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ORIGINAL REPORT

Institutional Clinical Trial Accrual Volume and Survival of Patients With Head and Neck Cancer

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See accompanying editorial on page 138; listen to the podcast by Dr Eisbruch at www.jco.org/podcasts

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ABSTRACT

Purpose
National Comprehensive Cancer Network guidelines recommend patients with head and neck cancer (HNC) receive treatment at centers with expertise, but whether provider experience affects survival is unknown.

Patients and Methods
The effect of institutional experience on overall survival (OS) in patients with stage III or IV HNC was investigated within a randomized trial of the Radiation Therapy Oncology Group (RTOG 0129), which compared cisplatin concurrent with standard versus accelerated fractionation radiotherapy. As a surrogate for experience, institutions were classified as historically low- (HLACs) or high-accruing centers (HHACs) based on accrual to 21 RTOG HNC trials (1997 to 2002). The effect of accrual volume on OS was estimated by Cox proportional hazards models.

Results
Median RTOG accrual (1997 to 2002) at HLACs was four versus 65 patients at HHACs. Analysis included 471 patients in RTOG 0129 (2002 to 2005) with known human papillomavirus and smoking status. Patients at HLACs versus HHACs had better performance status (0: 62% *v* 52%; $P = .04$) and lower T stage (T4: 26.5% *v* 35.3%; $P = .002$) but were otherwise similar. Radiotherapy protocol deviations were higher at HLACs versus HHACs (18% *v* 6%; $P < .001$). When compared with HHACs, patients at HLACs had worse OS (5 years: 51.0% *v* 69.1%; $P = .002$). Treatment at HLACs was associated with increased death risk of 91% (hazard ratio [HR], 1.91; 95% CI, 1.37 to 2.65) after adjustment for prognostic factors and 72% (HR, 1.72; 95% CI, 1.23 to 2.40) after radiotherapy compliance adjustment.

Conclusion
OS is worse for patients with HNC treated at HLACs versus HHACs to cooperative group trials after accounting for radiotherapy protocol deviations. Institutional experience substantially influences survival in locally advanced HNC.

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INTRODUCTION

Overall survival (OS) is improved for patients with cancer who undergo specialized surgical resection at hospitals that perform a large number of procedures (eg, pancreaticoduodenectomy or lung cancer resection).[1-6] Individual physician volume may also contribute to in-hospital mortality after cancer resection.[7] In a manner analogous to surgery, radiation therapy is a local modality with a high degree of user dependence. Treatment planning and patient care techniques can vary considerably among radiation oncologists. Because of its complexity, radiation therapy treatment planning for head and neck cancer (HNC) in particular has considerable interinstitutional and interphysician variation.[8,9]

In addition to complex treatment planning, HNC radiotherapy is frequently complicated by acute and chronic toxicities.[10] Therefore, robust multidisciplinary coordination of care may be particularly important in HNC. Indeed, current National Comprehensive Cancer Network (NCCN) guidelines recommend that all patients with HNC "need access to the full range of support services and specialists with expertise in the management of patients with HNC for optimal treatment and

follow-up."[11] The inference is that suboptimal outcomes may be more likely to occur for patients with HNC when high-volume specialization is not employed.

Therefore, we investigated whether institutional patient accrual volume was associated with OS or progression-free survival (PFS) for patients with HNC enrolled onto a prospective, multicenter, randomized controlled trial conducted by the Radiation Therapy Oncology Group (RTOG; protocol 0129).

PATIENTS AND METHODS

Study Population

RTOG 0129 was a phase III clinical trial conducted from 2002 to 2005 designed to evaluate whether accelerated fractionation (AFX) in comparison with standard fractionation (SFX) radiotherapy could improve OS of patients with HNC treated with concurrent high-dose cisplatin. The experimental design and primary results of the RTOG 0129 trial were published in 2010[12] and revealed similar 3-year OS in patients receiving AFX and SFX radiotherapy. RTOG 0129 was registered with the National Cancer Institute and approved by the institutional review boards at participating centers. All patients provided written informed consent. This retrospective analysis was not included in the original protocol.

Briefly, eligible patients for RTOG 0129 had untreated, pathologically confirmed, American Joint Committee on Cancer stage III or IV[13] squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx; had Zubrod performance status 0 to 1; were age ≥ 18 years; and had adequate bone marrow, hepatic, and renal function. Patients were randomly assigned to cisplatin concurrent with AFX by concomitant boost radiotherapy (72 Gy delivered in 42 fractions over 6 weeks, inclusive of twice-per-day irradiation for 12 treatment days) or SFX radiotherapy (70 Gy in 35 fractions over 7 weeks). Chemotherapy consisted of intravenous cisplatin 100 mg/m^2 of body-surface area on days 1 and 22 for patients assigned to AFX and on days 1, 22, and 43 for patients assigned to SFX.

Prior cigarette smoking in pack-years was obtained at enrollment by interviewer-administered questionnaire. To assess tumor status and late toxicity, follow-up examination and imaging studies were performed every 3 months for 2 years, every 6 months through year 5, and then annually.

Tumor Human Papillomavirus Status

Formalin-fixed, paraffin-embedded tumor specimens were evaluated for human papillomavirus (HPV) type 16 and 12 additional HPV types (types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) using the in situ hybridization–catalyzed signal amplification method for biotinylated probes (Dako GenPoint, Carpinteria, CA) as previously described.[14]

Radiation Therapy Compliance

Radiotherapy plans were reviewed for protocol compliance and categorized as per protocol (PP), acceptable variation (AV), or unacceptable deviation (UD) for total dose delivered, elapsed days, AFX completed, spinal cord dose, and field borders (Appendix Table A1, online only). Field borders were also scored based on adherence to protocol instructions by the principal investigator on primary tumor coverage, coverage of lymphatic space posterior to the spinal cord (right and left), and spinal cord and supraclavicular lymph node coverage.

