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Clinical Investigation

Randomized Trial of Hyperfractionation Versus Conventional Fractionation in T2 Squamous Cell Carcinoma of the Vocal Cord (RTOG 9512)

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Summary

A total of 250 patients with T2 vocal cord cancer were randomly assigned to hyperfractionation (HFX) or standard fractionation (SFX). The 5-year local control was modestly but not significantly higher with HFX (78% vs 70%; $P = .14$). Results are consistent with prior studies of hyperfractionation showing a benefit in local control. Substaging by T2a

Purpose: To compare hyperfractionation versus standard fractionation for T2N0 vocal cord carcinoma in a randomized controlled trial.

Methods and Materials: Patients with T2 vocal cord cancer were stratified by substage (T2a vs T2b) and randomly assigned to receive either hyperfractionation (HFX) to 79.2 Gy in 66 fractions of 1.2 Gy given twice a day, or standard fractionation (SFX) to 70 Gy in 35 fractions given once a day. The trial was designed to detect a 55% reduction in the local failure hazard rate with 80% statistical power.

Results: Between April 1996 and July 2003, a total of 250 patients were enrolled. Of 239 patients analyzable for outcomes, 94% were male, 83% had a Karnofsky performance status of 90-100, and 62% had T2a tumor. Median follow-up for all surviving patients was 7.9 years (range, 0.6-13.1 years). The 5-year local control (LC) rate was 8 points higher but not statistically significant ($P = .14$ for HFX [78%] vs SFX [70%]), corresponding to a 30% hazard rate reduction. The 5-year disease-free survival (DFS) was 49% versus 40% ($P = .13$) and overall survival (OS) was 72% versus 63%

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versus T2b carries prognostic value for DFS and OS. For cost and convenience reasons, other altered fractionation schedules (eg, 225/fraction) have been adopted in routine practice.

($P = .29$). HFX was associated with higher rates of acute skin, mucosal, and laryngeal toxicity. Grade 3-4 late effects were similar with a 5-year cumulative incidence of 8.5% (3.4%-13.6%) after SFX and 8.5% (3.4%-13.5%) after HFX.

Conclusions: The 5-year local control was modestly higher with HFX compared to SFX for T2 glottic carcinoma, but the difference was not statistically significant. These results are consistent with prior studies of hyperfractionation showing a benefit in local control. Substaging by T2a versus T2b carries prognostic value for DFS and OS. For cost and convenience reasons other altered fractionation schedules have been adopted in routine practice.

Introduction

Laryngeal carcinoma, approximately 23% of head and neck squamous cancer (1), may arise in any mucosal surface of the larynx, with the vocal cords (glottis) the most common subsite (75%). Treatment of early (T1-T2) glottic cancers generally results in high rates of local control and larynx preservation. Retrospective series show approximately 70% 5-year local control for T2 glottic lesions treated with conventional fractionation (2).

Hyperfractionation (HFX), that is, the use of doses per fraction of less than 1.8-2.0 Gy, was tested in clinical trials based on the hypothesized difference in fractionation sensitivity between late side effects and some tumor types, which should allow escalation of the biologically equivalent tumor dose for a fixed equivalent dose for late effects. In locally advanced head and neck squamous cell carcinomas (HNSCC), 2 large phase 3 trials, the European Organization for Research and Treatment of Cancer [EORTC] trial 22791 (3) and the Radiation Therapy Oncology Group [RTOG] trial 9003 (4) demonstrated significant improvement in loco-regional tumor control without significant increase in late toxicity. RTOG launched a prospective randomized trial, RTOG 9512, in 1996 to test whether HFX improves local control for T2 glottic carcinoma relative to standard once a day fractionation (SFX). Secondary objectives were to estimate disease-free survival, overall survival, and toxicity associated with each schedule.

Methods and Materials

Previously untreated patients with biopsy-proven T2N0 glottic carcinoma signed a study-specific consent form and were randomly assigned to SFX or HFX, stratified by substage T2a versus T2b. All patients had modified American Joint Committee on Cancer (AJCC) stage II tumor, Karnofsky performance status (KPS) $\geq$60, and no surgery except biopsy. Patients undergoing prior debulking or complete laser excision of the primary were ineligible. Cases were stratified by T-subcategory (T2a, extending above or below the vocal cord, or T2b, with impaired mobility), and were randomized according to Zelen's principle (5) to HFX or SFX with a 1:1 allocation ratio.

