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ORIGINAL REPORT

Postoperative Concurrent Chemoradiotherapy Versus Postoperative Radiotherapy in High-Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck: The Randomized Phase III TROG 05.01 Trial

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ABSTRACT

Purpose

To report the results of the Trans Tasman Radiation Oncology Group randomized phase III trial designed to determine whether the addition of concurrent chemotherapy to postoperative radiotherapy (CRT) improved locoregional control in patients with high-risk cutaneous squamous cell carcinoma of the head and neck.

Patients and Methods

The primary objective was to determine whether there was a difference in freedom from locoregional relapse (FFLRR) between 60 or 66 Gy (6 to 6.5 weeks) with or without weekly carboplatin (area under the curve 2) after resection of gross disease. Secondary efficacy objectives were to compare disease-free survival and overall survival.

Results

Three hundred twenty-one patients were randomly assigned, with 310 patients commencing allocated treatment (radiotherapy [RT] alone, n = 157; CRT, n = 153). Two hundred thirty-eight patients (77%) had high-risk nodal disease, 59 (19%) had high-risk primary or in-transit disease, and 13 (4%) had both. Median follow-up was 60 months. Median RT dose was 60 Gy, with 84% of patients randomly assigned to CRT completing six cycles of carboplatin. The 2- and 5-year FFLRR rates were 88% (95% CI, 83% to 93%) and 83% (95% CI, 77% to 90%), respectively, for RT and 89% (95% CI, 84% to 94%) and 87% (95% CI, 81% to 93%; hazard ratio, 0.84; 95% CI, 0.46 to 1.55; $P = .58$), respectively, for CRT. There were no significant differences in disease-free or overall survival. Locoregional failure was the most common site of first treatment failure, with isolated distant metastases as the first site of failure seen in 7% of both arms. Treatment was well tolerated in both arms, with no observed enhancement of RT toxicity with carboplatin. Grade 3 or 4 late toxicities were infrequent.

Conclusion

Although surgery and postoperative RT provided excellent FFLRR, there was no observed benefit with the addition of weekly carboplatin.

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ASSOCIATED CONTENT

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Appendix
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Data Supplement
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INTRODUCTION

Concurrent, platinum-based, postoperative chemoradiotherapy (CRT) has demonstrated improvement in locoregional control (LRC), progression-free survival, and overall survival (OS) compared with radiotherapy (RT) alone in patients with high-risk mucosal squamous cell carcinoma of the head and neck (SCCHN).[1,2] Although many have extrapolated the use of postoperative CRT from these studies to cutaneous SCCHN (cSCCHN), particularly in the presence of positive margins and extracapsular nodal extension (ECE), there is no high-level evidence to support its use in this setting.[3-5] The Trans Tasman Radiation Oncology Group (TROG) conducted a randomized phase III trial, known as

the POST (Postoperative Skin Trial) study, to determine whether the addition of concurrent carboplatin to postoperative RT improved LRC in high-risk cSCCHN (TROG 05.01; ClinicalTrials.gov identifier: NCT00193895).

PATIENTS AND METHODS

Study Population

Eligibility criteria included the following: histologically proven cSCCHN, complete macroscopic resection with or without microscopic positive margins, presence of a high-risk feature of either high-risk nodal disease and/or advanced primary disease (including in-transit disease) confined to above the clavicles, Eastern Cooperative Oncology Group performance status ≤ 2, adequate hematologic function and calculated creatinine clearance (Cockcroft-Gault) > 40 mL/min, no immunosuppression as a result of medication or medical condition, no distant metastases, no previous radical RT to the head and neck, and no prior cancers (except those diagnosed > 5 years ago with no evidence of recurrence).

High-risk nodal disease was defined as intraparotid nodal disease (any number or size of nodes, with or without ECE, and with or without an identifiable index lesion) and/or cervical nodal disease with a synchronous index lesion or previously resected primary tumor (< 5 years) within the corresponding nodal drainage and exclusion of a mucosal primary tumor with at least computed tomography (CT) scan and/or magnetic resonance imaging and panendoscopy. For cervical nodal disease to have been eligible, at least one of the following must have been present: two or more nodes, largest node ≥ 3 cm, or ECE.

Advanced primary disease was defined, as per the American Joint Committee on Cancer TNM staging system (sixth edition), as either being > 5 cm (T3) or invading surrounding cartilage, skeletal muscle, or bone (T4) of the head and neck and/or in-transit metastases.[6] All participants provided written informed consent, and the institutional ethics committees of participating centers approved the protocol.

Study Design

This was a multicenter, open-label, randomized, phase III clinical trial comparing RT and CRT in patients with high-risk cSCCHN. The trial was conducted under the auspices of TROG.

Study Treatment

Surgery consisted of resection of the primary lesion, any type of parotidectomy, and/or any type of neck dissection (ND). Participants with advanced primary disease without clinical evidence of nodal disease may have also undergone an elective parotidectomy and/or ND. Patients with intraparotid nodal disease without a synchronous primary lesion must have undergone some form of parotidectomy with or without a therapeutic or elective ND.