Statistical Methods

Our principal outcome was the effect of institutional expertise on OS. As a surrogate for institutional expertise, we used institutional accrual volume to 21 HNC clinical trials conducted by the RTOG during the 5-year period (July 30, 1997, to July 29, 2002) immediately before the activation of RTOG 0129. To do so, 3,007 patients enrolled from 303 centers were divided into three approximately equally sized cohorts: high (1,017 patients, 15 centers, ≥ 42 patients per center), middle (1,016 patients, 44 centers, 13 to 41 patients per center), and low (974 patients, 244 centers, one to 12 patients per center). RTOG 0129 outcomes in the middle and low cohorts were similar and combined. The final cohorts were denoted historically low (HLACs) and high accruing centers (HHACs).

OS was defined as time from random assignment to death resulting from any cause. Secondary end points were PFS, locoregional failure (LRF), and acute and chronic toxicities. PFS was defined as time from random assignment to local, regional, or distant progression or death resulting from any cause. LRF was defined as time from random assignment to local or regional disease progression; distant metastasis and death unrelated to the index cancer were competing risks. OS and PFS rates were estimated by the Kaplan-Meier method[15] and compared by log-rank test.[16] LRF rates were estimated by the cumulative incidence method[17] and compared by Gray's test.[18] Acute toxicity was evaluated weekly during the period of therapy according to the Common Toxicity Criteria for Adverse Events (version 2.0).[19] Late toxicities were recorded at each follow-up visit, with attention to soft tissue changes, bony necrosis, changes in central or peripheral nervous system function, and condition of the mucosa.

Analysis was restricted to patients with known HPV status (if oropharynx primary site) and known cigarette pack-years. To evaluate study population bias, pretreatment characteristics and survival outcomes were compared

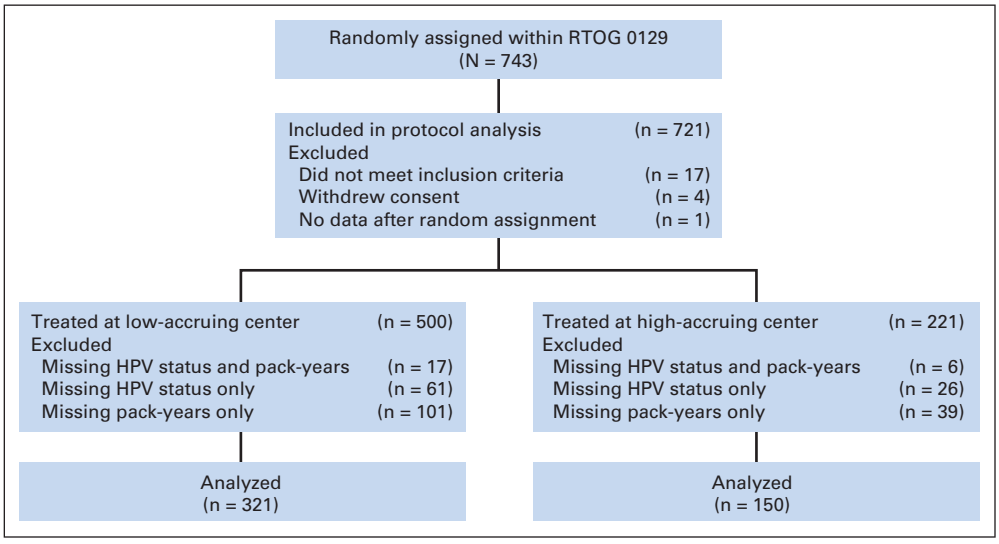

Fig 1. CONSORT diagram. HPV, human papillomavirus; RTOG, Radiation Therapy Oncology Group.

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for patients with complete versus missing data. Patient characteristics were compared by Pearson χ^2 or Fisher's exact test for categorical variables or Wilcoxon rank sum test[18] for ordinal and continuous variables. Cox proportional hazards models were used to evaluate the independent effect of accrual volume after accounting for treatment assignment and known prognostic factors: age, T stage, and N stage, Zubrod performance status, cigarette pack-years, and tumor HPV status. A second model including radiotherapy compliance estimated the percentage of the effect of accrual volume resulting from radiotherapy deviations. Sensitivity analysis was performed by: one, imputing missing values for HPV status (oropharynx only) and pack-years using the Markov chain Monte Carlo algorithm (with 20 imputations) to minimize potential bias from excluding patients from the analysis; two, lowering the HHAC threshold from 42 (top 5% of centers) to 25 patients (top 10% of centers); and three, considering historical accrual as a continuous variable.

RESULTS

Study Population

A total of 743 patients were enrolled, and 721 were eligible for protocol-specified end points (Fig 1). Of these 721, 250 (34.7%) had missing data for tumor HPV status (n = 110; oropharynx only) and/or cigarette smoking pack-years (n = 163). The remaining 471 patients were included. No statistically significant differences in patient or tumor characteristics or survival outcomes were observed for patients with complete versus missing data (Appendix Table A2; Appendix Figs A1 and A2, online only).

Median age of the analysis population was 56 years, and median number of smoking pack-years was 30. Thirty-eight percent of patients had HPV-positive oropharyngeal cancers, 19% had HPV-negative oropharyngeal cancers, and 44% had nonoropharyngeal primary cancers. Disease was staged as IVA for a majority of patients (77%).

