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Research Paper

The effect of treatment package time in head and neck cancer patients treated with adjuvant radiotherapy and concurrent systemic therapy

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Abstract *Objectives:* In patients with head and neck carcinoma, "treatment package time" (TPT) was proven to impact outcomes in cases receiving adjuvant radiotherapy alone. Its impact in patients receiving radiotherapy with concurrent systemic therapy has not been studied previously. The TPT influence on survival endpoints for patients treated with surgery followed by radiation and concurrent systemic therapy was analyzed.
Methods: Institutional database to identify head and neck carcinoma cases treated with definitive surgery followed by concomitant chemo(bio) radiotherapy (CRT) was used. TPT was the number of days elapsed between surgery and the last day of radiation. %FINDCUT SAS macro tool was used to search for the cutoff TPT that was associated with significant survival benefit. Kaplan–Meier curves, log-rank tests as well as univariate and multivariate analyses were used

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to assess overall survival (OS) and recurrence free survival (RFS).
Results: One hundred and three cases with a median follow up of 37 months were included in the study. Oropharyngeal tumors were 43%, oral cavity 40% and laryngeal 17% of cases. Concurrent systemic therapy included platinum and cetuximab in 72% and 28%, respectively. Optimal TPT was found to be < 100 days with significantly better OS ($P = 0.002$) and RFS ($P = 0.043$) compared to TPT $\geq$100 days. On multivariate analysis; TPT<100 days, extracapsular nodal extension, high-risk score, lymphovascular space and perineural invasion were independent predictors for worse OS ($P < 0.05$). T4, extracapsular nodal extension and high-risk score were all significantly detrimental to RFS ($P < 0.05$).
Conclusions: Addition of concomitant systemic therapy to adjuvant radiotherapy did not compensate for longer TPT in head and neck squamous cell carcinoma. Multidisciplinary coordinated care must be provided to ensure the early start of CRT with minimal treatment breaks.

Introduction

Head and neck squamous cell carcinomas (HNSCC) constitute a major problem in the United States with approximately 64 490 new cases and 13 740 deaths expected in 2018.[1] More than 75% of cases present with localized or regional disease with 5 year survival of around 80% and 60% for localized and regional disease respectively.[2] Combined modality therapy with surgery and postoperative radiation therapy (PORT) is recommended for a great proportion of these patients as it had been proven to be better than either treatment alone.[3–5] According to the combined analysis of the two major randomized trials addressing the role of postoperative therapy high risk features including extracapsular nodal extension (ECE), positive surgical margin (PM), pathological T3 or T4 tumor (T3/4), perineural invasion (PNI), lymphovascular space invasion (LVSI) and the invasion of two or more lymph nodes (N2+) were assessed for benefit of the addition of concurrent chemotherapy (CT) to adjuvant RT (CRT). Of these, only ECE and/or PM were associated with a significantly improved outcome with CRT with the remaining factors only showing a trend.[6–8] On this basis, the National Comprehensive Cancer Network (NCCN) and other guidelines developed their recommendations to administer adjuvant CRT for cases harboring ECE and/or PM reserving adjuvant radiotherapy (RT) alone for the other risk factors.[9,10]

In addition, the impact of treatment duration on outcomes has also been investigated. The three parameters studied included time from surgery to RT initiation, overall RT duration and treatment package time (TPT) that encompasses the whole interval between surgery date and the conclusion of RT course. Many studies showed that longer overall radiotherapy duration due to treatment interruptions and delays was detrimental for locoregional control.[11–13] As for surgery to radiotherapy initiation (SRT), improved outcomes were achieved with shorter wait times according to many studies.[11,14–18] Other studies did not come to the same conclusion.[19–22] A meta-analysis involving 851 patients reported that adjuvant RT should be initiated within 6 weeks of surgery for best results and this has been adopted by the NCCN.[9,23] Finally, the concept of TPT emerged which encompasses the influence of the two aforementioned time components (SRT + ORT) and was proven to correlate with outcomes even when any or both of them were not.[19,24,25] Optimal TPT cutoff varied between different studies with 100 days in classic studies[19,25,26] ranging between 77 and 105 in others.[27–30] In contrast, other studies refuted the significance of the TPT.[12,13]

