PRIMARY RADIOTHERAPY OF T1 AND T2 GLOTTIC CARCINOMA

Analysis of treatment results and prognostic factors in 223 patients

CLAES KLINTENBERG, JAN LUNDGREN, GUNNAR ADELL, MACIEJ TYTOR, LENA NORBERG-SPAAK, ROLF EDELMAN and JOHN M CARSTENSEN

Treatment results in 223 patients with T1 and T2 glottic carcinoma were analysed. A multivariate analysis was performed to evaluate the prognostic significance of factors related to tumour, patient and treatment. Locoregional control after radiotherapy was 90% for 129 patients with T1 tumours and 73% for 94 with T2 tumours. Disease-specific survival was 96% and 81% for patients with T1 and T2 tumours, respectively. In the multivariate analysis of locoregional control, subglottic extension contributed prognostic information to T-stage. In the univariate analysis, number of involved tumour sites, cord mobility and treatment interruption had a significant influence, which was lost in the multivariate analysis. Age gave additional prognostic information in the multivariate analysis of disease-specific survival. Significant adverse effects of radiotherapy were found in 9 patients (4%). Forty-nine patients (22%) had a second malignancy, 11 (5%) diagnosed before the glottic carcinoma.

Glottic carcinoma is often diagnosed at an early stage with the disease confined to the primary site (1, 2). Locoregional treatment by means of radiotherapy or surgery results in a high cure rate. Optimal treatment demands tumour control and preservation of laryngeal function. Radiotherapy offers the possibility of preservation of voice quality and local control rates between 80% to 95% and 65% to 85% for T1 and T2 tumours respectively (2–18). Factors related to tumour (6, 7, 10, 11, 13, 15, 19–21, 23), patient (15, 21, 23) and treatment (12, 14, 16–18, 22, 24–27), explaining the heterogeneity in treatment outcome, have been searched for, especially among T2 tumours. Primary radiotherapy reserving surgery for recurrent disease has been the treatment policy in the present series. Treatment results and analysis of factors with prognostic influence on locoregional control and disease-specific survival are reported.

From the Departments of Oncology (C. Klintenberg, G. Adell), Otorhinolaryngology (M. Tytor, L. Norberg-Spaak) and Radiophysics (R. Edelmann), Linköping University Hospital, Department of Health and Society, Linköping University (J.M. Carstensen), Department of Otorhinolaryngology, Huddinge University Hospital, Stockholm (J. Lundgren), Sweden.
Correspondence to: Dr. Claes Klintenberg, Department of Oncology, Linköping University Hospital, S-581 85 Linköping, Sweden.

Material and Methods

Between January 1969 and May 1991, 223 patients with early glottic carcinoma were treated with primary radiotherapy at Linköping University Hospital. The patients included 210 men, mean age 65.5 years (range 38–95 years, median 66 years) and 13 women, mean age 58.7 years (range 29–77 years, median 59 years). The tumours were staged according to the 1987 UICC TNM classification (29). T1a lesions were confined to one vocal cord, whereas T1b lesions had involvement of both vocal cords. T2 tumours with impaired cord mobility were classified as T2b. Diagnostic direct laryngoscopy and biopsy were performed in all patients. A further mapping of tumour extension was done by dividing the larynx into subsites and involvement of the sites was coded. Extension into the subglottic site was assessed and specified in millimetres below the medial edge of the vocal cord. Radiologic examinations included chest x-ray, laryngography, laryngeal tomography and/or computed tomography. A squamous

cell carcinoma was observed in 221 patients (60 well differentiated, 140 moderately differentiated and 21 poorly differentiated). One patient had a verruccous carcinoma and one patient a pleomorphic carcinoma. There were 129 patients with a T1 tumour, (110 T1a and 19 T1b) and 94 patients with a T2 tumour (76 T2a and 18 T2b).