Of the 471 patients, 321 were treated at one of 88 HLACs and 150 at one of 13 HHACs. Median accrual to RTOG 0129 from HLACs was two patients (range, one to 20), and median accrual to RTOG 0129 from HHACs was six patients (range, one to 44). Patient characteristics are listed in Table 1. Patients treated at HLACs and HHACs had similar distributions of treatment assignment, age, cigarette pack-years, tumor HPV status, and N stage. However, patients at HLACs had better performance status (Zubrod of 0: 62% *v* 52%; $P = .04$) and lower T stage (T4: 26.5% *v* 35.3%; $P = .002$).

Table 1. Patient and Tumor Characteristics by Accrual Volume

Characteristic	HHAC (n = 150) No.	%	HLAC (n = 321) No.	%	*P*
Assigned treatment					.83*
SFX plus cisplatin	75	50.0	164	51.1	
AFX-C plus cisplatin	75	50.0	157	48.9	
Age, years					.61†
Median	56		55		
Range	33-82		31-79		
Q1 to Q3	50-60		50-61		
Zubrod performance status					.04*
0	78	52.0	199	62.0	
1	72	48.0	122	38.0	
Cigarette pack-years					.75†
Median	30.5		30		
Range	0-152		0-137.5		
Q1 to Q3	1.5-50.4		6-49		
Primary site					.43*
HPV-positive oropharynx	62	41.3	116	36.1	
HPV-negative oropharynx	29	19.3	59	18.4	
Nonoropharynx	59	39.3	146	45.5	
T stage					.002†
T2	23	15.3	94	29.3	
T3	74	49.3	142	44.2	
T4	53	35.3	85	26.5	
N stage					.10†
N0	34	22.7	54	16.8	
N1	26	17.3	52	16.2	
N2a	11	7.3	31	9.7	
N2b	41	27.3	81	25.2	
N2c	27	18.0	73	22.7	
N3	11	7.3	30	9.3	
AJCC stage					.28*
III	40	26.7	71	22.1	
IV	110	73.3	250	77.9	

Abbreviations: AFX-C, accelerated fractionation with concomitant boost; AJCC, American Joint Committee on Cancer (ed 5); HHAC, historically high-accruing center; HLAC, historically low-accruing center; HPV, human papillomavirus; Q1, first quartile; Q3, third quartile; SFX, standard fractionation.
*Pearson χ^2 test.
†Wilcoxon rank sum test.

Survival and Treatment Efficacy Analyses

Median follow-up among surviving patients was 4.8 years (range, 1.1 to 6.5). There were 202 deaths among the cohort of 471 patients: 153 among patients treated at HLACs and 49 at HHACs. Patients treated at HLACs had significantly worse OS when compared with patients treated at HHACs (5 years: 51.0%; 95% CI, 45.1 to 56.8 *v* 69.1%; 95% CI, 61.6 to 76.7; $P = .002$; hazard ratio [HR], 1.67; 95% CI, 1.21 to 2.31). Patients treated at HLACs also had significantly worse PFS (5 years: 42.7%; 95% CI, 37.0 to 48.4 *v* 61.8%; 95% CI, 53.8 to 69.7; $P < .001$; HR, 1.64; 95% CI, 1.22 to 2.20). Kaplan-Meier curves for OS and PFS stratified by institutional accrual are shown in Figures 2A and 2B.

LRF rates were higher among patients treated at HLACs than HHACs (5 years: 36.4%; 95% CI, 30.9 to 41.9 *v* 20.8%; 95% CI, 14.1 to 27.5; $P < .001$). Among PFS events, the first failure event was locoregional in 43.3% of patients at HLACs compared with 33.9% at HHACs, distant in 25.0% and 30.5%, and death without documented progression in 31.7% and 35.6% ($P = .43$), respectively.

Treatment at an HLAC was associated with a 91% increased risk of death (HR, 1.91; 95% CI, 1.37 to 2.65; $P < .001$) and an 89% increase in progression or death (PFS: HR, 1.89; 95% CI, 1.39 to 2.56; $P < .001$) when compared with an HHAC (Table 2), after adjustment for age, T and N stages, performance status, smoking pack-years, tumor HPV status, and treatment assignment. Sensitivity analysis (adjusted for prognostic variables) confirmed the increase in risk of failure for both OS and PFS in patients treated at HLACs in all 721 patients (OS: HR, 1.57; 95% CI, 1.20 to 2.04; $P < .001$; PFS: HR, 1.56; 95% CI, 1.23 to 1.98; $P < .001$), when lowering the HHAC threshold to 25 patients (OS: HR, 1.53; 95% CI, 1.14 to 2.04; $P = .004$; PFS: HR, 1.69; 95% CI, 1.29 to 2.21; $P < .001$), and when historical accrual volume was considered a continuous variable (for every 10 patients; OS: HR, 0.93; 95% CI, 0.88 to 0.97; $P = .001$; PFS: HR, 0.92; 95% CI, 0.88 to 0.96; $P < .001$).