Patients were evaluated during radiation therapy and 4 weeks later for acute toxicity. Tumor control and late effects were evaluated clinically by mirror examination or clinic endoscopy every 3 months through year 1, every 4 months through year 2, twice in year 3, and then annually.

SFX consisted of 2 Gy per fraction, once a day to a total dose of 70 Gy in 35 fractions in 7 weeks. Two-dimensional RT using 2 or 3 coplanar portals was used. Field reduction at 50 Gy was permitted to reduce arytenoid dose. HFX consisted of 1.2 Gy per fraction, twice a day with a minimum interval of 6 hours, to a total dose of 79.2 Gy in 66 fractions in 6.5 weeks. Field reduction at 60 Gy was permitted. Beam energies were 4-6 MV or Cobalt-60. Portal dimension was generally 6 $\times$ 6 cm centered over the thyroid cartilage. Regional lymph nodes were not intentionally included, although some level II and III neck nodes were in the portals. Dose was prescribed at mid-depth along the central axis with the gross target volume receiving at least 95% of the prescribed dose. A thin (2- to 5-mm) bolus was used over the anterior larynx in patients with lesions involving the anterior commissure or in patients with thin soft tissue anterior to the thyroid cartilage.

The primary endpoint was local control at 5 years. The protocol specified a target sample size of 240 patients based on detecting a 55% reduction in local failure, corresponding to an improvement in 5-year local control from 70% to 85% or a hazard rate (HR) of 0.456. Statistical design parameters were overall significance level of .05 for the entire study, statistical power of 0.80, and three 2-sided significance tests. Two of these were interim tests after accruing 50% and 100% of the required sample size for possible early reporting if the nominal $P<.001$. The third (final) test, with nominal significance level 0.048, occurred after all patients had been potentially followed up for a minimum of 2 years. The sample size was increased by 10% to guard against patients retrospectively being reclassified as ineligible. Local control rates were estimated using the cumulative incidence method (6) to account for the competing risk of death without local failure. Patients were censored for locoregional control after 5 years. Disease-free and overall survival rates were estimated with the Kaplan-Meier method (7). The Cox proportional hazards model (8) with T-subcategory as a covariate was used to estimate and test the HR between the HFX and the

SFX arms. HR<1 indicates a reduction in failure rate after HFX.

Patients without clinical complete response (CR), that is, with persistent local disease, in the primary site were classified as having a local failure (LF), and the time of failure was backdated to study day 1. Patients with CR who subsequently experienced local recurrence were considered as failures on the date of reported relapse; otherwise patients were censored at their last follow-up visit. Patients were considered to be at risk for failure until they died. Since the study population had no nodal disease at entry, the only difference between a local and a locoregional failure occurred for patients who had nodal progression.

Second primaries in the head and neck region, as reported by the treating institution and not reviewed by the study chair, were not considered as local failures. One patient on the SFX arm, classified by the treating institution as dying of the index (study) cancer without specific documentation of disease progression, was not considered a local failure.

Disease-free survival (DFS) included local recurrence or persistent local disease, nodal failure, distant metastasis, second primary tumor of all sites, or death from any cause. The date of DFS failure was the first occurrence of any of these events; otherwise patients were censored at their last follow-up visit. Patient-reported voice quality was not measured.

Results

Between 1996 and 2003, a total of 87 institutions enrolled 250 patients with T2 glottic cancer. Of the 250 enrolled, 11 patients were excluded from all the treatment comparisons (4, SFX; 2, nodal disease; 2, restaged as T3-T4; 7, HFX; 3, nodal disease; 3, restaged as T3-T4; 1, withdrawn consent), leaving 239 patients to be analyzed. The median follow-up for all surviving patients was 7.9 years (range, 0.6-13.1 years). Pretreatment characteristics were well balanced between the trial arms (Table 1).

