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Clinical Investigation

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

David I. Rosenthal, MD,[*] Abdallah S.R. Mohamed, MD, MSc,[*,†] Adam S. Garden, MD,[*] William H. Morrison, MD,[*] Adel K. El-Naggar, MD,[‡] Mona Kamal, MD, PhD,[*,§] Randal S. Weber, MD,[‖] Clifton D. Fuller, MD, PhD,[*] and Lester J. Peters, MD[¶]

Departments of *Radiation Oncology, [‡]Pathology, and [‖]Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas; [†]Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, University of Alexandria, Alexandria, Egypt; [§]Department of Radiation Oncology, Ain Shams University, Cairo, Egypt; and [¶]Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

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Summary

We present the final report of a phase 3 trial to assess dose response for postoperative

Purpose: To present the long-term and final report of a phase 3 trial designed to assess dose-response relationship for postoperative radiation therapy (PORT) and pathologic risk groups in head and neck cancer.

Methods and Materials: Patients who underwent primary surgery for American Joint Committee on Cancer stage III or IV squamous cell carcinoma of the oral cavity,

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Reprint requests to: David I. Rosenthal, MD, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 97, Houston, TX 77030. Tel: (713) 563-2353; E-mail: dirosenthal@mdanderson.org

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radiation therapy in head and neck cancer. Primary sites and involved necks were independently assigned to higher- or lower-risk categories based on a point score system and then randomized to receive different dose levels. Increasing dose did not significantly improve tumor control, treatment package time was the only significant treatment variable, and positive surgical margins and extracapsular extension were the most significant pathologic factors.

oropharynx, hypopharynx, or larynx and who required PORT were eligible. Patients' primary sites and involved necks were independently assigned to higher- or lower-risk categories based on a cumulative point score representing increasing risk of recurrence. The sites in the lower-risk group were randomized to receive 57.6 or 63 Gy and those in the higher-risk group were randomized to receive 63 or 68.4 Gy, all at 1.8 Gy per fraction.
Results: A total of 264 patients were included. The actuarial 5-year locoregional control rate was 67%. A second primary cancer was documented in 27% of patients. The 5- and 10-year freedom−from−distant metastasis rates were 64% and 60%, respectively, whereas the 5- and 10-year overall survival rates were 32% and 20%, respectively. There was no statistically significant difference in tumor control between different dose levels in both the lower- and higher-risk groups. On multivariate analysis, nonwhite race ($P=.0003$), positive surgical margins ($P=.009$), extracapsular extension (ECE, $P=.01$), and treatment package time (TPT) $\geq$85 days ($P=.002$) were independent correlates of worse locoregional control, whereas age $\geq$57 years ($P<.0001$), positive surgical margins ($P=.01$), ECE ($P=.026$), and TPT $\geq$85 days ($P=.003$) were independently associated with worse overall survival.
Conclusions: This long-term report of PORT delivered at 1.8 Gy/d to total doses of 57.6 to 68.4 Gy without chemotherapy for head and neck squamous cell carcinoma demonstrated that increasing dose did not significantly improve tumor control. On multivariate analysis, the only significant treatment variable was TPT. The results confirm that positive surgical margins and/or nodal ECE remains the most significant predictive pathologic factors.

Introduction

Gilbert Fletcher introduced the concept of postoperative radiation therapy (PORT) for head and neck squamous cell carcinoma (HNSCC) in the 1950s to address observed high rates of postoperative recurrences (1). Subsequent reports confirmed that PORT can improve disease control—and probably survival—but there were no uniform or prospectively validated guidelines for fractional or total radiation dose selection (2-6). Fletcher (7) recommended a radiation dose of 60 Gy in the second edition of his *Textbook of Radiotherapy*. He posited in this era antedating segmental imaging that an incremental dose of 10 Gy was required to overcome relative hypoxia in the operative bed whereas nonoperated, non−tumor-bearing volumes could be reliably controlled with just 50 Gy. The University of Florida recommended that the dose be increased to 65 Gy at 1.7 to 1.8 Gy per fraction and that higher-risk areas, including positive margins, receive a definitive intent dose of 70 Gy (8). Thus, despite recognition of a benefit to PORT, questions regarding the ideal fractional dose and total dose, as well as the need for additional dose if clinical and pathologic features suggested a greater risk of recurrence, remained unanswered. To address these questions, investigators at The University of Texas MD Anderson Cancer Center evaluated the dose-response relationship for head and neck cancer PORT with this prospective, randomized study between 1983 and 1991. The question regarding fractional dose (ie, 1.8 Gy vs 2 Gy) was deemed less important, so these scientists focused on total dose, which varied dependent on a risk stratification formula based on the then-current understanding of clinical, surgical, and pathologic factors.

