Clinical and Translational Radiation Oncology 42 (2023) 100668

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Original Research Article

The impact of national holidays on postoperative radiotherapy of squamous cell carcinoma of the head and neck

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ARTICLE INFO

Keywords:
Head and neck cancer
Clinical oncology
Radiotherapy
Public health systems
Resource management
Accelerated radiotherapy

ABSTRACT

Background: Delays in starting postoperative radiotherapy (PORT) have been established as negative predictors for clinical outcomes in head and neck squamous cell carcinomas (HNSCC). Our study aimed to examine the effect of delays during PORT, and the impact of national holidays in Canada, a publicly funded system, on oncologic outcomes such as Overall Survival (OS) and Local Recurrence (LR).

Methods: The provincial cancer registry was queried to obtain demographic, pathologic, and outcomes data from cancer patients treated for all squamous cell carcinomas of the head and neck region treated between January 1, 2007 and November 30, 2019. All extracted information was cross-referenced and supplemented by chart review of patient electronic medical records. Extracted data were analyzed for OS and LR, in the context of Canadian national holidays causing delays during PORT.

Results: 1433 patients treated for HNSCCs were identified, of whom 338 were treated curatively with surgery followed by PORT. 68.6% of patients experienced at least one day of interruption during treatments due to holidays. LR was 15.4% and OS was 59.6% at 5 years. Treatment interruptions by holidays were predictive of local recurrence (HR, 2.38; 95% CI 1.17–4.83; $p = 0.017$). Patients that developed early recurrence prior to PORT had very poor oncologic outcomes.

Conclusion: Our findings were consistent with previously published studies in limiting the interval between surgery and PORT. We identified the novel finding of paired holidays as a significant predictor in determining LR, suggesting the importance of modifying RT delivery schedules and timing.

Introduction

The management of non-metastatic head and neck squamous cell carcinomas (HNSCC) is complex, and the decision-making for curative treatment depends on factors such as the patient performance status and age, extent of locoregional disease and probability of organ preservation. The decision between upfront radiation-based treatment or surgery depends on the various factors above [1]. For many patients, definitive management usually consists of surgical resection followed by postoperative radiotherapy (PORT) and concomitant platinum-based chemotherapy, except for nasopharyngeal carcinomas (NPC) where management is primarily with chemotherapy and radiation [2].

Retrospective studies have demonstrated a benefit of a shorter interval between surgery and PORT, but despite this, there remains controversy about what constitutes the ideal interval. The earliest work from Memorial-Sloan Kettering Cancer Center established 6 weeks or less as the ideal interval between surgical resection and PORT, although this finding was only seen in patients receiving doses of

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https://doi.org/10.1016/j.ctro.2023.100668
Received 1 April 2023; Received in revised form 25 July 2023; Accepted 4 August 2023
Available online 8 August 2023

radiotherapy<60 Gray [3]. An interval of 6 weeks or less is recommended by the National Comprehensive Cancer Network (NCCN) guidelines as of May 2022 [1]. More recently, a national database registry study by Harris et al. demonstrated a significant increase in mortality in patients treated beyond a 7-week interval, but no clinically relevant difference for patients that were treated before 7 weeks between surgery and PORT, and no difference in outcome in patients whose radiation started before a five-week interval [4]. As such, the optimal timing of PORT appears to be within the interval of 6 to 7 weeks from surgery to initiating radiotherapy.

But, what about delays during PORT? Another measure, the 'Treatment package time' (time from surgery to completion of PORT), has also been shown to be predictive of relapse [5]. Our study aimed to examine the impact of treatment breaks as a result of national holidays, in Canada, a publicly funded system. The primary objective of this study is to determine the probability of local recurrence (LR) in patients treated with surgery followed by PORT, in relation to the time elapsed between the date of surgery and start of radiotherapy. Secondary objectives include exploration of other variables that predict LR and overall survival (OS), including the effect of breaks in PORT due to national holidays.

Materials and methods

Patient selection

Institutional research ethics board approval was obtained, and a cohort was extracted from the provincial cancer registry selecting all squamous cell carcinomas (SCC) of the head and neck region diagnosed between January 1, 2007 and November 30, 2019, treated with definitive surgery followed by PORT in provincial radiotherapy centres. Extracted data included patient demographics, vital statistics, American Joint Committee on Cancer (AJCC) 7th staging classification, and dates of surgery, systemic therapies, and radiotherapy. Additional data were extracted from the Oncology Patient Information System (OPIS) regarding treatment-related details, including dates of surgery, systemic therapies, and radiotherapy appointments. A detailed chart review was conducted to obtain any missing information including smoking history, review of pathology reports, and recurrence data. Dates extracted from the provincial registry were cross-referenced with dates from individual chart review and verified treatment records.