Table 1 Pretreatment characteristics

	Once a day RT (n=119)	Twice a day RT (n=120)
Age (y)		
Median	65	64.5
Min - max	34-88	28-91
Q1 - Q3	57-73	57-73
Sex		
Male	110 (92.4%)	114 (95.0%)
Female	9 (7.6%)	6 (5.0%)
Race/ethnicity		
White	91 (76.5%)	104 (86.7%)
Hispanic	3 (2.5%)	2 (1.7%)
Black	21 (17.6%)	11 (9.2%)
Asian	2 (1.7%)	1 (0.8%)
Native American	1 (0.8%)	1 (0.8%)
Other	1 (0.8%)	1 (0.8%)
KPS		
50	1 (0.8%)	0 (0.0%)
60	3 (2.5%)	1 (0.8%)
70	5 (4.2%)	2 (1.7%)
80	13 (10.9%)	15 (12.5%)
90	63 (52.9%)	69 (57.5%)
100	34 (28.6%)	33 (27.5%)
Primary site		
Glottic larynx, NOS	17 (14.3%)	25 (20.8%)
Vocal cords	102 (85.7%)	95 (79.2%)
T stage		
T2a	74 (62.2%)	74 (61.7%)
T2b	45 (37.8%)	46 (38.3%)

Abbreviations: KPS = Karnofsky performance status; NOS = not otherwise specified; Ql = first quartile; Q3 = third quartile.

Quality assurance (RT fields, dose, tumor coverage) and compliance (treatment delivery) was performed in all cases; all patients randomized to SFX received it. Of the patients randomized to HFX, 96 (80%) received 2 daily fractions on all days, whereas 24 (20%) received 1 or more days with a single radiation fraction (18 patients, 1 or 2 days; 4 patients, 3 to 5 days; and 2 patients, >5 days). Five patients had major unacceptable deviations from protocol prescription, 2 in SFX and 3 in HFX, because of dose and/or field size and/or fractionation.

Tables 2 and 3 show acute and late toxicity. A higher incidence of acute grade 3 + toxicity, primarily laryngeal edema, mucosal, and skin reactions, was seen with HFX than with SFX (33.3% vs 22.7%; $P=.084$), but there was no difference in 5-year cumulative incidence of late grade 3 + toxicity (8.5% after SFX and 8.5% after HFX, including 3 cases requiring tracheostomy after SFX and 2 cases after HFX).

Figure 1 and Table 4 present local control, disease-free survival, and overall survival outcomes according to trial arm. In all, 67 patients experienced local failure by 5 years (35, SFX; 26, HFX). Local control was 70% versus 78% for SFX and HFX ($P=.14$; HR=0.70). In addition, 10 patients had isolated nodal relapse as site of first failure (4, SFX; 6, HFX). Locoregional control was 67% versus 73% (HR=0.77, $P=.26$). Of the 117 deaths, 25% were attributed to the study cancer, 20% to second primary cancers, 40% unrelated to cancer or treatment (comorbid conditions), and 15% unknown.

An analysis of outcome by subcategory T2b versus T2a was conducted with stratification for trial arm. The hazard rate for local control was higher in T2b compared with T2a disease (5-year: T2b 70.0% vs T2a 76.8%; HR=1.51, 95% CI 0.93-2.44; $P=.10$). Outcome was significantly worse in T2b disease for loco regional control (5-year: T2b 63.3% vs T2a 74.1%; HR=1.65, 95% CI 1.05-2.59; $P=.03$), disease-free survival (5-year: T2b 31.4% vs T2a 52.4%; HR=1.62; 95% CI 1.19-2.22; $P=.002$), and overall survival (5-year: T2b 50.0% vs T2a 77.5%; HR=2.06; 95% CI 1.43-2.97; $P=.0001$).

There were no signficiant differences in outcome by substage for local control for HFX versus SFX (T2a: HR=0.58; 95% CI 0.30-1.12; $P=.11$; T2b: HR=0.87; 95% CI 0.42-1.78; $P=.70$; P value for interaction, .42),

Table 2 Acute toxicity according to RTOG/EORTC Acute Toxicity Grading

	No. of patients with toxicity by type and grade									
	Once a day RT (n=119) Grade					Twice a day RT (n=120) Grade				
Acute radiation therapy toxicity	1	2	3	4	5	1	2	3	4	5
Hematologic	1	0	0	0	0	1	0	0	0	0
Skin	45	56	6	0	0	44	55	13	0	0
Mucous membrane/ stomatitis	28	36	5	0	0	19	46	10	0	0
Salivary gland	34	15	0	0	0	36	18	1	0	0
Pharynx/esophagus	35	53	4	0	0	30	64	4	0	0
Larynx	32	54	14	1	0	29	54	20	1	0
Subcutaneous tissue	5	0	0	0	0	5	0	0	0	0
Spinal cord	1	1	0	0	0	1	0	0	0	0
Other neurological	1	1	0	0	0	0	0	0	0	0
Upper gastrointestinal	11	5	0	0	0	10	9	1	0	0
Bone	1	0	0	0	0	1	0	0	0	0
Joint	1	0	0	0	0	0	0	0	0	0
Other	16	2	1	0	0	10	7	1	0	0