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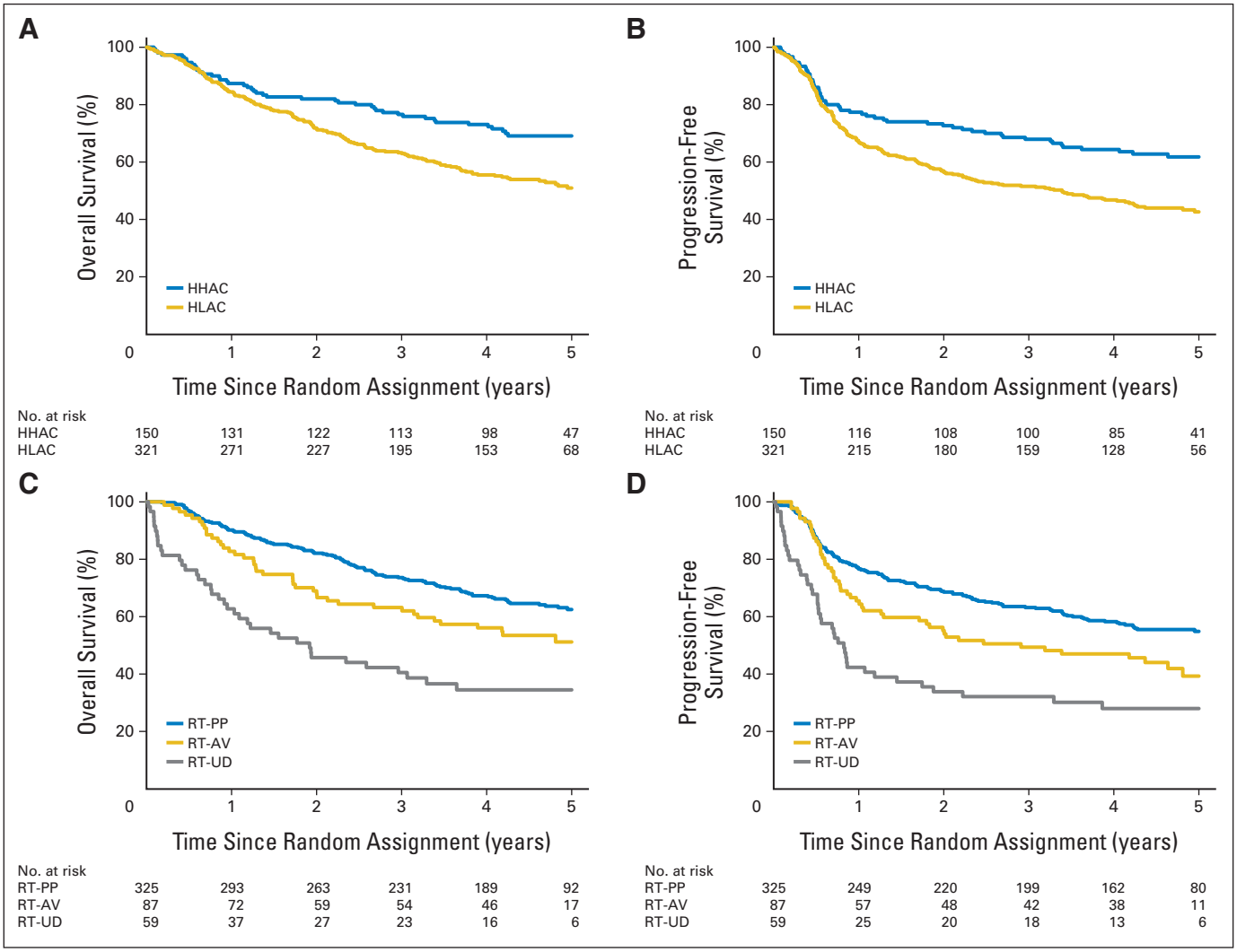

Fig 2. Kaplan-Meier estimates by (A, B) accrual volume and (C, D) radiotherapy (RT) compliance of (A, C) overall (OS) and (B, D) progression-free survival (PFS). Patients treated at historically low-accruing centers (HLACs) had significantly worse OS ($P = .002$) and PFS ($P < .001$) than patients treated at historically high-accruing centers (HHACs). (A) Five-year rates of OS were 51.0% (95% CI, 45.1 to 56.8) in HLAC group and 69.1% (95% CI, 61.6 to 76.7) in HHAC group. (B) Five-year rates of PFS were 42.7% (95% CI, 37.0 to 48.4) in HLAC group and 61.8% (95% CI, 53.8 to 69.7) in HHAC group. Patients with ≥ one RT compliance score of acceptable variation (AV) or with ≥ one RT compliance score of unacceptable deviation (UD) had significantly worse OS ($P = .007$ and $P < .001$) and PFS ($P = .01$ and $P < .001$) than patients treated per protocol (PP). (C) Five-year rates of OS were 63.0% (95% CI, 57.4 to 68.6) in PP group, 51.1% (95% CI, 40.1 to 62.3) in AV group, and 41.1% (95% CI, 26.6 to 55.6) in UD group. (D) Five-year rates of PFS were 55.6% (95% CI, 50.0 to 61.2) in PP group, 39.3% (95% CI, 28.0 to 50.7) in AV group, and 33.0% (95% CI, 19.2 to 46.8) in UD group.

Patient Population Analysis

Sociodemographic characteristics and medical comorbidities were compared for patients at HLACs versus HHACs to evaluate the possible contribution of these factors to observed survival differences (Table 3). HLACs had a higher proportion of uninsured patients (either self-pay or no means of payment) than HHACs (12.3% *v* 4.3%; $P = .009$), but no other differences were noted. Patients at HLACs and HHACs were also similar with regard to history of cardiovascular, respiratory, hepatic, renal, thromboembolic, hormonal, neurologic, and infectious illnesses.

