Stage IV cases (95.7%) per AJCC 8th version. This was driven mostly by ENE which is a surrogate for a higher pathological N stage, and consequently a higher stage group according to AJCC 8th edition [20]. Besides, the only significant difference between our TPT groups, was more T3-4 cases with TPT > 90 days, which may have resulted in a more extensive surgery and consequently to a longer course of post-operative healing, although we do not have details for this. This matches Guttman et al. who demonstrated that more advanced stages and readmissions were associated with significantly longer TPT. Meanwhile, longer TPT was more accentuated in OCSCC compared to other sites on MVA, resulting in worse OS by 4% for each week of delay [HR 1.04; 95% CI:1.03–1.05; *P < 0.001*] [25]. Moreover, unplanned reoperation was significantly higher with TPT > 90 days, and therefore, the interval to RT start was prolonged in comparison to TPT ≤ 90 days per our analysis. Graboyes et al. in another NCDB analysis demonstrated that longer length of postoperative hospital stay, as well as unplanned 30-day readmission, predicted longer wait times (from surgery to RT start) on MVA [9]. It is noteworthy that in another study by our group, authors demonstrated that failure to comply with two or more of quality metrics predicted worse outcomes for resected OCSCC. These metrics included adjuvant RT referral for stages III/IV, more extensive neck dissection, unplanned reoperations and unplanned readmissions postoperatively [26]. TPT > 90 days was not associated with any of these except for higher reoperations within 14 days.

Based on our results, the addition of concurrent chemotherapy did not seem to overcome the adverse impact of a prolonged TPT on survival. Both days to start RT and overall RT days were significantly longer in TPT > 90 days. All efforts need to be exerted to optimize baseline comorbidities, recovery from surgery, and healing issues to secure the delivery of adequate adjuvant therapy within accepted TPT limits [27]. Meanwhile, more care is needed to anticipate and manage RT related toxicities and to offer social support in order to avoid CRT long

Table 2
Multivariate analysis Cox regression models results for predictors of survival endpoints for the entire study cohort (n = 187).

Endpoint[i]	Variable	Response	HR (95% CI)	P-value
OS[ii]	TPT	10-D INC	1.14 (1.00–1.28)	0.043
	Perineural invasion	Present vs. Absent	2.05 (1.29–3.25)	0.002
	LN positive	Continuous	1.06 (1.02–1.09)	0.001
	Age	10 years increment	1.31 (1.07–1.57)	0.007
DFS[iii]	TPT	10-D INC	1.11 (0.98–1.23)	0.096
	Perineural invasion	Present vs. Absent	1.95 (1.28–2.97)	0.002
	Positive LN	Continuous	1.04 (1.01–1.08)	0.005
	Age	10 years increments	1.21 (1.02–1.42)	0.033
DMFS[iv]	Perineural invasion	Present vs. Absent	3.4 (1.48–7.81)	0.004
	Lympho-vascular space invasion	Present vs. Absent	1.76 (0.94–3.29)	0.078

Abbreviations: HR, Hazard ratio; CI, confidence interval; OS, overall survival; TPT, treatment package time; 10D-INC, 10-day increments; DFS, disease free survival; LN, lymph nodes; DMFS, distant metastases free survival

[i] For locoregional failure free survival there was no significant MVA model

[ii] Adjusted for lymphovascular space invasion and AJCC T-stage (8th edition)

[iii] Adjusted for lymphovascular space invasion

[iv] Adjusted for positive lymph node count

Table 3
Surgical details and rates of compliance with quality metrics among study TPT groups (≤90 days vs. > 90 days)*

Metric	TPT ≤ 90 days	TPT > 90 days	P-value
Median LN dissected	35 (range 13–86)	38 (range 9–199)	0.039
Bilateral LN dissection	12 (24.5%)	50 (40.3%)	0.050
Number of LN dissected ≥ 18	45 (84.9%)	119 (88.8%)	0.464
Unplanned re-admission within 30 days	2 (4.3%)	13 (11.9%)	0.136
Unplanned re-operation within 14 days	1 (2.1%)	14 (12.8%)	0.037

Abbreviations: TPT, treatment package time; LN, lymph node

interruptions and minimize TPT. These factors are modifiable and are best handled by a multidisciplinary team who coordinate to provide comprehensive care and avoid unnecessary delays or RT interruptions [28]. In addition to robust postoperative care, optimization of logistics needs special attention since the receipt of adjuvant IMRT as well as treatment in high-volume academic centers both were associated with longer waits beyond the recommended six weeks interval [9].