Data analysis and statistical methods

Baseline patient characteristics were compiled using summary statistics. The number of Canadian national holidays (days on which patients are not treated with radiotherapy) were analyzed for effect on local recurrence and overall survival, as a continuous variable, at various cut-points to dichotomize groups (e.g., 3 days missed versus 0–2 days missed, during a course of radiation). Data were also analyzed by whether or not the holidays occurred in a paired fashion or not, termed a 'paired holiday' (e.g., Good Friday and Easter Monday). The exact dates of holidays, by year, were determined using the SAS HOLIDAY function. National holidays included New Year's (January), Good Friday/Easter Monday (March/April), Victoria Day (May), Canada Day (July), Labour Day (September), Canadian Thanksgiving (October), Remembrance Day (November), and Christmas/Boxing Day (December). Overall treatment durations of courses of radiotherapy were analyzed to see if BID (twice daily) radiotherapy was used, to make up for the time lost due to holidays. The primary endpoints were measured from the date of surgery to either the event of interest, or the censoring date. Local control was estimated by competing risk time to event analysis, using the cumulative incidence method. The competing risks accounted for were non-cancer death and death from cancers other than HNSCC. Cox proportional hazard modeling with competing risks was used for multivariable modeling of local control, with selection of variables by stepwise regression, using a significance level of < 0.30 to enter the model and < 0.05 to stay in the model. Overall survival was estimated by the Kaplan-Meier method, and multivariable Cox proportional hazard modeling was used, with selection of variables by stepwise regression, using a significance level of < 0.30 to enter the model and < 0.05 to stay in the model. Patients that had evidence of clinically apparent regrowth of tumor after surgery, but before PORT were designated as patients who had 'early recurrence,' and were included in the analysis. This is similar to the definition by Hosni et al [6]. Variables that were analyzed were age, sex, smoking status, HPV status, site, T category, tumor size, N category, lymph node size, AJCC 8th edition stage, surgical margin status, presence of extranodal extension, presence of lymphovascular invasion, presence of perineural invasion, time from surgery to starting radiotherapy, the use of chemotherapy, and treatment during paired holidays. Local recurrence was considered in the overall survival multivariable model as a time dependent variable.

Statistical analysis was performed in SAS Version 9.4 (SAS institute, Cary, North Carolina, USA).

Results

Patient and treatment characteristics

A total of 1433 patients treated for HNSCC were identified through the provincial cancer registry, of whom 338 were treated with adjuvant PORT. We excluded patients that received either curative radiotherapy without surgery, or those who were treated with palliative radiotherapy alone.

The most common site of disease was the oral cavity, representing 41.4% of included patients. Most of the patients were pathologic stage IV (54.7%) at the time of diagnosis, which was determined based on the 2017 AJCC 7th edition staging.

HPV status was mostly undetermined in the provincial registry, with 70.7% of patients lacking this information. Most patients included in the study were recent ex-smokers (35.2%), or active smokers (29%) at the time of treatment. Patient and disease characteristics are summarized in Supplementary Table 1.

Median dose of radiotherapy delivered was 66 Gy (10 – 72 Gy), with a mean dose of 63 Gy. Radiotherapy delivery was mostly done through intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT), but 37 patients received 3D conformal radiotherapy (3DCRT) and 1 patient received 2D radiotherapy (2DRT). Only 74 patients (21.9%) received concurrent systemic therapies. Systemic therapy regimens included Cisplatin ($n = 77$), Carboplatin ($n = 3$), and weekly Cetuximab ($n = 4$). Patients who received systemic therapies had high risk features on pathology, including positive resection margins, extensive nodal disease, and extracapsular extension. Patients were excluded from systemic therapies if they were aged ≥ 70 years, those with comorbidities or poor performance status, which is consistent with our institutional policies.