Radiotherapy was accomplished with a linear accelerator in 216 patients (4MV 189 patients, 6MV 27 patients) and a ^{60}Co unit in 7 patients. In 196 patients the target volume was limited to the primary tumour and in 27 patients elective neck node irradiation was added. Patients were treated in supine position and individual plastic casts were made to facilitate a proper positioning. Between 1969 and 1978 individual dose plans were computed by hand in the central plane, based on orthogonal x-ray films and a patient surface contour. From 1978, we used computerized dose plans in three sections including the central plane, with appropriate inhomogeneity corrections, based on CT-scans with the patient in treatment position. The prescribed dose was represented by the isodose-line delineating the target. The maximum dose and the dose to the ICRU Reference Point were usually 5% higher than the prescribed doses. The ICRU Reference Point was located in the central part of the target. The primary tumour was treated using anterior oblique or lateral opposed wedge fields, sized between 4 × 4 cm and 7 × 7 cm (184/196 with fields between 5 × 5 cm and 6 × 6 cm). The neck nodes were irradiated through an anterior and two lateral oblique wedge fields, followed by a boost, with fields arranged and sized, like those used to treat the primary tumour. All patients were treated with a daily tumour dose of 2.0 Gy and 5 fractions/week. The total dose to the primary tumour varied between 60 and 72 Gy (mean 65.5 Gy, median 64 Gy), and the dose to the neck nodes varied between 30 and 64 Gy (mean 52.9 Gy, median 52 Gy) (Fig. 1). The irradiation was given as a continuous course in 148 patients (94 T1 tumours, 54 T2 tumours) and as a split course with a pause of between 7 and 38 days (mean 19.9 and median 17) in 75 patients (35 T1 tumours, 40 T2 tumours).

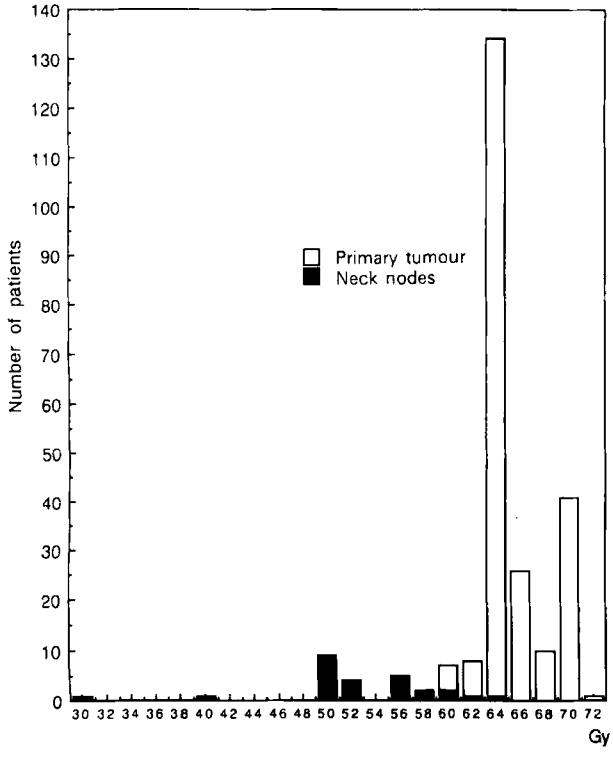

Fig. 1. Irradiation dose to the primary tumour (n = 23) and electively irradiated neck nodes (n = 27, 1 T1 tumour, 26 T2 tumours).

Local control and disease-specific survival after primary radiotherapy and salvage surgery were analysed using the actuarial method of Kaplan & Meier (30). The relationships between study variables, locoregional control and disease-specific survival were analysed using Cox's proportional hazards model (31).

Results

Locoregional control with primary radiotherapy was achieved in 187 out of the 223 patients. Twelve out of 129 (7%) patients with T1 tumours and 24 out of 94 (26%) with T2 tumours relapsed. In relapsing patients salvage surgery was performed in 11/12 patients with T1 tumours and in 16/24 patients with T2 tumours. Nineteen patients had a total laryngectomy, 5 a partial laryngectomy and 3 patients a neck node dissection. In 6 patients with T2 tumours palliative laser surgery was performed, while 3 patients (one with T1 and two with T2 tumours) had no surgery. Salvage surgery was successful in 18 patients (9 with T1 and 9 with T2 tumours.Ultimate local control was achieved in 126/129 (98%) patients with a T1 tumour and in 79/94 (84%) patients with a T2 tumour. Four patients developed neck node relapses, one with a T1 tumour in combination with a local relapse. Three with T2 tumours relapsed with neck nodes only.

Actuarial locoregional control and disease-specific survival at 2, 5 and 10 years are presented in Table 1. Actuarial locoregional control rate ($p = 0.0008$) and disease-specific survival ($p = 0.0001$) were significantly different for patients with T1 and T2 tumours (Fig. 2 and Fig. 3). Thirty-one out of the 36 recurrences (86%) were diagnosed within 2 years and the remaining 5 recurrences within 5 years from start of radiotherapy.