Importantly, other non-surgically related factors might have participated in the significant effect of longer TPT on OS which was not associated with a parallel impact on tumor-specific outcomes (LRFS and DMFS). Although baseline comorbidities, smoking and alcohol levels were not different across TPT groups; details of social support, overall functional status and other components of quality of life throughout treatment course were not available due to the multi-institutional nature of this study. In addition, systemic therapy and RT related toxicities were not captured for the study population. These factors have influence on both components of TPT (time to RT start and overall RT duration) and are associated with non-disease specific competing risks of death. It is noteworthy to state that in this homogenous high-risk population the risk of early recurrence before starting indicated adjuvant RT should not be disregarded. In our study 9 patients were excluded because of progression during the receipt of adjuvant therapy. A recent study by Yao et al. demonstrated early recurrence rate of 35% for surgically resected OCSCC with any high-risk feature by using PET/CT RT planning [29]. Although postoperative PET/CT is not yet a standard of care, masked early recurrences may be a strong confounding factor to the effect of TPT on tumor related events.

This study had some significant limitations that need to be highlighted, including the selection and reporting bias due to the retrospective nature. Although we had ten years' data of 6 academic institutes, we ended up with 187 candidates who fit our strict inclusion criteria. This tight selection prevented us from running subgroup analyses based on OCSCC subsite bearing in mind diverse pathogenesis and patients characteristics. Besides, the exact causes of unplanned RT breaks and failure patterns were not complete for all cases. Again, due to limited numbers, we were not able to run a subset analysis comparing outcomes for cisplatin vs. concomitant cetuximab (10%) or carboplatin (14%) which were prescribed based on contraindications to cisplatin.

Additionally, around 30% (n = 136) of our database high-risk population did not receive the planned concurrent chemotherapy, and another nine cases progressed while on CRT. In a recent French feasibility study, only 57.5% were able to complete the indicated course of CRT, and around 32% failed to receive the 3rd concomitant cisplatin dose [30]. Besides, 24.1% of the included cases received carboplatin or cetuximab, which are less effective. This was highlighted in a study that analyzed the patterns of utilization of chemotherapy among elderly cases (>70 years). Even though the benefit of CRT was maintained, only 42% of high-risk elderly patients received the indicated concurrent chemotherapy [31]. Upcoming trials incorporating more tolerable targeted agents and/or immunotherapy in the care of high-risk OCSCC need to recruit this elderly population. We hope results of these trials such as RTOG 1216 (NCT01810913) and the EORTC DUTRELASCO (NCT03784066) fill the gap and improve outcomes in high-risk patients who cannot tolerate full dose cisplatin.

Conclusion

In one of the largest collaborative multi-institutional cohorts of oral cavity squamous cell carcinoma treated optimally with surgical resection followed by adjuvant concomitant chemoradiotherapy using modern techniques and adequate doses, longer treatment package time was independently associated with decreased overall survival, with a non-significant impact on locoregional or distant recurrences. This underscores the significance of other non-cancer related deaths for this high-risk population. In a multidisciplinary setting, all efforts should be exerted to maintain a smooth perioperative course and optimize the general health condition throughout the treatment course and minimize toxicities to initiate adjuvant treatment as early as possible with minimal breaks.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Farzan Siddiqui reports Honoraria for lectures and travel reimbursement from Varian Medical Systems (unrelated to current work); Medical advisory board from Varian Noona. Jimmy J. Caudell reports COI from Varian Medical Systems (outside submitted work).The rest declare no conflict of interest].

Acknowledgements

None.

Role of funding source

No specific funding was disclosed.

Status

New submission. This work has not been previously published in any language anywhere and is not under simultaneous consideration or in press by another journal

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.

[2] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin. 2021;71(1):7–33. https://doi.org/10.3322/caac.21654. Epub 2021 Jan 12 PMID: 33433946.