The median time interval between surgery and PORT was 9 weeks, ranging from 4.6 to 21.4 weeks. The median treatment package time (TPT), defined as time from surgery to end of radiotherapy, was 15.1 weeks, ranging from 8.7 to 26.1 weeks. Most patients (68.6%) experienced at least one day of interruption in their radiotherapy, due to national holidays. Fifty-eight patients (17.2%) had treatment interruptions due to paired holidays, which included Christmas and Boxing Day and Good Friday and Easter Monday. Paired holidays often occurred in close proximity to the weekend, often resulting in a four-day interruption in treatment. One-hundred and sixty-five patients (48.8%) had BID treatments added in effort compensate for radiotherapy breaks. Treatment-related details are summarized in Supplementary Table 2.

Thirty-three patients were identified as having evidence of early recurrence, prior to the start of adjuvant radiotherapy. The mean time to start PORT was 9 weeks in patients without early recurrence, and 11.7 weeks with early recurrence ($p < 0.001$). Delays in treatment were

caused by additional confirmatory investigations including biopsy and imaging to establish a diagnosis of early recurrence.

Local recurrence

Overall LR for the entire cohort was 15.4% (95% confidence interval [CI]: 12–20%) at 5 years. Looking at different thresholds for time from surgery to starting PORT, the first statistically significant difference in LR occurred at 61 days. The 5-year LR was 10% (95% CI: 5.5–15%) for patients that received PORT within 61 days of surgery, and 20% (95% CI: 14.2–26.5%) for those that received it beyond 61 days (Fig. 1).

When analyzed as a continuous or dichotomous variable, the number of holidays during a course of radiotherapy, on univariable analysis was not associated with an increased risk of LR, even though there was a non-statistically significant trend (Hazard Ratio [HR] 1.21; 95% CI;p = 0.198) to a higher LR rate with more days missed due to holidays. On subgroups univariable analyses of local recurrence, there was a significantly worse LR rate in patients who did not have compensatory BID treatments (HR 1.56; 95% CI 1.01–2.41; p = 0.0449). Patients who were treated during paired holidays had a non-statistically significant increase in local recurrence (HR 1.72; 95% CI 0.91–3.27; p = 0.097). The adverse effect of paired holidays was further amplified by not having BID treatments, to account for the missing days with a subsequent LR hazard ratio of 2.94 (95% CI 1.29–6.68, p = 0.01).

Patients experiencing early recurrence experienced a particularly high rate of LR. LR at 5 years after radiotherapy, with or without systemic therapies was 54% (95% CI 33.4–70.7) versus 12% (95% CI 8.1–15.7) for patients without early recurrence, resulting in a HR of 7.79 (95% CI 4.16–14.56, p < 0.0001), illustrated in Fig. 2.

The multivariable analysis identified 5 factors predicting LR: prolonged time to start PORT (HR, 1.11; 95% CI, 1.01–1.22; P = 0.034), lower total RT dose (HR 0.91; 95% CI, 0.88–0.95; P < 0.0001), negative HPV status (Negative - HR, 8.14; 95% CI, 1.20–55.20; P = 0.032), early recurrence (HR, 10.9; 95% CI, 5.13–23.20; P < 0.0001), and paired holidays (HR, 2.38; 95% CI, 1.17–4.83; P = 0.017). Results from the univariable and multivariable analyses are summarized in Table 1.

Overall survival

OS for the entire cohort was 56.9% (95% CI: 51.0–62.2%) at 5 years. The earliest time from surgery to starting PORT in our patient cohort that demonstrated a statistically significant worse OS was at 84 days (12 weeks). The 5-year survival for patients treated with PORT<12 weeks from surgery was 59.6 % (95% CI: 53.3–65.3%) and for patients treated more than 12 weeks from surgery was 38.8% (95% CI: 23.7–53.6%; p = 0.0386). Holidays, in number of missed days (HR 1.06; 95% CI 0.89–1.26; p = 0.51), or as paired holidays did not predict OS (HR 1.09; 95% CI 0.70–1.67; p = 0.70). Both early recurrence and local recurrence at any point were strongly associated with OS, illustrated in Figs. 3 and 4.

