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● *Clinical Investigation*

INFLUENCE OF FRACTION SIZE, TOTAL DOSE, AND OVERALL TIME ON LOCAL CONTROL OF T1–T2 GLOTTIC CARCINOMA

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Purpose: To evaluate the influence of fraction size, overall time, total dose, and other prognostic factors on local control of T1 and T2 glottic carcinomas.

Methods and Materials: Between 1956 and 1995, 398 consecutive patients with early glottic carcinoma (315 T1 and 83 T2) were treated with once-a-day definitive radiotherapy at the University of California, San Francisco, and associated institutions. Treatment was delivered 5 days per week. Minimum tumor dose ranged from 46.6 to 77.6 Gy (median: 63 Gy). The fraction size was <1.8 Gy in 146; 1.8–1.99 Gy in 128; 2.0–2.24 Gy in 62, and ≥2.25 Gy in 62 patients. Overall time ranged from 34 to 75 days (median: 50 days). The majority of patients treated with a fraction size of 2.25 Gy completed therapy within 43 days. Median follow-up of all alive patients was 116 months (range 3–436 months).

Results: Five-year local control was 85% for T1 and 70% for T2 glottic carcinomas ($p = 0.0004$). For T1 lesions, within the dose and time range evaluated, there was no apparent relationship between fraction size, overall time, total dose, and local control on multivariate analysis. Treatment era was the only significant prognostic factor ($p = 0.02$), and anterior commissure (AC) involvement was of borderline significance ($p = 0.056$). Five-year local control was 77% for patients treated between 1956–1970, 89% for between 1971–1980, and 91% for between 1981–1995; 80% for patients with AC involvement and 88% for those without. For T2 lesions, prognostic factors for local control on multivariate analysis were: overall time ($p = 0.003$), fraction size ($p = 0.003$), total dose ($p = 0.01$), impaired vocal cord mobility ($p = 0.02$), and subglottic extension ($p = 0.04$). Five-year local control was 100% for T2 lesions treated with overall time ≤43 days vs. 84% for overall time >43 days; 100% for fraction size ≥2.25 Gy vs. 44% for fraction size <1.8 Gy; 78% for total dose >65 Gy vs. 60% for total dose ≤65 Gy; 79% for normal cord mobility vs. 45% for impaired cord mobility, and 58% for lesions with subglottic extension vs. 77% for those without. The severe complication rate for the entire group was low: 1.8%.

Conclusions: Total dose, fraction size, and overall time were significant factors for local control of T2 but not T1 glottic carcinomas. Anterior commissure involvement was associated with decreased local control for T1 but not T2 lesions. For T1 lesions, local control improved over the treatment era. For T2 lesions, local control decreased with impaired cord mobility and subglottic extension. © 1997 Elsevier Science Inc.

Early glottic carcinomas, Fraction size, Local control, Overall time, Radiotherapy, Total dose.

INTRODUCTION

Squamous cell carcinoma of the glottic larynx usually presents as localized disease and can be successfully treated with either radiotherapy or surgery. Radiotherapy has the advantage of preserving voice quality in the majority of the patients, and is therefore the treatment of choice for early-stage glottic carcinomas in most institutions. Initial local control rates with radiotherapy range from 80 to 95% for T1 (2, 4, 13, 14, 25, 37, 40, 42) and 50–80% for T2 lesions (12, 19, 21, 25, 39, 42), with an ultimate control rate of 90–95% after surgical salvage. Despite the high success rate in controlling early-glottic carcinomas, the importance of fraction size, total dose, and overall time is not well defined. At the University of California, treatment of early stage glottic carcinomas has evolved from small daily fractions and protracted treatment courses to larger daily fractions and shorter overall times over the past 4 decades. The purpose of this study was to review our experience in the treatment of T1 and T2 glottic carcinomas for the last 40 years, and to examine the influence of total dose, fraction size, overall time and other prognostic factors on local control.

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METHODS AND MATERIALS

Patient characteristics

From July 1956 to December 1995, 400 patients with T1 or T2 squamous cell carcinoma of the true vocal cord were irradiated with curative intent at the University of California, San Francisco, the Claire Zellerbach Saroni Tumor Institute, San Francisco, and the University of California, Davis. Three hundred and ninety-eight patients were treated with once-a-day fractionation and formed the population of this study. Two patients treated with hyperfractionation were excluded from the study. There were 363 male and 35 female patients with a male:female ratio of 10.4:1. Three hundred and twenty-two patients were white; 30 were African Americans; 20 were Asians, and 14 came from different ethnic backgrounds. Age ranged from 26 to 90 (median: 61). The median follow-up for alive patients was 116 months (range: 8–436 months), and one was lost to follow-up at 3 months.

Staging

Pretreatment evaluation included physical examination, complete blood cell count, serum chemistries, chest x-ray, direct laryngoscopy, and biopsy. The majority of patients had radiographic visualization of the larynx by laryngogram, or computed tomography (CT), or magnetic resonant imaging (MRI). All histopathological slides were reviewed by pathologists from our three institutions. Patients were staged according to the AJCC staging system (3). Stage T1 was defined as tumor limited to the true vocal cord(s) (may involve the anterior or posterior commissures) with normal mobility, and stage T2 as tumor extending to the supraglottis, and/or subglottis, and/or with impaired vocal cord mobility. T1 lesions were further subdivided into: T1a—tumor limited to one vocal cord, and T1b—tumor involving both vocal cords. Table 1 summarizes the patient and tumor parameters. Three hundred and fifteen patients had T1 lesions: 260 T1a and 55 T1b; 83 patients had T2 lesions. The anterior commissure was involved in 174 patients. One hundred and thirty-three patients had tumor invading the entire true vocal cord(s). Twenty-three T2 patients had impaired vocal cord mobility; 32 had subglottic extension, and 28 had supraglottic involvement. No patient presented with a clinically or histologically positive neck node.

Treatment

All patients were treated with megavoltage equipment using: 1 MV (109 patients), 4 MV (164 patients), 6 MV (11 patients), 8 MV (2 patients) X-rays, and ^{60}Co γ-rays (112 patients). Before 1970, most patients were treated with 1 MV x-rays. During that period, clinical setups at the machine were employed without the use of simulation apparatus or immobilization devices. After 1970, all patients were simulated and treated with opposed lateral fields. They were immobilized with either bite-blocks or aquaplast head masks. Field size ranged from 12–120 cm^2 (median: 27.5 cm^2) for T1, and 14–195 cm^2 (median: 36 cm^2) for T2 lesions. Two patients with T1 and 30 with T2 tumors had elective neck irradiation. Wedge filters or compensators were employed in 224 cases to improve dose homogeneity. Two hundred and fifty patients had one field treated each day, and 148 had both fields treated daily.