A preliminary report on the first 240 of 302 patients was published in 1993 with a median follow-up period of 22 months (9). The authors recommended a dose of 57.6 Gy for "intermediate-risk" volumes and 63 Gy for "high-risk" volumes delivered at 1.8 Gy per fraction, 5 days per week. More complete long-term follow-up data were collected but not reported. The authors recognized that treatment time factors were important and, in fact, addressed these in their next trial, randomizing patients to standard or accelerated fractionated PORT.

We analyzed the >20-year follow-up on the original dataset for the complete cohort and performed further unplanned exploratory statistical analyses in light of the current understanding of risk factors to better appreciate the time-dose-response relationships for PORT in HNSCC. Our specific aims include:

1. Long-term and final reporting of this prospective, risk-adaptive trial
2. Confirmation of tumor risk factors affecting outcomes after PORT without chemotherapy
3. Identification of time- and/or dose-dependent outcomes in PORT without chemotherapy
4. Identification of treatment package time (TPT, from surgery to completion of PORT) thresholds for PORT in HNSCC

Methods and Materials

The details of the study design, inclusion criteria, risk stratification, and radiation therapy (RT) techniques were

described in detail in the first report (9). In brief, eligible patients had HNSCC in primary tumors of the oral cavity, oropharynx, hypopharynx, or larynx or neck nodes of unknown primary that required PORT. Patients had their primary tumor and disease in the neck assessed separately, and each was assigned to either a lower− or higher−dose risk group by use of a separate empirical point system for each (Fig. 1). The dose to be treated for sites in the lower-risk group was randomized between dose levels A (57.6 Gy in 32 fractions over a period of 6 weeks) and B (63 Gy in 35 fractions over a period of 7 weeks), whereas the dose to be planned for sites in the higher-risk group was randomized to dose level B or C (68.4 Gy in 38 fractions over a period of 7.5 weeks). It should be noted that dose level A was initially 52.2 to 54 Gy, but after the first interim analysis showed several early recurrences, the minimal dose was changed to 57.6 Gy. Data regarding tobacco use were not collected.

Statistical analysis

The Kaplan-Meier product-limit test was used to calculate, from the date of surgery, rates of 5- and 10-year overall survival (OS), local control (LC), regional control (RC), locoregional control (LRC), freedom from distant metastasis (FDM), and cancer-specific survival (CSS, death from primary cancer coded as an event and censoring all others). Comparison of disease control by risk category and dose level was performed based on intention-to-treat assignment.

Competing risk analyses of failure and death were performed with Weibull parametric fitting using cause of failure and cause of death, respectively, as a competing risk variable for uncensored data. Univariate Cox proportional hazards assessments were performed to determine the correlation of patient-, disease-, and treatment-related variables with disease control and survival endpoints. For continuous variables that demonstrated a significant association with an outcome in the initial univariate analysis, a subsequent recursive partitioning analysis (RPA) was implemented to identify the appropriate cutoff point; continuous variables were then converted to binary levels based on the resultant cutoff to be included in the final model. Eventually, all the following variables were examined: age (<57 years vs ≥57 years); sex (male or female); race (white vs other); T category (T1-T2 vs T3-T4); N category (N0 vs N+); margin status (positive vs other [comprising "negative, converted, and close"]); number of positive nodes (0-1 vs ≥2); number of nodal groups (0-1 vs ≥2); extracapsular extension (ECE) (positive vs other); nerve invasion (positive vs negative); nodal direct invasion (positive vs negative); biologically effective dose (BED), as a linear-quadratic−based formula with an overall time factor included for both primary and neck RT (10); and TPT (<85 days vs ≥85 days). Age and TPT binary levels were RPA driven. The number of nodal groups was recorded but not the named neck levels. Multivariate survival analyses were performed with Cox

Recurrence risk at primary site

Criteria	Points				
	0	1	2	3	4
Stage	T1-T2	–	T3	–	T4
Margins	-ve	–	Mucosa +ve-> -ve	Deep +ve -> -ve	Close final margins (< 5 mm)
Nerve invasion	-ve	–	Minor nerve(s) +ve	Minor nerve(s) +ve	Major nerve +ve
Neck nodes	N0	N1	≥N2	–	–

Recurrence risk in the neck

Criteria	Points				
	0	1	2	3	4
N. Of nodes	0	1	2-3	≥4 or matted	–
N. Of nodal groups	0-1	2	3	≥4	–
Size/ECE	–	<3 cm without ECE	>3 cm without ECE	<3 cm with ECE	3-6 cm with ECE
Direct invasion	–	–	–	Muscle; skin; nerve; vein	Carotid; base of skull