Abbreviations: EORTC = European Organization for the Research and Treatment of Cancer; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group.

locoregional control (T2a: HR=0.61; 95% CI 0.33-1.14; P=.12; T2b: HR=1.00; 95% CI 0.52-1.93; P=.99; P value for interaction, .28), disease-free survival (T2a: HR=0.74; 95% CI 0.49-1.11; P=.15; T2b: HR=0.86; 95% CI 0.54-1.38; P=.54; P value for interaction, .63), or overall survival (T2a: HR=0.65; 95% CI 0.39-1.08; P=.10; T2b: HR=1.06; 95% CI 0.62-1.79; P=.84; P value for interaction, .19).

Table 3 Late toxicity

	No. of patients with toxicity, by type and grade									
	Once a day RT (n=118) Grade					Twice a day RT (n=119) Grade				
Late radiation therapy toxicity	1	2	3	4	5	1	2	3	4	5
Hematologic	18	0	0	0	0	13	0	0	0	0
Skin	41	5	0	1	0	41	14	1	1	0
Mucous membrane/ stomatitis	30	7	2	0	0	22	7	2	1	0
Salivary gland	42	7	0	0	0	34	11	1	0	0
Pharynx/esophagus	40	9	2	1	0	30	15	3	0	0
Larynx	51	28	5	4	0	54	33	3	3	0
Subcutaneous tissue	25	4	1	0	0	25	10	0	0	0
Spinal cord	16	2	0	0	0	16	0	0	0	0
Other neurological	14	1	0	0	0	16	1	0	0	0
Upper gastrointestinal	18	0	1	0	0	13	1	0	0	0
Bone	16	0	0	0	0	13	1	0	0	0
Joint	16	0	0	0	0	14	0	0	0	0
Other	20	5	3	1	0	22	8	1	0	0

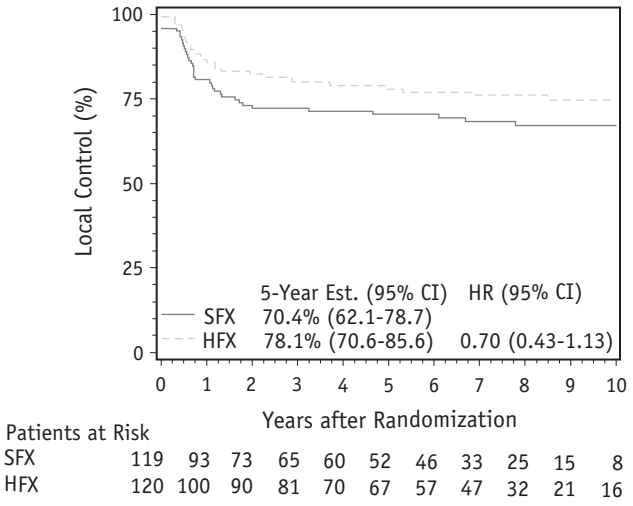

Fig. 1. Local control (actuarial).

Discussion

RTOG 9512 is the only prospective trial of HFX conducted specifically in T2N0 glottic cancer. Results show an 8-point difference in local control (78% vs 70%) at 5 years favoring HFX (P=.14), corresponding to a 30% reduction in the hazard rate (HR=0.70) as well as a trend for improved disease-free survival. There were no significant differences in outcomes between SFX and HFX by substage (T2a vs T2b). Acute toxicity was slightly higher with HFX but very acceptable; there was no difference in severe late effects. Long-term voice quality was not measured, but >85% of patients had only mild to moderate hoarseness or edema by toxicity critieria. This was achieved with conventional 2-dimensional radiation therapy techniques. Current intensity modulated radiation therapy (IMRT) techniques might enhance outcomes further, but these data have not been reported in early glottic cancers.

