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RADIATION TREATMENT OF LARYNGEAL CARCINOMA WITH SPECIAL REFERENCE TO CRE VALUES

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Abstract

In a retrospective analysis of 203 cases of laryngeal carcinoma treated with radiation therapy, conventional absorbed dose levels and CRE calculations were compared as regards the prediction of treatment failure, tumor recurrences and major complications. The recurrence rate for T1 and T2 tumors was 14 per cent and for T3–4 tumors 26 per cent. Poorly differentiated (grade 3) tumors had a significantly higher recurrence rate than well and moderately well differentiated (grades 1 and 2) ones. Corrected 10-year survival rates were 89, 82 and 52 per cent, respectively for T1, T2 and T3–4 tumors. There was a significant relationship between the recurrence rate and the CRE level while the total absorbed dose in Gy or the size of the treatment field could not be correlated to treatment failure. Major complications occurred in 8 (3.9%) patients and they had all received treatment giving CRE values of 1920 reu or more.

For many years radiation therapy has been considered the treatment of choice for early cases of squamous cell carcinomas of the larynx (18). Tumor engagement of the vocal cords gives rise to a specific symptom (hoarseness) at an early stage. Lymph node involvement and distant metastases are rare for small tumors involving only the true vocal cords. Larger tumors of the vocal cords and those of the supraglottic larynx are, however, more difficult to control with either radiation therapy alone or with combined surgery and irradiation (5). Laryngeal carcinoma is a highly rewarding tumor for radiation therapy with a high cure rate and, in contrast to surgery, preserved good quality of the voice (14). Treatment failures can be salvaged successfully by laryngectomy, and in some cases even limited surgery is possible after radiation therapy (3). Using the nominal standard dose (NSD) concept (4), a number of authors have tried to find a dose response curve (6, 8, 9) and a risk level of major complications (1). ARISTIZABAL & CALDWELL (1) showed an apparent correlation between NSD values and the rate of necrosis and recurrence.

In a retrospective analysis of 203 cases of supraglottic and glottic laryngeal carcinomas, basic data on survival and local treatment failure (persistent tumor and recurrence) were analysed in relation to tumor stage, histologic grade, total dose in Gy and CRE level (10). An attempt is made to recommend an optium level for radiation treatment of T1N0M0 glottic carcinomas.

Material and Methods

During the period from January 1, 1959 to December 31, 1980, 203 patients with laryngeal carcinomas were treated at the Department of Oncology. For the present investigation all the cases, except 4 TXN0M0 tumors were restaged according to the TNM classification (17) (Table 1). There were 111 patients with T1 lesions, 42 with T2 lesions and 46 with T3–4 lesions. Twenty-one of the tumors were considered to be primarily supraglottic. In most analyses the glottic and supraglottic tumors were

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grouped together as it was sometimes difficult to separate them accurately during the restaging procedure. Eleven patients had lymph node metastases initially.

The median age of the patients was 73.0 years (range 59–81 years). In the total series there were 190 men and 13 women (6.4%). Six of the women had T1, 3 T2 and 4 T3–4 tumors.

The treatment policy for T1N0M0 tumors was primary radiation therapy with surgery being reserved for recurrent disease. One patient, however, had recently been operated upon as a biopsy, erroneously, had indicated malignant fibrous histiocytoma. The radiation treatment was given with a ^{60}Co unit until 1980. The SSD was 100 cm. Two wedged fields with an individual size of 4–6 cm × 6–8 cm were used. The treatments were given with the patient in supine position. The total delivered midline tumor dose until 1972 was 60 to 65 Gy given in 5–6 weeks, 2.0 to 2.5 Gy per fraction and 4 to 5 treatments per week. After 1972 a dose corresponding to CRE = 1950 reu (10) was given with various fractionation schedules. Beginning in 1980 the treatment was given with a Microtron (Scanditronix, Sweden) accelerator using 10 MV photon beams against two opposed lateral fields and an 8 MeV electron beam against an anterior field. The field sizes and fractionation schedules were about the same as before.

Of the T2 tumors 26 (61.9%) were treated only with radiation therapy using the technique described for T1N0 tumors. The mean size of the treatment fields was larger for T2 tumors (47.1 cm^2) than for T1 tumors (32.7 cm^2). The remaining 16 T2 tumors as well as 35 (76.1%) of the T3 tumors were subjected to preoperative radiation therapy, 40 to 45 Gy in 4 weeks (CRE approx. 1500 reu), and subsequent laryngectomy.