Nevertheless, none of these studies analyzed time factors for cases treated using adjuvant radiation therapy with concomitant systemic therapy. In the present study we investigated the influence of TPT on outcomes of a high-risk population of surgically resected head and neck squamous cell carcinoma treated by adjuvant chemoradiotherapy.

Methods

After obtaining Institutional Review Board approval, we queried our prospectively maintained head and neck cancer database to identify HNSCC cases of oral cavity, oropharynx and larynx/hypopharynx treated with curative intent by surgical resection followed by adjuvant CRT. The decision to add CT to PORT was undertaken in the setting of multidisciplinary tumor board based mainly on close/involved margin and/or ECE in surgical specimen.[6–8] All cases without curative intent surgery, those treated with adjuvant radiotherapy alone as well as patients receiving induction chemotherapy were excluded from our analysis. In addition, cases who had not received the planned RT dose or systemic therapy cycles were not included. Patients were preferentially recommended concurrent cisplatin. Concurrent cetuximab was delivered in patients who could not tolerate cisplatin due to pre-existing renal, cardiac or hearing issues. For each case we calculated a provisional risk score (RS) based on NCCN defined indications for adjuvant treatment.[9] Two points each were assigned for PM and ECE and 1 point for each of the remaining adverse features (T3/4, N2+, PNI and LVSI) reaching a maximum possible score of 8. Then we categorized RS as low (<2), intermediate (2–4) and high (4–8). We did not include nodal involvement of level IV and V as this factor is not prognostic for laryngeal/hypopharyngeal tumors that we

Table 1 Demographic, pathologic and treatment characteristics of the two study groups with TPT<100 days or TPT≥100 days.

Variable	TPT[i] <100 days (n = 62)	TPT≥ 100 days (n = 41)	P value
Median age in years	59 (range 36.0–84.0)	56 (range 36.0–79.0)	0.401
Gender			0.091
Male	50 (81%)	27 (66%)	
Female	12 (19%)	14 (34%)	
Race			0.622
White	39 (63%)	25 (60%)	
Black and others	23 (37%)	16 (40%)	
Smoking status			0.012
Non-smoker	22 (35%)	4 (10%)	
Smoker≤ 20 packs years	11 (18%)	12 (29%)	
Smoker> 20 packs years	29 (47%)	25 (61%)	
Alcohol status			0.481
None	21 (34%)	12 (29%)	
Social drinker/infrequent	20 (32%)	18 (44%)	
Alcoholism	21 (34%)	11 (27%)	
Charlson comorbidity score			0.0572
0	32 (52%)	18 (44%)	
1-2	18 (29%)	16 (39%)	
3+	12 (19%)	7 (17%)	
HNSCC[a] location			0.002
Oral cavity	19 (31%)	22 (54%)	
Oropharynx	35 (56%)	9 (22%)	
Larynx/hypopharynx	8 (13%)	10 (24%)	
HPV[b] status			0.311
Positive	17 (27%)	6 (15%)	
Negative	12 (19%)	9 (22%)	
Not-tested	33 (53%)	26 (63%)	
Histological grade			0.167
1	13 (21%)	5 (13%)	
2 & 3	49 (79%)	36 (87%)	
Pathological T stage			0.033
T1/2	29 (47%)	13 (32%)	
T3	7 (11%)	3 (7%)	
T4	26 (42%)	25 (61%)	
Pathological N stage			0.668
N0/N1	19 (31%)	10 (25%)	
N1/N2	43 (69%)	31 (75%)	
Median +ve[c] LN[d]	2 (0–20)	3 (0–91)	0.282
+ve ECE[e]	30 (48%)	25 (61%)	0.210
Final surgical margins			0.289
Negative	25 (40%)	23 (56%)	
Close	15 (24%)	7 (17%)	
Involved	22 (36%)	11 (27%)	
+ve LVSI[f]	24 (39%)	20 (49%)	0.312
+ve PNI[g]	24 (39%)	24 (59%)	0.048
Mean risk score (RS, *Mean* ± *SD*)	3.7 ± 1.6	4.3 ± 2.1	0.155
Concomitant systemic treatment			0.122
Platinum based	48 (77%)	26 (63%)	
Cetuximab	14 (23%)	15 (37%)	
LN dissection			0.036
Unilateral	27 (44%)	9 (22%)	
Bilateral	35 (56%)	32 (78%)	
RT[h] treatment interruptions	7 (11%)	15 (37%)	0.002
Median time to recurrence (months)	8	6	0.171
Alive at last follow up	48 (77%)	20 (49%)	0.003