The rationale for hyperfractionation for our trial was drawn from 2 large fractionation studies enrolling mostly nonlarynx cases, EORTC 22791 and RTOG 90 03 (3, 4)

Table 4 Treatment outcomes at 5 years

	Once a day RT (n=119)	Twice a day RT (n=120)	
Local control	70%	78%	P=.14; HR=0.70
Local-regional control	67%	73%	P=.26, HR=0.77
Disease-free survival	40%	49%	P=.13; HR=0.79
Overall survival	63%	72%	P=.29; HR = 0.82

Abbreviation: HR = hazard rate.

(Horiot, Beitler, in press). Direct comparison with those trials is problematic; the former was limited to the oropharynx, and the latter was in advanced disease. Nonetheless, the hazard rate in RTOG 9512 at 0.70 compares favorably with these trials (HR = 0.68 and HR = 0.81, respectively) as well as the meta-analysis estimates for hyperfractionation by Bourhis et al (9) at 0.77. Since the design and conduct of this trial, other fractionation schedules have been tested and implemented in early-stage glottic cancer.

Accelerated fractionation using 225 cGy per fraction (slight hypofractionation) also appears to be effective at increasing local control with acceptable toxicity. Yamazaki et al showed a significant benefit from accelerated fractionation in a randomized trial of 180 T1 glottic carcinomas using 2.25 Gy per fraction up to 63 to 66 Gy (LC, 92% vs 77%; $P = .004$) (10). Moon et al (11) also compared 225 cGy fractions to 63 to 67.5 Gy for T1-T2 glottic cancers in a 156-patient randomized trial. Local progression−free survival was 11 points higher (89% vs 78%) in the hypofractionated arm; however, the study, like our trial, was underpowered to show significance ($P = .213$). Hliniak et al (12) randomized 395 patients with T1-T3, N0 glottic and supraglottic cancers to 66 Gy in 33 fractions over 45 days or accelerated treatment of 66 Gy in 38 days by delivery twice a day on Thursdays. There was no benefit in overall locoregional control ($P = .37$), but in the subset of glottic cancers (292 patients), LRC was higher ($P = .04$). These studies, including ours, also highlight the challenge of conducting randomized trials in head and neck subsites with small patient numbers. DAHANCA 6 and 7 randomized 908 larynx (690 glottic and 218 supraglottic) cancers to 66 Gy at 2 Gy per fraction accelerated (in 5.5 weeks) versus conventional (6.5 weeks). The 5-year larynx preservation was 80% versus 68% ($P = .007$) (13).

Retrospective analysis at several centers have found that 225 cGy fractions over 25-28 treatments produce excellent outcomes. Chera et al (14) reviewed 585 T1-T2 patients and found overall treatment time to be a significant factor and better outcomes with 225-cGy fractions. Le (15) found that fraction size, total dose, and overall time had impacts on the control of 83 T2 glottic cancers. Garden et al (16) found approximately 80% local control in 228 T2 glottic cancers with both hyperfractionation and hypofractionation. Severe late effects in these series are low (2%-8%) despite a slightly larger fraction size, because of the small volume irradiated and slightly lower total dose. Reports from these centers indicate that 225 cGy per fraction is their preferred treatment for T2 glottic cancers.

Outcomes with concurrent chemotherapy in early-stage glottic cancer have not been reported. However, becaues of less than optimal outcomes in T2b tumors, concurrent chemotherapy may be considered (14). Surgical techniques for early larynx cancers have also evolved with greater use of laser resection, with good tumor control and acceptable voice quality (17).

The possible prognostic importance of impaired cord mobility in T2 glottic cancer (18) was evaluated by McCoul and Har-El (19), who pooled data from 21 reports and found a statistically better outcome in T2a disease. Our data confirm a prognostic difference based on substage, including a trend for better local control in T2a versus T2b disease, and significant differences in locoregional control, disease-free survival, and overall survival, but no differential effect by fractionation. We encourage the American Joint Committee on Cancer to consider T2a versus T2b substaging of glottic carcinoma for inclusion in the Cancer Staging Manual.

Conclusion

RTOG 9512 tested an HFX schedule in T2 glottic tumors similar to schedules tested in more locally advanced disease in RTOG 9003 and EORTC 22791. Although the difference between treatment arms did not reach statistical significance, the trial outcome is consistent with gains observed for hyperfractionation in more locally advanced disease, enhancing local control by 8 points. This was achieved with low acute and late toxicity. Other effective and more convenient fractionation schedules in the management of early glottic cancer include hypofractionation at 225 cGy per fraction. Outcomes in patients with T2b tumors remain suboptimal and may benefit from concurrent chemotherapy.

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