Point range = 0- 14; Low risk = 1-6; High risk 7- 14

Any final positive margin automatically connotes high risk

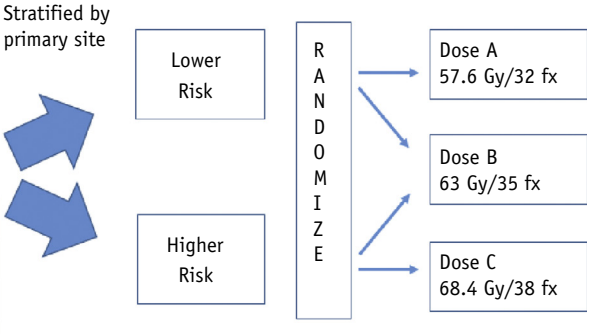

Fig. 1. Risk scoring criteria for primary site and neck. Patients' primary sites and involved necks were independently assigned to higher- or lower-risk categories based on the cumulative point score representing lower versus higher risk of recurrence and then randomized to different dose levels. *Abbreviations:* ECE = extracapsular extension; fx = fractions.

regression and included all variables with $P<.30$. Survival distributions between various risk groups were compared with the log-rank test. Data were analyzed by use of JMP 11.2 Pro statistical software (SAS Institute, Cary, NC), and statistical significance was determined using a specified non−Bonferroni-corrected α of .05.

Results

Patients

From 1983 to 1991, 301 patients were enrolled. Of these, 26 were excluded because of interval disease recurrence after surgery and prior to RT start, 8 were excluded because of refusal to start RT, and 3 were excluded because of a major protocol violation, leaving 264 patients included in the current analysis. The median age was 61 years (range, 34-86 years), and 195 patients (74%) were men. Table 1 summarizes patient and disease characteristics.

Table 1 Patient and disease characteristics

Characteristic	Data
Age, median (range), y	61 (34-86)
Sex, n (%)	
Male	197 (75)
Female	67 (25)
Ethnicity, n (%)	
White	205 (78)
African American	30 (11)
Hispanic	28 (11)
Other	1 (<1)
Primary site, n (%)	
Oral cavity	74 (28)
Oropharynx	49 (19)
Hypopharynx	47 (18)
Larynx	92 (35)
Unknown	2 (<1)
T category, n (%)	
T0	2 (<1)
T1	4 (1)
T2	50 (19)
T3	143 (55)
T4	65 (25)
N category, n (%)	
N0	107 (41)
N1	51 (19)
N2	67 (25)
N3	39 (15)
Surgical margins, n (%)	
Negative	124 (47)
Close	67 (26)
Positive -> negative	44 (18)
Positive	24 (9)
NA	2 (<1)
ECE, n (%)	
No nodal disease	61 (28)
Negative	75 (24)
Positive	128 (48)
Nerve invasion, n (%)	
Absent	195 (74)
Present	67 (26)
NA	2 (<1)

Abbreviations: ECE = extracapsular extension; NA = not available.

Overall oncologic and survival data

At the time of final study analysis, 7 patients were alive approximately 25 years after study closure, 4 patients were lost to follow-up, and 253 patients were deceased. The actuarial 5- and 10-year OS rates were 32% and 20%, respectively, and the actuarial 5- and 10-year CSS rates were 48% and 46%, respectively. In 75 patients (28%), local and/or regional failure was documented; 64 of these recurrences (85%) occurred in the first 2 years of follow-up. The actuarial 5-year LRC rate was 67%, and there were no events beyond 5 years. There were 83 total distant recurrences (31%), with 5- and 10-year FDM rates of 64% and 60%, respectively. For patients with LRC (n = 189), the 5- and 10-year FDM rates were 67% and 63%, respectively. The actuarial 5- and 10-year relapse free survival (RFS) rates were 47% and 44%, respectively. A second primary cancer was documented in 70 patients (27%). Figure 2 shows the Kaplan-Meier curves of oncologic and survival outcomes for all patients.

Assessment of competing causes of death for all patients revealed the predominance of cancer mortality throughout the entire follow-up duration, followed by non−cancer-related death and death from second primary cancer (Fig. 3A). In addition, assessment of competing causes of first failure for all patients revealed the slight numerical predominance of locoregional failure throughout the entire follow-up duration, followed by distant metastasis (Fig. 3B).

Disease control by risk group and dose level

Local recurrence developed in 42 patients (16%): 19 of 135 in the lower-risk group (14%) and 23 of 129 in the higher-risk group (18%) of primary site recurrence based on the study-designed risk scoring system for primary recurrence. Except for patients who were treated prior to 1985 with lower dose level A <54 Gy (n = 17), there were no statistically significant differences in the 5-year LC rates between the different dose levels in both the lower- and higher-risk groups (Table E1; available online at www.redjournal.org; Fig. 4A).