[a] Head and neck squamous cell carcinoma.
[b] Human papilloma virus.
[c] Positive.

[d] Lymph nodes.
[e] Extracapsular nodal extension.
[f] Lymphovascular space invasion.
[g] Perineural invasion.
[h] Radiation therapy.
[i] Treatment package time.

included, and it was not consistently recorded in our database.

Treatment package time (TPT), representing the number of days elapsed between surgery date and the last day of CRT was calculated for each case of the study cohort. We used %FINDCUT SAS macro tool to define TPT optimal cutoff point to the nearest 10 days that was correlated with the most significant difference in overall survival (OS) and recurrence free survival (RFS).[31,32] After establishment of the cutoff value 2 groups were created and all demographic, pathological and treatment data was compared.

Chi-squared and Fisher's Exact tests for categorical and Wilcoxon test for continuous variables were performed to analyze differences in distribution of variables by TPT cutoff, with the generation of two-sided *P*-values. Statistical significance was defined at *P* value of $\leq$0.05. OS and RFS were assessed by Kaplan–Meier and log-rank tests for the study groups. Univariate and multivariate modeling (MVA) with Cox regression analysis were performed to identify statistically significant predictors of OS and RFS for the entire cohort. All statistical analyses were performed using Statistical Analysis Software, version 9.4 (SAS Institute, Inc. Cary, NC, USA).

Results

Out of a total of 300 cases managed with curative surgery and adjuvant RT, we identified 103 cases treated between 2010 and 2015 that utilized adjuvant CRT who has met our inclusion criteria. Of the total, 44 cases (43%) were oropharyngeal (OP) primaries, 41 cases (40%) were oral cavity (OC) and 17% were laryngeal/hypopharyngeal (LA). Mean RS was 4.0 $\pm$ 1.8 (median 4). All cases received a complete RT course to the tumor bed and neck using intensity modulated radiation treatment (IMRT) prescribed to the PTV. High dose regions received 60–66 Gy with low risk areas receiving 45–54 Gy. All cases received 2 Gy per fraction, five fractions per week with median dose 65 Gy, mean (62.5 $\pm$ 6.6) Gy concomitant with either platinum based chemotherapy (72%) or cetuximab (28%). Median TPT for the entire study cohort was 91 (57–168) days and mean was (95.8 $\pm$ 24.0) days.

Using the %FINDCUT SAS macro tool we evaluated 80, 90, 100 and 110 days as cutoff points for TPT. Optimal TPT was found to be $<$ 100 days (n = 62) with significantly better OS (P = 0.002) and RFS (P = 0.043) compared to TPT$\geq$100 days (n = 41). The two study groups were well-balanced for the majority of demographic and pathological features including RS (mean: 3.7 vs 4.3; P = 0.15) except that TPT$\geq$100 days was associated with higher smoking history, OC location, T4 disease and bilateral neck dissection ($P < 0.05$). TPT$<$100 days had less interruptions during RT and significantly more oropharyngeal cases (P = 0.002); nevertheless, there was no difference in the distribution of HPV positive and negative disease between the two study groups (P = 0.31) as portrayed in Table 1. Causes for TPT$\geq$100 days were RT interruptions (15; 37%) and/or longer surgery to RT initiation (34; 83%) as portrayed in Table 2.

