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Hypofractionated Radiotherapy for Patients with Early-Stage Glottic Cancer: Patterns of Care and Survival

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Abstract

Background: Radiotherapy alone is often used to treat early-stage glottic cancer (ESGC); however, the optimal radiation treatment schedule remains unknown. The National Comprehensive Cancer Network (NCCN) guidelines recommend both hypofractionated radiotherapy (HFX) and conventionally fractionated radiotherapy (CFX). We compared overall survival (OS) and treatment patterns among patients treated with HFX vs CFX for ESGC using a large national database.
Methods: We identified patients diagnosed with stage I–II (cT1-2N0M0) glottic cancer from 2004 to 2013 within the National Cancer Data Base who were treated with either HFX (2.25 Gy/fraction to 63–65.25 Gy) or CFX (2.0 Gy/fraction to 66–70 Gy). The overall survival of patients receiving HFX vs CFX was compared using the log-rank test, multivariable Cox proportional hazards regression, and propensity score matching. All statistical tests were two-sided.
Results: Among 10 212 included patients, 4030 patients (39.5%) received HFX and 6182 patients (60.5%) received CFX. Predictors for receipt of HFX included clinical T1 disease, recent year of diagnosis, and treatment at academic and higher-volume centers (all $P < .001$). Patients treated with HFX increased from 22.1% in 2004 to 58.0% in 2013. HFX was associated with improved OS compared with CFX on univariate (five-year OS = 77.1%, 95% CI = 75.2% to 78.8%, vs 73.5%, 95% CI = 72.1% to 74.8%, respectively, log-rank $P < .001$) and multivariable analysis (HR = 0.89, 95% CI = 0.81 to 0.98, $P = .02$), a finding confirmed on propensity score matching.
Conclusions: HFX is associated with improved survival compared with CFX among patients treated with definitive radiotherapy for ESGC, particularly among patients with cT2 disease. HFX utilization increased over the study period; however, 40% of patients in our cohort did not receive HFX in the most recent year of our analysis.

Early-stage glottic cancer is often treated with radiotherapy (RT) alone in the United States (1). A variety of radiotherapy fractionation schedules have been used, and several studies have demonstrated that altered fractionation regimens are associated with improved local control (LC) when compared with conventional fractionation regimens (2–13). In addition to improved LC, some randomized trials comparing fractionation regimens have demonstrated trends suggesting an overall survival (OS) advantage associated with hyperfractionated or hypofractionated RT; however, these trials have not been powered to detect such a difference (7,14). Furthermore, a large meta-analysis of patients with primarily advanced-stage, oropharyngeal, and laryngeal cancers has demonstrated an OS benefit associated with altered fractionation regimens (15).

Despite evidence suggesting improved outcomes with altered fractionation regimens, controversy regarding the optimal RT regimen for early-stage glottic cancer remains (16). This is demonstrated by the National Comprehensive Cancer Network (NCCN) guidelines, which recommend either conventionally fractionated radiotherapy (CFX; 2 Gy/fraction to 66–70 Gy) or hypofractionated radiotherapy (HFX; 2.25 Gy/fraction to 63–65.25 Gy) for the management of early-stage, node-negative glottic cancer (17).

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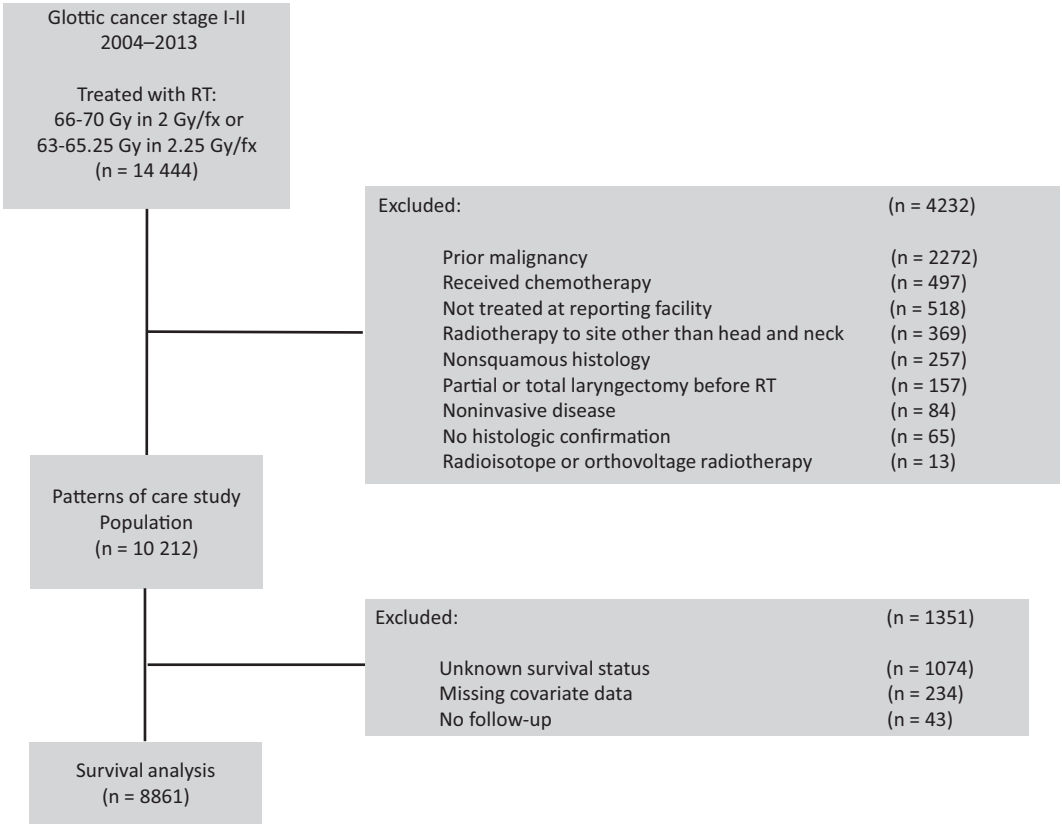