Neck recurrences occurred in 47 patients (18%): 21 of 148 in the lower-risk group (14%) and 26 of 116 in the higher-risk group (22%) of neck recurrence based on the study-designed risk scoring system for neck recurrence. There were no statistically significant differences in the 5-year RC rates between different dosing levels in both the lower- and higher-risk groups (Fig. 4B). In addition, the significant dose response demonstrated in the initial report for patients with ECE was no longer noted in the current analysis. There was

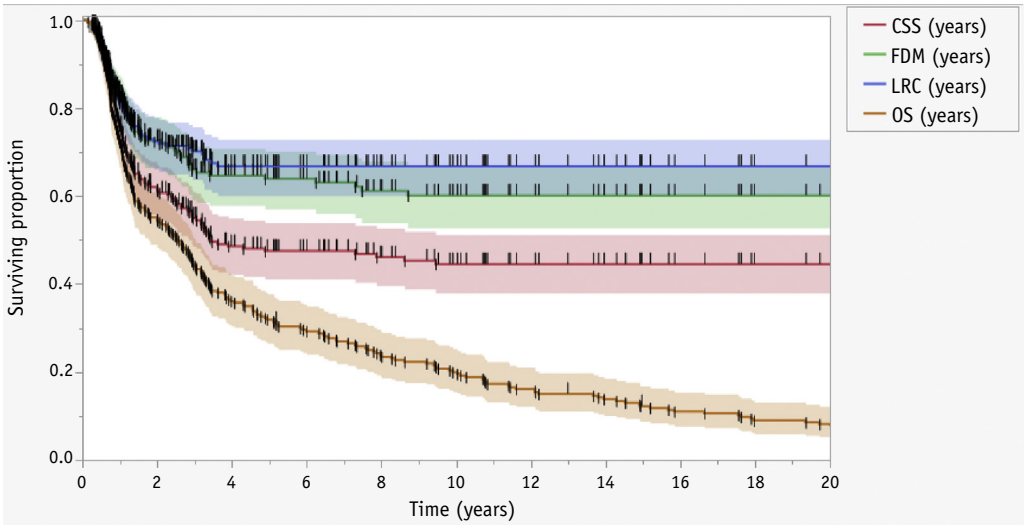

Fig. 2. Kaplan-Meier curves calculated for all patients (N = 264), showing locoregional control (LRC), freedom from distant metastasis (FDM), cancer-specific survival (CSS), and overall survival (OS). Short vertical lines represent censored data, and shaded colors represent 95% confidence intervals.

no significant dose response above 57.6 Gy for patients with ECE (n = 15), with a 5-year RC rate of 71% compared with 67% for ≥63 Gy (n = 112, $P = .9$).

Late toxicity

Severe late complications (ie, grades 3 and 4 as per the Radiation Therapy Oncology Group [RTOG] late toxicity scoring system) were recorded in 30 patients (11%). There was no grade 5 toxicity. The most frequently encountered late toxicities were pharyngeal stricture and dysphagia in 17 patients, osteoradionecrosis of the mandible in 8 patients, severe neck fibrosis in 3 patients, and pharyngocutaneous fistula in 2 patients. There was no dose-response relationship for late toxicities when analyzed by the maximum dose delivered, as there was no statistically significant difference in the distribution of late toxicity events between the 3 groups ($P = .9$). The frequency was 4 of 43 (9.3%) for maximum dose ≤57.6 Gy, 15 of 128 (11.7%) for 63 Gy, and 11 of 93 (11.8%) for 68.4 Gy.

Outcome correlates

Locoregional control

Univariate analysis revealed that all of the following variables were significantly associated with improved LRC: white race, nonpositive surgical margins, no ECE, negative nodal staging, higher neck RT BED, and package time <85 days ($P < .05$ for all). On multivariate analysis, white race (hazard ratio [HR], 0.4; 95% confidence interval [CI], 0.2-0.6; $P = .0003$); negative surgical margins including "negative, converted, and close margins" (HR, 0.4; 95% CI, 0.2-0.8; $P = .009$); no ECE (HR, 0.4; 95% CI, 0.2-0.8; $P = .01$); and TPT <85 days (HR, 0.5; 95% CI, 0.3-0.8; $P = .002$) were independent correlates of better LRC.

Distant control

Univariate analysis revealed that all of the following variables were significantly associated with improved distant control: N0 stage, nonpositive margins, lower number of positive nodes, lower number of nodal groups, no ECE, primary RT BED, and neck RT BED ($P < .05$ for all). However, on multivariate analysis, lower number of nodal groups (ie, 0-1 vs ≥2) was the only covariate that remained significant (HR, 0.4; 95% CI, 0.2-0.6; $P = .0003$).

Cancer-specific survival

Univariate analysis revealed that all of the following variables were significantly associated with improved CSS: white race, nonpositive surgical margins, lower number of positive nodes, lower number of nodal groups, no ECE, neck RT BED, primary RT BED, and package time <85 days ($P < .05$ for all). On multivariate analysis, white race (HR, 0.5; 95% CI, 0.4-0.8; $P = .001$), nonpositive surgical margins (HR, 0.4; 95% CI, 0.3-0.8; $P = .004$), and package time <85 days (HR, 0.7; 95% CI, 0.5-0.9; $P = .03$) were independently associated with improved CSS.