After a median follow up time of 37 months (3–72); nearly a third of the population (31%) had a recurrence most of which (78%) included distant metastases that were fatal. Salvage surgeries with or without re-irradiation were performed only in 6 subjects (18.8%) and the remaining cases either received palliative systemic therapy (37.4%) or only supportive measures (43.8%). Kaplan–Meier curve for OS shows significant benefit for TPT$<$ 100 days at 1 & 2 years [91% (95% *CI*: 82–97) vs. 68% (95% *CI*: 52–80) & 90% (95% *CI*: 79–95) vs. 56% (95% *CI*: 39–69), $P < 0.01$] as in Fig. 1A. Similar findings were detected for RFS with TPT$<$100 days at 1 & 2 years [89% (95% *CI*: 78–94) vs. 71% (95% *CI*: 54–82) & 80% (95% *CI*: 68–88) vs. 60% (95% *CI*: 44–74), $P < 0.05$] as depicted in Fig. 1B.

Meanwhile, subgroup analyses showed that two-year OS was worse for TPT$\geq$100 vs $<$ 100 days for both oral cavity (P = 0.03) and oropharynx (P = 0.02).Similar findings were detected among both smokers (P = 0.003) or non-smokers (P = 0.02). This significant difference persisted within cases that received platinum after we excluded cases that utilized cetuximab (P = 0.002). A secondary analysis for risk score categories expressed a highly significant detrimental effect on OS and RFS for higher RS ($P < 0.0001$) as in Fig. 2.

On MVA for OS for the whole cohort (n = 103); TPT $\geq$100 days and high RS were independent predictors for worse OS ($P < 0.05$) after adjusting for all other factors. In another MVA model including RS components and excluding RS total score: ECE, LVI & PNI were all detrimental for OS ($P < 0.05$) as shown in Table 3. In an exploratory MVA for RFS: T4 vs T1/2, +ve ECE and high RS were significantly related to

Table 2 Causes of TPT$\geq$100 days [n(%)].

Overall causes of TPT[a]≥100 days(n = 41)	N (%)
Long SRT[b]	26 (71)
RT[c] treatment interruptions	7 (17)
Long SRT and RT treatment delays	8 (12)
Causes of long SRT[b] (n = 34)	
Wound healing problems	21 (62)
Insurance and socioeconomic issues	10 (29)
Medical comorbidities	3 (9)

[a] Treatment package time.
[b] Surgery to radiation therapy interval.
[c] Radiation therapy.