Figure 1. Study flow diagram. fx = fraction; RT = radiotherapy.

The goal of our study was to determine whether HFX is associated with improved OS compared with CFX among patients with early-stage glottic cancer. We also sought to characterize the utilization of HFX over time among patients treated in the United States.

Methods

Study Design and Data Source

We used National Cancer Data Base (NCDB) registry data for patients diagnosed from 2004 to 2013 to perform a retrospective study of patients diagnosed with early-stage glottic cancer in the United States. The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons (ACS) and the American Cancer Society. It contains de-identified information from approximately 70% of newly diagnosed cancers in the United States. The data used are derived from a de-identified NCDB file. The ACS and the CoC have not verified and are not responsible for the analytic or statistical methodology used or the conclusions drawn from these data by the investigators. The Yale Human Investigations Committee determined that this study was exempt from review given that existing and de-identified data were used.

Study Cohort

We selected patients with stage I (cT1N0M0) or II (cT2N0M0) glottic cancer, diagnosed from 2004 to 2013, who were treated with RT. Inclusion and exclusion criteria are summarized in Figure 1. Consistent with the radiotherapy fraction sizes and total doses recommended by the NCCN, patients comprising the CFX group included those treated with 2.0 Gy per fraction to a total dose of 66 to 70 Gy; patients treated with 2.25 Gy per fraction to a total dose of 63 to 65.25 Gy comprised the HFX group. Primary site code C320 and squamous cell carcinoma histology codes of 8052, 8070 to 8079, 8083, and 8084 were used. Patients with incomplete treatment details were excluded. All treatments were delivered at the reporting facility. Patients with unknown or missing data for any of the inclusion variables above were excluded.

Construction of Variables

Patient, tumor, and treatment information was recoded into meaningful groups and/or dichotomized when possible. Race was recoded as white non-Hispanic, Black, Hispanic, and other/unknown. Facility classification was recoded as academic and nonacademic. Facility volume was estimated by calculating the annual number of cases of glottic cancer treated with HFX or CFX at each facility appearing in the NCDB. Facilities were dichotomized into higher- and lower-volume facilities, with higher-volume facilities defined a priori as those belonging to the 75th percentile or greater of annual RT volume. Facility locations were recoded as Northeast, South Atlantic, Midwest, South, and West. Charlson-Deyo score was recoded as 0 or 1 or higher. All other covariates were analyzed in the form in which they were received from the NCDB. Other demographic

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Table 1. Baseline demographics and clinical characteristics for patients treated with either conventionally fractionated radiotherapy or hypofractionated radiotherapy

