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Treatment package time in high-risk oral cavity squamous cell carcinoma: where are we failing and at what cost?

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ABSTRACT

Background: The gold-standard of treatment for oral cavity squamous cell carcinoma (OCSCC) is surgery and adjuvant chemoradiotherapy (CRT) in the sub-group of high-risk patients. In this group of patients, treatment time is an important factor in clinical outcomes. We aim to study the influence of the treatment package time (TPT).

Materials and methods: We conducted a retrospective study of patients with high-risk OCSCC managed with surgery followed by adjuvant CRT between January 2017 and December 2020. TPT was defined as the time between surgery and the last fraction of radiotherapy. We categorized TPT according to an optimal cut-off point. The Kaplan-Meier methodology was used to calculate 5-year survival.

Results: We included 79 patients, median age: 60 years (range: 39–70 years), majority were male (84.8%, n = 67) and smokers (73.4%, n = 58). Extra-nodal extension (ENE) and positive resection/< 1 mm margin were found in 51.9% (n = 41) and 84.8% (n = 67) of cases, respectively. Median radiotherapy dose: 66 Gy. Median cisplatin dose: 300 mg/m^2. Median TPT time was 109 days. The optimal cut-off point was 104 days. 5-year overall survival (OS) with TPT ≤ 104 days was 77.4% and 46.7% with TPT > 104 days, with similar results for disease-free survival (DFS).

Conclusions: Our institution cohort of high risk OCSSC treated with surgery followed by adjuvant CRT had a prolonged TPT (median 109 days). Within our cohort, a TPT > 104 days was found to have a worse OS and DFS, with a nonsignificant impact on locoregional or distant disease-free survival. This highlights the need to optimize the multimodal cancer care pathway.

Keywords: oral cavity; adjuvant chemoradiotherapy; treatment package time

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Introduction

Oral cavity cancer is a group of rare neoplasms, representing 2% of new cancer diagnoses worldwide and 1.8% of cancer related deaths [1]. In Portugal there were 1103 diagnoses of oral cavity cancer and 382 deaths caused by it in 2020 [2].

The gold-standard of treatment for oral cavity squamous cell carcinoma (OCSCC) is surgery. According to pathological criteria, surgery is followed by adjuvant treatment with Radiotherapy (RT) with or without concomitant systemic treatment [3]. Despite multimodal treatment plans, results remain discouraging, highlighting the need to identify prognostic factors and therapeutic strategies to improve outcomes.

Adjuvant treatment with chemoradiotherapy (CRT) for OCSCC is, nowadays, the standard of care in the sub-group of high-risk patients. Two main studies demonstrated the benefit of this combined approach: Radiation Therapy Oncology Group (RTOG) 9501 and European Organisation for. Research and Treatment of Cancer (EORTC) 22931. These were analysed together by Bernier in 2005 who concluded that adjuvant CRT is superior to RT in locoregional control and disease-free survival (DFS) in high-risk head and neck cancer patients, namely those with extra-capsular lymph node extension or positive surgical margins. In this group, there was a 10% survival benefit at 5 years when compared with radiotherapy alone, with patients without these risk factors not benefiting from the combination of CRT in adjuvant treatment [4, 5].

Data from RTOG 0951 were updated and a 10-year follow-up demonstrated no difference in loco regional control, DFS or overall survival (OS). However, when analysing the subgroup of patients with positive surgical margins and/or extracapsular extension, patients who underwent CRT had better outcomes, namely better local control [21.0% *vs.* 33.1%, hazard ratio (HR), p = 0.02), DFS (18.4% *vs.* 12.3%, HR, p = 0.05) and OS (27.1% *vs.* 19.6%, HR, p = 0.07) [6].

In patients who have undergone surgery and need adjuvant radiotherapy, treatment time is an important factor in clinical outcomes. The time to start adjuvant treatment (from the day of surgery until the start of radiotherapy treatments) should be under 6 weeks, as this leads to better outcomes [3]. The treatment package time (TPT) is the time from the day of surgery to the last day of radiotherapy treatment and should be under 11 weeks / 77 days [7]. This appears possible in a scenario where the patient's surgical recovery occurs between 4 and 6 weeks (28 to 42 days) and radiotherapy treatments run uninterrupted for 40 to 45 days, for a treatment dose of 60–66 Gy, allowing for an optimal TPT of 68 to 87 days.