Every attempt was made to commence RT within 6 weeks, but no later than 9 weeks, after surgery. The trial was initiated before the universal availability of intensity-modulated RT (IMRT); therefore, patients were treated with three-dimensional conformal RT. Planning and prescribing were according to the International Commission on Radiation Units and Measurements 50 and 62 guidelines.[7,8] Initially, RT in both arms consisted of conventionally fractionated daily treatment to a total of 60 Gy in 30 fractions over 6 weeks to the site of previous gross disease. However, a modification to include the option of 66 Gy in 33 fractions over 6.5 weeks was included in November 2008 because of concerns by investigators that 60 Gy may have been a suboptimal dose in the presence of microscopic positive margins. To avoid bias in the treatment arms, investigators were required to nominate the total RT dose before random assignment. RT quality assurance (QA) was performed by the TROG QA team. RT variables assessed after therapy included volumes, dosimetry, technique, and

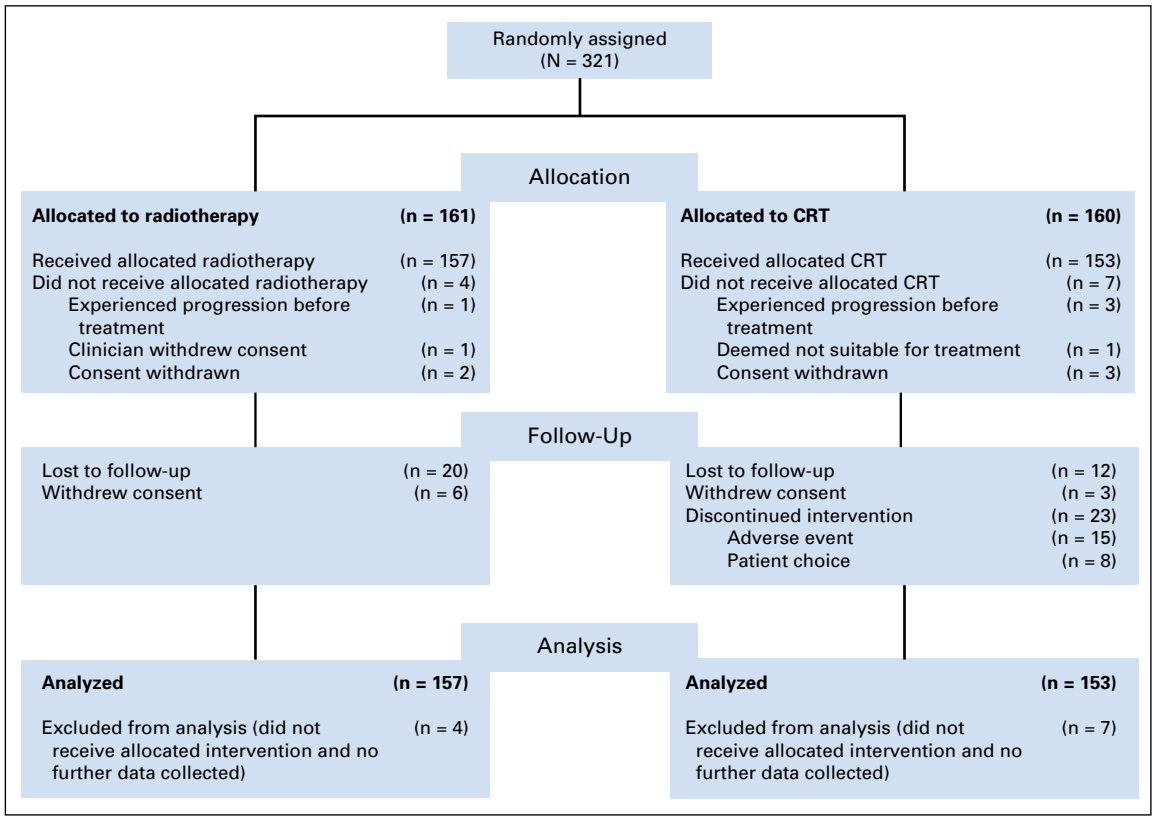

Fig 1. CONSORT diagram. CRT, chemoradiotherapy.

Table 1. Patient, Tumor, and Treatment Characteristics

Characteristic	RT Arm (n = 157)	CRT Arm (n = 153)
Median age, years (range)	65 (37-83)	63 (32-85)
Sex		
Male	147 (94)	140 (92)
Female	10 (6)	13 (8)
ECOG PS		
0	144 (92)	133 (87)
1	12 (8)	20 (13)
2	1 (1)	0 (0)
High-risk feature		
High-risk nodal	122 (78)	116 (76)
Advanced primary/in transit	29 (18)	30 (20)
T3	3	1
T4	17	24
In transit	9	4
In transit/T4	0	1
High-risk nodal and advanced primary/ in transit	6 (4)	7 (5)
T3	1	1
T4	4	6
In transit	1	0
High-risk nodal with synchronous nonadvanced primary	11 (9)	16 (14)
TX	1	3
T1	4	6
T2	6	7
Nodal surgery performed (elective or therapeutic)	144 (92)	136 (89)
ND only	44 (31)	33 (24)
ND and P	82 (57)	81 (60)
P	18 (12)	22 (16)
P performed		
Superficial	64 (64)	71 (69)
Partial	8 (8)	9 (9)
Total	25 (25)	20 (19)
Missing	3 (3)	3 (3)
Nodal pathology status		
ND positive	37 (26)	19 (14)
ND and P positive	16 (11)	77 (57)
P positive	68 (47)	24 (18)
ND and/or P negative	23 (16)	16 (12)
Extracapsular extension		
Absent	58 (40)	57 (42)
Present	86 (60)	79 (58)
Advanced primary (T3-4) margin status with or without high risk nodal disease	25 (16)	33 (22)
Positive	10	16
≤ 5 mm	7	12
> 5 mm/clear	3	2
Missing	5	3
RT dose*		
Median, Gy (range)	60 (60-70)	60 (50-66)
66 Gy	23 (15)	22 (14)
Planned RT delivered	151 (96)	143 (93)
Delayed RT start (> 6 weeks)	17 (11)	19 (12)
Carboplatin (AUC 2)		
5 cycles	—	12 (8)
6 cycles	—	128 (84)
Other	—	13 (8)

NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviations: AUC, area under the curve; CRT, chemoradiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ND, neck dissection; P, parotidectomy; RT, radiotherapy.
*Five patients received < 60 Gy as a result of discontinuance, whereas three patients (all in the RT arm) received a dose > 66 Gy as a result of protocol deviation (68 Gy, n = 1; 70 Gy, n = 2).

verification with compliance graded as acceptable, minor, major, or missing/not evaluable.