Characteristic	Conventionally fractionated radiotherapy (n = 6182) No. (%)	Hypofractionated radiotherapy (n = 4030) No. (%)	P*
Age at diagnosis, y			.24
Median	66	65	
IQR	58–74	58–74	
Age at diagnosis, y			.08
≤49	476 (7.7)	289 (7.2)	
50–59	1355 (21.9)	928 (23.0)	
60–69	1992 (32.2)	1362 (33.8)	
70–79	1611 (26.1)	966 (24.0)	
≥80	748 (12.1)	485 (12.0)	
Sex			.87
Male	5341 (86.4)	3477 (86.3)	
Female	841 (13.6)	553 (13.7)	
Year of diagnosis†			<.001
2004	748 (12.1)	212 (5.3)	
2005	692 (11.2)	244 (6.1)	
2006	729 (11.8)	299 (7.4)	
2007	665 (10.8)	298 (7.4)	
2008	603 (9.8)	377 (9.4)	
2009	659 (10.7)	408 (10.1)	
2010	581 (9.4)	453 (11.2)	
2011	542 (8.8)	513 (12.7)	
2012	512 (8.3)	603 (15.0)	
2013	451 (7.3)	623 (15.5)	
Clinical T stage			<.001
T1	4738 (76.6)	3313 (82.2)	
T2	1444 (23.4)	717 (17.8)	
Tumor size, cm			.18
0–1.0	679 (11.0)	457 (11.3)	
1.1–2.0	286 (4.6)	150 (3.7)	
2.1–3.0	49 (0.8)	27 (0.7)	
3.1–4.0	17 (0.3)	11 (0.3)	
>4.0	10 (0.2)	12 (0.3)	
Unknown	5141 (83.2)	3373 (83.7)	
Radiotherapy dose, Gy			
63	0 (0)	3208 (79.6)	
65.25	0 (0)	822 (20.4)	
66	3461 (56.0)	0 (0)	
68	619 (10.0)	0 (0)	
70	2102 (34.0)	0 (0)	
Race			.003
White non-Hispanic	4756 (76.9)	3108 (77.1)	
African American	553 (9.0)	410 (10.2)	
Hispanic	209 (3.4)	155 (3.9)	
Other/unknown	664 (10.7)	357 (8.9)	
Charlson/Deyo score			.82
0	5031 (81.4)	3287 (81.6)	
≥1	1151 (18.6)	743 (18.4)	
Facility classification			<.001
Academic	1416 (22.9)	1304 (32.4)	
Nonacademic	4766 (77.1)	2726 (67.6)	
Facility case volume			<.001
Lower-volume facility	4881 (79.0)	2762 (68.5)	
Higher-volume facility	1301 (21.0)	1268 (31.5)	
Facility location			<.001
Northeast	1264 (20.7)	853 (21.4)	
South Atlantic	1213 (19.8)	1017 (25.6)	
Midwest	2013 (32.9)	946 (23.8)	
South	946 (15.5)	544 (13.7)	
West	682 (11.2)	621 (15.6)	

(continued)

Table 1. (continued)

Characteristic	Conventionally fractionated radiotherapy (n = 6182) No. (%)	Hypofractionated radiotherapy (n = 4030) No. (%)	P*
Insurance			.02
Private	2392 (38.7)	1594 (39.6)	
Medicare	3112 (50.3)	1920 (47.6)	
Medicaid	248 (4.0)	193 (4.8)	
Uninsured	192 (3.1)	138 (3.4)	
Other government or unknown	238 (3.9)	185 (4.6)	
Proportion without high school degree in patient's area of residence†			.001
≥21%	1102 (18.1)	742 (18.6)	
13%–20.9%	1815 (29.8)	1031 (25.9)	
7%–12.9%	1975 (32.4)	1357 (34.0)	
<7%	1206 (19.8)	856 (21.5)	
Income†			<.001
<$38,000	1268 (20.8)	736 (18.5)	
$38 000–$47 999	1625 (26.7)	987 (24.8)	
$48 000–$62 999	1620 (26.6)	1102 (27.7)	
≥$63 000	1583 (26.0)	1159 (29.1)	

*All *P* values were two-sided; *P* values were calculated using the Pearson's chi-square test for categorical variables and the independent sample *t* tests for continuous variables. IQ = interquartile range.

†Chi-square tests compared 2004 to 2008 with 2009 to 2013 for year of diagnosis; ≥13% vs < 13% for proportion without high school degree in patient's area of residence; and ≥$48k vs <$48k for income.

variables included age, year of diagnosis, insurance status, income, and education.

Statistical Analysis

Categorical variables were compared using chi-square tests, and continuous variables were compared using independent sample *t* tests. Multivariable logistic regression was used to determine factors associated with the receipt of HFX vs CFX. Variables were included in the multivariable regression analysis if they were found to be associated with fractionation ($P < .15$) on univariate analysis. OS was defined as the time from diagnosis until death or last follow-up. Patients diagnosed in 2013 lacked vital statistics and were omitted from outcome analysis. The Kaplan-Meier method and log-rank test were used to estimate OS and compare survival between subgroups. Multivariable Cox proportional hazards modeling was used to determine statistically significant contributors to differences in OS. The proportional hazards assumption was checked graphically using log-log survival plots and by calculating Schoenfeld residuals. Variables were included in the multivariable analysis if they were found to be associated with OS ($P < .15$) on univariate analysis. We also stratified patients by clinical T stage and performed subset analyses among patients with cT1 disease and cT2 disease.

Because the NCDB does not record the number of radiotherapy fractions delivered per week, we used total days of treatment and the dose and fractionation scheme to identify patients who may have received accelerated RT. We conducted sensitivity analyses by excluding these patients and performing the survival analyses described above.

Propensity score matching was performed by bootstrapping with 1:1 nearest-neighbor matching without replacement to match the cohorts receiving HFX and CFX. Variables used for matching were selected from among variables that were found to be statistically significant predictors of receipt of HFX on univariate analysis and included clinical T stage, year of diagnosis, race, and facility classification. Race and year of diagnosis had been previously demonstrated to be associated with survival (18). Patients were also matched by facility classification given the observed differences in rates of treatment with HFX by facility classification in our patterns of care analysis.