Table 1. Patient and tumor parameters

Parameter	Stage T1 No. of pts. (%)	Stage T2 No. of pts. (%)
Total	315	83
T1a	260	
T1b	55	
Gender		
Male	291 (92)	72 (87)
Female	24 (8)	11 (13)
Grade		
Well differentiated	138 (44)	23 (28)
Moderately differentiated	136 (43)	47 (56)
Poorly differentiated	18 (6)	9 (11)
Unknown	23 (7)	4 (5)
Anterior commissure involved		
Yes	116 (37)	58 (70)
No	199 (63)	25 (30)
Subglottis extension		
Yes	N/A	32 (39)
No		51 (61)
Entire cord involved		
Yes	85 (27)	48 (58)
No	230 (73)	35 (42)
Impaired mobility		
Yes	N/A	23 (28)
No		60 (72)

pts.: patients.

All patients received continuous course radiotherapy with once-daily fractionation. Table 2 shows the treatment parameters for the group. Three hundred sixty-one patients were treated with five fractions per week, and 37 with four fractions per week. The overall time ranged from 34–70 days (median: 50 days) for T1, and 37–75 days (median: 52 days) for T2 lesions. The majority of patients (90%) treated with a fraction size $\geq$2.25 Gy completed therapy within 43 days. For the purpose of this study, isodose curves were reviewed and, if absent, were recalculated for all patients. The fraction size and the minimum tumor dose (specified at smallest isodose line that encompassed the entire true cord) were recalculated if necessary. The fraction size ranged from 1.33 to 2.43 Gy (median: 1.8 Gy) for both T1 and T2 lesions. It was $<$1.8 Gy in 122 T1 and 24 T2; 1.8–1.99 Gy in 93 T1 and 35 T2; 2.0–2.24 Gy in 49 T1 and 13 T2, and $\geq$2.25 Gy in 51 T1 and 11 T2 lesions. Among the 1.8–1.99 Gy group, 88% (112 of 128) of the patients had a fraction size of 1.8 Gy. Similarly, of the 2.0–2.24 Gy group, 76% (47 of 62) of the patients had a fraction size of 2.0 Gy. The median tumor dose was 63 Gy (range:

Table 2. Treatment parameters

Parameter	Stage T1 No. of pts. (%)	Stage T2 No. of pts. (%)
Field size		
≤30 cm^2	191 (61)	17 (20)
>30 cm	124 (39)	66 (80)
Median total dose (Gy)	63.0	65.2
(Dose range)	(46.6–75.4)	(51.2–76.6)
Beam energy		
1 MV	91 (29)	19 (23)
≥4 MV	133 (42)	43 (52)
^{60}Co	91 (29)	21 (25)
Overall time		
≤43 days	48 (15)	7 (9)
44–50 days	132 (42)	25 (30)
>50 days	135 (43)	51 (61)
Fraction size (Gy)		
<1.8	122 (39)	24 (30)
1.8–1.99	93 (29)	35 (42)
2.0–2.24	49 (16)	13 (15)
≥2.25	51 (16)	11 (13)
Beam modifiers*		
Yes	171 (54)	53 (64)
No	144 (46)	30 (36)
Both fields treated/day		
Yes	115 (37)	33 (40)
No	200 (63)	50 (60)

* Wedges or compensators.

46.6–75.4 Gy) for T1, and 65.2 Gy (range: 51.2–76.6 Gy) for T2 lesions.

Statistical methods

Estimates of initial local control, ultimate local control, overall survival, and cause-specific survival were computed using the Kaplan-Meier product limit method (18). Outcomes were measured from the first date of radiation treatment to the date of failure for local control, and the last date of follow-up for survival analysis. For local control evaluation, the first local failure was scored. Patients who died of intercurrent disease were censored at the last follow-up. For overall survival, all causes of death were considered. For cause-specific survival, only deaths from tumor-related causes were evaluated. Log rank statistics (7) and Cox proportional hazard model (6) were employed to identify important prognostic factors for local control on univariate analysis. Step-wise Cox regression hazard model (6) was used for multivariate analysis. Patient, treatment, and tumor parameters evaluated included: age (on a continuum), gender, tumor grade (poorly differentiated vs. the rest), anterior commissure involvement, involvement of the entire length of the vocal cord(s), unilateral or bilateral vocal cord(s) involvement (for T1 only), subglottic extension (for T2 only), impaired vocal cord(s) mobility (for T2 only), daily fraction size (on a continuum), minimum tumor dose (on a continuum), overall time (on a continuum), field size (on a continuum), beam energy (1 MV photon vs. others), use of beam modifier(s), and the year of radiotherapy (on a continuum). Stata (5) and S-Plus for Window (35) statistical software's were used for statistical calculations.

RESULTS

Pattern of initial failure

Table 3 shows the initial sites of failure, salvage treatment, and the ultimate salvage rates for patients with early glottic carcinomas. The first sites of relapse included: vocal cord(s) only in 73, regional lymph nodes only in 1, and vocal cord(s) plus regional lymph nodes in five patients. No patient whose primary site was controlled had distant metastasis.

Among patients without recurrence at the primary site, the neck failure rate was 1/264 (0.4%) for T1 and 0/56 for T2 lesions. However, among those with recurrence at the primary site, the neck failure rate was 10/51 (20%) for T1 and 4/27 (15%) for T2 lesions.

Local control

Local failure occurred in 78 patients (51 T1 and 27 T2). The median time to local recurrence was 12.5 months (range: 0–105 months). Eighty-five percent (66 of 78) of local relapses occurred within 5 years of treatment. Although some of the late recurrences may represent new primaries, they were scored as treatment failures for this analysis because we had no way of distinguishing the two. The 5- and 10-year actuarial local control rates for all patients were 82% (95% CI: 78–86%) and 77% (95%

Table 3. Initial treatment failures and ultimate salvage rates

			No. salvaged/No. attempted							
Stage	Initial site of failure	No. of pts.	VC Stripping	Cordecttomy	HL	TL	TL + ND	ND only	None	Total (%)
T1	Primary only	47	0/2	7/7	9/10	21/26	2/2			41/47 (87)
	Primary + lymphnode	4					1/4			1/4
	Lymphnode only	1						1/1		1/1
T2	Primary only	26		1/1	3/3	15/18	1/1		0/3	20/26 (77)
	Primary + lymphnode	1					0/1			0/1

HL: Hemilaryngectomy; ND: Neck dissecion; TL: Total laryngectomy, VC: Vocal cord.