In the CRT arm, participants were planned to receive weekly carboplatin commencing on day 1, 2, or 3 of the RT and repeated on the same day each week to a maximum of six doses. The drug was administered intravenously over 20 to 30 minutes before and within 4 hours of receiving RT. Carboplatin commenced with a dose calculated according to the Calvert formula to target an area under the curve of 2.0 using a calculated creatinine clearance.[9,10] The calculated dose at baseline was used in all cycles unless there was a weight change of > 10% from baseline or serum creatinine changes by > 0.02 mmol/L.

Pretreatment and Follow-Up Evaluations

Pre–random assignment assessment included clinical history, physical examination, blood tests, CT of head and neck, CT of the chest or chest x-ray, and health-related quality of life (HRQoL) using the Functional Assessment of Cancer Therapy–Head and Neck (FACT-HN) and Functional Assessment of Cancer Therapy–General questionnaires.[11,12] During treatment, toxicity was graded weekly according to the Common Terminology Criteria for Adverse Events (version 3.0), and blood tests were performed weekly in patients randomly assigned to the CRT arm. Follow-up assessments were performed at 4, 8, and 12 weeks and then 6, 9, 12, 16, 20, and 24 months after the completion of treatment and every 6 months thereafter up to 5 years or until the close-out date. Toxicity was classified as acute or late based on whether it occurred up to or beyond 12 weeks after the completion of treatment.[13]

HRQoL was assessed at baseline and 12 weeks and then 6, 12, and 24 months after completion of treatment and at recurrence, with the option of annual assessment until the close-out date or 5 years. Upon suspicion of suspected recurrence, patients underwent histologic confirmation (where feasible), photo documentation, and/or tumor diagram and restaging CT imaging.

End Points

The primary end point, freedom from locoregional relapse (FFLRR), was measured from the date of random assignment until the first evidence of locoregional relapse (LRR). If distant relapse occurred, the patient continued to be observed for subsequent LRR. Therefore, distant relapse was not a censoring event. Death without preceding LRR was a censoring event for the primary analysis, but a sensitivity analysis was performed considering death as a competing event.

LRR was defined as a local (or in-transit) and/or regional relapse. In-transit relapse was defined as dermal or subcutaneous relapse between the primary site and the adjoining nodal basin. Disease-free survival (DFS) was measured from the date of random assignment until first relapse at any site or death from any cause.

OS was measured from the date of random assignment until the date of death from any cause. For all of the time-to-event end points (FFLRR, DFS, and OS), patients who did not experience the respective event by the study close-out date were censored.

The frequency, severity, and relatedness of treatment-related adverse events (AEs; Common Terminology Criteria for Adverse Events version 3.0) were recorded. The FACT-HN trial outcome index was the primary HRQoL outcome, scored according to the standard algorithm specified by the instrument's developers.[11,12] A change in score of 5% was considered clinically meaningful.[14,15]

Random Assignment and Stratification

Participants were randomly assigned in a ratio of 1:1 to RT or CRT. Stratified random assignment was used to balance the arms according to high-risk nodal disease and advanced primary/in-transit disease and institution. In cases where participants had both risk categories, patients were stratified to the high-risk nodal group.