Overall survival

Univariate analysis revealed that all of the following variables were significantly associated with improved survival: age <57 years, N0 stage, negative surgical margins, lower number of positive nodes (0-1 vs ≥2), smaller number of positive nodal groups (0-1 vs ≥2), higher neck RT BED, and shorter package time (<85 days) ($P < .05$). On multivariate analysis, age <57 years ($P < .0001$), negative surgical margins ($P = .011$), negative ECE ($P = .027$), and package time <85 days ($P = .003$) were independently associated with improved survival. Table 2 shows the details of the Cox regression analyses. Figure E1 (available online at www.redjournal.org) depicts the Kaplan-Meier

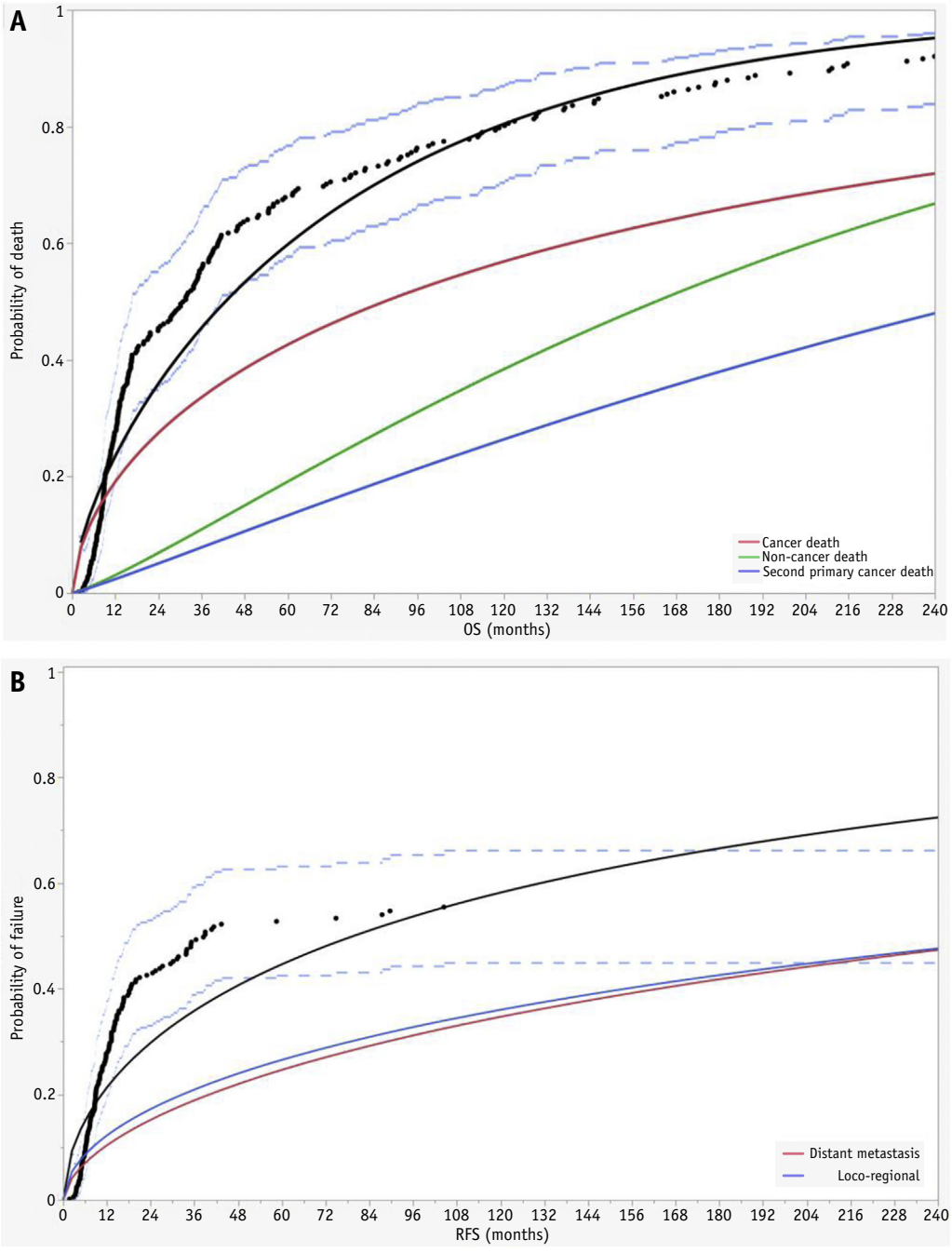

Fig. 3. Competing risk analysis for all patients. (A) Competing risk of cancer mortality predominates throughout the entire follow-up duration, followed by non−cancer-related death and death from second primary cancer. (B) Competing risk of failure in which locoregional failure slightly exceeds the risk of distant metastasis. The black dots represent aggregated data points, the black lines represent the fitted lines of the aggregated data points, and the dashed blue lines represent 95% confidence intervals. *Abbreviations:* OS = overall survival; RFS = relapse free survival. (A color version of this figure is available at www.redjournal.org.)

survival curves for all patients by margin status, ECE, and TPT.