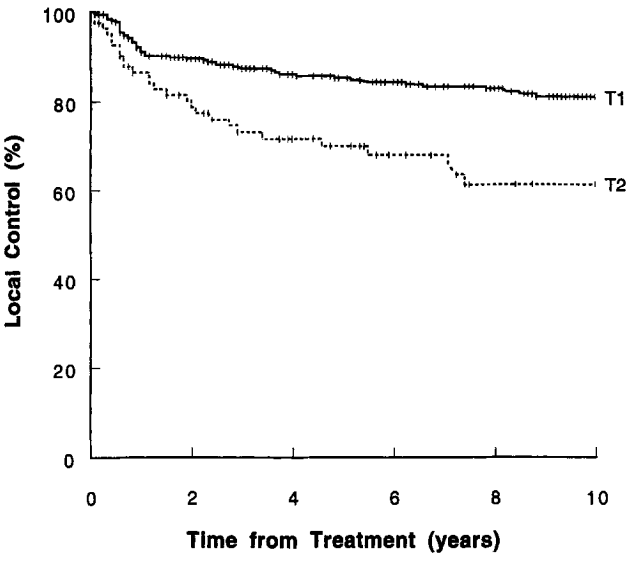


Fig. 1. Local control by tumor stage, $p = 0.0004$.

CI: 72–81%), respectively. There was a significant decrease in local control for T2 when compared to T1 lesions: 70% (95% CI: 58–79) vs. 85% (95% CI: 81–89%) at 5 years, and 61% (95% CI: 48–72%) vs. 81% (95% CI: 76–85%) at 10 years ($p = 0.0004$) (Fig. 1).

Factors influencing local control for T1 lesions

Fifteen patient, tumor, and treatment parameters (listed in the methods section) were evaluated for prognostic significance on local control. For T1 lesions, factors correlated with local control on univariate analysis were: treatment era ($p = 0.02$), involvement of the anterior commissure (AC) ($p = 0.03$), and fraction size ($p = 0.04$) (Table 4). Total dose (on a continuum) was of borderline significance ($p = 0.09$). Overall time did not reach statistical significance ($p = 0.34$) when it was analyzed as a continuous variable; however, when it was divided into three separate subsets as shown in Table 4, the difference in local control rates of the three groups was statistically significant ($p = 0.04$).

Five-year local control according to fraction size is shown in Fig. 2A. Most of the patients in the 1.8–1.99 Gy group were treated with 1.8 Gy/fraction, and the majority of the patients in the 2.0–2.24 Gy cohort received 2.0 Gy/fraction. In patients with T1 lesions, there was a significant difference in local control between the <1.8 Gy group and the >2.25 Gy group (79 vs. 94% at 5 years,

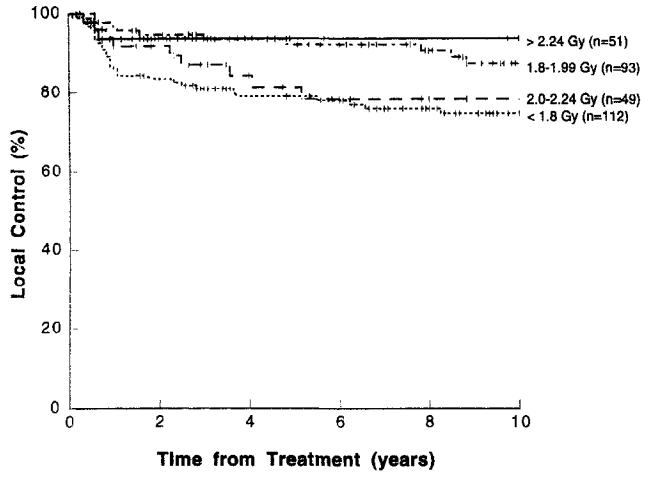
Table 4. Prognostic factors for local control of T1 and T2 glottic carcinomas on univariate and multivariate analyses

	T1					T2				
Treatment and tumor parameter	No. of pts.	Med. F-U (month)	% 5-year LC	Univ. *p*-value	Mult.* *p*-value	No. of pts.	Med. F-U (month)	% 5-year LC	Univ. *p*-value	Mult.* *p*-value
Fraction size (Gy)										
<1.8	122	131	79			24	170	44		
1.8–1.99	93	145	92	0.04	NS	35	136	79	0.007	0.003
2.0–2.24	49	96	81	(0.05)*		13	70	73	(0.002)*	
≥2.25	51	31	94			11	27	100		
Overall time (day)*										
≤43	48	35	98	0.04		7	34	100	0.25	
44–50	132	116	83	(0.34)*	NS	25	171	70	(0.06)*	0.003†
>50	135	129	84			51	88	66		
Total dose (Gy)*										
≤65	222	120	83	0.15	NS	39	124	60	0.24	0.01
>65	93	104	90	(0.09)*		44	85	78	(0.20)*	
Treatment period*										
1965–1970	123	147	77	0.02		24	121	60	0.20	
1971–1980	94	149	89	(0.01)*	0.02	33	176	72	(0.17)*	NS
1981–1995	98	45	91			26	50	78		
AC involvement										
Yes	116	102	80	0.03	0.056†	58	102	65	0.43	NS
No	199	120	88			25	86	81		
Subglottic extension										
Yes	N/A	N/A	N/A	N/A	N/A	32	81	58	0.02	0.04
No						51	116	77		
Impaired cord mobility										
Yes	N/A	N/A	N/A	N/A	N/A	23	75	45	0.008	0.02†
No						60	113	79		

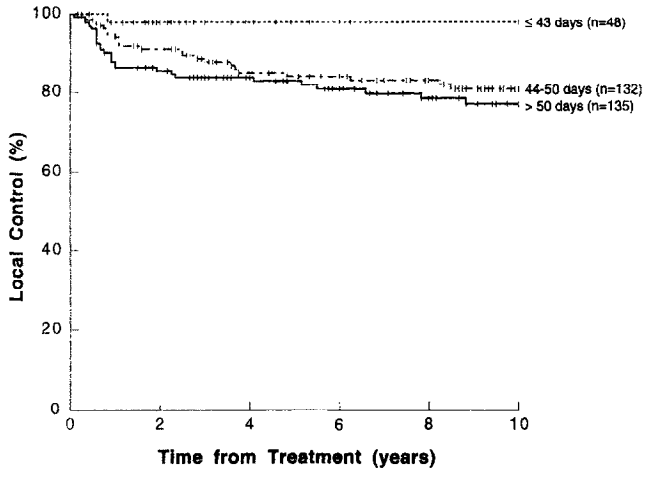
* Parameter analyzed as a continuous variable.

† Significant on multivariate analysis when only patients treated after 1970 were evaluated.

AC: Anterior commissure, Med. F-U: Median follow-up: Mult.: multivariate: NS: Not statistically significant; Pts.: patients; Univ.: univariate; Yr: year.