Survival was measured according to the actuarial life-table method and differences were tested by the log-rank method (15). Linear regression models as well as χ^2 and Student's t-test were used in the statistical analysis. The cumulative radiation effect (CRE) was calculated according to the formula given by KIRK et coll. (10).

Results

The crude and corrected survival rates for the different tumor stages are presented in Fig. 1. Corrected survivals of T1 and T3–4 tumor patients differed significantly ($p<0.001$), while the T1 versus T2 and T2 versus T3–4 only differed with a p-value at the 10 per cent level when tested with the log-rank technique. The 5-year survival rates were 91, 82 and 63 per cent, respectively for T1, T2 and T3–4 when corrected for the intercurrent deaths. The survival curves for T1 and T2 were practically flat between 5 and 10 years after treatment while for T3–4 the survival rate fell to 52 per cent at 10 years of observation. The local recurrence-free survival rates in subgroups of T1 tumor patients obtaining different CRE levels (>1900 or <1900 reu) are illustrated in Fig. 2. The difference between these two survival curves was highly significant ($p<0.001$). Among the 111 patients with T1 tumors 16 (14.4%) had recurrences and 11 (68.8%) of these occurred within the first 2 years. The latest recurrence seen in this group occurred 8 years after the primary treatment (Fig. 3). Three (2.7%) T1 tumors, 2 glottic and one supraglottic tumor, failed initially with persistent tumor. Of the 16 patients with recurrences, 9 underwent laryngectomy and they were alive, NED, 5 to 119 months after surgery. The remaining 7 (43.8%) patients all died with uncontrolled disease.

Six (14.3%) of 42 patients with T2 tumors had recurrences. Among the 26 T2 tumors subjected to radiation therapy only, there were 4 (15.4%) recurrences. Among the 16 T2 tumors treated by preoperative irradiation and laryngectomy there were one recurrence in the stoma and one, probably secondary, hypopharyngeal carcinoma 136 months after the primary treatment. Five (11.9%) patients did not achieve primary cure and 4 of these were regarded as supraglottic tumors. The histopathologic speci-

Table 1

Tumor stage (UICC TNM classification) distribution in the complete series of 203 cases

TNM stage	Glottic carcinomas		Supraglottic carcinomas	
	No.	Per cent	No.	Per cent
T1N0M0	107	52.7	2	1.0
T1N1M0	0		2	1.0
T2N0M0	34	16.7	4	2.0
T2N1M0	1	0.5	3	1.5
T3-4N0M0	34	16.7	7	3.4
T3-4N1M0	2	1.0	3	1.5
TXN0M0	4	2.0	0	

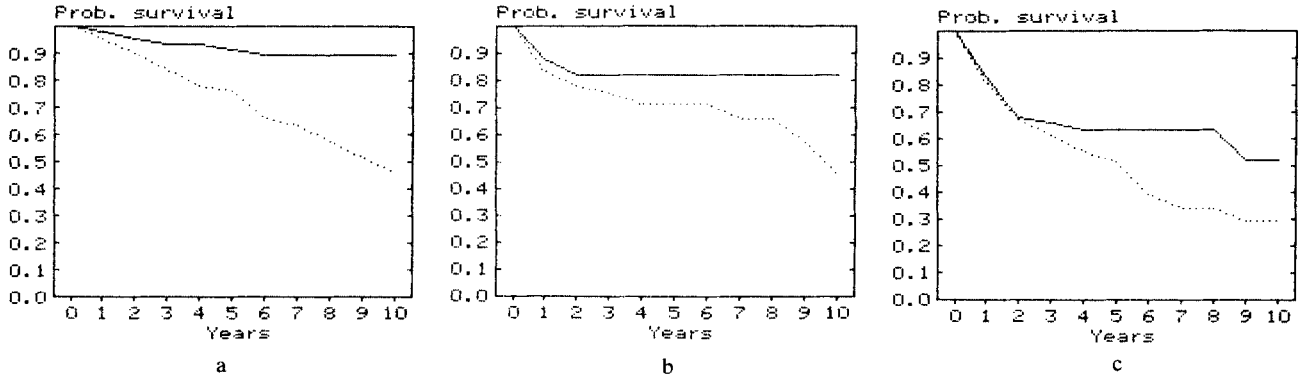

Fig. 1. Crude (. . . .) and corrected (——) actuarial survival cures for a) 111 patients with T1 tumors, b) 42 with T2 tumors and c) 46 with T3–4 tumors.