Treatment package time

As the overall treatment time was inherently longer with dose C (38 fractions), as compared with dose B (35 fractions) and dose A (32 fractions), we further analyzed the impact of the identified TPT per each dose group. Because primary sites and involved necks were independently assigned to higher- or lower-risk categories based on a cumulative point score, patients' inclusion in each dose group was based on the maximum dose assignment per patient. The distributions of TPT and its components (time from surgery to RT start and RT total time) for each dose

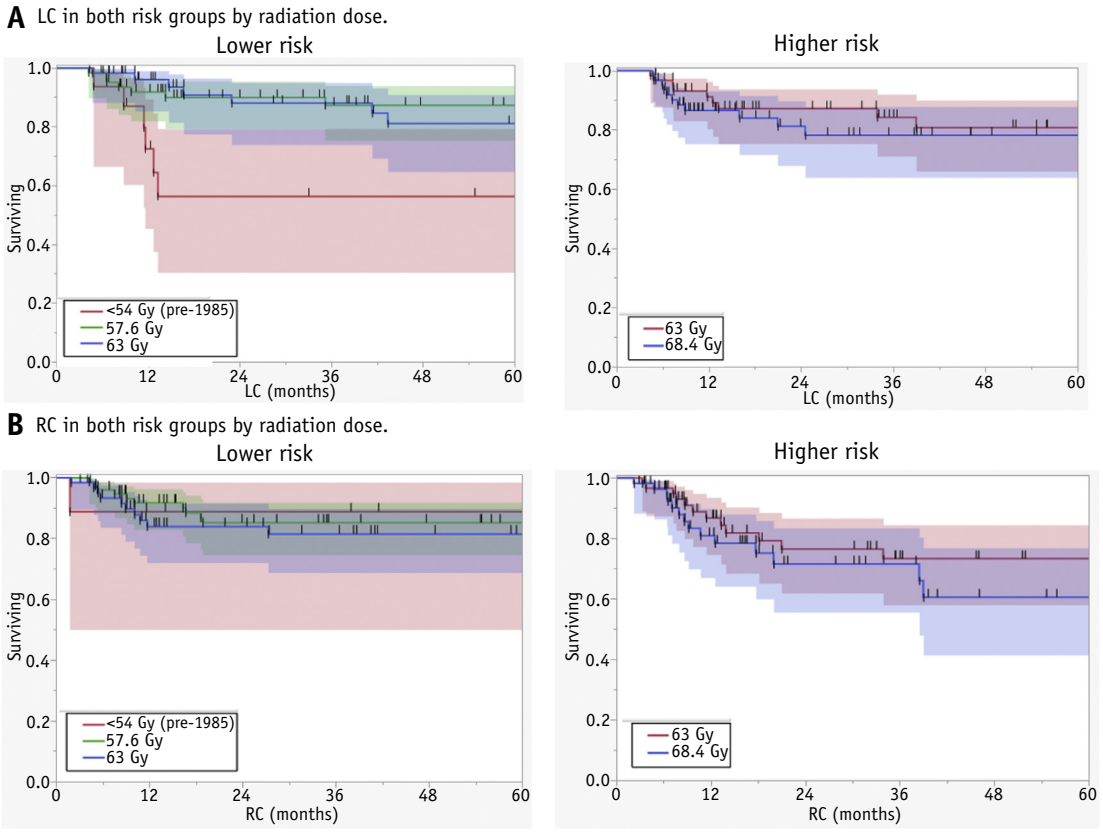

Fig. 4. Kaplan-Meier curves for local control (LC) in both risk groups by radiation dose (A) and regional control (RC) (B). There were no statistically significant differences in LC or RC rates between different dose levels in both the lower- and higher-risk groups except for LC in patients who were treated prior to 1985 with lower dose level A <54 Gy (n = 17).

group are presented as box plots (Fig. E2; available online at www.redjournal.org). Figure E2 demonstrates that time from surgery to RT start was more variable in each dose group compared with RT total time, which showed a relatively tighter distribution. On univariate survival analysis, TPT as a continuous variable remained significant in the dose A group ($P = .004$) but it did not reach statistical significance in the other 2 dose groups. However, when Kaplan-Meier curves were plotted by the identified TPT cutoff binary variable of 85 days for each dose group (Fig. E3; available online at www.redjournal.org), this showed a separation of curves in the 3 dose groups in favor of TPT <85 days that reached statistical significance in the dose A group for both LRC and, notably, OS endpoints. Kaplan-Meier curves also separated in dose groups B and C in favor of TPT <85 days, but this did not reach statistical significance.

Discussion

This was the first prospective, multidisciplinary, risk-based personalized trial to evaluate the effect of radiation dose on the outcomes of PORT for HNSCC. Herein, we present the final report with long-term follow-up of the complete cohort that also allows for the re-evaluation of the data within the current contextual understanding of risk factors for recurrence and death. The most important finding is that radiation dose, within the ranges used (1.8 Gy/d to total doses between 57.6 and 68.4 Gy and no concurrent chemotherapy), simply did not significantly affect LC, LRC, or OS. However, the finding of our secondary analysis is consistent with other reports that the overall TPT, not radiation dose, drives LRC, CSS, and OS.