All analyses were performed using Stata SE version 13.0 (Stata, College Station, TX). All statistical tests were two-sided, and a *P* value of less than .05 was considered statistically significant.

Results

Study Cohort Characteristics

We identified 10 212 patients diagnosed between 2004 and 2013 with early-stage glottic cancer who were treated with HFX or CFX. Overall, 4030 patients (39.5%) received HFX and 6182 patients (60.5%) received CFX. Clinical and demographic characteristics are provided in Table 1. Median follow-up was 5.0 years for all patients; median follow-up durations for patients treated with HFX and CFX were 4.1 and 5.5 years, respectively. Median age was 66 years among all patients. Patients receiving HFX were more likely to have clinical stage T1 disease than those receiving CFX (82.2% vs 76.6%, $P < .001$).

Utilization of Hypofractionation Over Time

The proportion of patients treated with HFX increased during the years included in the study from 22.1% in 2004 to 58.0% in 2013 (Figure 2A). Adoption of HFX by clinical stage, facility case volume, and facility classification is displayed in Figure 2, B, C, and D, respectively. The percentage of patients receiving HFX was higher among academic and higher-volume facilities for all years

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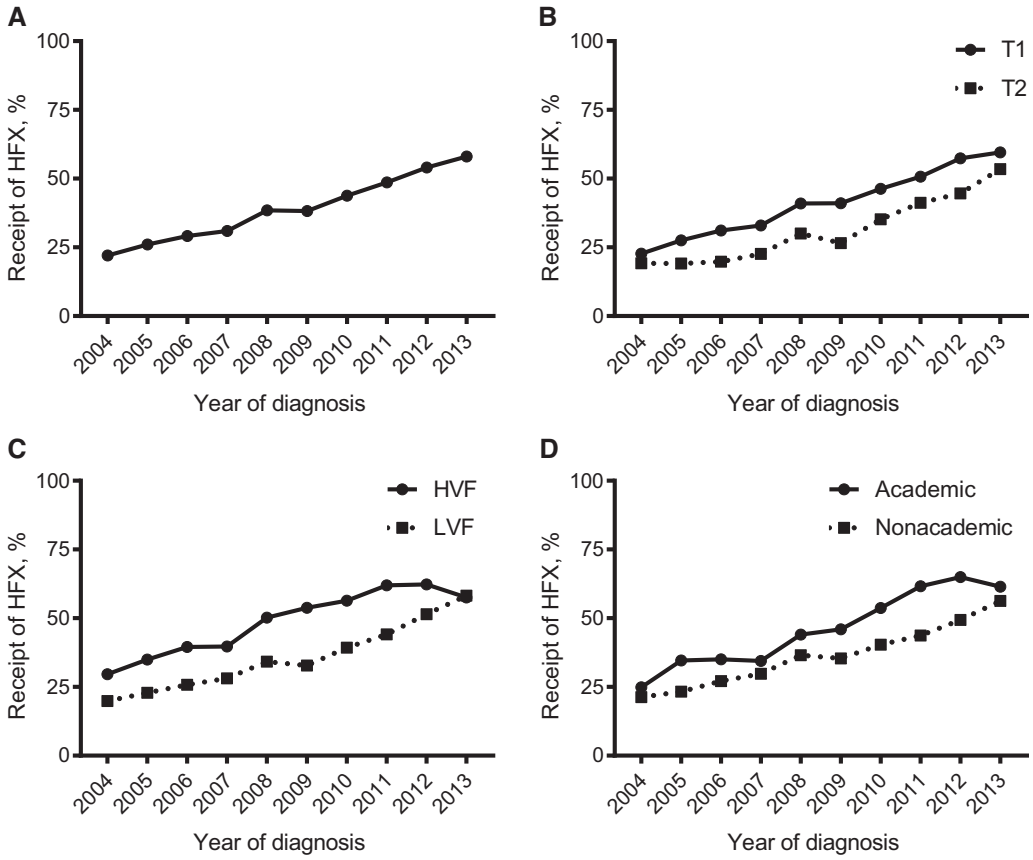

Figure 2. Utilization of hypofractionated radiotherapy. Utilization among **(A)** overall cohort and patients stratified by **(B)** T stage, **(C)** higher- and lower-volume treatment centers, and **(D)** academic and nonacademic facility type. HFX = hypofractionated radiotherapy; HVF = higher-volume facility; LVF = lower-volume facility.

analyzed, but by the end of the study period differences were more narrow. Adoption of HFX occurred more quickly among academic centers, and rates of HFX were higher among patients with stage I disease in all years analyzed. Rates of treatment by average radiotherapy dose per fraction used among patients with T1–2N0, T1N0, and T2N0 glottic cancer treated from 2004 to 2013 are presented in Supplementary Table 1 (available online).