The multivariable model identified 7 factors affecting OS: increasing age at surgery (HR, 1.05; 95% CI, 1.03–1.06; P < 0.0001), prolonged time to start PORT (HR, 0.91; 95% CI, 0.88–0.95; P = 0.048), increasing tumor size (HR, 1.014; 95% CI, 1.005–1.022; P = 0.002), negative HPV status (negative – HR, 3.37; 95% CI, 1.52–7.49; P < 0.003), early recurrence (HR, 3.23; 95% CI, 1.94–5.37; P = 0.003), extracapsular extension (HR, 1.54; 95% CI, 1.08–2.18; P = 0.017), and local recurrence (HR, 5.22; 95% CI, 3.61–7.57; P < 0.0001). Results from the univariable and multivariable models are summarized in Table 2. The analyses, for both local recurrence and overall survival, were repeated using treatment package time, yielding nearly identical results, due to the relative homogeneity of the radiation dose and fractionation.

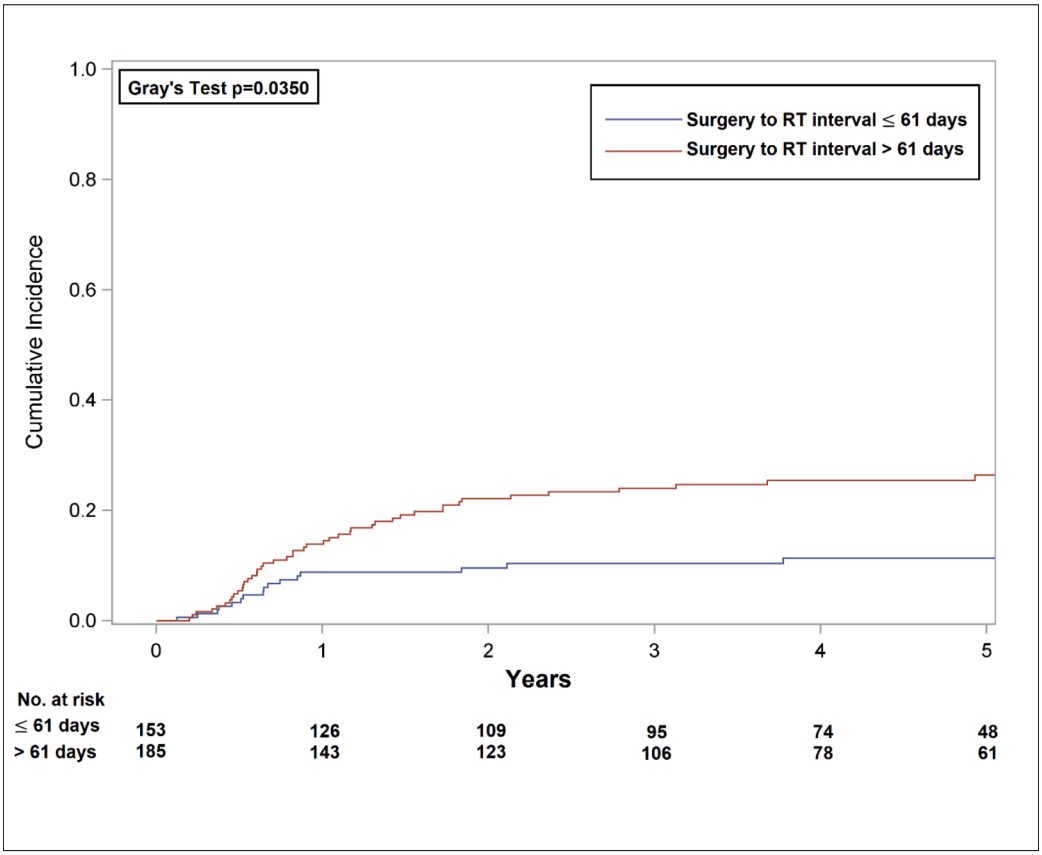

Fig. 1. Local recurrence for patients treated with postoperative radiotherapy within 61 days or beyond 61 days of surgery.