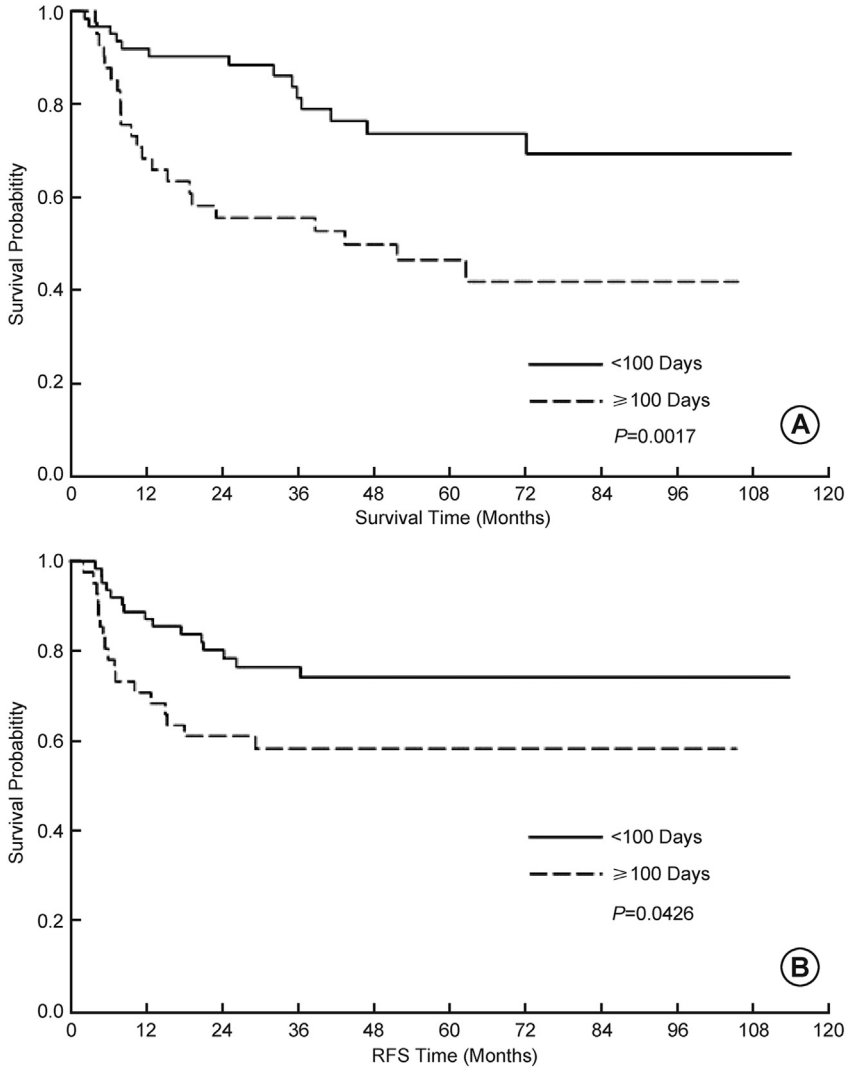

Fig. 1 Kaplan–Meier curves for overall survival (A) and recurrence free survival (B) for the two TPT groups.

inferior RFS ($P < 0.05$); however, TPT was not independently associated with RFS.

Discussion

To our knowledge, this is the first analysis examining timing factor for patients treated with postoperative radiotherapy utilizing modern IMRT technique with concurrent systemic therapy. Harris et al in a recently published national cancer database (NCDB) study which included more than 25 000 HNSCC cases treated with adjuvant RT, comprised 57% cases that received concomitant chemotherapy. Nevertheless, only SRT interval was studied and no separate analysis was provided for the cases only treated with adjuvant CRT.[18] Cases managed with adjuvant CRT represented 43% ($n = 118$) of Tribius et al study, albeit no separate results for TPT$<$ or $\geq$87 days were presented for this subgroup.[29]

We hypothesized that higher total dose 60–66 Gy and sensitizing concomitant systemic therapy will achieve an acceptable level of locoregional control and survival independent of TPT. However, TPT$<$100 days was proven to have superior overall and recurrence free survival and this cutoff time point was not much different from the 87–100 days that prevailed in classic studies.[20,25,27] TPT of 87 days was calculated in modern series in Tribius et al that included CRT cases and the most recent report on the MD Anderson randomized trial of PORT and both resorted to recursive partitioning analysis to determine the cutoff level.[29,30] TPT$\geq$100 days was independently associated with worse OS but not for RFS. This may be as the MVA model for RFS was only exploratory due to inadequate recurrence events which was not the case for OS.