(a)



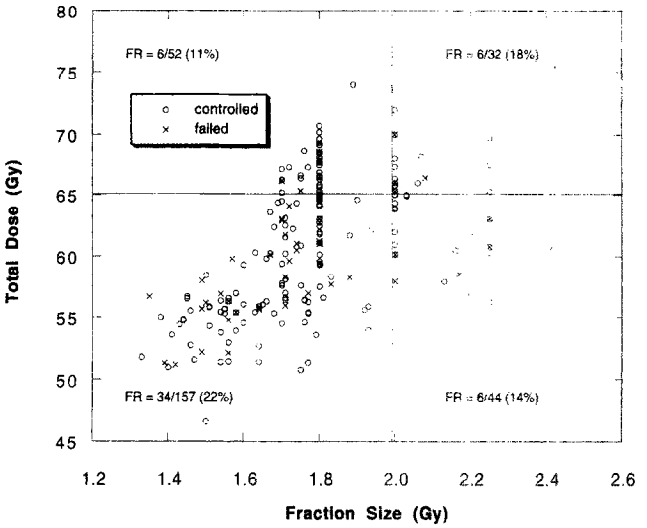
(b)

Fig. 2. (a) Local control of T1 lesions by fraction size (n = number of patients in each group). (b) Local control of T1 lesions by overall time (n = number of patients in each group).

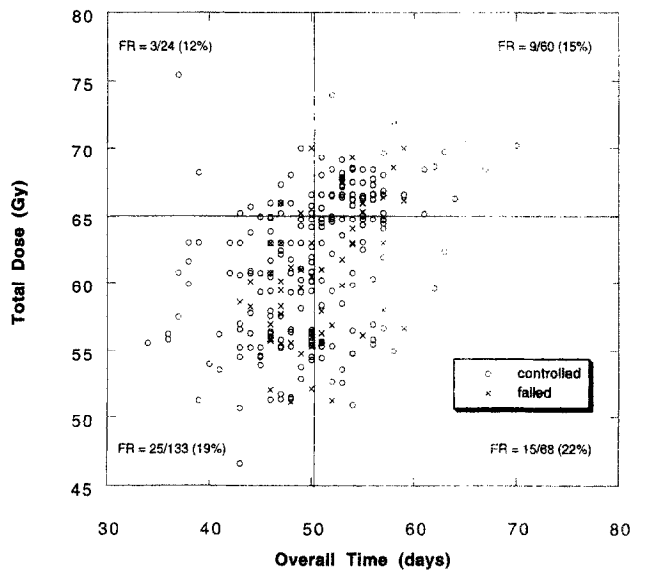
p = 0.04). Among the three larger fraction size groups (1.8–1.99 Gy, 2.0–2.24 Gy, ≥2.25 Gy), we observed a trend for improved local control with fraction size ≥2.25 Gy; however, the difference did not achieve statistical significance.

The relationship between overall time and local control is shown in Fig. 2B. We used 43 days as the first cutoff because over 90% of the patients treated with a fraction size of 2.25 Gy, 5 days a week, completed therapy within 43 days. The second cutoff of 50 days represented the median overall time for the group. On univariate analysis, the 5-year local control rate was superior for patients treated with overall time <43 days compared to overall time = 44–50 days or overall time >50 day (98 vs. 83–84%, p = 0.04). However, the follow-up for the first group was significantly shorter than that for the others.

A scatter plot of local control in relation to fraction size and tumor dose is shown in Fig. 3A. Because most local relapses occurred within the first 2 years, we only included patients who had at least 2 years of follow-up in this analysis. The patients were divided into four subgroups: 1) total dose >65 Gy and fraction size <2.0 Gy; 2) total dose >65 Gy and fraction size ≥2.0 Gy; 3) total dose ≤65 Gy and fraction size ≥2.0 Gy; 4) total dose ≤65 Gy and fraction size <2.0 Gy. No obvious total dose, fraction size, and local control relationship was observed for T1 lesions. Figure 3B is a scatter plot of local control in relation to overall time and total dose. Again, the patients were divided into four subgroups by a total dose of 65 Gy and an overall time of 50 days. The highest failure rate was seen in the group with total dose ≤65 Gy and overall time >50 days, although the difference was not statistically significant by chi-square tests.



(a)



(b)

Fig. 3. (a) Local control of T1 lesions in relation to total dose and fraction size (F.R.: failure rate). (b) Local control of T1 lesions in relation to total dose and overall time (F.R.: failure rate).

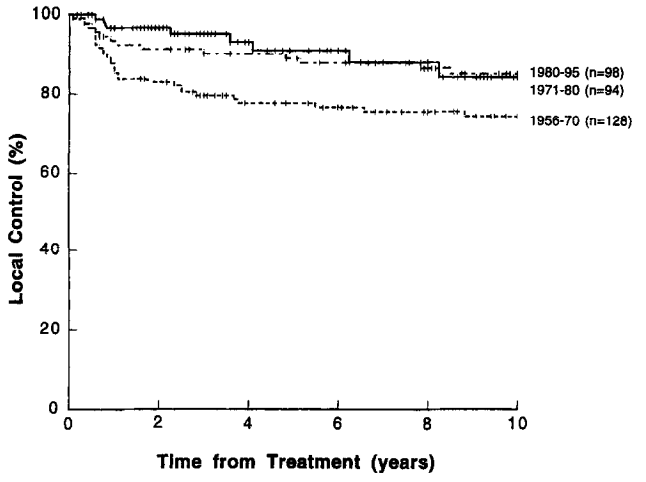


Fig. 4. Local control of T1 lesions by treatment era (n = number of patients in each group).

Because fraction size was strongly correlated with total dose, we carried out two separate multivariate analyses: one evaluating fraction size with other parameters, and one evaluating total dose with the same set of parameters. The only important factor for local control of T1 lesions from both analyses was the treatment era ($p = 0.02$) (Fig. 4). Anterior commissure involvement was of borderline significance ($p = 0.056$). In a subset analysis of patients treated after 1970 when adequate total dose and fraction size were delivered, the only important prognostic factor for local control of T1 glottic carcinomas was anterior commissure involvement ($p = 0.04$). No other tumor or treatment parameters reached statistical significance on multivariate analysis.

Factors influencing local control for T2 lesions

A similar analysis was carried out for T2 lesions. As shown in Table 4, fraction size (on a continuum) ($p = 0.002$), subglottic extension ($p = 0.02$), and decreased vocal cord(s) mobility ($p = 0.008$) were important for local control on univariate analysis; overall time (on a continuum) was of borderline significance ($p = 0.06$).

Figure 5A shows local control according to fraction size for this group. Similar to patients with T1 lesions, those treated with fraction size ≥2.25 Gy had the best local control rate, and those treated with fraction size <1.8 Gy, the worst. When we compare the ≥2.25 Gy group with the 1.8–1.99 Gy and the 2.0–2.24 Gy groups, there was a trend for improved local control with fraction size ≥2.25 Gy, but the number of patients in each group was too small to show a statistical significance.