We aim to investigate the impact of TPT on survival in a single institution cohort of surgically resected high-risk OCSCC patients who received adjuvant CRT.

Materials and methods

Population

We analysed radiation treatment courses in our department's internal database and cross-linked them with the institution's medical records of patients with non-metastatic high-risk OCSCC managed with surgery followed by adjuvant CRT between January 2017 and December 2020. Inclusion criteria were age ≥ 18 years, histological diagnostic of OCSCC, surgical resection and pathological high-risk criteria for adjuvant CRT (extracapsular extension or positive/< 1 mm margin). Exclusion criteria included patients treated outside this time frame, an unknown total TPT, no pathological high-risk criteria, histologies other than SCC and no concomitant chemotherapy.

Study variables

Data collection included patient [sex, date of birth, Eastern Cooperative Oncology Group Performance Status (ECOG PS), smoking history, alcohol consumption, haemoglobin at diagnosis], tumour (location of primary tumour, degree of histological differentiation, Tumor–Node–Metastasis (TNM) stage, number of positive nodes in the surgical specimen, extra-nodal extension (ENE), positive or < 1 mm surgical margins (PM), perineural invasion, lympho-vascular invasion] and treatment (date of surgery, mandibular segmentectomy, levels of lymph node dissection, number of resected lymph nodes, number of positive lymph nodes, date of pathological report, date of the multidisciplinary team decision for CRT, start date of RT, end date of RT, total RT dose, used chemotherapy and cumulative CT dose) characteristics. Whenever applicable,

the clinical reasons that justified the postponement of procedures necessary for the continuity of oncological care (e.g. clinical and non-clinical complications) were documented. The date of local or distant disease progression and date of death were also collected.

Outcome definitions

TPT was defined as the number of days between the date of surgery and the date of the last fraction of RT. A patient was considered ready for RT planning if simultaneously had a multidisciplinary therapeutic meeting, pathological report, and clinical condition for planning. OS was defined as the time between the date of surgery and the date of death from any cause. DFS was defined as the time between the date of surgery and the date of death from any cause or disease relapse in any location. Locoregional disease-free survival (LRDFS) was defined as the time between the date of surgery and the date of the loco-regional disease recurrence. Distant disease-free survival (DDFS) was defined as the time between the date of surgery and the date of distant recurrence.

Statistical analysis

The analysis of TPT and OS and DFS association was carried out by adjusting Cox proportional hazards models. This analysis was carried out considering TPT as a continuous variable. The categorization of the TPT will be made based on the optimal cut-off point, i.e., the cut-off point that maximizes the separation between groups in terms of the analysed endpoints. The Kaplan-Meier methodology was used to calculate 5-year survival in the global sample and in the subgroups of interest. The analysis of **TLDLR and TLDD** outcomes was carried out using the Fine and Gray regression model, which allows evaluating the time until the first event considering the competitive events: locoregional recurrence; distant metastasis; and death without recurrence. A descriptive study was carried out on the time between surgery and pathological staging, surgery and the holding of a multidisciplinary meeting, and between surgery and the start of RT.

A significance level of 5% will be considered (except when expressly stated otherwise). The analysis will be done using the R program (https://www.r-project.org/).

Results

Baseline characteristics

We identified a total of 79 patients portrayed in Table 1. The median age was 60 years (range: 39–70 years), with a majority of male patients (84.8%, n = 67) and a smoking history (73.4%, n = 58). Almost all patients had a ECOG PS of 0 or 1 (97.5%, n = 77).