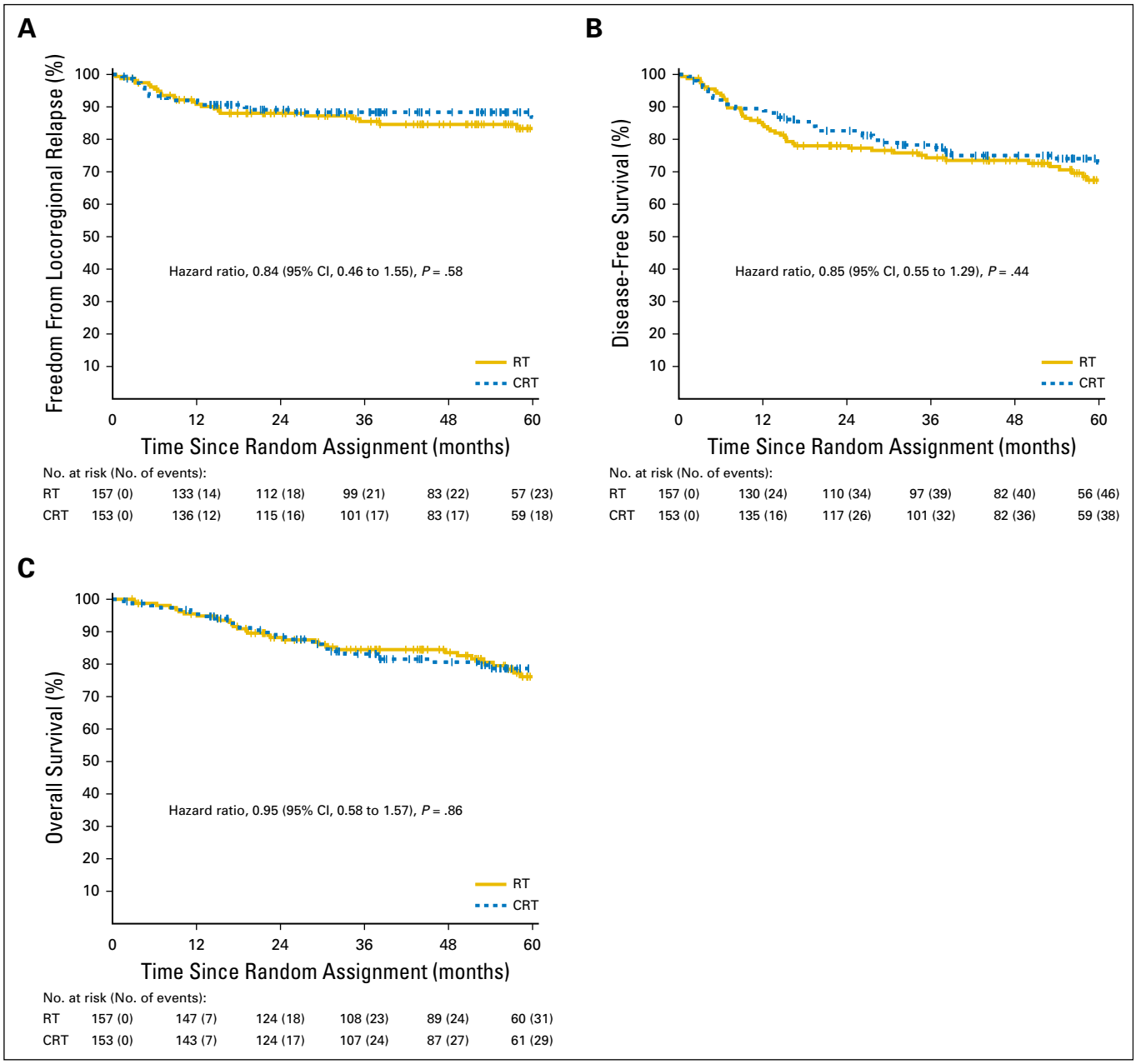

Fig 2. Kaplan-Meier estimates of (A) freedom from locoregional relapse, (B) disease-free survival, and (C) overall survival by treatment arm. CRT, chemoradiotherapy; RT, radiotherapy.

Sample Size

The targeted sample size of 265 patients was determined to detect a difference of 15% in FFLRR at 2 years (70% and 85% for RT and CRT, respectively), corresponding to a hazard ratio (HR) of 0.46. It was assumed that the FFLRR curve for the RT group exhibits an exponential decline to a plateau at 40% (cure fraction) and that the majority of LRRs occur by 12 months.[16,17] With an accrual rate of 45 to 50 patients per year, a further 2 years of follow-up after accrual, a power of 80%, and a significance level of 5%, 237 patients were required. To allow for some censored observations, 265 patients were planned for recruitment. After a clinical impression by the Trial Management Committee (TMC) during the conduct of the study that the overall LRR rate seemed to be lower than expected, data relevant to the primary outcome for the RT arm only were extracted in August 2011 for the purpose of a sample size reassessment. The trial chairs and TMC were blinded to this assessment, which was overseen by the Independent Safety and Data Monitoring Committee. On the basis of these results, an assumed accrual rate of 45 patients per year, and an unchanged clinically important HR of 0.46, the sample size was recalculated to a total of 350 patients. The Independent Safety and Data Monitoring Committee recommended the trial continue with the revised target accrual. The recruitment rate from 2011 onward was noted to be substantially reduced, as a result of factors such as the introduction of IMRT as standard of care for most head and neck cancers (HNCs). The TMC elected not to seek an amendment to include IMRT because it may have affected the secondary outcomes, complicating the analysis. In 2014, the Independent Safety and Data Monitoring Committee agreed with the TMC that based on the reduced accrual rate, the trial was unlikely to meet the revised target and the trial ceased, with 321 patients being recruited.

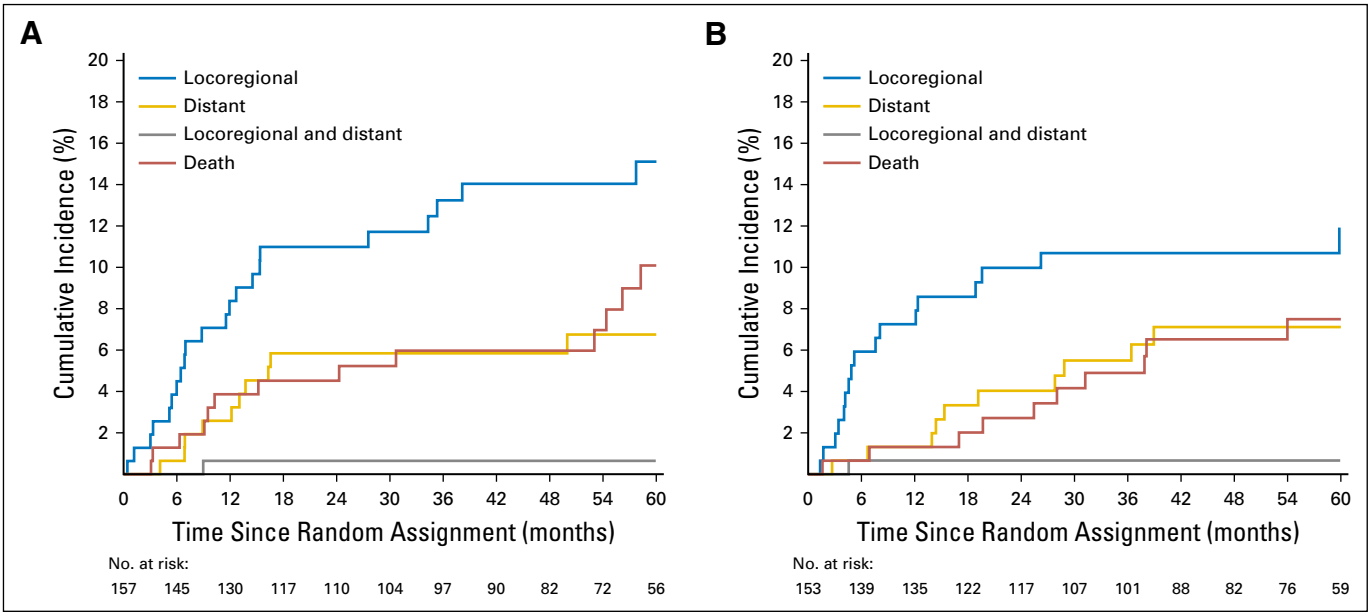

Fig 3. Cumulative incidence of first failure in the (A) radiotherapy arm and (B) chemoradiotherapy arm.