[3] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in oncology: head and neck cancer Version 3.2021. Available from: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf [Accessed On: 22 October, 2021].

[4] Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004;350(19):1937–44. https://doi.org/10.1056/NEJMoa032646.

[5] Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre J-L, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350(19):1945–52. https://doi.org/10.1056/NEJMoa032641.

[6] Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005;27(10):843–50. https://doi.org/10.1002/hed.20279.

[7] Cooper JS, Zhang Q, Pajak TF, Forastiere AA, Jacobs J, Saxman SB, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys. 2012;84:1198–205. https://doi.org/10.1016/j.ijrobp.2012.05.008. Epub 2012 Jun 30 PMID: 22749632.

[8] Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. J Clin Oncol. 2003;21(3):555–63. https://doi.org/10.1200/JCO.2003.04.171. PMID: 12560449.

[9] Graboyes EM, Garrett-Mayer E, Ellis MA, Sharma AK, Wahlquist AE, Lentsch EJ, et al. Effect of time to initiation of postoperative radiation therapy on survival in surgically managed head and neck cancer. Cancer 2017;123(24):4841–50. https://doi.org/10.1002/cncr.30939.

[10] Harris JP, Chen MM, Orosco RK, Sirjani D, Divi V, Hara W. Association of survival with shorter time to radiation therapy after surgery for US patients with head and neck cancer. JAMAOtolaryngol Head Neck Surg 2018;144:349–59. https://doi.org/10.1001/jamaoto.2017.3406. PMID: 29522072.

[11] Suwinski R, Sowa A, Rutkowski T, Wydmanski J, Tarnawski R, Maciejewski B. Time factor in postoperative radiotherapy: a multivariate locoregional control analysis in 868 patients. Int J Radiat Oncol Biol Phys. 2003;56:399–412. https://doi.org/10.1016/S0360-3016(02)04469-3. PMID: 12738315.

[12] Fujiwara RJT, Judson BL, Yarbrough WG, Husain Z, Mehra S. Treatment delays in oral cavity squamous cell carcinoma and association with survival. Head Neck 2017;39(4):639–46. https://doi.org/10.1002/hed.24608.