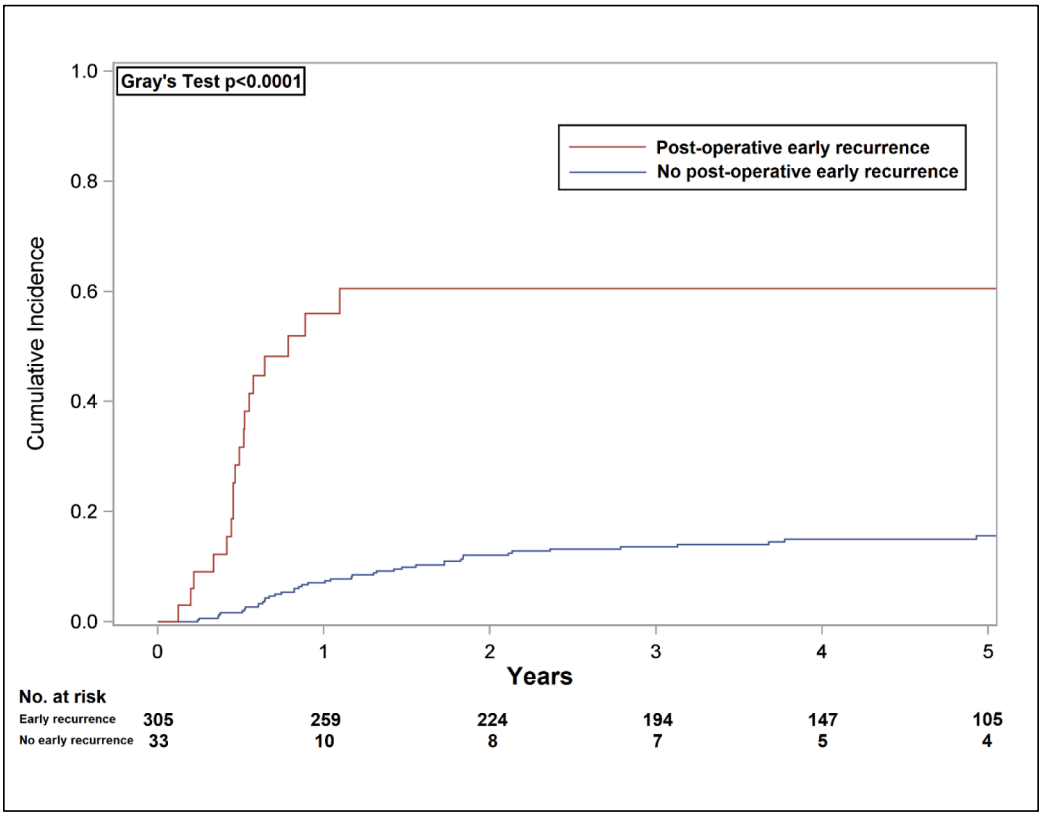

Fig. 2. Local recurrence for patients with early recurrence prior to PORT, compared to patients without early recurrence.

Table 1
Univariable and Multivariable analysis to identify factors of local recurrence.

Covariate	Univariable Analysis HR (95% CI)	P value	Multivariable Analysis HR (95% CI)	P value
Time to start RT	1.24 (1.11–1.38)	<0.0001	1.11 (1.01–1.22)	0.034
Total RT dose	0.97 (0.93–1.02)	0.28	0.91 (0.88–0.95)	<0.0001
HPV Status				
Positive	Reference12.70		Reference8.14	
Negative	(2.31–69.69)	0.003	(1.20–55.20)	0.032
Unknown	8.31 (2.04–33.83)	0.003	9.76 (2.03–46.8)	0.004
Early post-op recurrence	7.79 (4.16–14.56)	<0.0001	10.9 (5.13–23.20)	<0.0001
Yes	Reference		Reference	
No				
Perineural Invasion	2.29 (0.77–6.85)0.81	0.72	3.39 (0.88–13.06)	0.098
Positive	(0.19–0.64)	0.14	1.50 (0.39–5.82)	0.6314
Negative	Reference		Reference	
Unknown				
Paired Holidays	1.72		2.38	
Yes	(0.91–3.27)	0.097	(1.17–4.83)	0.017
No	Reference		Reference	

Analyses excluding patients with early recurrence

Due to the unique behavior of patients with early recurrence, the analyses of local control and overall survival were repeated, excluding 33 patients with early recurrence.

With respect to local control, the detrimental effect of paired holidays on the subgroup of patients who did not have compensatory BID treatments still held statistically significant results on univariate competing risk analysis at 5 years (15.6% vs 35.2% local recurrence; Gray's test p = 0.0415). When early recurrence patients were excluded from the multivariable analysis of local control, the only 3 variables that remained significant for adverse local control was HPV negativity (HR 6.75; 95% CI 0.94–48.31; p = 0.0056), perineural invasion (HR 2.26; 95% CI 1.25–4.11; p = 0.001), and smoking at any time (HR 3.59; 95% CI 1.11–11.61; p = 0.0226). Temporal factors did not retain significance due to the lack of events, including the time from surgery to radiation (HR 1.086; p = 0.1802) and treatment during paired holidays (HR 1.60; p = 0.1864).