Statistical Methods

Time-to-event outcomes (FFLRR, DFS, and OS) were estimated using the Kaplan-Meier method, with corresponding 95% CIs. The close-out date was March 30, 2016. Stratified Cox proportional hazards models were used to estimate the HR and compare the treatment arms, with the presence of high-risk nodal disease (yes or no) as a stratification variable. A sensitivity analysis for FFLRR was carried out using competing risks regression with death as the only competing event.

Patients who withdrew from the trial before treatment who had no postbaseline data available were excluded from the analysis. All other patients were analyzed according to treatment arm, regardless of treatment compliance.

The worst grades of acute and late toxicities were recorded and described as percentages of the total evaluable patients. Rate of toxicities were compared between arms using generalized linear models.

HRQoL was analyzed using linear mixed models (LMM) with time (as factor) included as a fixed effect and patient included as a random effect. No within-group correlations were assumed, with the model being fitted by maximizing the restricted log-likelihood. No imputation for missing values was used. Means and 95% CIs were estimated from the linear mixed models contrasts.

A post hoc analysis was performed comparing the arms based on the following subgroups: margin status of resected primary disease, presence of ECE, number of positive nodes, and size of largest involved node. All statistical analyses were performed in R version 3.2.3 (www.r-project.org).[18]

RESULTS

Patient Characteristics

From April 2005 to July 2014, 321 patients from 22 Australian and New Zealand sites were randomly assigned. CONSORT flowchart is shown in Figure 1. A total of 11 patients did not receive the allocated treatment and had no further data collected (RT, n = 4; CRT, n = 7), leaving 310 evaluable patients (RT, n = 157; CRT, n = 153). The two arms were balanced with respect to demographic and tumor characteristics (Table 1). The median age was 65 and 63 years for the RT and CRT arms, respectively. The majority of patients were men, the predominant Eastern Cooperative Oncology Group performance status was 0, and the median follow-up time was 60 months (range, 1.6 to 91.4 months). Two hundred thirty-eight patients (77%) had high-risk nodal disease, 59 (19%) had high-risk primary or in-transit disease, and 13 (4%) had both. Superficial parotidectomy was the most common regional nodal surgery performed. ECE was present in 86% and 79% of patients in the RT and CRT arms, respectively. Of the 251 patients (81%) with high-risk nodal disease, a synchronous primary tumor (advanced or nonadvanced) or in-transit disease was present in 16% (Table 1). It was not always possible to obtain a reliable T stage for primary lesions when they were metachronous in patients with advanced nodal disease for various reasons (eg, lesions treated by a wide range of external centers with T stage not recorded at initial diagnosis, topical agents used as definitive therapy, and/or a history of previous multiple lesions making it difficult to identify the index lesion). For patients with advanced primary disease (T3-4) in whom the margin status was known, a positive margin was seen in 40% (10 of 25 patients) and 48% (16 of 33 patients) of patients in the RT and CRT arms, respectively (Table 1).

Treatment Compliance

The median RT dose was 60 Gy. The prescribed RT dose was delivered in 96% and 93% of patients in the RT and CRT arms, respectively. Commencement of RT was delayed (> 6 weeks) in 11% and 12% of patients in the RT and CRT arms, respectively. Six doses of chemotherapy were administered to 84% of the patients in the CRT arm, with 11% requiring a dose reduction (Table 1).

Efficacy Outcomes

FFLRR, DFS, and OS curves for RT and CRT patients are shown in Figures 2A, 2B, and 2C, respectively. The 2- and 5-year

Table 2. Acute Treatment-Related Adverse Events (CTCAE V3.0; worse grade) by Arm (from commencement to within 12 weeks of completing treatment)

Adverse Event	No. of Evaluable Patients (%)			
	RT (n = 156)		CRT (n = 152)	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
Dermatitis*	80 (51)	76 (49)	94 (62)	58 (38)
Salivary gland	149 (96)	0	141 (93)	0
Otitis externa	109 (70)	1 (1)	92 (61)	1 (1)
Mucositis	131 (84)	16 (10)	118 (78)	16 (11)
Dysphagia	113 (72)	5 (3)	106 (70)	5 (3)
Constipation†	1 (1)	0	32 (21)	1 (1)
Fatigue†	7 (4)	0	40 (26)	1 (1)
Edema	132 (85)	2 (1)	123 (81)	2 (1)
Otitis media	2 (1)	0	2 (1)	0
Dysgeusia†	8 (5)	0	20 (13)	0
Lhermitte	2 (1)	0	2 (1)	0
Chemotherapy related adverse events‡				
Hemoglobin			23 (16)	0
Neutrophils			10 (7)	1 (1)
Platelets			26 (18)	1 (1)
Febrile neutropenia			1 (1)	1 (1)
Infection with normal ANC or grade 1 or 2 neutrophils			16 (11)	1 (1)
Infection with unknown ANC			5 (3)	1 (1)
Nausea			81 (55)	3 (2)
Vomiting			22 (15)	1 (1)

NOTE. Two patients did not have acute RT-related adverse events recorded (RT, n = 1; CRT, n = 1).
Abbreviations: ANC, absolute neutrophil count; CRT, chemoradiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; RT, radiotherapy.
*Dermatitis grade 3 or 4: *P* between arms = .065.
†Presence of toxicity (grade ≥ 1) between arms was significant for constipation ($P < .001$), fatigue ($P < .001$), and dysgeusia ($P = .018$)
‡Chemotherapy-related adverse events were not recorded in five patients (evaluable, n = 147).