Factors Affecting Treatment Selection

Treatment selection was associated with both clinical and socioeconomic factors (Table 2). On multivariable logistic regression, the odds of receiving HFX decreased with clinical stage T2 disease, treatment at a nonacademic facility, receipt of treatment in the Midwest region, and higher patient education level. The strongest predictor of receipt of HFX was diagnosis in more recent years (2009–2013), followed by treatment in the West region and treatment at a higher-volume facility. Age, insurance status, and income were statistically significant on univariate analysis but did not remain independently associated with treatment selection on multivariable analysis.

Survival Outcomes

A total of 8861 patients diagnosed from 2004 to 2013 were included in the survival analysis. In the entire cohort, the unadjusted five-year survival rates were 77.1% (95% CI = 75.2% to 78.8%) for patients receiving HFX and 73.5% (95% CI = 72.1% to 74.8%) for patients receiving CFX ($P < .001$) (Figure 3A). On multivariable analysis, patients treated with HFX had improved OS compared with those receiving CFX (HR = 0.89, 95% CI = 0.81 to 0.98, $P = .02$) on multivariable analysis (Table 3). Other factors associated with improved OS on multivariable analysis included female gender, age younger than 50 years, clinical stage T1 disease, Charlson-Deyo score of 0, and private insurance.

We performed separate subset analyses to evaluate the impact of fractionation on OS among patients with clinical stage T1 disease and patients with clinical stage T2 disease. Among the 7032 patients with clinical T1 disease, 2747 patients (39.1%) were treated with HFX and 4285 (60.9%) were treated with CFX. The five-year OS rates for patients with clinical stage T1 disease were 78.2% (95% CI = 76.2% to 80.1%) for patients treated with HFX vs 76.0% (95% CI = 74.5% to 77.4%) for patients treated with CFX (log-rank $P = .05$) (Figure 3B). On multivariable analysis, HFX did not reach statistical significance (HR = 0.93, 95% CI = 0.84 to 1.03, $P = .17$) (Supplementary Table 2, available online).

When the cohort was limited to patients with clinical T2 disease (n = 1829), we identified 553 (30.2%) patients who received HFX and 1276 (69.8%) who received CFX. Five-year OS was 70.8% (95% CI = 65.5% to 75.4%) for patients receiving HFX and 64.5% (95% CI = 61.3% to 67.5%) for patients who received CFX (log-rank $P = .02$) (Figure 3C). HFX remained statistically significantly associated with improved OS (HR = 0.79, 95% CI = 0.65 to 0.96, $P = .02$) on multivariable analysis (Supplementary Table 3, available online).

Propensity score matching created a cohort of 6242 patients matched on race, year of diagnosis, clinical disease stage, and

Table 2. Multivariable analysis of predictors of treatment with hypofractionated radiotherapy

Variable	OR (95% CI)	P*
Age, y		
<50	1.00 (ref)	
50–59	1.07 (0.88 to 1.29)	.50
60–69	1.06 (0.88 to 1.28)	.53
70–79	0.95 (0.77 to 1.17)	.65
≥80	1.05 (0.84 to 1.32)	.66
T stage		
cT1	1.00 (ref)	
cT2	0.64 (0.58 to 0.71)	<.001
Race		
White non-Hispanic	1.00 (ref)	
Black	1.09 (0.94 to 1.27)	.25
Hispanic	0.93 (0.74 to 1.17)	.54
Other/unknown	0.91 (0.79 to 1.05)	.19
Year of diagnosis		
2004–2008	1.00 (ref)	
2009–2013	2.35 (2.16 to 2.56)	<.001
Facility classification		
Academic	1.00 (ref)	
Nonacademic	0.63 (0.57 to 0.69)	<.001
Facility volume		
<3.4 cases/y	1.00 (ref)	
≥3.4 cases/y	1.62 (1.47 to 1.79)	<.001
Location		
Northeast	1.00 (ref)	
South Atlantic	1.38 (1.21 to 1.57)	<.001
Midwest	0.78 (0.69 to 0.89)	<.001
South	0.99 (0.85 to 1.15)	.89
West	1.75 (1.51 to 2.03)	<.001
Insurance		
Private	1.00 (ref)	
Medicare	0.98 (0.88 to 1.10)	.77
Medicaid	1.11 (0.89 to 1.37)	.35
Uninsured	1.04 (0.82 to 1.33)	.73
Other government/unknown	1.04 (0.83 to 1.30)	.73
Med income		
>$48 000	1.00 (ref)	
<$48 000	0.98 (0.88 to 1.08)	.64
Proportion without high school degree in patient's area of residence		
≥13%	1.00 (ref)	
<13%	0.83 (0.75 to 0.92)	.001

*All P values are two-sided and derived from a multivariable Cox proportional hazards analysis. CI = confidence interval; OR = odds ratio.

facility classification. Supplementary Table 4 (available online) demonstrates the well-matched nature of the propensity-matched cohorts. Patients treated with HFX experienced improved overall survival (log-rank $P = .02$) (Supplementary Figure 1, available online).