In fact, sequential CT before RT yielded no benefit in terms of OS or DFS compared to PORT alone as per Intergroup 0034 study that was mainly owing to increased treatment package time in chemotherapy arm by at least 9 weeks.[33] Similar outcomes for sequential CT were reported by Muriel et al;[34] taking into consideration that chemotherapy was only effective in the CRT setting as long as RT starts within maximum of 8 weeks per inclusion criteria for the RTOG 95-01 study.[7] RTOG 0024 also examined both short postoperative and concomitant CT without increasing TPT; however no superior results were attained compared

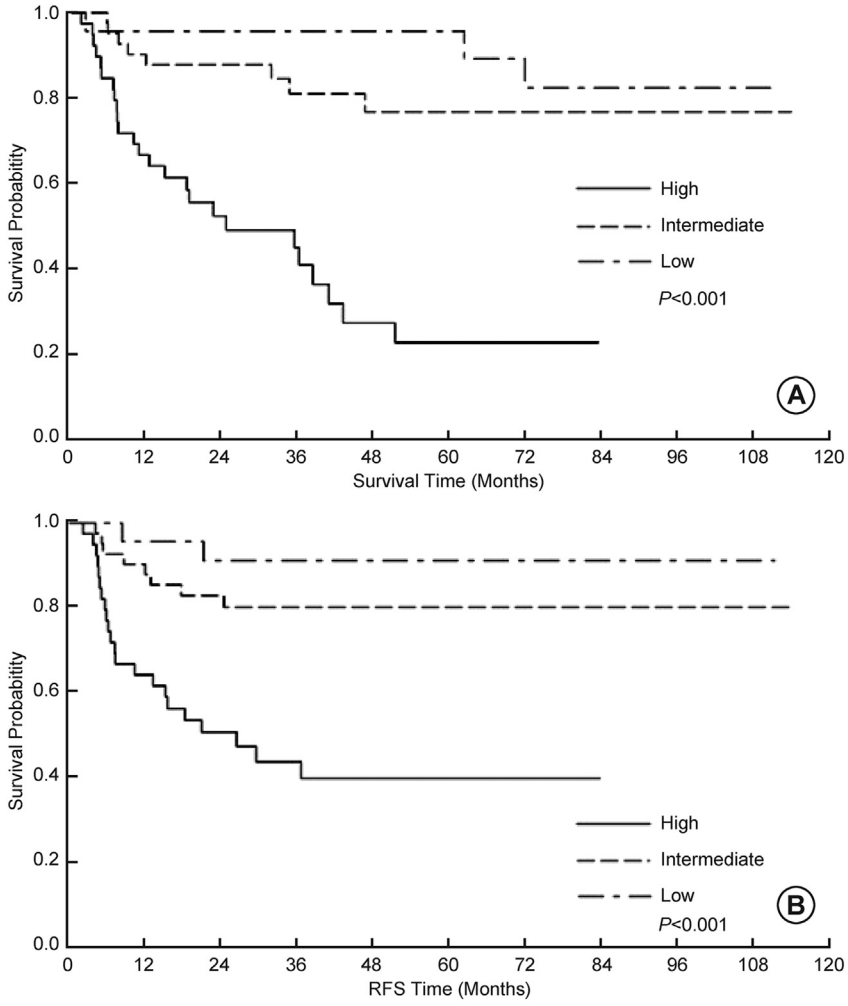

Fig. 2 Kaplan–Meier curves for overall survival (A) and recurrence free survival (B) for risk score (RS) categories.

Table 3 Multivariable analysis models for predictors of recurrence free survival and overall survival for the entire study cohort (n = 103) including all components of RS and excluding RS (A), including RS as continuous or categorical and excluding its components (B).