The most frequent primary tumor locations were the oral tongue (35.4%, n = 28), gum/buccal

Table 1. Population characteristics of the study cohort

Characteristic	N = 79 N (%)
Median age in years (range)	60 (39–70)
Male	67 (84.8)
Heavy smokers*	58 (73.4)
Heavy alcohol consumption**	46 (58.2)
PS ECOG 0–1	77 (97.5)
Hg < 14.5 g/dL in men and < 13 g/dL in women	35 (44.3)
Oral cavity subsite	
Retromolar trigone	6 (7.6)
Oral tongue	28 (35.4)
Floor of mouth	22 (27.8)
Gum/buccal mucosa	23 (29.1)
Performed staging PET-CT	3 (3.8)
Histological grade	
Grade 1–2	53 (67.1)
Grade 3	26 (32.9)
pT stage* **	
1–2	19 (24.1)
3–4	60 (75.9)
pN stage* **	
0–1	33 (41.8)
2	20 (25.3)
3	26 (32.9)
Disease stage* **	
I–II	4 (5.1)
III	12 (15.2)
IVa	37 (46.8)
IVb	26 (32.9)
Median dissected LN (range)	42 (0–104)
Median positive LN (range)	2 (0–19)
Positive LN/dissected LN > 7%	30 (38.0)

Table 1. Population characteristics of the study cohort

Characteristic	N = 79 N (%)
High-risk features	
Extra-nodal extension	41 (51.9)
Positive final/< 1 mm surgical margin	67 (84.8)
Perineural invasion	36 (45.6)
Lympho–vascular invasion	35 (44.3)
Median time to start RT in days (range)	62 (41–115)
Median RT treatment duration in days (range)	45 (39–65)
Median TPT in days (range)	109 (85–159)
Median RT dose delivered in Gy (range)	66 (60–70)
Concomitant cisplatin	69 (87.3)
Median cumulative dose of cisplatin in mg/m^2 (range)	300 (100–300)

PS ECOG — performance status according to Eastern Cooperative Oncology Group; Hg — hemoglobin; PET-CT — positron emission tomography/computed tomography; LN — lymph node; RT — radiotherapy; TPT — treatment package time. *> 10 Median Smoking index (pack-years); **men: ≥ 5 drinks/day, women ≥ 4 drinks/day; ***the American Joint Committee on Cancer (AJCC) 8th ed

mucosa (29.1%, n = 23) and floor of the mouth (27.8%, n = 22). According to American Joint Committee on Cancer (AJCC), 8th edition classification, pathological staging of the primary was pT3–pT4 in 75.9% of patients (n = 60), and 79.7% (n = 63) patients were stage IV at diagnosis (IVa = 46.8%, IVb = 32.9%). ENE and PM were present in 51.9% (n = 41) and 84.8% (n = 67) of cases, respectively.

The median radiotherapy dose was 66 Gy (range: 60–70 Gy) and the median cisplatin cumulative dose was 300 mg/m^2 (range: 100–300 mg/m^2).

Treatment package time and oncological outcomes

An optimal cut-off point of 104 days was found for TPT.

5-year OS was 77.4% [95% confidence interval (CI): 61.8–97.1%] for patients with TPT ≤ 104 days and 46.7% (95% CI: 33.5–65.0%) for patients with TPT > 104 days. In a univariable analysis it was found that the risk of death for patients with TPT > 104 days was 2.4 times higher (95% CI: 0.98–5.89; p = 0.0547). In a multivariable analysis controlled for confounding factors [T stage (T1/2 *vs.* T3/4), surgery with/without mandibular segmentectomy, bilateral lymph node dissection present/absent), the risk of death in the group with TPT > 1 04 days was 3.13 times higher (95% CI: 1.23–7.94; p = 0.0165).

5-year DFS for patients with TPT ≤ 104 days was 73.4% (95% CI: 57.2–94.2%) and 40.5% (95% CI: 27.8–59.1%) for patients with TPT > 104 days. In a univariable analysis, risk of death for TPT > 104 days was 2.46 times higher (95% CI: 1.11–5.42; p = 0.0262). In a multivariable analysis, using a model stratified by T stage (T1/2 *vs.* T3/4) and controlling for previously mentioned confounding factors, risk of death was 3.44 times higher with TPT > 104 days (95% CI: 1.50–7.87; p = 0.0035).