With respect to tumor factors, we confirm that the 2 now generally accepted "high-risk" factors of margin status and ECE were the only independent tumor-related risk factors predicting LRC and OS. Because only the number of nodal groups was recorded and not the named neck level, we could not make a conclusion as to whether low neck disease portends poorer outcomes. In addition, when we evaluated ECE only in patients with positive neck dissection findings, a numerical trend rather than statistical significance was shown for the positive ECE subcohort (Fig. E4; available online at www.redjournal.org). Patients with initial positive margins, either mucosal or deep, that are converted to negative, as well as <5 mm but negative ("close") margins (groups 2, 3, and 4 in the original publication), had similar LRC and OS to those with initial negative margins (9). Moreover, it was seen that the presence of a single involved lymph node did not worsen outcomes, but any multilevel nodal

Table 2 Univariate and multivariate analyses of OS

	Univariate		Multivariate	
Characteristics	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age				
≥57 y	1		1	
<57 y	0.6 (0.4-0.7)	.0001*	0.5 (0.4-0.7)	<.0001*
Sex				
Male	1		-	
Female	0.96 (0.7-1.3)	.790	-	
Race				
White	1		-	
Other	1.1 (0.8-1.5)	.495	-	
Site				
Oropharynx	1		1	
Oral cavity	1.1 (0.8-1.6)		1.1 (0.8-1.6)	
Larynx	0.97 (0.7-1.4)		0.9 (0.6-1.4)	
Hypopharynx	1.5 (1-2.3)	.069	1.1 (0.8-1.8)	.410
T category				
T1-T2	1		-	
T3-T4	1.0 (0.8-1.4)	.798	-	
N category				
N1-N3	1		1	
N0	0.7 (0.6-0.96)	.024*	0.91 (0.7-1.2)	.463
ECE				
Positive	1		1	
Negative	0.6 (0.5-0.8)	.0002*	0.9 (0.6-1.2)	.026*
Margins status				
Positive	1		1	
Other	0.5 (0.4-0.8)	.007*	0.5 (0.3-0.85)	.011*
Nerve invasion				
Negative	1		1	
Other	1.2 (0.9-1.6)	.213	1.2 (0.8-1.6)	.385
No. of positive nodes				
≥2	1		1	
0-1	0.5 (0.4-0.7)	<.0001*	0.7 (1.3-3.6)	.098
No. of nodal groups				
≥2	1		1	
0-1	0.5 (0.4-0.7)	<.0001*	0.8 (0.5-1.3)	.391
Direct invasion				
Yes	1		1	
No	0.8 (0.6-1.1)	.0842	1.0 (0.7-1.6)	.655
Primary RT BED				
Continuous		.0911		.757
Neck RT BED				
Continuous		<.0001*		.097
Package time				
≥85 d	1		1	
<85 d	0.6 (0.5-0.8)	.0003*	0.7 (0.5-0.9)	.003*

Abbreviations: BED = biologically effective dose; CI = confidence interval; ECE = extracapsular extension; HR = hazard ratio; OS = overall survival; RT = radiation therapy.

* Statistically significant.

disease of any number did observably increase the risk of distant metastasis. This was likely though more driven by ECE. Other than margin status and ECE, none of the pathologic risk factors evaluated—the factors we now consider "intermediate risk factors" and current indications for single-modality PORT—were detectably associated with elevated risk of local or regional recurrence in the context of PORT. This does not mean that those risk factors do not predict for postoperative recurrence, but that they were adequately addressed by the PORT given, regardless of dose within the range evaluated.

The fact that dose escalation in this study was not successful has been attributed to tumor cell regeneration

during the additional time required to deliver doses >57.6 Gy at <2 Gy per fraction because repopulation offsets any putative benefit of higher radiation dose during the additional time required for delivery (11). However, to evaluate this concern, we performed a BED analysis with correction for time (10) to interrogate the effect of the received dose as an outcome driver in the current dataset. On multivariate analysis, BED was not an independent driver of any of the tested outcomes.

When this study was initiated, the common belief was that patients might not be able to tolerate PORT at 2 Gy per fraction, so 1.8 Gy was chosen. However, it is now well recognized that dose per fraction also affects overall treatment time, and prolongation of time may lead to decreased tumor control. Subsequent prospective studies for the definitive radiation treatment of HNSCC confirmed that strategies used to address time factor challenges including hyperfractionation and accelerated fractionation improved at least LC (12-14), adding to the milieu suggesting time and fractionation, rather than dose per se, are drivers of RT response. These findings and the recognized tolerance of PORT led to an empirical increase in fractional dose for PORT from 1.8 to 2 Gy that is now accepted as the standard (15, 16). However, to further improve the therapeutic index, risk stratification based on biological rather than conventional clinical and pathologic factors may be needed.