To examine the effect of separate variables on local control and disease-specific survival, a Cox regression analysis was performed. Covariates studied were: T-stage, subglottic extension, supraglottic extension, cord mobility, number of tumour-involved sites, involvement of the anterior commissure, histologic grade, total dose, treatment pause and age. In the univariate analysis, stage, subglottic extension, number of tumour-involved sites,

Table 1

Actuarial locoregional recurrence-free survival and disease-specific survival.

T-stage	Number of patients	Locoregional control			Disease-specific survival		
		2-year %	5-year %	10-year %	2-year %	5-year %	10-year %
T1	129	92	92	90	100	100	96
T1a	110	92	91	91	100	100	97
T1b	19	89	89	89	100	94	94
T2	94	78	73	73	93	83	81
T2a	76	79	75	75	92	83	83
T2b	18	60	60	60	100	79	79

cord mobility and treatment pause all had a significant impact on locoregional control, and T-stage, subglottic extension, number of tumour-involved sites, cord mobility and age on disease-specific survival (Table 2). In the multivariate analysis of locoregional control, only subglottic extension ($p = 0.0001$) had significant prognostic value (Fig. 4), in addition to T-stage. In the analysis of disease-specific survival, age only added prognostic information ($p = 0.0020$) to T-stage (Fig. 5).

Nine patients (4%) suffered from significant adverse effects. Two patients developed aryoedema, 5 chondritis, 1 chondronecrosis and 1 patient had a fistula. A second malignancy was diagnosed in 49 patients (22%) (Table 3).

Discussion

Radiotherapy of patients with T1 glottic carcinoma has been reported to give a high cure rate with few late complications (2,3,7,10–12,15–18). Several series with local control rates in excess of 90% have been reported (5,12,15,16,20,25,26). Survival after salvage surgery is reported as being close to 100% (12,16,20). In patients with T2 tumours the results are less favourable. Thus, local control is reported between 60 and 85% (5,10,15,20,23,24–26) and survival after salvage surgery between 80 and 94% (10, 20, 23).

The present results are in good agreement with these figures. Thus, local control was 90% and survival after

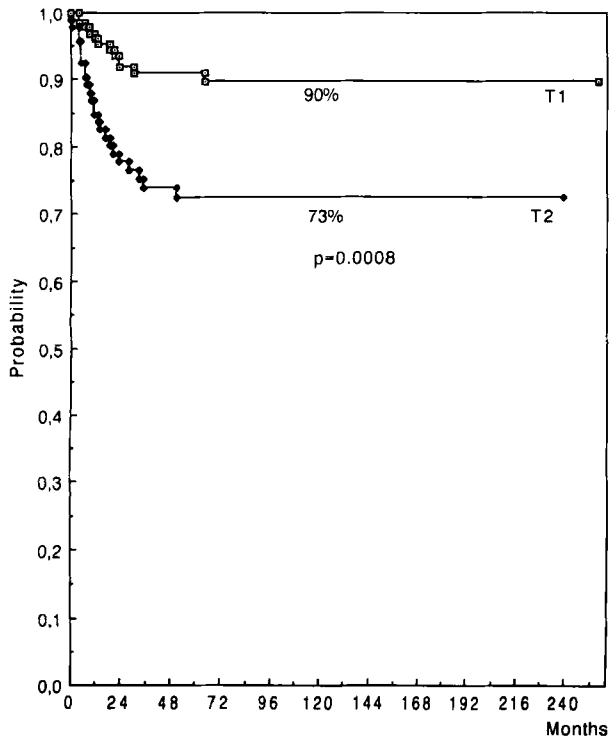

Fig. 2. Actuarial locoregional control among 129 patients with T1 tumours and 94 with T2 tumours, treated with radiotherapy.