In the sample, 15 events of local recurrence, 14 events of distant recurrence, and 10 events of death without previous recurrence were observed. Given the smaller number of events of interest under analysis, the adjustment of the multivariate models was made considering only the T stage confounding factor (T3/4 *vs.* T1/2). In line with the analysis performed for OS and DFS, the TPT variable was categorized considering the cut-off point of 104 days (> 104 days *vs.* ≤ 104 days). In a univariable analysis it was not possible to demonstrate an association between TPT and time to locoregional (p = 0.594) or distant recurrence (p = 0.283). A multivariable analysis controlling for T stage also did not allow us to highlight statistically significant differences (time until locoregional recurrence: HR = 1.47; 95% CI: 0.46–4.72; p = 0.510; time until distant recurrence: HR = 3.04; 95% CI: 0.68–13.5; p = 0.140).

Multimodal cancer care pathway metrics

In the entire cohort, median TPT time was 109 days (range: 85–159 days). Median time from surgery to start of RT was 62 days and median RT treatment time was 45 days.

Dividing patients according to TPT (Tab. 2), patients with TPT ≤ 104 days, 2 (7.7%) patients started radiotherapy 42 days after surgery, while most patients (88.5%) were ready to plan CRT in under 6 weeks. Median time from surgery to pathological report was 19 days (Fig. 2A). Median time from surgery to the multidisciplinary team decision was 27 days (Fig. 2B). Median time from surgery to first RT appointment was 38 days and median time from surgery to start of RT was 53 days (Fig. 2C). Median time from the multidisciplinary team decision and first RT appointment was 7 days and median time from first RT appointment to start of RT was 15 days. Most patients (69.2%) had a total RT treatment time of 45 days or less.

Table 2. Surgical and institutional details concerning quality metrics among treatment package time (TPT) groups (≤ 104 days *vs.* > 104 days)

Characteristic		TPT ≤ 104 days (n = 26)	TPT > 104 days (n = 53)
Bilateral LN dissection		11 (42.3%)	30 (56.6%)
> 17 LN dissected		23 (88.5%)	48 (90.6%)
Pos-operative hospital stay >15 days		11 (42.3%)	24 (45.3%)
Difficult healing/dehiscence		8 (30.8%)	7 (13.2%)
Infection		2 (7.7%)	17 (32.1%)
Other		1 (3.8%)	0 (0.0%)
Re-admission within 10 days		0 (0.0%)	2 (3.8%)
Re-operation		1 (3.8%)	9 (17.0%)
Surgery and start of RT ≤42 days		2 (7.7%)	0 (0.0%)
Referred to and fulfilling all prerequisites for CRT < 6 week		23 (88.5%)	27 (50.9%)
Not ready	No clinical status	0 (0.0%)	4 (7.5%)
	No multidisciplinary decision	3 (11.5%)	25 (47.2%)
	No pathological result	0 (0.0%)	10 (18.9%)
Ready	Median days between multidisciplinary decision and 1st RT appointment (range)	7 (3–23)	14 (2-27)
	Median days between 1st RT appointment and start of RT (range)	15 (8–28)	22 (9-67)
Median time between surgery and pathological staging (days) (range)		19 (4–31)	26 (4–68)
Median time between surgery and multidisciplinary decision (days) (range)		27 (14–38)	34 (17–97)
Median time between surgery and 1st RT appointment (days) (range)		38 (23–43)	46 (29–102)
Median time between surgery and start of RT (days) (range)		53 (41–59)	67 (45–115)
Median time between multidisciplinary decision and 1st RT appointment (days) (range)		7 (2–19)	11 (2–36)
Median time between 1st RT appointment and start of RT (days) (range)		15 (8–28)	22 (7–67)
Total time of RT treatment ≤ 45 days		18 (69.2%)	26 (49.1%)