On multivariate analysis using the two separate models mentioned above, factors associated with increased local failure in all patients with T2 lesions were: prolonged overall time ($p = 0.003$), smaller fraction size ($p = 0.003$), lower total dose ($p = 0.01$), impaired vocal cord mobility ($p = 0.02$), and subglottic extension ($p = 0.04$) (Table 4). Of the patients treated after 1970, overall time ($p = 0.02$) and impaired vocal cord mobility ($p = 0.02$) were the only important factors for local control of T2 lesions on multivariate analysis.

Figure 5B shows the relationship between overall time and local control for T2 lesions. There was no failure in the seven patients who had an overall time ≤43 days, and there was a trend for increased local relapse with longer overall time. Again, the median follow-up for the first group was significantly shorter than that for the other two groups (34 months vs. 88–171 months).

Figure 6 shows scatter plots of local control in relation to total dose and fraction size (Fig. 6A), and total dose and overall time (Fig. 6B) for T2 lesions. Local relapse increased in patients treated with fraction size <2.0 Gy and total dose ≤65 Gy. No difference in local failure was observed in the other three groups. There was no treatment failure when the overall time was <50 days and the total dose was >65 Gy. The majority of

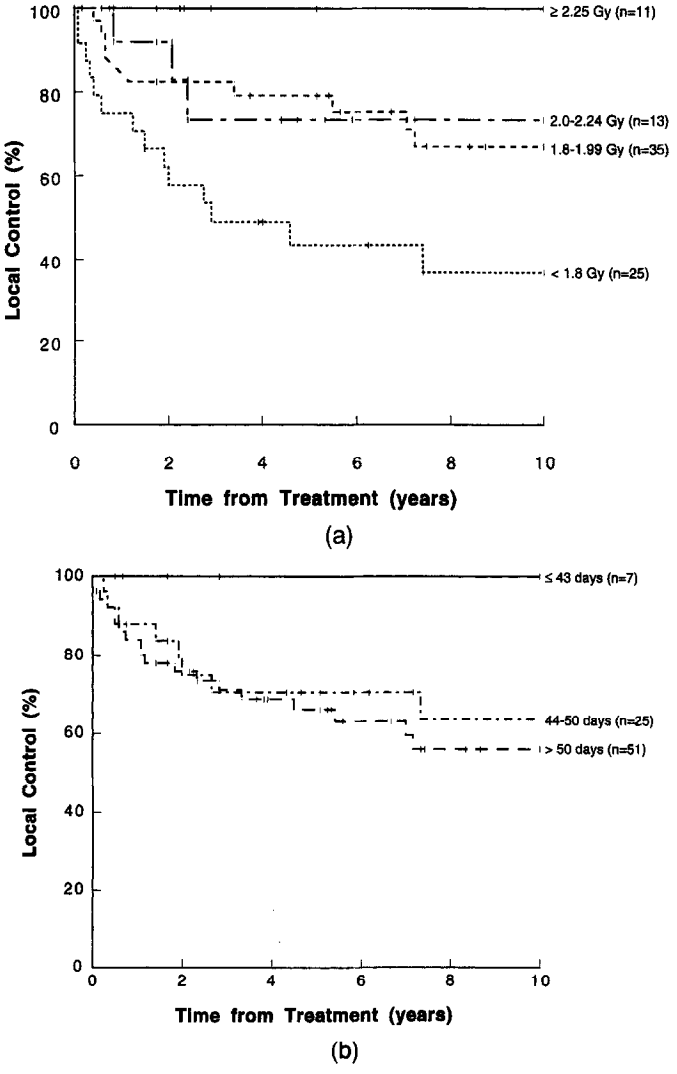


Fig. 5. (a) Local control of T2 lesions by fraction size (n = number of patients in each group). (b) Local control of T2 lesions by overall time (n = number of patients in each group).

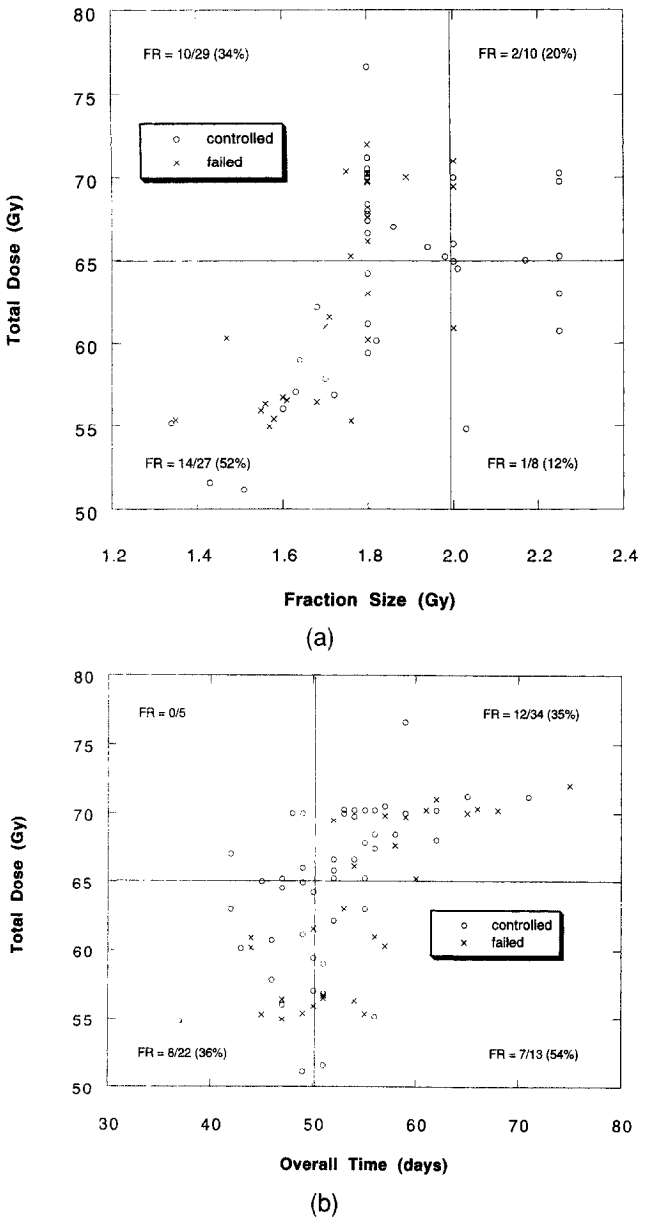


Fig. 6. (a) Local control of T2 lesions in relation to total dose and fraction size (F.R.: failure rate). (b) Local control of T2 lesions in relation to total dose and overall time (F.R.: failure rate).

relapses occurred in patients treated with a total dose ≤65 Gy and an overall time >50 days. The failure rates were equivalent for the remaining two groups. Within the group receiving a total dose >65 Gy, there was again a significant association between local relapse and overall time. No failure (0 of 5) occurred when the overall time was ≤50 days; 6 of 24 (25%) patients failed when the overall time was between 51 and 60 days, and 6 of 12 (50%) patients failed when the overall time was >60 days ($p = 0.04$).