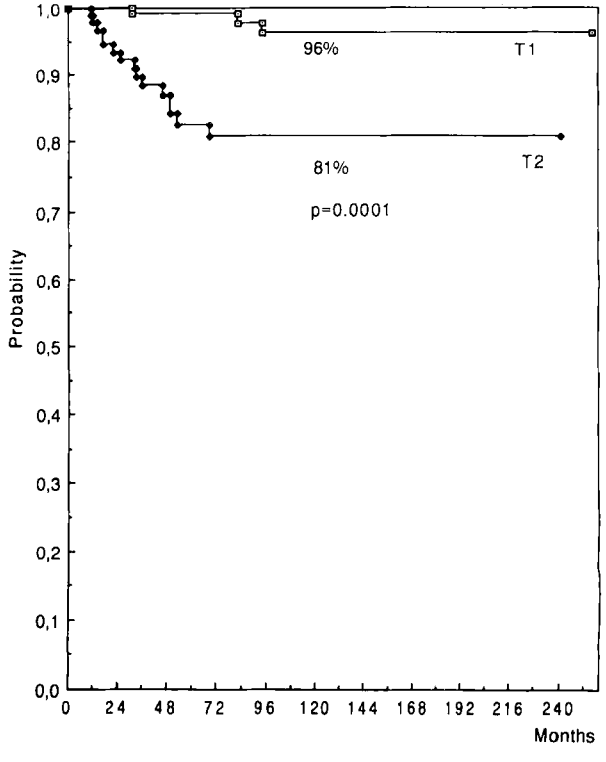

Fig. 3. Actuarial disease-specific survival among 129 patients with T1 tumours and 94 with T2 tumours, treated with radiotherapy. Salvage surgery was performed in 27/36 recurrent cases.

Table 2

Locoregional and disease-specific survival. Univariate analysis. 223 patients

		Locoregional control (36 recurrences)			Disease-specific survival (18 dead of disease)		
	n	Risk-ratio	95% CI	P-value	Risk-ratio	95% CI	P-value
Variable							
T-stage				0.0007			0.0002
T1a	110	1.0	–		1.0		
T1b	19	1.1	0.2–5.1		2.8	0.3–31.1	
T2a	76	2.9	1.3–6.2		9.6	2.2–43.1	
T2b	18	4.5	1.6–12.2		11.4	1.9–68.5	
Subglottic extension mm				0.000			0.0003
0	137	1.0	–		1.0	–	
1–4	38	1.7	0.7–4.6		4.1	1.0–16.4	
5–9	31	3.4	1.5–8.0		8.0	2.3–27.7	
>9	17	7.0	2.9–17.0		8.4	1.9–37.6	
Number of tumour involved sites				0.0004			0.0001
<4	114	1.0	–		1.0	–	
>4	109	3.5	1.6–7.5		9.3	2.1–40.4	
Cord mobility				0.0240			0.0363
normal	199	1.0	–		1.0	–	
impaired	24	2.7	1.2–6.0		3.4	1.2–9.6	
Age				0.0790			0.0024
<60	63	1.0	–		1.0	–	
60–70	85	1.2	0.5–3.0		0.9	0.2–4.4	
>70	75	2.0	0.9–4.8		4.8	1.3–30.5	
Treatment pause >7 days				0.0242			0.2699
No	148	1.0	–		1.0	–	
Yes	75	2.1	1.1–3.9		1.7	0.7–4.3	

n = number of patients, CI = confidence interval.

salvage surgery 96% for patients with T1 tumours. Corresponding figures for patients with T2 tumours were 73% and 81%. Eighty-one percent disease-specific survival among patients with T2 tumours reflects the fact that only 16 out of 24 patients with recurrent tumours received salvage surgery.

Table 3

Incidence of second malignancies

	Relation to glottic carcinoma		
Tumour type	before	after	Total (%)
Genito-urinary	2	16	18 (8)
Gastrointestinal	5	9	14 (6.5)
Lung	1	4	5 (2)
Head and neck	2	3	5 (2)
Skin	1	3	4 (2)
Breast	0	2	2 (1)
CNS	0	1	1 (0.5)
	11 (5)	38 (17)	49 (22)

A number of factors with possible influence on the difference in treatment outcome between patients with T1 and T2 tumours have been reported. Tumour-related factors with prognostic value usually reflect different aspects of tumour extension on and beyond the true vocal cord (10–12, 16, 17, 19, 20). Impaired cord mobility has been described as a significant risk factor in several reports (10, 15, 17, 19, 23), and a subdivision of T2 tumours into a T2b group with impaired mobility has been proposed (2). Other tumour-related factors discussed are tumour size (21), involvement of the anterior commissure (7, 8, 15, 20), and histologic grade (6, 10, 16, 21).

In the present series, as based on the univariate analysis, tumour-related factors with influence on local control all reflected tumour extension. These were T-stage, number of involved sites, cord mobility and subglottic extension. Subglottic extension has been recognized by others as a possible risk factor of unclear significance (7, 10, 19, 20).