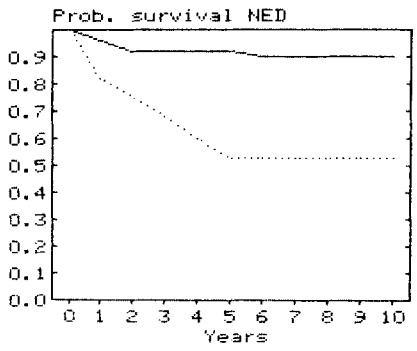

Fig. 2

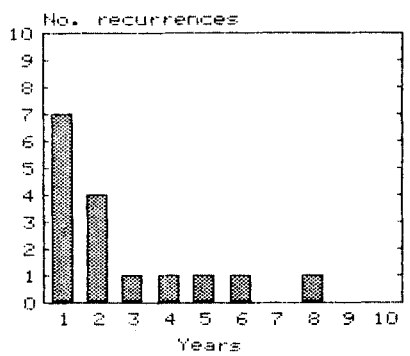

Fig. 3

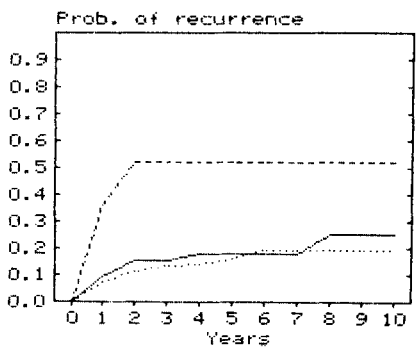

Fig. 4

Fig. 2. Local recurrence-free survival rates for two subgroups of T1 tumors according to the CRE level (<1 900 . . ., >1 900 — reu) reached at radiation therapy. The cut level was set to 1 900 reu.

Fig. 3. The time distribution of recurrences among T1 tumors. Seventy per cent of the recurrences occurred within the first two years after treatment.

Fig. 4. The probability of tumor recurrences is highly dependent on the histopathologic degree of differentiation. Poorly differentiated (grade 3 – – –) tumors have a recurrence rate that is three times higher than that of well and moderately well (grade 1 — and grade 2 . . .) differentiated tumors.

Table 2

Histologic tumor grade

Grade	Stage					
	T1		T2		T3	
	No.	Per cent	No.	Per cent	No.	Per cent
1	40	43	11	31	8	24
2	40	43	18	50	17	50
3	12	13	7	19	9	26

mens from the 16 cases with combined treatment were examined with a whole organ section technique (Department of Pathology, Regionsjukhuset, University Hospital, Linköping). Only one specimen was free from residual carcinoma after the preoperative irradiation.

Twelve (26.1%) patients with T3–4 tumors had recurrences and 8 (17.4%) never achieved primary cure. Eleven T3–4 tumors were only treated with radiation (mean dose 59.8 Gy and mean CRE 1 803 reu) and the failure rate was 45.5 per cent. The remaining 35 patients had been treated with preoperative irradiation (mean dose 49.9 Gy and mean CRE 1 582 reu) and laryngectomy. The failure rate for this group of T2–4 tumors was 20.0 per cent. Ten of the 12 patients with recurrences died while 2, at the time of writing, are alive with disease.

Of the 21 patients with supraglottic tumors, 5 (23.8%) got recurrences and another 7 (33.3%) never achieved primary cure. All patients with persisting tumors died within 17 months from primary treatment. The histologic tumor grade distribution is shown in Table 2. Grade 3 (poorly differentiated) tumors constituted 13 per cent of the T1 tumors and 26 per cent of the T3–4 tumors. Grade 3 tumors had a significantly higher probability of recurrence ($p<0.001$) than grade 1 and 2 tumors (Fig. 4). The recurrence rate of poorly differentiated tumors was