LN — lymph node; CRT — chemoradiotherapy; RT — radiotherapy

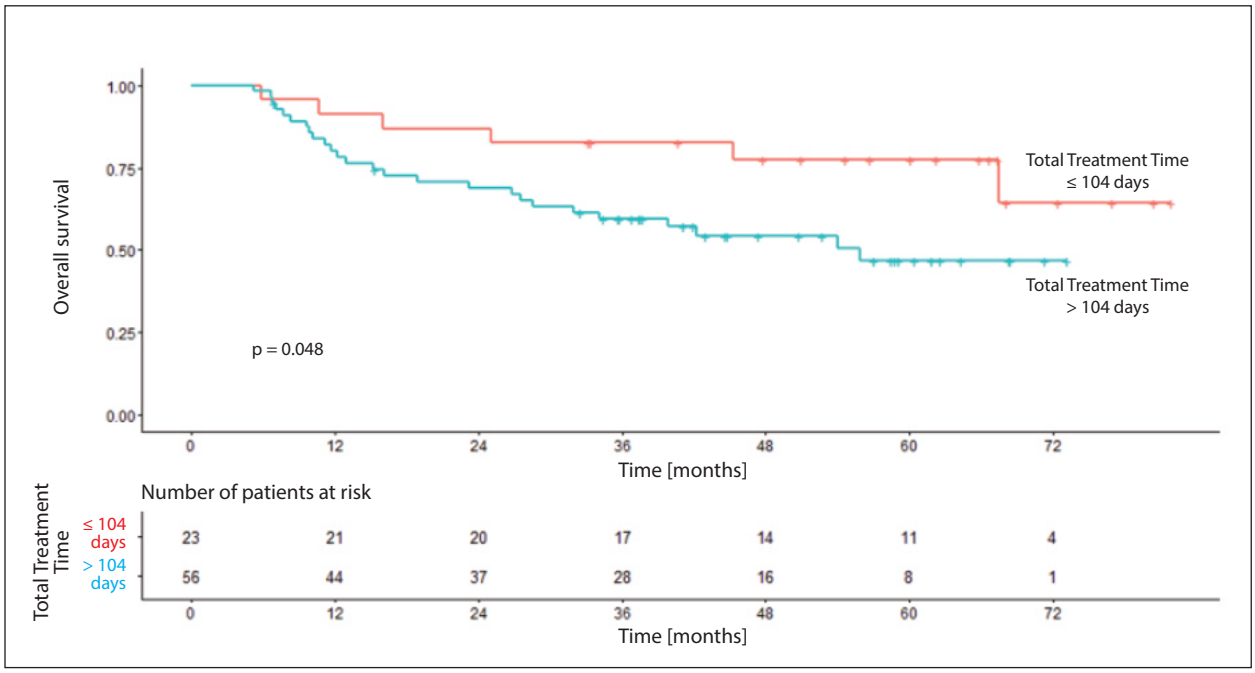

Figure 1. Overall survival by treatment package time (TPT) groups (≤ 104 days *vs.* > 104 days)