The concept of "treatment package time" was introduced to define the interval from surgery to the completion of PORT (17). We evaluated the TPT in this dataset as a continuous variable, and we were able to identify the cutoff point of 85 days using RPA analysis that showed it was an independent predictor of LRC, CSS, and OS for the entire dataset. However, after stratification by each dose group, TPT showed a higher impact at the lowest dose level (ie, dose A). This finding confirms that TPT independently affects outcomes for PORT delivered at 1.8 Gy/d without chemotherapy especially when lower total doses (ie, <60 Gy) are prescribed. The principal driver of variation in TPT in our study after control for risk assignment was the interval between surgery and start of RT (Fig. E2; available online at www.redjournal.org). Thus, although it is tempting to attribute outcomes to TPT, the observation may just be a statistical correlate, and increasing time between surgery and RT may reflect other hidden factors selecting for patients with worse outcomes. Subsequent studies, however, do suggest the importance of minimizing TPT. The original investigators incorporated treatment time into their next prospective trial randomizing patients to PORT with standard or accelerated fractionation (11). Their study showed accelerated fractionation led to better LRC, but only for patients with a delay to start of RT >6 weeks. Outcomes were best if RT was completed within <11 weeks from surgery. In a retrospective cohort from the University of Pennsylvania, treatment time of ≤100 days led to better LRC and OS (18). Finally, a prospective Italian phase 3 multicenter trial also showed that accelerated PORT led to better LRC for patients with a delay to start of RT >6.9 weeks (19).

Other strategies to address the risk of repopulation as a function of time include concurrent and "sandwich" chemotherapy. RTOG 9501 and EORTC (European Organisation for Research and Treatment of Cancer) 22931 used concurrent chemotherapy that has the potential for greater cell kill to compensate for interval subclinical clonogenic proliferation (15, 16). Patients enrolled in RTOG 9501 were allowed to recover from surgery without active treatment for up to 8 weeks before RT began. In RTOG 0024, weekly chemotherapy was given starting in the second week postoperatively to suppress clonogenic repopulation during the interval in which patients were recovering from surgery—and before postoperative chemo-RT started. The RTOG 0024 regimen was well tolerated and had better risk-adjusted LRC, disease-free survival, and OS compared with concurrent therapy alone in RTOG 9501 (20).

There are 3 main limitations of this study. First, the high-risk group did not undergo testing at 57.6 Gy. It is conceivable that 63 Gy might not have an advantage over 57.6 Gy for even the high-risk group and that no dose-response relationship above 57.6 Gy exists for PORT. Second, patients were classified as "low" versus "high" risk independently for the primary site and neck. Thus, the same patient may have been classified as both low risk in the neck and high risk at the primary site, or vice versa, and assigned different doses to those sites. Separating out the differences in control within those different volumes after treatment in the 2-dimensional era using opposed laterals and electrons—and without segmental imaging—is impossible. Finally, our concepts of dose today, with 3- and 4-dimensional radiation target definition, and sophisticated computerized treatment planning are not the same as 30 years ago, when the delivered doses were likely less precise.

Now that 2 Gy per fraction is used, the empirical doses used for PORT are 56 Gy for intermediate-risk areas and 60 Gy for high-risk areas. RTOG trials allowed for additional boosting to as high as 66 Gy (15, 20, 21), but this is optional and empirical and the potential benefit has not been validated by prospective trials. Non−tumor-bearing, nonoperated contiguous or adjacent areas considered to be at risk, albeit "lower," are given 50 to 54 Gy. In the context of integrated planning, the common doses used are 60, 57, and 54 Gy for clinical target volumes 1, 2 and 3, respectively, in 30 fractions.

This and other trials did not address radiation dosing in the context of concurrent chemotherapy. The radiation doses used with concurrent chemotherapy (eg, cisplatin) are the same as those used without chemotherapy (15, 16). The reason the radiation doses were kept the same as with RT alone in initial chemo-RT trials evaluating the addition of chemotherapy is that RT was considered the gold standard treatment, so its full robustness was maintained, while chemotherapy dose intensity was reduced when necessary. Current and future related studies are and will be evaluating the relative importance of specific aspects and degrees of margin status and ECE, as well as chemotherapy and RT dose reduction, in the setting of human papillomavirus−driven HNSCC (E3311)

and whether the addition of concurrent cetuximab adds to PORT for intermediate-risk cancers (RTOG 0920).

In conclusion, this long-term report of a radiation dose seeking trial of PORT for HNSCC demonstrated that increasing dose did not significantly improve tumor control. The likely explanation is that in fractionated irradiation, increasing the total time likely offsets any benefit of increased dose, as well as adds to toxicity. The question of dose (and time) remains unanswered because although the standard of care for patients with "high-risk" features is currently concurrent chemo-RT, the 2 seminal trials used differing doses (60 Gy vs 66 Gy in 6 or 6.5 weeks).

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