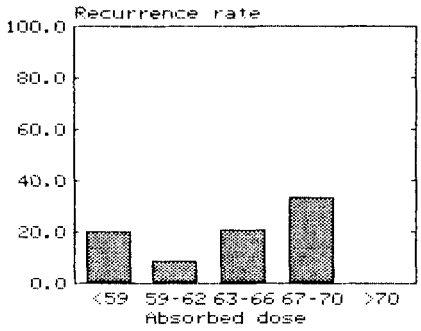

Fig. 5

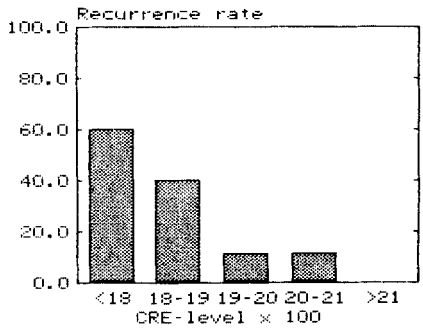

Fig. 6

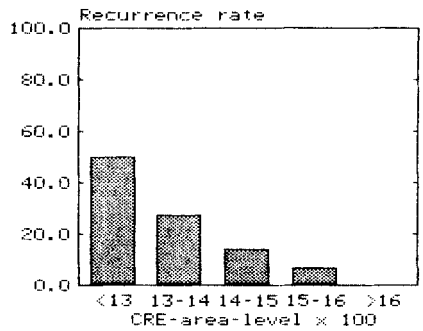

Fig. 7

Fig. 5. Rate of recurrences versus the total absorbed dose in Gy.

Fig. 6. Rate of recurrences versus the CRE level.

Fig. 7. Rate of recurrences versus the CRE_{area} level.

52 per cent within 5 years and most recurrences had occurred already within 2 years. No relationship could be found between the total absorbed dose in Gy and the rate of recurrence (Fig. 5). There was, however, a significant correlation between increasing CRE value and decreasing recurrence rate in T1 tumors (Fig. 6). For T2 and T3–4 tumors no such relationship could be found. Area corrected CRE values (CRE_{area}) were also calculated according to KIRK et coll. (10). Patients with CRE_{area} values above 1 500 reu and T1 tumors had a recurrene rate of 5.3 per cent compared with 18.0 per cent for CRE_{area} values below 1 500 reu and 29.2 per cent of those below 1 400 reu (Fig. 7).

The correlation coefficient (calculated by linear regression analysis) between CRE and CRE_{area} for T1 tumors was $r=0.28$ ($p<0.01$). A CRE_{area} value of 1 500 reu corresponds to a CRE value of 2 040 reu. No recurrences occurred above CRE 2 020 reu.

No correlation at all could be found in this series between field size and recurrence rate. For T1 tumors and field size <25 cm^2 and >26 cm^2 the recurrence rates were 8.0 per cent and 18.2 per cent, respectively. The corresponding percentages for <35 cm^2 and >36 cm^2 were 15.8 and 16.7.

Thirty patients (14.8%) developed a secondary malignancy; basal cell carcinomas excluded. Four carcinomas of the hypopharynx were diagnosed 111, 113, 120 and 136 months after the primary irradiation. Pulmonary carcinomas were also rather frequent (Table 3).

Eight (3.9%) treatment-related major complications were recorded in this series (Table 4). The total absorbed dose in these cases ranged between 58 Gy and 68 Gy (mean 62.9 Gy), the CRE values

Table 3

Secondary malignancies occurring after treatment of 203 cases of laryngeal carcinoma

Type of malignancy	No.	Per cent
Tumors in upper alimentary tract	7	23.3
Hypopharyngeal carcinoma	4	
Tongue carcinoma	2	
Tonsillar carcinoma	1	
Esophageal carcinoma	2	6.7
Lung carcinoma	5	16.7
Gastrointestinal carcinoma	6	20.0
Prostate carcinoma	5	16.7
Other malignancies	5	16.7
Abdominal liposarcoma	1	
Malignant melanoma	1	
Cerebral tumor	1	
Leukemia NUD	1	
Carcinoma of the urinary bladder	1	