The conclusions from the multivariable analysis for overall survival remained unchanged. With the exclusion of 33 patients with early recurrence, the factors that remained significant were: age at time of surgery (p < 0.0001), tumor size (p = 0.004), AJCC clinical stage (p = 0.0001), perineural invasion (p = 0.019) and local recurrence (p < 0.0001). Temporal factors including the number of missed treatment days and treatment during paired holidays did not demonstrate statistical significance. The results of this analysis are summarized in Supplementary Table 3.

Discussion

The present study's findings are consistent with existing literature, demonstrating that the ideal interval between surgery and PORT is likely around the 6–7 week threshold, to optimize OS and LR for patients with HNSCC. We were able to demonstrate the novel finding of the adverse effect of paired holidays on local recurrence, even in the context of the multivariable model for LR.

To the best of our knowledge, this is the first study to show increased risk of LR from breaks in PORT due to paired holidays. Patients treated during paired holidays had worse LR rates, but this detriment was not demonstrated for OS. This is likely attributed to the low number of local failures compared to the nearly two-fold occurrence of distant metastases and non-H&N cancer-related deaths that contributed to all-cause mortality. It did appear that performing BID treatments to account for treatment days missed due to holidays did mitigate some of the

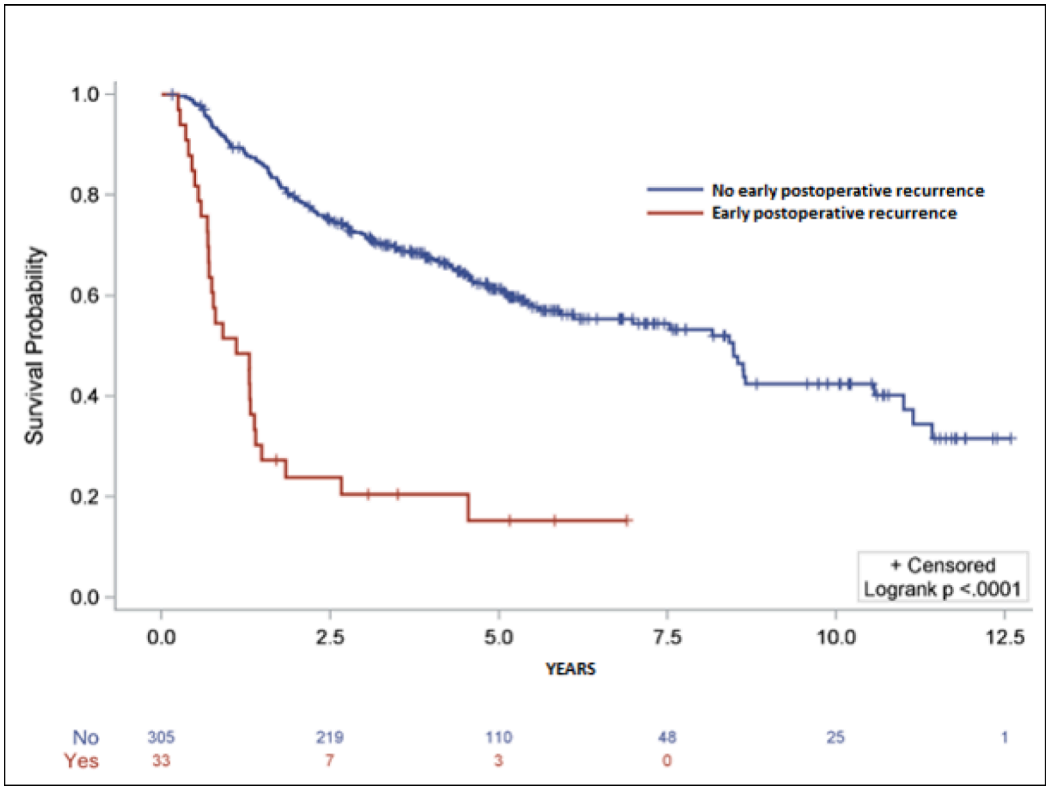

Fig. 3. Kaplan-Meier survival curve as a function of early postoperative recurrence.