On sensitivity analyses, when excluding patients whose total treatment time suggested the possibility of an accelerated course of treatment, we found that our results remained robust (data not shown).

Discussion

Using a large national hospital-based database, we compared two commonly used RT treatment regimens recommended by the NCCN guidelines for early-stage glottic cancer and found the use of HFX to be associated with improved survival when compared with CFX. On subset analysis, this benefit persisted among patients with T2 disease but did not reach statistical significance among patients with clinical T1 disease. To our knowledge, this is the largest study of its kind and first study to demonstrate an OS benefit for HFX in the treatment of early-stage glottic cancer.

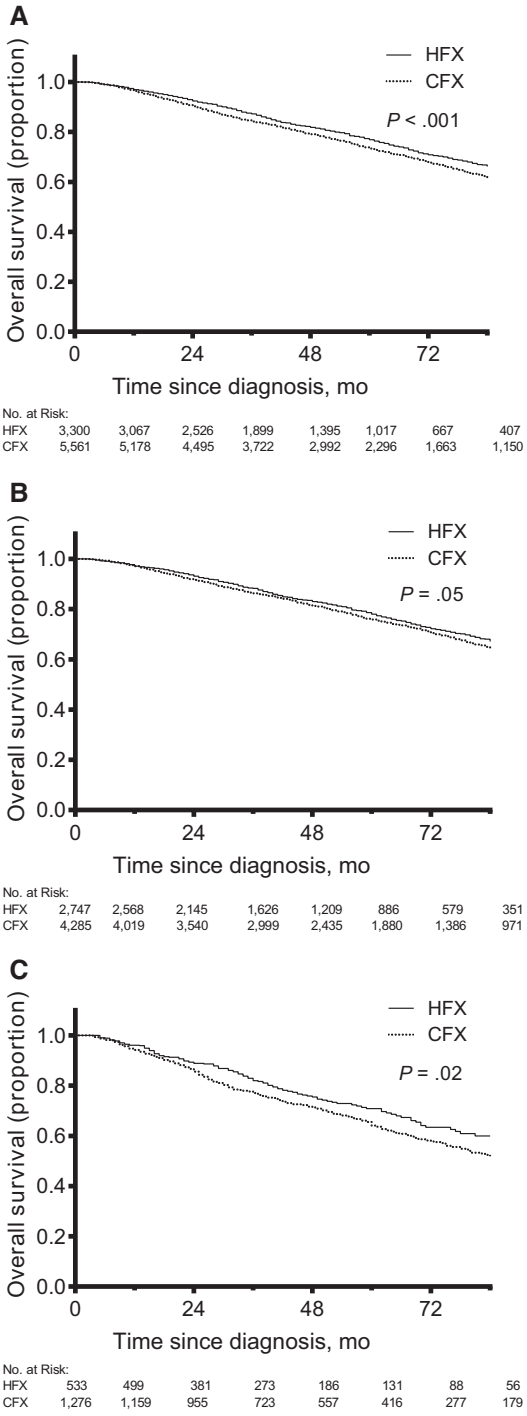

Figure 3. Kaplan-Meier curves comparing overall survival by hyperfractionated radiotherapy (HFX) vs conventionally fractionated radiotherapy (CFX) treatment regimens. Results are shown for analysis of the **(A)** overall cohort, **(B)** subset of patients with stage I glottic cancer, and **(C)** subset of patients with stage II glottic cancer. *P* values are two-sided and derived from log-rank tests.

Table 3. Univariate and multivariable analyses of predictors of overall survival among all patients