FFLRR rates for RT were 88% (95% CI, 83% to 93%) and 83% (95% CI, 77% to 90%), respectively, whereas for CRT, they were 89% (95% CI, 84% to 94%) and 87% (95% CI, 81% to 93%; HR, 0.84; 95% CI, 0.46 to 1.55; $P = .58$), respectively. The results from the sensitivity analysis with death as a competing event were almost identical (HR, 0.85; 95% CI, 0.47 to 1.56; $P = .60$).

The 2- and 5-year DFS rates for RT were 78% (95% CI, 72% to 85%) and 67% (95% CI, 60% to 76%), respectively, whereas for CRT, they were 83% (95% CI, 77% to 89%) and 73% (95% CI, 66% to 81%; HR 0.85; 95% CI, 0.55 to 1.29; $P = .44$), respectively. The 2- and 5-year OS rates for RT were 88% (95% CI, 83% to 93%) and 76% (95% CI, 69% to 84%), respectively, whereas for CRT, they were 88% (95% CI, 83% to 94%) and 79% (95% CI, 72% to 86%; HR, 0.95; 95% CI, 0.58 to 1.57; $P = .86$), respectively.

Cumulative incidence of site of first failure by arm is shown in Figure 3. Isolated LRR was the most common site of first failure. Isolated distant failure occurred in 7% of patients in both arms. No significant treatment effect for the primary end point was identified in any subgroup (Appendix Fig A1, online only).

AEs

There were no treatment-related deaths. Skin reaction was the most common AE, whereas the most common chemotherapy-related

Table 3. Late (≤ 3 years) Treatment-Related Adverse Events (new or worsening of existing adverse event; CTCAE V3.0)

Toxicity	No. of Evaluable Patients (%)			
	RT (n = 145)		CRT* (n = 149)	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
Skin atrophy	51 (35)	0	52 (35)	0
Xerostomia	16 (11)	3 (2)	12 (8)	0
Induration/fibrosis	44 (30)	3 (2)	42 (28)	2 (1)
Telangiectasia	60 (41)	0	78 (52)	0
Trismus	3 (2)	0	1 (1)	0
Osteoradionecrosis	5 (3)	0	4 (3)	1 (1)
Cataract	1 (1)	0	0	0
Ocular surface disease	5 (3)	0	5 (3)	1 (1)
Hearing loss	9 (6)	0	7 (5)	1 (1)
Tinnitus	2 (1)	1 (1)	3 (2)	0
Neuropathy, sensory	3 (2)	0	1 (1)	0

Abbreviations: CRT, chemoradiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; RT, radiotherapy.
*In CRT arm, one patient experienced a grade 3 CNS necrosis.