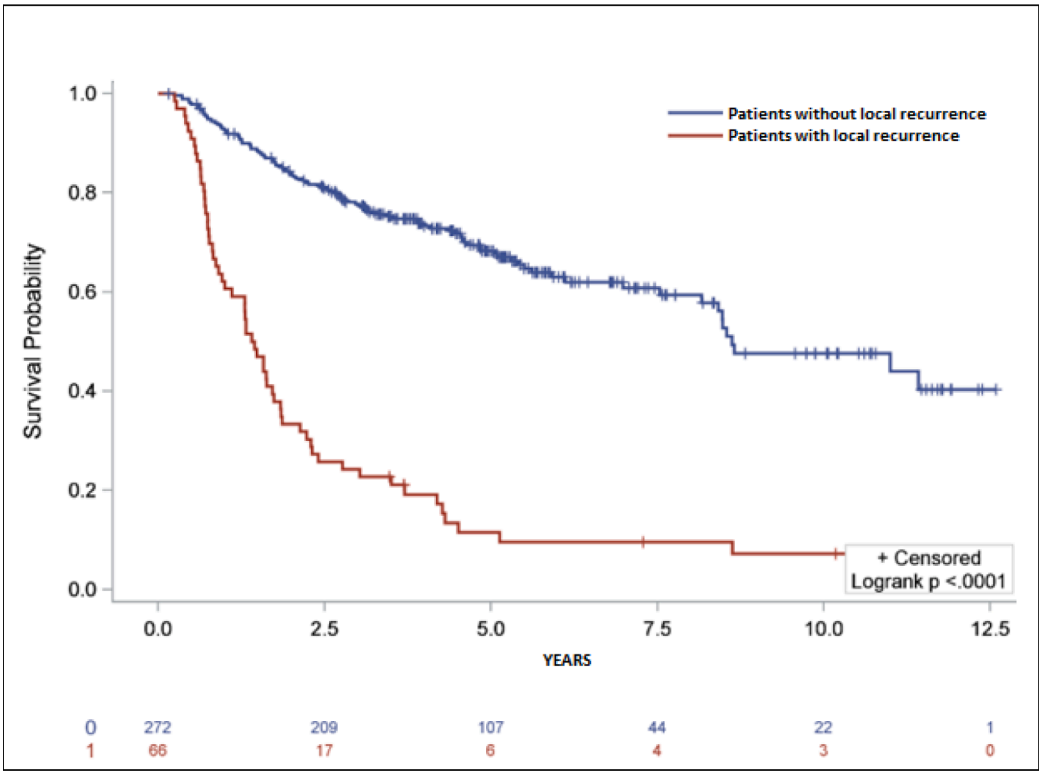

Fig. 4. Kaplan-Meier survival curve as a function of local recurrence.

detrimental effects on outcome. This work has changed the policy in our institution, so that patients will no longer have a planned 4-day break in treatment, due to holidays.

Early recurrence was found to be an important predictor for both LR and OS. This was previously defined by Hosni et al. as tumor recurrence after surgical resection, prior to the initiation of planned PORT, in the

Table 2
Univariable and Multivariable analysis to identify factors of overall survival.

Covariate	Univariable Analysis HR (95% CI)	P value	Multivariable Analysis HR (95% CI)	P value
Age at surgery	1.04 (1.02–1.06)	<0.0001	1.05 (1.03–1.06)	<0.0001
Time to start RT	1.068 (1.007–1.134)	0.03	0.931 (0.868–0.999)	0.048
Tumor size	1.02 (1.01–1.03)	<0.0001	1.014 (1.005–1.022)	0.002
HPV Status				
Positive	Reference7.45		Reference3.37	
Negative	(3.54–15.7)3.25	<0.0001	(1.52–7.49)2.14	0.003
Unknown	(1.90–5.57)	<0.0001	(1.22–3.75)	0.008
Early post-op	4.99		3.23	
recurrence	(3.26–7.64)	<0.0001	(1.94–5.37)	<0.0001
Yes	Reference		Reference	
No				
Perineural	1.99		1.38	
Invasion	(1.44–2.75)	<0.0001	(0.98–1.95)	0.07
Positive	Reference0.83		Reference0.55	
Negative	(0.43–1.62)	0.58	(0.26–1.16)	0.12
Unknown				
Extracapsular	1.30		1.54	
Extension	(1.93–1.82)	0.12	(1.08–2.18)	0.017
Positive	Reference1.13		Reference1.56	
Negative	(0.60–2.12)	0.70	(0.78–3.13)	0.21
Unknown				
Local	5.26	<0.0001	5.22	<0.0001
Recurrence*	(3.78–7.32)		(3.61–7.57)	
No. of missed	1.06	0.51	Not applicable	0.31
treatment days	(0.89–1.26)			
Paired Holidays				
Yes	1.09 (0.70–1.67)	0.70	Not applicable	0.76
No	Reference		Reference	