Variable	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P*	HR (95% CI)	P*
Fractionation				
CFX				
HFX	0.86 (0.78 to 0.94)	.001	0.89 (0.81 to 0.98)	.02
Sex				
Male				
Female	0.80 (0.71 to 0.91)	.001	0.78 (0.69 to 0.89)	<.001
Age, y				
<50				
50–59	1.34 (1.04 to 1.74)	.02	1.32 (1.02 to 1.71)	.03
60–69	1.94 (1.52 to 2.47)	<.001	1.67 (1.30 to 2.14)	<.001
70–79	3.01 (2.36 to 3.83)	<.001	2.32 (1.79 to 3.01)	<.001
≥80	5.85 (4.57 to 7.49)	<.001	4.53 (3.47 to 5.90)	<.001
T stage				
cT1				
cT2	1.52 (1.38 to 1.67)	<.001	†	
Tumor size, cm				
0–1.0				
1.1–2.0	1.36 (1.07 to 1.73)	.01	1.25 (0.98 to 1.59)	.07
2.1–3.0	1.89 (1.22 to 2.93)	.01	1.52 (0.98 to 2.37)	.06
3.1–4.0	2.01 (1.03 to 3.92)	.04	2.02 (1.04 to 3.95)	.04
>4.0	2.25 (1.16 to 4.39)	.02	1.99 (1.02 to 3.90)	.04
Unknown	1.21 (1.05 to 1.39)	.01	1.24 (1.08 to 1.43)	.003
Race				
White non-Hispanic				
Black	1.03 (0.90 to 1.19)	.66	1.05 (0.91 to 1.21)	.51
Hispanic	0.75 (0.58 to 0.97)	.03	0.84 (0.65 to 1.09)	.20
Other/unknown	0.83 (0.73 to 0.96)	.01	0.90 (0.78 to 1.03)	.12
Year of diagnosis				
2004–2008				
2009–2013	1.12 (1.02 to 1.24)	.02	1.09 (0.98 to 1.20)	.10
Charlson/Deyo score				
0				
≥1	1.66 (1.51 to 1.83)	<.001	1.41 (1.28 to 1.56)	<.001
Facility classification				
Academic				
Nonacademic	1.18 (1.07 to 1.30)	.001	1.06 (0.96 to 1.17)	.25
Facility volume				
Lower-volume facility				
Higher-volume facility	0.99 (0.90 to 1.09)	.82		
Location				
Northeast				
South Atlantic	1.04 (0.92 to 1.18)	.55	1.07 (0.94 to 1.22)	.30
Midwest	1.07 (0.95 to 1.20)	.28	1.07 (0.95 to 1.21)	.27
South	1.24 (1.09 to 1.42)	.002	1.29 (1.12 to 1.48)	<.001
West	1.05 (0.91 to 1.22)	.48	1.05 (0.90 to 1.21)	.54
Insurance				
Private				
Medicare	2.48 (2.25 to 2.73)	<.001	1.50 (1.33 to 1.70)	<.001
Medicaid	2.06 (1.67 to 2.55)	<.001	1.98 (1.60 to 2.45)	<.001
Uninsured	1.36 (1.00 to 1.84)	.05	1.40 (1.03 to 1.91)	.03
Other government/unknown	1.94 (1.56 to 2.41)	<.001	1.64 (1.31 to 2.04)	<.001

*All *P* values are two-sided and derived from univariate and multivariable Cox proportional hazards analyses. CI = confidence interval; HR = hazard ratio.
†The multivariable model was stratified by T stage because it was found to be a time-dependent variable.

Our findings build on previously published trials and retrospective studies that have suggested improved disease control and survival when using altered-fractionation RT schedules compared with conventional RT schedules among patients with early-stage glottic cancer (see Table 4). Despite limited statistical power, these studies suggest that altered-fractionation RT is associated with improved outcomes. Similar to RTOG 95-12, in which a trend toward a 9% absolute survival difference was observed among patients with T2N0 glottic cancer receiving hyperfractionation, we observed a 6.3% survival benefit in our subset analysis of patients with T2N0 disease who were treated with HFX (7). Likewise, among patients with T1N0 disease, we

Table 4. Clinical trials comparing altered and conventional fractionation radiotherapy treatment regimens*

Study	Year	Patients	Clinical stage(s)	Experimental RT arm	Conventional RT arm	Local control (exp. vs CFX)	DFS	OS (exp. vs CFX)
Yamazaki et al. 2006 (6)	2006	180	T1N0	2.25 Gy/fx up to 63 Gy	2 Gy/fx up to 66 Gy	5-y: 92% (95% CI = 86% to 98%) vs 77% (95% CI = 67% to 87%; P = .004)		88% vs 87% (NS)
Moon et al. 2014 (14)	2013	156	T1–T2 (90% T1)	T1: 63 Gy/28 fx T2: 67.5 Gy/30 fx	T1: 66 Gy/33 fx T2: 70 Gy/35 fx	5-y LPFS: 88.5% vs 77.8% (P = .19)		86.6% vs 82.5% (P = .36)
RTOG 95-12 2014 (7)	2014	250	T2N0	79.2 Gy/66 fx (1.2 Gy BID)	70 Gy/35 fx	5-y: 78% vs 70% (P = .14)	5-y: 49% vs 40% (P = .13)	72% vs 63% (P = .29)
DAHANCA 6 2015 (9)	2015	690	T1–T4 (86% T1–T2; 3% N+)	62–68 Gy in 2 Gy/fx, delivered in 6 fx/wk	62–68 Gy in 2 Gy/fx, delivered in 5 fx/wk	Local failure (T1–T2): 11.0% vs 19.4% LRF: T1a: 13.8% (95% CI = 8.8% to 19.8%) vs 13.8% (95% CI = 8.8% to 19.9%); T1b: 13.8% (95% CI = 5.0% to 26.9%) vs 30.3% (95% CI = 15.8% to 46.2%); T2: 16.3% (95% CI = 10.0% to 24.0%) vs 34.1% (95% CI = 25.3% to 43.0%)		Not reported for T1–T2

*BID = twice daily; CI = confidence interval; DFS = disease-free survival; fx = fraction; LPFS = local progression-free survival; LRF = loco-regional failure; NS = statistically nonsignificant; OS = overall survival; RT = radiotherapy.

observed a statistically nonsignificant overall survival difference favoring HFX. Moon et al. demonstrated a 4.1% OS difference favoring patients treated with hypofractionation among patients with T1–T2N0 disease, though this study closed early because of poor accrual (14). In our study, we observed a statistically significant 3.5% absolute survival difference among all patients with T1–T2N0 disease.