Salvage treatment and ultimate local control

Seventy-six patients underwent salvage treatment for radiation failures. Two patients died of intercurrent disease prior to salvage attempts. One patient refused salvage surgery and died of metastatic disease. Table 3 shows the result of salvage therapy for initial treatment failures. Salvage attempts were ultimately successful in 63 patients: 43 of 52 (83%) in patients with T1, and 20 of 27 (74%) in patients with T2 lesions. In the other 13 patients, disease continued to progress with subsequent nodal and/or distant dissemination. The 10-year actuarial ultimate local-regional control rates were: 96% (95% CI: 92–98%) for T1, and 91% (95% CI: 82–96%) for T2 glottic carcinomas. There was no significant difference in the ultimate local-regional control rates between T1 and T2 lesions.

Second primaries

Ninety-five patients developed a second primary cancer during follow-up. Ten had more than one new primary, resulting in a total of 105 second malignancies (26%). The second primary was in the upper aerodigestive tract in 56 (53%), in the gastrointestinal tract in 22 (21%), in the gentitourinary tract in 17 (16%), in the reticuloendothelial system in 2 (2%), in the central nervous system in 1 (1%), and as melanoma in 2 (2%). Overall, second carcinomas accounted for 66 deaths in our patients.

Survival

At the last follow-up, 224 patients had died: 15 from glottic carcinomas, 3 from complication of salvage treatment, 66 from a second primary, and 140 from intercurrent disease. Figure 7 showed overall survival and cause-specific survival for patients with T1 and T2 lesions. The actuarial 10-year overall survival was 65% (95% CI: 59–71) for patients with T1 and 63% (95% CI: 51–73%) for patients with T2 lesions. The actuarial 10-year cause specific survival (CSS) was 96% (95% CI: 93–98%) for patients with T1 and 91% (95% CI: 81–96%) for patients

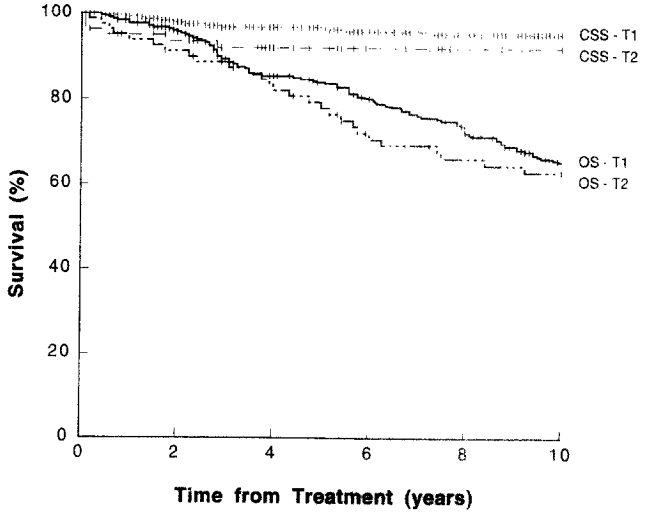


Fig. 7. Overall (os) and cause-specific survival (CSS) for patients with T1–T2 glottic carcinoma.

with T2 tumors. The difference in cause-specific survival between patients with T1 and T2 glottic carcinomas was not statistically significant.

Complications

There were 7 (1.8%) documented severe complications that required surgical intervention. The type of complication, tumor stage, treatment parameters, surgical intervention, and the length of follow-up of these patients are shown in Table 5. There was no obvious correlation between fraction size or tumor dose to the development of severe complications. The incidence of severe complications was 1.9% (6 of 321) in patients treated with fraction size ≤2.0 Gy vs. 1.2% (1 of 77) in those with a larger fraction size. None of the patients with a complication received a tumor dose >70 Gy. There was a trend for increased complications with increase of field size: 1% (2 of 108) complication rate for field size ≤30 cm^2 vs. 2.6% for larger field sizes. The incidence of severe complications was also found to be higher in patients treated before 1971 (2.7 vs. 1.2%), during which period most patients were treated with lower energy (1 MV), one field each day, without proper immobilization devices, and without the use of wedge filters to improve dose homogeneity. Of note, two patients also had repeated glottic biopsies after radiotherapy to rule out tumor recurrence. These surgical procedures may have exacerbated the existing glottic edema and resulted in further respiratory compromise.

Voice quality was not well documented in all patient records. In 340 patients with larynx preservation, voice quality was deemed adequate to good in 249 (73%) and poor in 91 (27%).

DISCUSSION

Our results demonstrate that radiotherapy is an effective treatment for early-stage glottic carcinomas. Our 5-year local control rates of 85% for T1 and 70% for T2 lesions are in agreement with published results in the literature. Our ultimate 5-year local control rates of 97% for T1 and 91% for T2 lesions reflect the high salvage rate of these tumors after radiotherapy failed.

The pattern of failure in our patients paralleled those reported in the literature (16, 24). Local relapse was the initial site of involvement in 99% of treatment failures. Only one patient who had a small T1a lesion developed an isolated neck recurrence. No other case of regional or distal relapse was observed in patients whose primary lesion never recurred. Given the low neck failure rate, routine elective neck irradiation is not warranted in patients with T1–T2 glottic carcinomas who present with N0 disease.

The median time to local relapse was 1 year, which is in accordance with those found in other studies (29, 36). Yet, similar to the experience at the M. D. Anderson Cancer Center (16), we did have some "late failures" (up to 9 years). It is not possible to determine whether these late relapses represent indolent tumors or new primaries. Most of these patients continued to smoke and drink after radiotherapy. We recommend continued long-term follow-up for patients with early glottic carcinomas. This patient population is also at a high risk for developing new primary tumors in the upper aerodigestive tract. They are candidates for chemoprevention trials.

T1 glottic carcinomas

The role of fraction size on local control of T1 lesions has been controversial. A relationship between larger fraction size and higher tumor control rates have been observed by some. Schwaibold *et al.* (30) reported a 100% 3-year local control rate for patients treated with fraction size ≥2.0 Gy vs. 75% (21 of 28) for those with smaller fractions. Kim *et al.* (20) observed a 96% local control rate for patients treated with fraction of 2.0 Gy vs. 79% for those with fraction of 1.8 Gy. Mendenhall *et al.* (25) found an association between larger fraction size and improved local control only for small to intermediate T1a (10–15 mm) lesions. Such a relationship was not seen in

Table 5. Severe complications

Complication	T-Stage	RT year	Fx. size (Gy)	Total dose (Gy)	Field size (cm^2)	Energy (MV)	Wedges	2 fd/d	Surgical intervention	F-U duration (months)
Cord fixation and chronic aspiration	1	1956	2.07	68.17	35	1	No	No	Perm trach	254
Laryngeal sicca and edema	2	1957	1.86	67.02	36	1	No	No	Temp Trach	155
Severe laryngeal edema	1	1957	1.80	57.51	36	1	No	No	Temp Trach	173
Larngeal incompetence*	1	1967	1.54	56.34	30.25	1	No	No	Tot Laryngect	343
Laryngeal necrosis	1	1979	1.8	61.95	25	4	No	No	Perm Trach	148
Cricoarytenoiditis and severe laryngeal edema	1	1986	1.8	64.80	25	^{60}Co	Yes	Yes	Temp Trach	109
Severe laryngeal edema*	2	1995	2.0	66.0	39	6	Yes	Yes	Temp Trach	10

* Multiple biopsies after completion of radiotherapy.