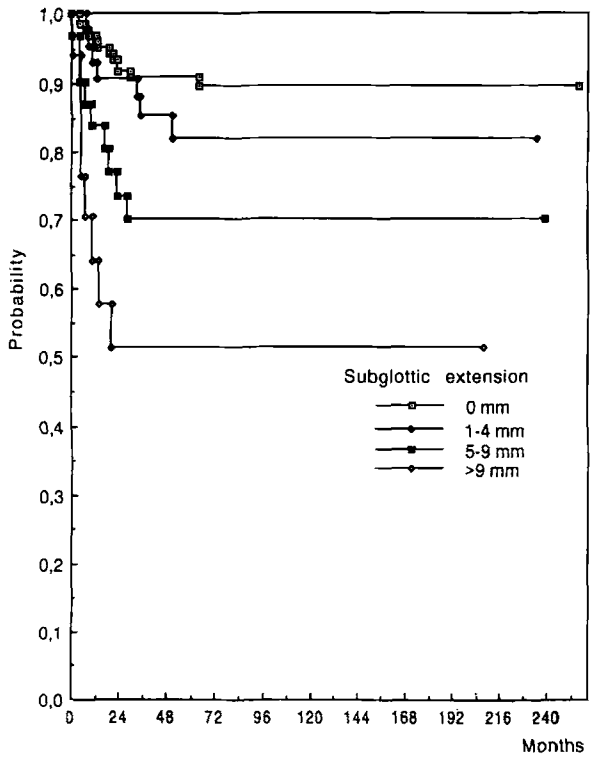

Fig. 4. Locoregional control after radiotherapy in relation to subglottic extension.

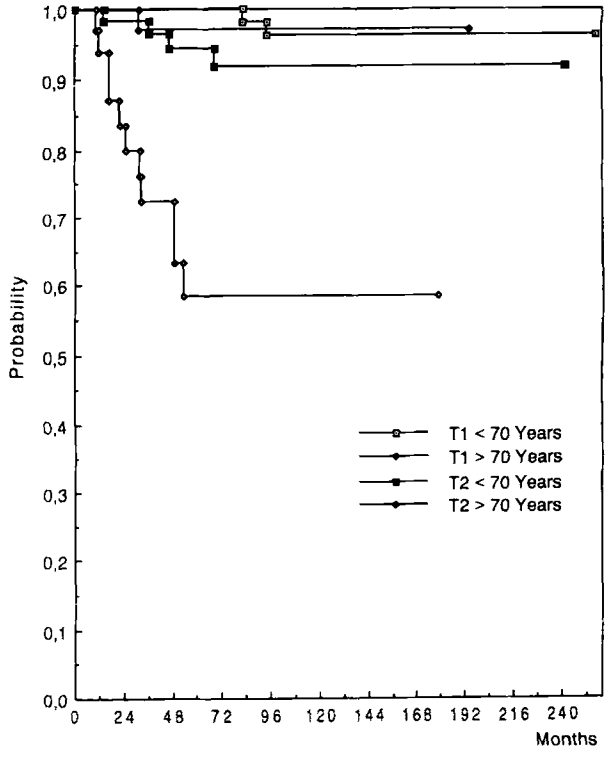

Fig. 5. Disease-specific survival after radiotherapy and salvage surgery in relation to age. Surgery was performed in 27/36 recurrent cases.

Eighty-six out of the 94 T2 tumours had subglottic extension between 2 and 20 mm. In the multivariate analysis this factor added significant prognostic information ($p = 0.0001$) to T-stage, while the others did not. Histologic grade had no significant influence on local control or survival, in accordance with some previous reports (10, 16) but not with others (6, 21).

Seventy-five patients were treated with a split-course irradiation, a regimen that was in use in our department between 1977 and 1987. In the univariate analysis a treatment interruption of 7 days or more showed a significant impact, but this was lost in the multivariate analysis. Several authors have shown total treatment time to predict treatment outcome and therefore treatment interruptions are not recommended (16, 18, 22, 24, 25, 27).

In this series the total irradiation dose did not influence local control or survival, probably reflecting the uniformity in dose prescription. A dose response relationship has been demonstrated by some authors (8, 17, 24, 26).

In the analysis of disease-specific survival, T-category was the strongest predictor, and in the multivariate analysis age only contributed prognostic information in addition to T-stage. Because of advanced age and often poor general condition, a number of patients with recurrences were not offered salvage surgery.

In conclusion, this study of T1 and T2 glottic carcinoma shows that T-stage is the most reliable predictor of treatment outcome. Factors reflecting aspects of tumour extension (in this material subglottic extension) may add prognostic information. Since treatment interruptions were unfavourable in univariate analysis we recommmend that prolonged total treatment time is avoided. This appears to be of particular importance for patients with T2 tumours.

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