Variable	Response	Overall survival			Recurrence free survival (exploratory)		
(A)	–	*HR*	95% *CI* of *HR*	*P* value	*HR*	95% *CI* of *HR*	*P* value
ECE[a]	Yes	2.92	1.35–6.33	0.0065	3.78	1.56–9.11	0.0031
LVSI[b]	Yes	2.69	1.26–5.77	0.0108	2.22	0.94–5.25	0.0687
PNI[c]	Yes	2.45	1.08–5.57	0.0319	–	–	–
Pathological T stage	T1 vs T4	–	–	–	0.19	0.04–0.89	0.0353
	T2 vs T4	–	–	–	0.42	0.14–1.32	0.1384
(B)							
RS[d]	Continuous	1.53	1.28–1.83	<0.0001	1.59	1.29–1.95	<0.0001
RS category	High vs Low	11.54	3.36–39.64	0.0001	9.05	2.1–38.95	0.0031
	Intermediate vs Low	2.92	0.75–11.42	0.1229	2.93	0.61–13.96	0.1777
TPT[e]	≥100 vs 100	2.37	1.17–4.83	0.0170	1.6	0.78–3.31	0.2021

[a] Extracapsular nodal extension.
[b] Lymphovascular space invasion.
[c] Perineural invasion.
[d] Treatment package time.
[e] Risk score.

to RTOG 95—01 controls except in cases with ECE or PM.[7,35] Consequently, both the theoretical postoperative proliferation of residual tumor cells as well as the rapid repopulation occurring during RT does not seem to be robustly counteracted by CT neither in the sequential setting nor concurrently with RT especially if long gaps occur.

TPT has two components namely surgery to RT interval (SRT) and interruption occurring during the course of RT. In our study TPT≥100 days was associated with more delays during RT (37% vs 11%, $P = 0.002$). Moreover, prolonged SRT was identified in 83% of TPT≥100 days mainly due to wound healing problems (62%) or insurance issues and other medical conditions (38%). This is in agreement with factors associated with for longer TPT reported in other studies.[25,30] It is noteworthy to report that T4 disease and oral cavity location were more associated with longer TPT in our results as these cases are managed with more extensive surgery resulting in higher chances of complicated wound healing that is even worsened by higher smoking index that prevailed in that group. T4 disease, insurance and facility issues as well as the use of concomitant chemotherapy were all significantly associated with prolonged TPT as seen in our study.[12,14,25] Whether adjuvant CRT should commence before maximal healing needs to be examined in a prospective setting. Nevertheless, robust pre-operative optimization in addition to adequate perioperative care need to be stressed as both will help in getting the patients through treatment as early as possible and hence limiting total package time.

Another crucial observation in our work in high risk population is that there was significant difference in outcomes among groups harboring multiple compared to fewer NCCN indications for RT ± CT as manifested in our provisional risk score (RS) which was independent of any other factors. Other studies that grouped cases according to number or weighting of risk factors confirmed this finding.[13,25,27,36] Moreover, none utilized concomitant chemotherapy and most used suboptimal doses of RT. This finding persisted in our study despite the receipt of standard of care with currently recommended dosage and fractionation of RT and concomitant CT. Consequently, new trials need to be designed to address cases with multiple risk factors including those with ECE and involved margins to explore further dose escalation or other treatment options for this group.

Some limitations of this study ought to be mentioned. As with any non-randomized retrospective study, selection and reporting bias limit the study. However due to ethical reasons no prospective trial can be designed to explore the timing factors. Although the time frame of this study is nearly 6 years, treatment recommendations have not changed much during that time. Having relatively low number of cases prevented us from designing robust subgroup analyses for different HNSCC subsites bearing in mind that we had proportionally fewer larynx cases as laryngeal preservation is sought as possible. However, this is a single institution study and this high risk population is often low in number Although TPT≥100 days was associated with significantly less oropharyngeal cancers and more T4 disease, longer TPT was detrimental on OS after adjusting for all other factors. Neither tumor location nor T-stage were independent factors for OS in our study and also HPV status was not significantly different among study groups.

Conclusion

Addition of concomitant systemic therapy to adjuvant RT did not compensate for longer TPT in HNSCC with high risk features. Multidisciplinary coordinated care and support programs must be provided to ensure as early as possible start of CRT with minimal treatment breaks. The co-existence of multiple surgical and pathological risk factors is related to worse outcomes and this population needs to be encountered in the setting of dedicated prospective studies.

Conflict of interest

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