[13] Mazul AL, Stepan KO, Barrett TF, Thorstad WL, Massa S, Adkins DR, et al. Duration of radiation therapy is associated with worse survival in head and neck cancer. Oral Oncol 2020;108:104819. https://doi.org/10.1016/j.oraloncology.2020.104819.
[14] Ang KK, Trotti A, Brown BW, Garden AS, Foote RL, Morrison WH, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;51(3):571–8.
[15] Rosenthal DI, Liu Li, Lee JH, Vapiwala N, Chalian AA, Weinstein GS, et al. Importance of the treatment package time in surgery and postoperative radiation therapy for squamous carcinoma of the head and neck. Head Neck 2002;24(2):115–26. https://doi.org/10.1002/hed.10038.
[16] Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million RR. An analysis of factors influencing the outcome of postoperative irradiation for squamous cell carcinoma of the oral cavity. Int J Radiat Oncol Biol Phys 1997;39:137–48. https://doi.org/10.1016/s0360-3016(97)00152-1. PMID: 9300748.
[17] Peters LJ, Withers HR. Applying radiobiological principles to combined modality treatment of head and neck cancer-the time factor. Int J Radiat Oncol Biol Phys 1997;39:831–6. https://doi.org/10.1016/s0360-3016(97)00466-5. PMID: 9369130.
[18] Tribius S, Donner J, Pazdyka H, Münscher A, Gröbe A, Petersen C, et al. Survival and overall treatment time after postoperative radio(chemo)therapy in patients with head and neck cancer. Head Neck 2016;38(7):1058–65. https://doi.org/10.1002/hed.24407.
[19] Rosenthal DI, Mohamed ASR, Garden AS, Morrison WH, El-Naggar AK, Kamal M, et al. Final Report of a Prospective Randomized Trial to Evaluate the Dose-Response Relationship for Postoperative Radiation Therapy and Pathologic Risk Groups in Patients With Head and Neck Cancer. Int J Radiat Oncol Biol Phys. 2017;98(5):1002–11. https://doi.org/10.1016/j.ijrobp.2017.02.218. Epub 2017 Jul 10 PMID: 28721881.
[20] Ridge JA, Lydiatt WM, Patel SG, Glastonbury CM, Brandwein-Gensler M, Ghossein RA, et al. In: AJCC Cancer Staging Manual. Cham: Springer International Publishing; 2017. p. 79–94. https://doi.org/10.1007/978-3-319-40618-3_7.
[21] Tam M, Wu SP, Gerber NK, Lee A, Schreiber D, Givi B, et al. The impact of adjuvant chemoradiotherapy timing on survival of head and neck cancers. Laryngoscope. 2018;128(10):2326–32.
[22] Goel AN, Frangos MI, Raghavan G, Lazaro SL, Tang B, Chhetri DK, et al. The impact of treatment package time on survival in surgically managed head and neck cancer in the United States. Oral Oncol. 2019;88:39–48. https://doi.org/10.1016/j.oraloncology.2018.11.021.
[23] Ghanem AI, Schymick M, Bachiri S, Mannari A, Sheqwara J, Burmeister C, et al. The effect of treatment package time in head and neck cancer patients treated with adjuvant radiotherapy and concurrent systemic therapy. World J Otorhinolaryngol Head Neck Surg. 2019;5(3):160–7. https://doi.org/10.1016/j.wjorl.2018.09.005.
[24] Chen MM, Harris JP, Orosco RK, Sirjani D, Hara W, Divi V. Association of Time between surgery and adjuvant therapy with survival in Oral cavity cancer. Otolaryngol Head Neck Surg. 2018;158(6):1051–6. https://doi.org/10.1177/0194599817751679. Epub 2018 Jan 9 PMID: 29313448.
[25] Guttmann DM, Kobie J, Grover S, Lin A, Lukens JN, Mitra N, et al. National disparities in treatment package time for resected locally advanced head and neck cancer and impact on overall survival. Head Neck. 2018;40(6):1147–55. https://doi.org/10.1002/hed.25091.
[26] Liu SW, Woody NM, Wei W, Appachi S, Contrera KJ, Tsai JC, et al. Evaluating compliance with process-related quality metrics and survival in oral cavity squamous cell carcinoma: Multi-institutional oral cavity collaboration study. Head Neck 2021;43(1):60–9.
[27] Dort JC, Farwell DG, Findlay M, Huber GF, Kerr P, Shea-Budgell MA, et al. Optimal Perioperative Care in Major Head and Neck Cancer Surgery With Free Flap Reconstruction: A Consensus Review and Recommendations From the Enhanced Recovery After Surgery Society. JAMAOtolaryngol Head Neck Surg 2017;143(3):292. https://doi.org/10.1001/jamaoto.2016.2981.
[28] Friedland PL, Bozic B, Dewar J, Kuan R, Meyer C, Phillips M. Impact of multidisciplinary team management in head and neck cancer patients. Br J Cancer 2011;104:1246–8. https://doi.org/10.1038/bjc.2011.92. PMID: 21448166.
[29] Yu Y, Schöder H, Kang J, McBride SM, Tsai CJ, Chen L, et al. Postoperative PET/CT for detection of early recurrence (ER) after surgery for squamous cell carcinomas (SCC) of the oral cavity (OC). J Clin Oncol. 2021;39(15_suppl):6060. https://doi.org/10.1200/JCO.2021.39.15_suppl.6060.
[30] Humbert M, De La Losa M, Gery B, Florescu C, Thariat J, Rambeau A. Routine feasibility of postoperative chemoradiotherapy in head and neck squamous cell carcinoma at high risk of recurrence [published online ahead of print, 2020 Apr 11]. Eur Ann Otorhinolaryngol Head Neck Dis. 2020;S1879–7296(20):30088. https://doi.org/10.1016/j.anorl.2020.03.012. PMID: 32291205.
[31] Woody NM, Ward MC, Koyfman SA, Reddy CA, Geiger J, Joshi N, et al. Adjuvant Chemoradiation After Surgical Resection in Elderly Patients With High-Risk Squamous Cell Carcinoma of the Head and Neck: A National Cancer Database Analysis. Int J Radiat Oncol Biol Phys. 2017;98(4):784–92. https://doi.org/10.1016/j.ijrobp.2017.03.019.