2 Fd/d: Both fields treated each day; F-U: Follow-up; Fx.: fraction; Perm trach: Permanent tracheotomy; RT: Radiotherapy; Temp trach: Temporary tracheotomy; Tot Laryngect: Total laryngectomy.

larger T1a (>15 mm) or T1b lesions. He attributed this discrepancy to the small number of treatment failures in these subsets. Of note, all of these studies employed only univariate analysis. They did not take into consideration other confounding treatment and tumor variables such as overall time, total dose, tumor size, tumor location, and treatment techniques. In contrast, a number of other series failed to show a relationship between fraction size and tumor control for T1 disease. Fein *et al.* (8), in his review of 109 patients treated at Fox Chase Medical Center for T1–T2 glottic carcinomas, did not observe a correlation between fraction size and local control. Small *et al.* (34) found no difference in the dose per fraction between patients with recurrence and those without. Our data, likewise, failed to demonstrate a relationship between fraction size and tumor control in T1 lesions on multivariate analysis. There was a trend for higher local control in patients treated with fraction size ≥2.25 Gy when compared to others; yet the difference did not reach statistical significance, and the short follow-up in this subgroup precluded a meaningful comparison. Given the low recurrence rate in T1 lesions, it would be difficult to demonstrate a significant relationship between fraction size and local control short of a randomized trial with a large number of patients.

Similar to Lustig *et al.* (22) and Schwaibold *et al.* (30), we did not detect an independent effect of total dose on local control for T1 lesions on univariate or multivariate analysis. However, over $\frac{2}{3}$ of our patients received a tumor dose >60 Gy, and in many cases the total dose was tailored to the lesion size and the tumor response during radiotherapy (i.e., lower total dose for small lesions with rapid tumor response and vice-versa). Given the excellent control rate for T1 lesions, and the wide variability in the fraction size, and the overall time used in our patients, a larger sample size and longer follow-up may be necessary to delineate the effect of total dose on local control for these tumors.

Overall time also did not appear to influence local control for T1 lesions in our study. This is in agreement with Wang *et al.* (40) and Inoue *et al.* (17). There was a trend to improved tumor control in patients who completed their radiotherapy within 43 days. However, the follow-up for this subgroup was too short for a meaningful comparison, and the sample size of the group was too small to reach a statistical significance on multivariate analysis. On scatter plots, the majority of failures occurred in the subgroup of patients irradiated with a fraction size <2.0 Gy, a total dose ≤65 Gy, and an overall time >50 days. Therefore, we continue to maintain our current treatment policy of using a fraction size of 2.25 Gy to a total dose of 63 Gy for T1 lesions.

The influence of anterior commissure involvement on local control has also been controversial. The thyroid cartilage lacks a protective perichondrial lining as a potential tumor barrier. Because the anterior commissure is attached to the thyroid cartilage, tumor involvement of the anterior commissure has been implicated as a poor prognostic factor for local control (31). Amornmarn *et al.* (1) reported a 14.7% failure rate in patients with AC involvement vs. 1.9% in those without. Olszewski *et al.* (27) showed an 8% increased in local recurrence with tumor extension to the AC. In the study by Mantravardi *et al.* (23), the local control rate decreased from 90 to 71% in patients with AC involvement. Other studies failed to show AC involvement as a poor prognostic factors (11, 15). In a previous review of our experience, Woodhouse *et al.* (42) did not find any significant difference in local control rate with respect to AC involvement. With a larger number of patients and a longer follow-up, we observed a small but borderlinely significant decrease in local control with AC involvement (80 vs. 88%, $p = 0.056$ on multivariate analysis) for T1 lesions. When the effect of treatment era was eliminated by analyzing only patients treated after 1970, AC involvement became the only significant parameter on multivariate analysis. The discrepancy between the results of these analyses can be explained as follows: before 1971, the effect of AC involvement on local control of T1 lesions was masked by the low local control rate achieved at that time. After 1970, with improved treatment results for T1 lesions (as discussed below), the effect of AC involvement on local control became more prominent (5-year local control rate of 91% for patients with AC involvement vs. 80% for those without). The anterior commissure is a troublesome area as it is difficult to examine by indirect methods, and is a location where minimal anterior tumor extension may result in thyroid cartilage involvement. Many of patients with AC involvement also had a larger tumor burden anteriorly, and in some cases unrecognized subglottic extension. These patients are at higher overall risk for treatment failure, and their management requires appropriate treatment planning to insure adequate tumor coverage anteriorly. Inspite of the fact that AC involvement was associated with a small increased risk of local failure, over 80% of these patients were controlled with radiotherapy alone. Radiotherapy should, therefore, be the initial treatment of choice for all T1 glottic carcinomas regardless of AC involvement.

Radiotherapy for early glottic carcinomas at our institution has evolved over time. Before 1971, it was our policy to treat patients with low daily dose and protracted treatment time to avoid mucosal reaction (38). In general, a fraction size ≤1.8 Gy a total dose ≤65 Gy were used. Many patients were set up clinically, in chick-wing position with neck turned. There was no routine use of simulation apparatus and patient immobilization devices. Reproducibility of patients positioning required maximal technical skill and patient cooperation. Most patients were treated with 1 MV X-ray using a nonisocentric technique. Many patients with early tumor response had their treatment terminated prematurely at a lower total dose. With such treatment schemes, the initial failure rates were high, ranging from 20% for T1 to 48% for T2 lesions (42). From 1971 onward, simulation and patient immobilization were routinely used. Most patients were

treated on isocentric 4 MV linear accelerators or ^{60}Co machines, and the fraction size was increased to ≥1.8 Gy. Patients were also treated with higher total dose or shorter overall time. Since 1988, we have been using fraction sizes ≥2.1 Gy for the treatment of early-stage glottic carcinomas in view of the excellent tumor control rates reported from the University of Florida (25). In addition, many patients in the later era were evaluated with modern imaging techniques (CT or MRI), which provided better tumor delineation and staging. Although statistical analysis failed to detect a significant improvement in local control of T1 lesions with individual technical changes, the local failure rate decreased over time (on both univariate and multivariate analysis), suggesting that a combination of technical innovations and modern imaging techniques adopted at our institution had a positive effect on local control of these lesions. One may argue that shorter follow-up was the reason for the observed improved tumor control over time. Yet, patients treated between 1971–1980 also had a significantly better control rate than those treated before 1971, and the median follow-up of the two groups was identical (147 vs. 149 months). Our results suggest that patients treated in the 1990s can expect a local control rate >90% compared to 77% for those treated before 1971.