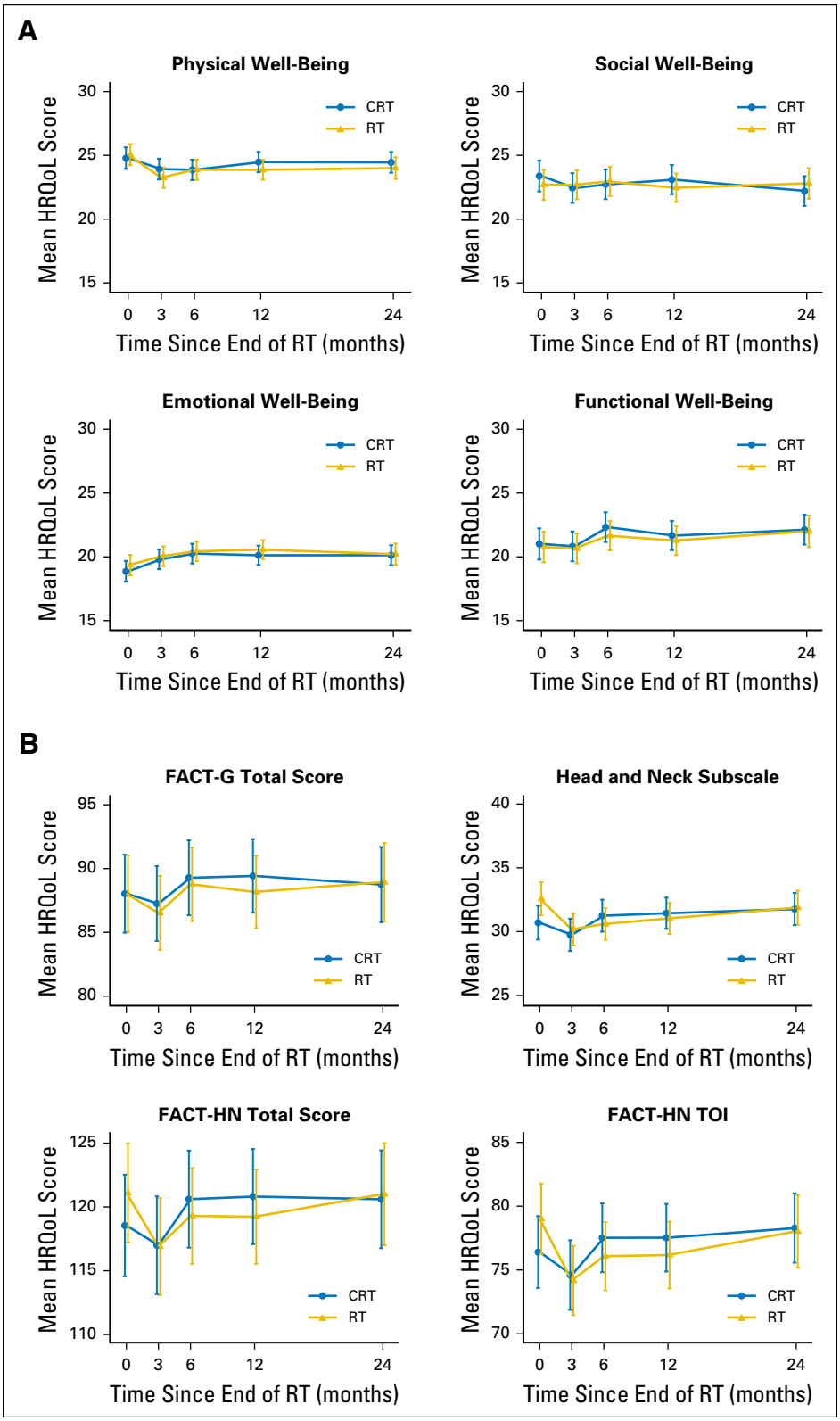

Fig 4. Health-related quality-of-life (HRQoL) mean scores (95% CIs) by treatment arm from baseline to 2-year follow-up. (A) Functional Assessment of Cancer Therapy–General subscales. (B) Functional Assessment of Cancer Therapy–Head and Neck total scores and subscale. CRT, chemoradiotherapy; RT, radiotherapy; TOI, trial outcome index.

AE was nausea (grade 1 or 2; Table 2). Constipation ($P < .001$), fatigue ($P < .001$), and dysgeusia ($P = .018$) were more common in the CRT arm. Excluding skin reaction, grade 3 or 4 AEs were uncommon.

The most common late AEs were telangiectasia, skin atrophy, and induration or fibrosis. Grade 1 or 2 osteonecrosis was seen in 3% of patients in both arms (Table 3).

RT QA

TROG conducted QA in 301 patients (RT, n = 151; CRT, n = 150), examining 3,172 variables (Appendix Tables A1 and A2, online only). Major protocol deviations occurred in 33 patients (11%), with only 19 deviations (6%) related to dose compliance within the planning target volumes. The remaining 14 deviations (5%) were mainly associated with field verification protocol compliance.

Quality of Life

HRQoL compliance was low at all visits, 44% at baseline, and similar on both arms (reasons for noncompliance were not recorded; Appendix Table A3, online only). The FACT-HN trial outcome index and all the subscales results were similar between arms (Fig 4).

DISCUSSION

In this first reported randomized phase III trial of CRT in high-risk cSCCHN, the 2- and 5-year FFLRR rates after surgery and postoperative RT were high, and the addition of concurrent carboplatin did not improve FFLRR, DFS, or OS. On the basis of retrospective single-institution case series and extrapolation from mucosal HNC studies, the National Comprehensive Cancer Network guidelines recommend postoperative RT for positive margins, ECE, two or more involved nodes, or involved node > 3 cm,[3,16,17,19-29] and that the addition of concurrent chemotherapy should be considered in the presence of ECE.[1,2,4,5]

Although this was a negative study, there were a number of potential limitations that affected the outcome. Consideration should be given to the following factors: the study was not powered to detect and cannot exclude a smaller benefit from chemotherapy; carboplatin was used rather than cisplatin; and despite the best available evidence at the time, the population did not seem to be as high risk for locoregional failure as originally anticipated.

At the time of trial design, series reported LRC rates of 40% to 45% with surgery alone depending on extent of nodal disease, with a 15% to 20% benefit with the addition of postoperative RT.[16,20,21] Our initial study design made an assumption of a 2-year FFLRR of 70% with postoperative RT alone. The higher than expected FFLRR rate in the RT arm of 88% at 2 years now sets the benchmark for future studies and establishes the control arm in any subsequent randomized trial testing the addition of other agents in the adjuvant setting in immunocompetent patients.

On the basis of the available evidence, we assumed the addition of concurrent platinum-based chemotherapy would improve 2-year FFLRR by 15%.[1,2] At the time of trial design, there were limited data on the use of systemic therapy for cSCCHN, and anti–epidermal growth factor receptor agents and immunotherapies had not entered the clinical domain.[30,31] The majority of studies, but not all, demonstrating superiority of concurrent CRT in mucosal SCCHN have used cisplatin; however, it was anticipated that many patients eligible for this study were likely to be elderly with coexisting medical comorbidities precluding its use.[32-34] Hence, we elected to use carboplatin given once weekly during RT in the experimental arm. Our results do not preclude the possibility that cisplatin may be efficacious in the postoperative cSCCHN setting in patients who do not have a contraindication to cisplatin, but this remains unproven. Although adjuvant treatment was well tolerated, a higher rate of non–RT-related AEs was seen in the CRT arm. Severe chemotherapy and late RT toxicity was uncommon, with no enhancement of late RT toxicity seen with the addition of carboplatin. There was no apparent difference in HRQoL; however, results should be interpreted with caution because of potential nonignorable missing data and low questionnaire completion rates. The importance of RT quality in HNC has been well documented.[35] The low rate of major RT protocol deviations confirmed the high quality of the treatment delivered, which may have contributed to the higher than expected FFLRR.

Given the high LRC, interventions that may affect both LRC and distant metastases would be preferable for future adjuvant trials. Promising results with immune checkpoint inhibitors in advanced cSCCHN warrant further evaluation in the adjuvant setting.[31]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Manuscript writing: All authors
Final approval of manuscript: All authors
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Postoperative Concurrent Chemoradiotherapy Versus Postoperative Radiotherapy in High-Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck: The Randomized Phase III TROG 05.01 Trial