*Local recurrence modeled as a time-dependent covariable in the overall survival model.

absence of a second head and neck primary tumor [6]. Our investigation identified a group of patients that developed early post-operative recurrence, who had far worse outcomes than any other patients. Their treatment was also delayed on average by 2.7 weeks, due to additional investigations including biopsies and imaging to establish the diagnosis of early post-operative recurrence. Despite addition of systemic therapy and accelerated fractionation schedules to limit overall treatment time, patients still had poor outcomes, suggesting that these patients may require a novel treatment paradigm altogether. This was also examined by Kibe et al., who suggest that standard adjuvant regimens may not be enough to treat early recurrences [7]. Hosni et al.'s study identified the oral tongue site, microscopic positive margins, and higher TNM staging (pT3-4, pN2-3) as significant predictors of early postoperative recurrence, which may lay the groundwork for additional investigations. Apart from early recurrence, all forms of local recurrence had a large impact on overall survival, a finding demonstrated in a retrospective study by Weckx et al. previously [8]. This highlights how critical it is to optimize local control at the patient's first presentation, and not to rely on salvage treatments at time of relapse.

Our study had several limitations that influenced our results, largely due to sample size issues. While our multivariable models demonstrated findings consistent with existing literature, showing that the ideal interval between surgery and PORT is likely between 6 and 7 weeks, but due to our smaller sample size, resolving clinically and statistically significant benefits at the 6- or 7-week threshold could not be achieved. We were also unable to demonstrate a benefit for adding systemic therapy, which has long been established to improve both OS and locoregional control [9,10]. Our study had low utilization rates of concurrent systemic therapies at 21.9% compared to the study by Harris et al. at 53–63%, but similar to that of Hosni et al., who also reported rates of utilization for systemic therapies at 19% in the adjuvant setting and 23% overall, including patients receiving palliative and salvage treatments [4,6]. The indication for systemic therapies in the study by Hosni et al. was high risk features (extranodal extension, and/or positive resection margins), excluding patients aged $\geq$ 70 years, those with comorbidities or poor performance status, which is consistent with our institutional policies. This suggests a difference in practice between Canada and the United States of America in recommending adjuvant systemic therapies in the management of HNSCC.

Conclusion

Our findings were consistent with previously published studies in limiting the interval between surgery and post-operative radiotherapy. Early recurrence was associated with very poor oncologic outcomes, indicating the need for early recognition, and new treatment paradigms in this subpopulation. We identified the novel finding of paired holidays as a significant predictor in determining local recurrence, meaning that radiotherapy centres may be able to improve patient outcomes by making feasible and practical changes to their RT delivery schedules and timing.

Data availability statement for this work

This study was based on the Nova Scotia provincial cancer registry data. The authors do not own these data and hence are not permitted to share them in the original form (only ina aggregate form, eg publications). At the time of request data were provided by the Nova Scotia Provincial Cancer Registry and maintained by the Nova Scotia Health Authority.

Conflict of interest

None.

Funding

None.

CRediT authorship contribution statement

Michael S. Kim: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Margaret Sheridan:** Data curation, Writing – review & editing. **Murali Rajaraman:** Writing – review & editing. **Helmut Hollenhorst:** Writing – review & editing. **Amanda Caissie:** Writing – review & editing. **Ashraf Mahmoud-Ahmed:** Writing – review & editing. **Nathan Lamond:** Writing – review & editing. **Stephanie Snow:** Writing – review & editing. **Martin Corsten:** Writing – review & editing. **S. Mark Taylor:** Writing – review & editing. **Jonathan R.B. Trites:** Writing – review & editing. **Matthew H. Rigby:** Writing – review & editing. **Martin Bullock:** Writing – review & editing. **Derek Wilke:** Conceptualization, Methodology, Software, Formal analysis, Writing – review & editing, Visualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Gordon Walsh.
Ron Dewar.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100668.

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