Despite the results of these studies, the appropriate fractionation regimen for early-stage glottic cancer remains controversial (16). HFX is recommended by the American College of Radiology Expert Panel on Radiation Oncology—Head and Neck Cancer, though NCCN guidelines currently recommend both hypofractionated and conventional fractionated RT as appropriate fractionation regimens (16,17,19). Our data suggest that a substantial proportion of practioners continue to favor conventional fractionation.

Identifying an optimal fractionation regimen for patients with early-stage glottic cancer is important as disease control is critical to avoid the morbidity of salvage treatments that are often not curative. In DAHANCA 6, a randomized trial comparing an accelerated course of RT with conventional RT among patients with nonmetastatic glottic cancer (86% T1–T2), 177 of 690 patients failed after RT. Of the 128 offered a salvage procedure, 75 (59%) were successfully salvaged, resulting in an overall salvage rate of only 42%. Of the 102 patients who were not offered or failed salvage only two (2%) were alive at five years. A retrospective study from the Cleveland Clinic reported the outcomes of patients with laryngeal cancer who recurred after RT or chemoradiation and underwent salvage partial or total laryngectomy. Among patients who developed recurrence after treatment for early-stage laryngeal cancer, over half presented with stage III/IV disease at recurrence, 28% of patients failed after salvage surgery, and five-year disease-specific survival was 70% (20). We suspect that the overall survival difference observed in our study is due to the improved disease control achieved with HFX, though we cannot confirm this with our data because the NCDB does not collect data regarding disease control or cause-specific survival.

Because of its increased convenience and decreased cost, once-daily hypofractionated RT has been more commonly adopted over other altered fractionation schedules as the preferred RT regimen (7). We found a relatively linear increase in utilization of HFX over the study period, from 22.1% of patients in 2004 to 58.0% of patients in 2013. Interestingly, HFX was more commonly used among patients with T1 disease and those treated at academic or higher-volume centers. However, in the most recent year of our analysis (2013), these differences diminished as the rates of HFX among higher-volume and academic centers declined for unclear reasons. Future data will provide a better understanding of whether this is an anomaly or whether the use of HFX is no longer increasing among these centers.

The greatest strength of this study lies in its uniquely large sample size, which may have facilitated the detection of an OS benefit with HFX that has been repeatedly suggested in the literature but never statistically confirmed. Limitations of this study include the possibility of treatment allocation bias related to unmeasured confounders, such as functional status, nutritional data, or provider-level variables such as for-profit facility status, years of practice, cumulative case volume, and board certification. Without data regarding recurrence or salvage laryngectomy, it is difficult to demonstrate with certainty whether or not the improvement in OS observed among patients receiving HFX is primarily due to improved local control. Other

variables that may have affected clinician choice of fractionation were not available and may have provided additional insight into treatment utilization. Tumor size was available for a limited number of patients. Median follow-up was shorter among patients treated with HFX; this is likely because HFX has been used more frequently in recent years. However, differences in survival were apparent by 24 months after diagnosis, and the number of patients at risk at five years was over 1000 in each treatment group. We were not able to identify patients treated with regional nodal irradiation; however, we suspect that the percentage of patients receiving regional nodal irradiation was low as this practice is not recommended because of the low risk of regional nodal involvement in early-stage glottic cancer (3,16,19,21,22). It is theoretically possible that a small number of patients in the CFX group may have received accelerated RT. However, our sensitivity analyses suggest that excluding these patients did not affect our results.

In conclusion, we found HFX to be associated with an OS benefit among patients with early-stage glottic cancer when compared with CFX. Despite increasing adoption of HFX over our decade-long study period, more than 40% of patients did not receive HFX in the most recent year of our analysis (2013). Although the optimal RT regimen for early-stage glottic cancer remains controversial, we believe that the data from our study, combined with those from previous clinical trials, provide support for HFX as the standard of care for early-stage glottic cancer.

Notes

Trevor J. Bledsoe, MD, and John M. Stahl, MD, have no conflicts of interest to report. Wendell G. Yarbrough and Barbara A. Burtness also have not conflicts to disclose. Henry S. Park, MD, MPH, has received honoraria and travel expenses from Varian Medical Systems as a speaker. Roy H. Decker, MD, PhD, reports research grants from Merck and 21st Century Oncology. Zain A. Husain, MD, reports research funding from Merck.

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