Toxicity and Protocol Compliance Analysis

Incidences of grade ≥ 3 acute toxicity (any), acute mucositis, and late toxicity were similar between the groups (Table 4). Incidence of late mucositis was higher at HHACs but low in both groups (HHACs, 6.8%; HLACs, 2.9%; $P = .08$).

Patients treated at HLACs and HHACs received similar cisplatin doses and cycles and radiation doses and numbers of fractions, but duration of therapy was longer at HLACs (range, 0 to 120 *v* 30 to 71 days; first to third quartile, 44 to 52 *v* 43 to 50; median, 49 *v* 47 days; $P = .004$; Table 4). The overall radiotherapy plan score at HLACs was more likely than at HHACs to deviate from protocol (inclusive of AV and UD; 18.1% *v* 6%; $P < .001$). In general, there were more cases of protocol variation (considered within acceptable range) in the HLAC group for total dose, field border, fractionation, and elapsed days. At least one component of the treatment plan or delivery was scored as UD more often at HLACs versus HHACs (11% *v* 5%; $P = .04$). Common causes of UD included an excess of elapsed days of treatment (HLAC *v* HHAC, 3%; n = 10 *v* 0.7%; n = 1) and field borders not PP (HLAC *v* HHAC, 8%; n = 26 *v* 5%; n = 7).

An analysis of the effect of treatment compliance on outcome revealed OS and PFS to be significantly lower among patients with AV

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Table 2. Multivariable Analysis

End Point	Patients With Complete Data (n = 471)			All Patients With Data Imputed (n = 721)		
	HR	95% CI	*P*	HR	95% CI	*P*
OS						
Accrual volume (HLAC *v* HHAC)	1.91	1.37 to 2.65	< .001	1.57	1.20 to 2.04	< .001
Assigned treatment (SFX *v* AFX-C)	0.94	0.71 to 1.25	.69	1.07	0.85 to 1.35	.56
Age, years (continuous)	1.03	1.01 to 1.04	.002	1.02	1.01 to 1.03	.002
Zubrod performance status (1 *v* 0)	1.53	1.16 to 2.04	.003	1.65	1.30 to 2.09	< .001
Cigarette pack-years (continuous)	1.01	1.00 to 1.01	.01	1.01	1.00 to 1.01	.008
T stage (T4 *v* T2-3)	2.08	1.55 to 2.79	< .001	1.84	1.45 to 2.34	< .001
N stage (N2b-N3 *v* N0-N2a)	1.59	1.18 to 2.12	.002	1.64	1.29 to 2.09	< .001
HPV status (HPV-negative OP *v* HPV-positive OP)	2.34	1.52 to 3.61	< .001	2.22	1.48 to 3.33	< .001
HPV status (non-OP *v* HPV-positive OP)	2.46	1.68 to 3.60	< .001	2.48	1.78 to 3.46	< .001
PFS						
Accrual volume (HLAC *v* HHAC)	1.89	1.39 to 2.56	< .001	1.56	1.23 to 1.98	< .001
Assigned treatment (SFX *v* AFX-C)	0.87	0.67 to 1.13	.30	0.98	0.79 to 1.20	.83
Age, years (continuous)	1.02	1.01 to 1.04	.003	1.02	1.00 to 1.03	.006
Zubrod performance status (1 *v* 0)	1.62	1.24 to 2.10	< .001	1.63	1.31 to 2.02	< .001
Cigarette pack-years (continuous)	1.01	1.00 to 1.01	.001	1.01	1.00 to 1.01	.005
T stage (T4 *v* T2-3)	1.75	1.33 to 2.31	< .001	1.54	1.23 to 1.92	< .001
N stage (N2b-N3 *v* N0-N2a)	1.59	1.21 to 2.07	< .001	1.55	1.25 to 1.93	< .001
HPV status (HPV-negative OP *v* HPV-positive OP)	2.09	1.42 to 3.08	< .001	2.05	1.46 to 2.87	< .001
HPV status (non-OP *v* HPV-positive OP)	2.06	1.46 to 2.89	< .001	2.14	1.60 to 2.86	< .001

Abbreviations: AFX-C, accelerated fractionation with concomitant boost; HHAC, historically high-accruing center; HLAC, historically low-accruing center; HPV, human papillomavirus; HR, hazard ratio; OP, oropharynx; OS, overall survival; PFS, progression-free survival; SFX, standard fractionation.

or UD when compared with patients treated PP (Figs 2C and 2D). Effect of historical accrual volume did not differ by fractionation arm. Therefore, we evaluated whether the differences in OS and PFS for patients treated at HLACs versus HHACs could be explained by radiotherapy compliance.

Accrual volume remained independently associated with OS and PFS in multivariable analysis after consideration of treatment compliance effect (OS: HR, 1.72; 95% CI, 1.23 to 2.40; PFS: HR, 1.73; 95% CI, 1.28 to 2.36). UD (but not AD) from radiotherapy protocol independently increased the risk of death (OS: HR, 2.56; 95% CI, 1.75 to 3.74) and progression or death (PFS: HR, 2.31; 95% CI, 1.62 to 3.30) when compared with PP radiation therapy. By comparing the HR for accrual volume before and after the addition of radiotherapy compliance with the multivariable model, we estimated that only 21% and 18% of the effect of accrual volume on OS and PFS, respectively, resulted from radiotherapy protocol noncompliance.

DISCUSSION

In a secondary analysis of RTOG 0129, we observed significantly worse OS and PFS among patients with HNC treated at institutions with historically low- as compared with historically high-volume accrual to RTOG trials. Risk of death or progression was 90% greater for patients at HLACs. There were higher locoregional recurrence rates at HLACs compared with HHACs. Deviations from protocol therapy were more common at HLACs than HHACs and independently increased risk of death but did not entirely explain the survival benefit from HHAC treatment. These findings suggest that experienced providers likely execute superior treatment plans and may better support patients through treatment.