T2 glottic carcinoma

Poor prognostic factors for local control of T2 lesions on multivariate analysis were: protracted overall time, smaller fraction size, lower tumor dose, impaired vocal cord mobility, and subglottic extension. Overall time was one of the most significant variables (p = 0.003, hazard ratio = 1.1). This is in agreement with Wang *et al.* (40), who showed that prolonged treatment course adversely affected local control for T2b lesions. Overgaard *et al.* (28) also reported a higher failure rate in laryngeal cancer patients treated with split-course radiotherapy (longer overall time) than with continuous course (shorter overall time). In a review of 496 cases of T2–T3 laryngeal cancer treated with definitive radiotherapy at the Christie Hospital, Slevin *et al.* (32) showed that a time factor of 0.5–0.6 Gy/day was required to overcome the adverse effect of accelerated tumor repopulation when the overall time was longer than 3 weeks. Our data, likewise, suggested that for optimal tumor control, higher total dose was necessary when overall time was prolonged. No one failed when the overall time was <50 days and the total dose was >65 Gy. In contrast, 54% of the patients failed when the overall time was >50 days and the total dose was ≤65 Gy. Within the high total dose group (>65 Gy), we observed more local relapses when the overall time was prolonged. Fifty percent (6 of 12) of the patients with an overall treatment time >7.5 weeks relapsed even with a total dose ≥70 Gy. This is a retrospective study, and various forms of biases might have occurred in the practice at our institutions in the earlier years. Specifically, higher total doses were prescribed to larger tumors, and more slowly responding tumors were given a few extra treatments at the end. After 1970, the treatment policy was more uniform; higher total dose or larger fraction size was used. Yet, the effect of overall time on local control of T2 lesions remained strongly significant over time. In a subset analysis of the patients treated after 1970, overall time remained an independent prognostic factor for local control on multivariate analysis, while the effect of total dose and fraction size became less significant. Therefore, to maximize tumor control with radiotherapy for T2 glottic carcinomas, we recommend that the overall time be kept short, preferentially <50 days.

Fraction size was another important prognostic factor for local control of T2 lesions (p = 0.003). This is consistent with the results reported by Mendenhall *et al.*, who showed an increase in local control for T2a lesions with larger fraction size (25). In our study, patients treated with fraction size <1.8 Gy had the highest failure rate. There was a trend for improved local control in patients treated with fraction size ≥2.25 Gy when compared to the other two groups; however, these patients had shorter follow-up than the remainder of the series, and the sample size was too small to provide a valid comparison of treatment efficacy.

Total dose appeared to have a beneficial effect on local control for T2 lesions independent of overall time. Such an effect has been explored in hyperfractionated radiotherapy, which theoretically allows for an increased tumor dose without increasing late normal tissue injury, while keeping the overall time the same or shorter. Fein *et al.* (9) reported an increase in 5-year local control from 81 to 91% in patients treated with hyperfractionation (1.2 Gy twice-daily to 74.4–76.8 Gy) when compared to those treated with once-daily fractionation (2.25 Gy to 63–67.5 Gy). A retrospective review from the M. D. Anderson Cancer Center (41) also showed a higher local control rate for patients treated with twice-a-day fractionation when compared to historical controls treated once-a-day. The overall time is also shorter in these twice-a-day hyperfractionated regimens. Currently, the RTOG is conducting a prospective randomized trial comparing hyperfractionation (1.2 Gy b.i.d. to 79.2 Gy/6.5 weeks) to conventional fractionation (2 Gy/fraction/day to 70 Gy/7 weeks) for T2 glottic carcinomas (RTOG 95-12). Results of this study should establish the relative efficacy of hyperfractionation vs. conventional fractionation in the radiotherapy of these lesions.

Impaired vocal cord mobility confers poor prognosis. In fact, decreased mobility alone automatically upstages a lesion from T1 to T2. However, vocal cord mobility can be observer dependent. This is probably one of the reasons for the lack of consensus in the literature regarding the effect of impaired vocal cord mobility on

local control of T2 glottic carcinomas. While Hardwood *et al.* (12) and Slevin *et al.* (33) demonstrated a 22–28% decrease in local control at 5 years with impaired mobility, Howell-Burke *et al.* (16) and Mendenhall *et al.* (26) did not find an association between impaired mobility and lower local control. In our experience, patients with T2 lesions and decreased cord mobility did significantly worse than those with normal mobility (5-year local control rate of 79 vs. 45%). This difference persisted on multivariate analysis for all patients as well as for those treated after 1970 when higher total dose and fraction size were utilized.

Subglottic extension for T2 lesions is defined as tumor extending to >1 cm below the apex of the ventricle or >5 mm below the free edge of the true vocal cord as documented on laryngoscopy or imaging. Subglottic extension is, therefore, a reflection of tumor burden. The lower control rate of T2 lesions with subglottic involvement in our study and others (1, 10, 39) may be due to a larger tumor bulk and/or possible geometric miss. With the introduction of modern imaging techniques, subglottic extension and tumor volume can be quantified more readily. In patients with T2 glottic carcinomas, CT and/or MRI are useful in evaluating tumor extent and in radiotherapy treatment planning. They should be performed whenever possible.

CONCLUSION

Total dose, fraction size, and overall time were significant factors for local control of T2 but not T1 glottic carcinomas within the dose range and time range evaluated. Anterior commissure involvement was associated with decreased local control for T1 but not T2 lesions. For T1 lesions, local control improved over the treatment era. For T2 lesions, local control decreased with impaired vocal cord mobility and subglottic extension.

Our current policy is to treat patients with T1 glottic carcinomas with 2.25 Gy/fraction/day, 5 days/week, to a total dose of 63 Gy, and to enroll those with T2 lesions in the RTOG randomized trial (RTOG 95-12) comparing twice-a-day hyperfractionated radiotherapy to conventional fractionated radiotherapy whenever possible. Off protocol, patients with T2 lesions can be treated with either 2 Gy/fraction/day, 5 days/week, to a total dose of 70 Gy or 2.25 Gy/fraction/day, 5 days/week, to a total dose of 65.25 Gy. Although our data have not established that the 2.25 Gy/fraction/day regimen is superior to other regimens used in the treatment of early glottic carcinomas, we offer this treatment to patients off protocol because it allows patients to complete their therapy with a shorter overall time and with no increase of long term complications.

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