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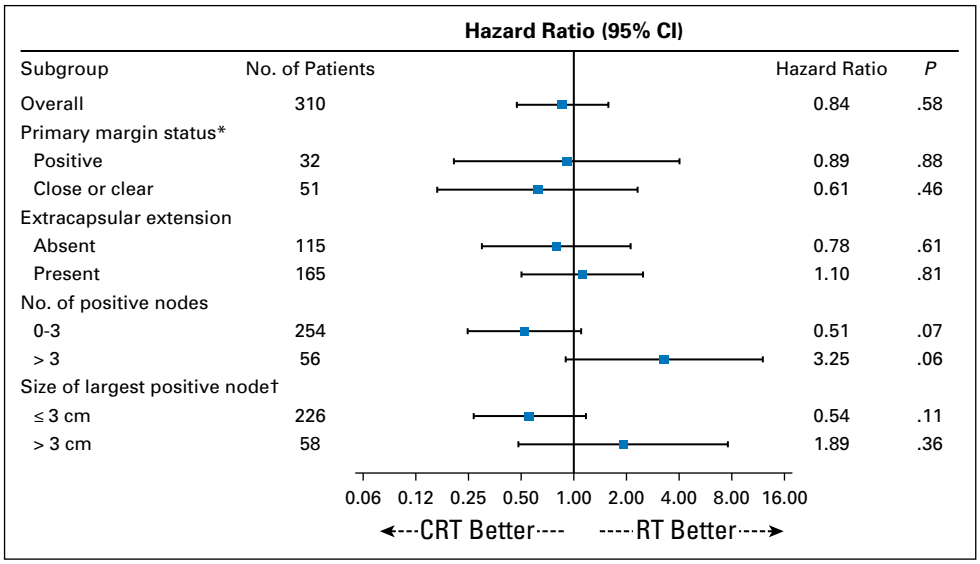

Fig A1. Forest plot of freedom from locoregional relapse comparing chemoradiotherapy (CRT) and radiotherapy (RT) alone in patient subgroups. (*) Primary margin status for advanced primary or in-transit and high-risk nodal disease with either synchronous advanced primary (T3-4) or nonadvanced (< T3) primary disease (n = 99). Margin status was unknown or missing in 16 patients. Clear margin was defined as > 5 mm. Close margin was defined as ≤ 5 mm but not extending to the resection edge. Positive margin was defined as microscopic extension of disease to resection edge. Nodal size based on the largest diameter of either high risk or low risk nodal disease

Table A1. TROG Quality Assurance Radiotherapy Compliance Report

	No. of Patients (%)				
Category	Variables Reviewed	Acceptable	Minor	Major	Missing/Unevaluable
Schedule	453	444	5	3	1
Dose	906	813	23	19	51
Technique	1,209	1,027	57	1	124
Verification	604	591	0	10	3
Total	3,172	2,875 (91)	85 (3)	33 (1)	179 (6)

NOTE. The first five patients from each site were reviewed after treatment. This was followed by a minimum of a one in three random sampling. Parameters reviewed and variation definitions are listed in Appendix Table A2.

Table A2. Radiotherapy Variables and Definitions

Parameter	Acceptable	Minor	Major
Schedule			
Treatment duration, days			
PTV3 60 Gy	≤ 44	45-46	> 46
PTV3 66 Gy	≤ 47	48-49	> 49
Total No. of fractions			
PTV3 60 Gy	29-31	27-28 or 32 -33	< 27 or > 33
PTV3 66Gy	32-34	30-31 or 35-36	< 30 or > 36
All fields prescribed for 1 fraction per day	Yes	—	No
Dose			
Total dose within PTVl to ICRU reference point, Gy	47.5-52.5	45-47.4 or 52.6-55	< 45 or > 55
Total dose within PTV2 to ICRU reference point, Gy	51.3-56.7	48.6-51.2 or 56.8-59.4	< 48.6 or > 59.4
Total dose within PTV3 to ICRU reference point, Gy			
PTV3 60 Gy	57-63	54-56.9 or 63.1-66	< 54 or > 66
PTV3 66 Gy	62.7-69.3	59.5-62.6 or 69.4-72.7	< 59.5 or > 72.7
Minimum dose to PTV3, Gy			
PTV3 60 Gy	≥ 54	51-53.9	< 51
PTV3 66 Gy	≥ 59.5	56.5-59.4	< 59.4
Maximum dose to PTV3, Gy			
PTV3 60 Gy	< 67.3	67.3-70.2	> 70.2
PTV3 66 Gy	< 74.1	74.1-77.8	> 77.8
Dose per fraction, Gy	1.9-2.1	1.8-1.89 or 2.11-2.2	< 1.8 or > 2.2
Technique			
PTVl compliant with protocol	Acceptable	Marginal	Inadequate
PTV2 compliant with protocol	Acceptable	Marginal	Inadequate
PTV3 compliant with protocol	Acceptable	Marginal	Inadequate
CT planning used	Yes	—	Other
Surgical scar marked on plan CT	Yes	No	
Maximum dose to spinal cord, Gy	< 47.25	47.5-50	> 50
Maximum dose to brainstem, Gy	54	54.1-56.7	56.8
Maximum dose to optic chiasm, Gy	54	54.1-56.7	56.8
Verification			
Reference image provided	Sim x-ray or DRR	—	No image provided
Portal images (day 1) taken	Yes	—	No
Portal images (weekly) taken	Yes	—	No
Reference image for electron fields	Yes	—	No

Abbreviations: CT, computed tomography; DRR, digitally reconstructed radiograph; ICRU, International Commission on Radiation Units; PTV, planning target volume; PTV1, 50 Gy; PTV2, 54 Gy; PTV3, 60 (66) Gy.

Table A3. Health-Related Quality-of-Life Questionnaire Compliance

	RT			CRT		
Visit	Expected (No.)*	Received No.	Return Rate (%)	Expected (No.)*	Received No.	Return Rate (%)
Before treatment	157	68	43	153	67	44
12 weeks	154	75	49	150	75	50
6 months	153	76	50	148	76	51
12 months	146	81	55	143	81	57
24 months	128	62	48	124	74	60

Abbreviations: CRT, chemoradiotherapy; RT; radiotherapy.
*Expected numbers represent the number of patients alive, not lost to follow-up, and not having withdrawn consent at the specific time point.