Prior publications have associated patient volume with HNC survival outcome. Population-based data from the National Cancer Data Base demonstrated that treatment at high-volume research facilities was associated with higher 90-day, 1-year, and 4-year survival for patients with locally advanced laryngeal cancer.[20] Furthermore, an analysis of HNC outcomes in a SEER-Medicare database demonstrated that patients treated at high-volume hospitals had a trend toward better survival compared with patients treated at low-volume hospitals, even though they were not more likely to receive NCCN guideline therapy.[21] This growing body of evidence suggests patients with HNC who are treated at high-volume centers have better outcomes.

Our results are also supported by a prior report from the Trans Tasman Radiation Oncology Group (TROG 02.02), in which major radiation plan deficiencies in HNC treatment were strongly associated with institutional enrollment volume. Major deficiencies were reported for 5.4% of patients at sites contributing ≥ 20 patients versus 29.8% of patients at sites contributing < five patients.[22] Furthermore, patients treated with major radiation plan deficiencies had an absolute OS reduction of 20% (50% *v* 70%; $P < .001$) and locoregional control reduction of 24% (54% *v* 78%; $P < .001$) at 2 years. The RTOG 0129 protocol included several predefined quality measures for radiotherapy (eg, total dose delivered, elapsed days, hyperfractionation completed, spinal cord dose, and boost field borders) but did not include minimal dose to the gross and planning target volumes, which were analyzed in the TROG 02.02 study. Therefore, we were unable to use identical metrics. These or other unmeasured quality indices may account for some of the outcome differences between HLACs and HHACs not explained by the available compliance measures in RTOG 0129.

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Table 3. Socioeconomic and Comorbidity Status by Accrual Volume

Factor	HHAC (n = 150) No.	%	HLAC (n = 321) No.	%	*P*
Highest educational level completed					.11*
Grade 1 to 8	1	0.7	22	6.9	
Grade 9 to 11	22	14.7	46	14.3	
High school graduate or GED	54	36.0	123	38.3	
Vocational school	10	6.7	20	6.2	
Associate's degree or some college	17	11.3	46	14.3	
Bachelor's degree	18	12.0	30	9.3	
Advanced degree	9	6.0	14	4.4	
Other	2	1.3	6	1.9	
Unknown/prefer not to answer	17	11.3	14	4.4	
Insurance status					.009†
Other	30	20.0	44	13.7	
Private insurance	78	52.0	135	42.1	
Medicare	12	8.0	21	6.5	
Medicare and private insurance	5	3.3	8	2.5	
Medicaid	4	2.7	25	7.8	
Medicaid and Medicare	1	0.7	3	0.9	
Military or VA	2	1.3	35	10.9	
Self-pay	1	0.7	11	3.4	
No means of payment	5	3.3	27	8.4	
Unknown	12	8.0	12	3.7	
History of heart problems					.75‡
No	135	90.0	284	88.5	
Yes	15	10.0	37	11.5	
History of lung problems					.36‡
No	136	90.7	299	93.1	
Yes	14	9.3	22	6.9	
History of high blood pressure					.83‡
No	106	70.7	222	69.2	
Yes	44	29.3	99	30.8	
History of bleeding problems					.45‡
No	149	99.3	314	97.8	
Yes	1	0.7	7	2.2	
History of circulation problems					.56‡
No	138	92.0	301	93.8	
Yes	12	8.0	20	6.2	
History of liver problems					.60‡
No	146	97.3	308	96.0	
Yes	4	2.7	13	4.0	
History of diabetes or sugar in urine					.13‡
No	135	90.0	302	94.1	
Yes	15	10.0	19	5.9	
History of kidney or urine problems					1.00‡
No	147	98.0	314	97.8	
Yes	3	2.0	7	2.2	
History of stroke					.77‡
No	145	96.7	312	97.2	
Yes	5	3.3	9	2.8	
History of thyroid problems					.24‡
No	148	98.7	310	96.6	
Yes	2	1.3	11	3.4	
History of seizure					.41‡
No	147	98.0	309	96.3	
Yes	3	2.0	12	3.7	
History of HIV/AIDS					.32‡
No	149	99.3	321	100.0	
Yes	1	0.7	0	0.0	
History of frequent infections					1.00‡
No	149	99.3	318	99.1	
Yes	1	0.7	3	0.9	
History of psychological problems					1.00‡
No	144	96.0	308	96.0	
Yes	6	4.0	13	4.0	
History of other illness					.08‡
No	142	94.7	287	89.4	
Yes	8	5.3	34	10.6	

Abbreviations: GED, General Educational Development; HHAC, historically high-accruing center; HLAC, historically low-accruing center; VA, Veterans Affairs.

*Wilcoxon rank sum test; other and unknown were excluded.

†Fisher's exact test of self-pay and no means of payment versus all others; unknown was excluded.

‡Fisher's exact test.