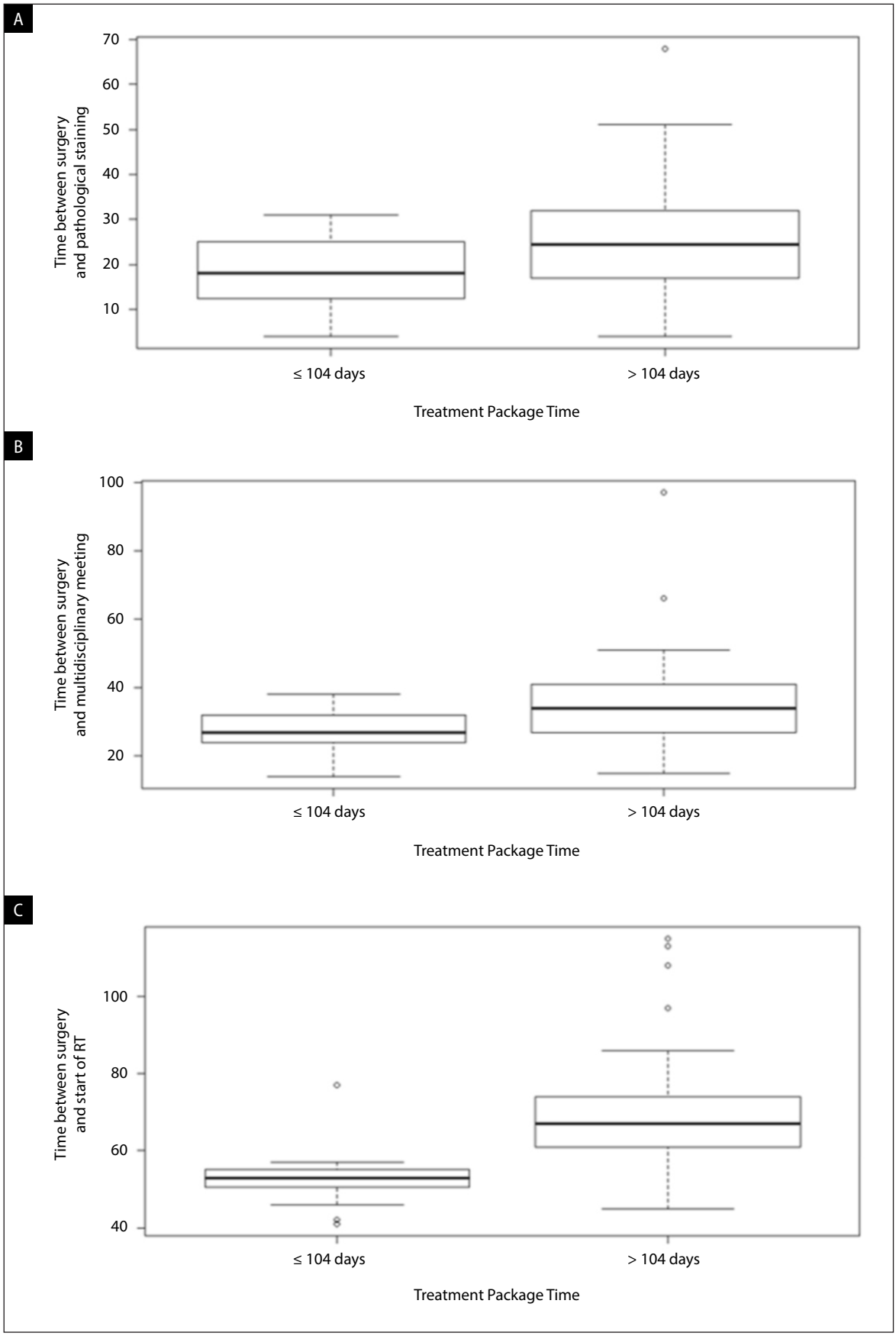

Figure 2A–C. Boxplot showing the time between surgery and pathological staging, multidisciplinary meeting, and the start of radiotherapy (RT), respectively

Patients with TPT > 104 days, none had started radiotherapy 42 days after surgery and half of the patients (50.9%) were ready to plan CRT 6 weeks after surgery. Median time from surgery to pathological report was 26 days (Fig. 2A). Median time from surgery to the multidisciplinary team decision was 34 days (Fig. 2B). Median time from surgery to first RT appointment was 46 days and median time from surgery to start of RT was 67 days (Fig. 2C). Median time from the multidisciplinary team decision to first RT appointment was 11 days and median time from first RT appointment to start of RT was 22 days. Nearly half the patients (49.1%) had a total RT treatment time of 45 days or less.

More than half of the patients in the entire cohort (n = 50, 63.3%) were ready for RT planning at 6 weeks. In the TPT of ≤ 104 days group the majority (n = 23, 88.7%) of patients were ready for RT planning at 6 weeks, while patients with TPT > 104 days, about half of the patients (n = 27, 50.9%) were ready for RT planning at 6 weeks.

Discussion

The importance of timing in the adjuvant setting of head and neck cancer has long been a subject of study. An interval between the surgery and adjuvant treatment under six weeks is known to provide better outcomes [8]. Although not the main aim of our study, this interval was increased in our cohort with a mean of 62 days, which contributed to a prolonged TPT. The duration of radiotherapy treatment, which takes into account unplanned pauses during RT and, consequently. the prolongation of treatment time, has been shown to have a deleterious effect on clinical outcomes, which is more significant in higher-risk patients undergoing treatment with a radiation dose > 60 Gy [9]. While not being the main aim of our study, in our cohort this metric was within the established time, with a mean of 45 days from start to finish of RT, therefore not being the main reason for a prolonged TPT.

Some studies have looked specifically at TPT as an important factor in head and neck cancer. Rosenthal et al. demonstrated that TPT was a treatment variable that had an impact on disease control, determining an optimal TPT of 85 days. However, this study only evaluated patients undergoing adjuvant RT, and did not take into account patients treated with CRT, not evaluating patients with a worse prognosis [10]. Other studies analysed all head and neck cancer patients treated with adjuvant CRT, not just a subgroup of patients with oral cavity cancer who normally have a longer surgical recovery time [11, 12]. One of these studies demonstrated that a TPT of up to 97 days has an impact on overall survival. However, this study included patients proposed for adjuvant CRT for prognostic factors other than pathological high risk criteria [13].