All patients treated in RTOG 0129 received three-dimensional conformal radiotherapy. Because modern intensity-modulated radiation therapy (IMRT) requires a higher level of expertise than three-dimensional conformal radiotherapy, our analysis may have underestimated the impact of provider expertise in the IMRT era. IMRT allows for a substantial reduction in parotid dose and therefore subjective and objective improvements in xerostomia without loss of efficacy.[23-25] However, IMRT substantially increases the complexity of contouring and treatment planning. In fact, target delineation is often nonuniform; Hong et al[26] observed major differences in delineated clinical target volumes from a predefined gross tumor volume, even among recognized experts in HNC. Furthermore, the first RTOG study to evaluate the feasibility of IMRT for early-stage oropharyngeal carcinoma (RTOG 0022) observed higher treatment failure rates among patients treated with major dosimetric protocol deviations.[27] Given that target delineation deviations were observed more frequently at HLACs than HHACs with three-dimensional conformal therapy, the increased complexity of target delineation associated with IMRT may exacerbate outcome differences. However, RTOG currently collects more dose-volume histogram data on individual plans, a factor that may reduce variation in treatment planning.

In our analysis, measured deviations from protocol therapy did not entirely explain differences in OS and PFS by accrual volume. Only approximately 20% of the effect of accrual volume on OS and PFS could be explained by poor compliance with protocol-specified radiotherapy. HHACs were frequently synonymous with academic tertiary care centers, including members of NCCN and National Cancer Institute–designated cancer centers. A myriad of additional institution-specific factors that may contribute to outcomes were not assessed, including presence of tumor board, number of colleagues, years of practice, presence of a residency training program, and ancillary support services such as speech and swallowing therapists, dietetics and nutritional support, and specialized nursing—all of which may be more robust at HHACs compared with HLACs. Such support services may limit

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Table 4. Toxicity and Treatment Compliance by Accrual Volume

Toxicity/Compliance	HHAC		HLAC		*P*
	No.	%	No.	%	
Acute grade 3 to 5 toxicity	118 of 150	78.7	255 of 321	79.4	.85*
Acute grade 3 to 5 mucositis	57 of 150	38.0	106 of 321	33.0	.29*
Late grade 3 to 5 toxicity†	42 of 146	28.8	106 of 310	34.2	.25*
Late grade 3 to 5 mucositis†	10 of 146	6.8	9 of 310	2.9	.05*
No. of cisplatin cycles delivered					.91‡
0	0	0.0	2	0.6	
1	10	6.7	29	9.0	
2	91	60.7	176	54.8	
3	> 49	32.7	114	35.5	
Cisplatin dose delivered, mg/m^2					.99‡
Mean	221.4		219.6		
SD	57.1		64.0		
Median	200.0		200.0		
Range	100.0-301.8		0.0-308.6		
Q1 to Q3	200.0-300.0		198.9-299.1		
Radiation total dose, Gy					.32‡
Median	70.79		71.5		
Range	44.1-74.85		0-76.02		
Q1 to Q3	70-72		70-72		
Radiation total fractions					.71‡
Median	35		35		
Range	25-42		0-51		
Q1 to Q3	35-42		35-42		
Radiation therapy elapsed days					.004‡
Median	47		49		
Range	30-71		0-102		
Q1 to Q3	43-50		44-52		

Abbreviations: HHAC, historically high-accruing center; HLAC, historically low-accruing center; Q, quartile; SD, standard deviation.
*Pearson χ^2 test.
†Late period defined as > 90 days after start of radiation therapy.
‡Wilcoxon rank sum test.

treatment interruptions through advanced management of toxicities. Indeed, a slight but significant increase in treatment duration was observed at HLACs versus HHACs. However, the reported acute toxicities did not differ.

We cannot entirely exclude a possible contribution of referral bias leading to differences in patient populations treated at HLACs versus HHACs and hence differences in outcomes. However, we note that the higher numbers of individuals with poor performance status and T4 tumors at HHACs versus HLACs would bias toward poorer survival. In contrast, patients treated at HLACs were more likely to be uninsured, and socioeconomic status[28-31] and uninsured status[32] has been associated with less favorable outcomes in HNC. However, insurance status had no effect on PFS or OS (data not shown). We observed no differences in the prevalence of comorbidities or deaths resulting from unknown causes at HLACs versus HHACs. A limitation to our analysis is that accrual to RTOG clinical trials may not be an entirely accurate measure of overall treatment volume at some centers, because of competing institutional protocols and/or treatment volume off protocol.

Nevertheless, our comparative effectiveness research data provide direction toward improvements in research and treatment for patients with HNC. First, cancer centers and training programs should prioritize specialization, particularly in HNC management. Second, clinical trialists should consider the possible contribution of accrual volume on outcome through stratification or other means. Third, clinicians and patient advocates should take steps to improve access of patients with HNC to oncologists who specialize in HNC and who treat patients at high volume centers. Additional alternatives to mitigate this disparity in outcomes include: increased access to and use of contouring atlases to reduce differences in target delineation and normal tissue contouring, validation and implementation of autocontouring software, and continuing medical education focused on target delineation and treatment planning in HNC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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GLOSSARY TERMS

accelerated fractionation: radiation dose fractionation schedule with an effective rate of dose accumulation exceeding the traditional 10 Gy delivered in five fractions per week.

comparative effectiveness research: the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of comparative effectiveness research is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at the individual and population levels.

conformal radiation therapy: an irradiation technique developed to limit the highest radiation dose to volumes at risk for tumors while sparing surrounding normal tissues. Treatment planning is based on three-dimensional reconstructions of individual patient anatomy.

multivariate proportional hazards model: a general method in medical statistics used to analyze the influence of several (patient-specific) covariates on time-to-event end points. No assumption is made concerning the form of the underlying time-to-event curve. The only assumption made is that the effect of the covariates on the hazard rate in the study population is multiplicative and does not change over time.