Two studies focused exclusively on oral cavity carcinomas and the impact of adjuvant RT treatment times, not including patients who underwent CRT. One of the studies analysed around 4800 patients from the National Cancer Data Base diagnosed between 1998 and 2011 and attempted to associate different time intervals of the therapeutic plan with an impact on OS, namely the interval between diagnosis and surgery, the interval between surgery and the start of radiotherapy, the duration of radiotherapy, the TPT and the interval between diagnosis and the end of RT. This study did not demonstrate an association between TPT and OS; however, it did verify an association between the duration of RT and OS – patients with shorter treatment times (i.e., without treatment interruptions) had better survival. This study did not, however, evaluate disease-free survival, a relevant endpoint in this context [14]. Another study analysed 132 patients treated at the same institution diagnosed between 2008 and 2016. It was found that a TPT greater than 11 weeks was a factor independently associated with worse OS (HR: 6.68) and worse DFS (HR: 2.94) [15].

The study most closely related to ours, focusing on high-risk OCSCC who underwent adjuvant CRT showed that 5-year OS was worse for TPT > 90-days (45% *vs.* 62%; p = 0.05), with similar results for DFS [16].

In our study of high-risk OCSCC treated with adjuvant CRT, TPT > 104 days was associated with worse OS and DFS. We acknowledge the potential confounding factor where patients with larger tumours may experience greater physical impairment. This leads to more extensive surgical resections, a higher risk for postoperative complications and can result in delays in the initiation or completion of planned treatment. To minimize this confounding factor, we have stratified patients by tumour stage (T1/T2 *vs.* T3/T4).

It is also important to look at the time metrics within the different steps of the multimodal patient care flow. While the time metrics of the TPT group > 104 days were worse, median time from surgery to the pathological report (Fig. 2A) and median time from surgery to the multidisciplinary team decision (Fig. 2B) had a smaller impact on the delay than the median time from surgery to start of RT (Fig. 2C), where a more pronounced difference in times was noticed. This seems to point out that these patients were inherently more complex, but also adds to the fact that RT could not compensate or neutralize the negative effect within the department timings. The discrepancy between the number of patients ready to plan RT at 6 weeks and those who started RT at 42 days (7 weeks) after surgery should also be noticed. This may be explained by an extremely ambitious timeframe in which the RT first appointment and the start of RT should happen within 7 days, meaning that radiotherapy referral should be optimized to no later than 5 weeks after surgery to comply with optimized timings.

Finally, a non-randomized, retrospective study had a selection and reporting bias, which pose a limitation. The cohort itself limited the study since the median TPT was very distant from what is considered ideal and, therefore, conclusions about TPT cut-off should not be effectively extrapolated.

Conclusion

Our institution cohort of high risk OCSSC treated with surgery followed by adjuvant CRT had a prolonged TPT (median 109 days). Within our cohort, a TPT > 104 days was found to have a worse OS and DFS, with a nonsignificant impact on locoregional or DFS. This highlights the need to optimize the multimodal cancer care pathway, namely within the radiotherapy care path.

Disclaimers

This article was partly based on a conference poster presented at ICHNO 2024, Barcelona. The poster abstract was published in The Green Journal - Radiotherapy and Oncology, https://www.sciencedirect.com/science/article/pii/S0167814024004973.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Author contributions

P.F.: manuscript preparation, data collection, and literature search; S.E.: statistical analysis and manuscript revision; M.V.: manuscript revision; P.M.: manuscript revision; M.R.: manuscript revision; S.M.: manuscript revision; I.S: manuscript revision; R.C.: manuscript revision; E.N.: manuscript revision and literature search. All authors read and approved the final manuscript.

Ethical declaration

The ethical approval to conduct this study has been granted by the ethical committee of the Instituto Português de Oncologia de Lisboa Francisco Gentil (approval UIC/1646 – 9th May 2024).

Data Availability

All data generated or analysed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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