planning target volume (PTV): volume encompassing the clinical target volume that is introduced for radiation treatment planning and evaluation to ensure that the prescribed absorbed dose will actually be delivered to all parts of the clinical target volume with a clinically acceptable probability. It takes into account uncertainties and variations in set-up, positioning, and target motion.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Institutional Clinical Trial Accrual Volume and Survival of Patients With Head and Neck Cancer

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Appendix

Table A1. Radiation Therapy Scoring Criteria

Parameter	PP	AV	UD
Total dose	≤ 4% variation	> 4% to 9% variation	> 9% variation
Elapsed days			
SFX	46-52	53-60	> 60
AFX-C	39-49	50-57	> 57
Hyperfractionation	≤ 2 days missed	3-5 days missed	> 5 days missed
Spinal cord dose, Gy	< 47	47-50	> 50

Abbreviations: AFX-C, accelerated fractionation with concomitant boost; AV, acceptable variation; PP, per protocol; SFX, standard fractionation; UD, unacceptable deviation.

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Table A2. Missing Data Analysis

Factor	Complete Data (n = 471) No.	Complete Data (n = 471) %	Missing HPV Status* and/or Cigarette Pack-Years (n = 250) No.	Missing HPV Status* and/or Cigarette Pack-Years (n = 250) %	*P*
Assigned treatment					.62†
SFX plus cisplatin	239	50.7	122	48.8	
AFX-C plus cisplatin	232	49.3	128	51.2	
Age, years					.31‡
Median	56		56		
Range	31-82		26-82		
Q1 to Q3	50-61		49-63		
Zubrod performance status					.47†
0	277	58.8	140	56.0	
1	194	41.2	110	44.0	
T stage					.08‡
T2	117	24.8	51	20.4	
T3	216	45.9	112	44.8	
T4	138	29.3	87	34.8	
N stage					.28‡
N0	88	18.7	48	19.2	
N1	78	16.6	29	11.6	
N2a	42	8.9	18	7.2	
N2b	122	25.9	67	26.8	
N2c	100	21.2	73	29.2	
N3	41	8.7	15	6.0	
AJCC stage					.14†
III	111	23.6	47	18.8	
IV	360	76.4	203	81.2	
Accrual volume					.34†
HHAC	150	31.8	71	28.4	
HLAC	321	68.2	179	71.6	
OS					.76§
5-year estimate, %	56.9		57.9		
95% CI	52.2 to 61.6		51.3 to 64.4		
HR	Reference		0.96		
95% CI			0.76 to 1.22		
PFS					.96§
5-year estimate, %	48.8		47.1		
95% CI	44.1 to 53.5		40.4 to 53.8		
HR	Reference		0.99		
95% CI			0.80 to 1.23		

Abbreviations: AFX-C, accelerated fractionation with concomitant boost; AJCC, American Joint Committee on Cancer; HHAC, historically high-accruing center; HLAC, historically low-accruing center; HPV, human papillomavirus; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; Q, quartile; SFX, standard fractionation.

*Oropharynx only.

†Pearson χ^2 test.

‡Wilcoxon rank sum test.

§Log-rank test.

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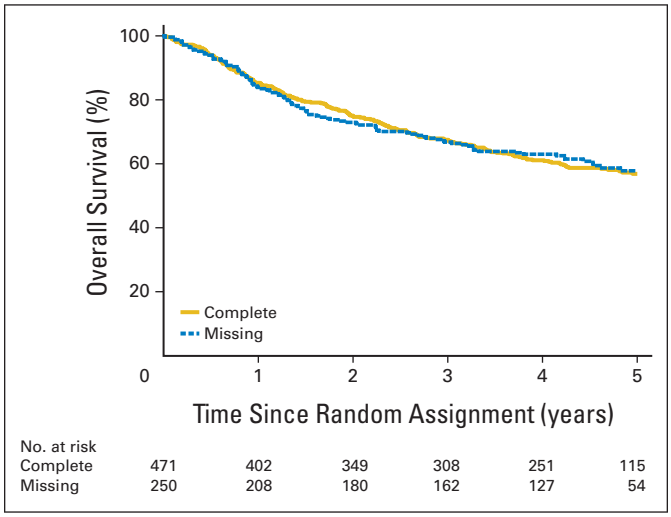

Fig A1. Kaplan-Meier estimates of overall survival for patients with complete data versus missing data.

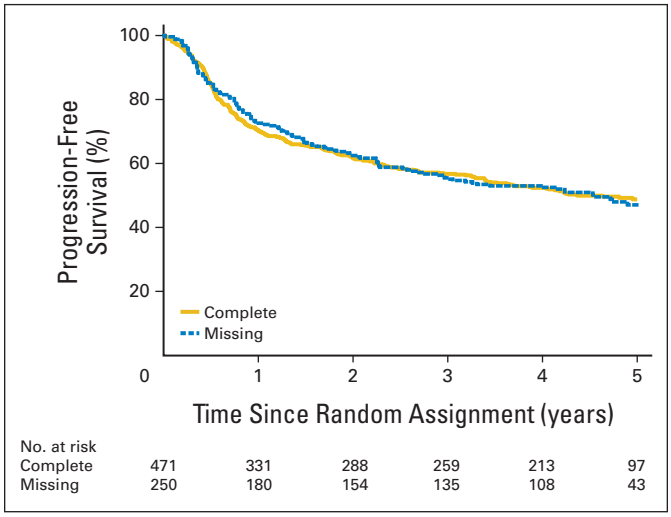

Fig A2. Kaplan-Meier estimates of progression-free survival for patients with complete data versus missing data.

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