Table 4

Major treatment-related complications

Type of complication	Total dose (Gy)	CRE (reu)	CRE_{area} (reu)
Permanent tracheostomy	60	1940	1470
Tracheostomy	68	1960	1578
Subchronic chondritis	66	1920	1455
Advanced radiation changes	59	1950	1437
Bilateral vocal cord paresis	58	2190	1556
Unilateral vocal cord paresis	63	1930	1500
Hoarseness	64	1970	1499
Esophageal constriction	65	1760	1476

between 1 760 and 2 190 reu (mean 1 953 reu) and the CRE_{area} values between 1 437 and 1 578 reu (mean 1 496 reu). The mean values of the total absorbed dose in Gy and the CRE values in these cases were almost identical with the corresponding values for the total of T1 and T2 tumors. There was, however, a tendency ($p=0.063$) towards a higher mean CRE_{area} value for those with major complications (1 496 reu) than for the total T1 tumor series (1 466 reu).

Discussion

Survival rates in treated laryngeal carcinomas are highly dependent on the primary tumor stage (Fig. 1) and on the localization of the tumor (supraglottic or glottic). Only one third of the patients in the present investigation with supraglottic tumor survived without recurrences. A 5-year survival rate of approximately 25 per cent has been reported in supraglottic carcinomas by severeal authors (2, 12, 13, 16). Five-year survival twice or three times as high have often been reported in glottic carcinomas (14, 19). Compared with the vocal cords the supraglottic region is richly supplied with lymphatics and the risk of lymphatic spread is much greater for tumors with this site. Supraglottic tumors also tend to be more anaplastic and may—unlike the glottic tumors—be symptomless when they are small. When the tumors are detected they have therefore often reached an advanced stage (14). In the present series 10 of 21 supraglottic tumors were in stage T3–4 and 8 (38.1%) had positive lymph nodes; 33.3 per cent were poorly differentiated (grade 3), compared with only 17.3 per cent in the total series. In a report by HORIOT et coll. (8) the incidence of failures could not be correlated with the degree of differentiation. In the present series, however, grade 3 tumors had a significantly higher recurrence rate than grade 1 and 2 tumors and poorly differentiated tumors were more common in the higher tumor stages.

A relationship was found between CRE level and recurrence rate in T1 tumors. A similar correlation was reported by KIM et coll. (9) between NSD value and local failure rate. After 1900 ± 50 ret, their failure rate was 11.1 per cent while in the present series the total failure rate after 1 901 to 2 000 reu was 11.5 per cent. HARWOOD & TIERIE (6), on the contrary, in early glottic carcinoma found no correlation between failure rate and NSD value in the range 1 650 to 2 050 ret and therefore recommended a moderate radiation dose (55 Gy in 5 weeks) and partial laryngectomy for post-irradiation recurrences. They also found a relation between field size and local control and were of the opinion that local failure often was due to underdosage (geographic misses). In the present series there was no significant relationship between field size and local recurrence rate. An explanation of this may be the higher doses, which can have decreased the risk of underdosage. Area-corrected CRE values had a similar inverse relationship to the recurrence rate as for the 'uncorrected' CRE values but was not superior in the search for an optimun dose level concerning local control of T1N0M0 tumors. A recommended CRE level of 2 000 reu should, in the present series have given a recurrence rate of about 8 per cent and the corresponding percentage for a CRE_{area} level of 1 500 reu should have been about 5. According to ARISTIZABAL & CALDWELL (1), the tolerance of the larynx remained constant up to approximately 2 040 ret and they recommended an NSD level of 1920 to 2 040 ret for T1N0 and T2N0 tumors. All patients with major complications in the present series had CRE >1 920 reu, except for one patient with a T2N0 tumor who developed an esophageal constriction just below the larynx after 65 Gy and CRE=1 760 reu. The treatment field had been 48 cm^2 and CRE_{area} was 1 476 reu. The lowest recorded CRE_{area} value for a patient with a major complication (advanced radiation damage) was 1 437 reu. The CRE_{area} level seemed to be a useful parameter as regards the risk of major radiation complications. In T1N0 and T2N0 glottic tumors a recommended CRE level of 1 900 reu seems to be a reasonable compromise between the probability of recurrence (45.0% below 1 900 reu and 11.0% above this level) and of major complications (3.9% above 1 920 reu). This level corresponds to CRE_{area} 1 450 reu. In T3N0 lesions a somewhat higher dose is probably required for optimum results. ARISTIZABAL & CALDWELL (1) recommended for instance an NSD value of about 2 100 ret. In the present series, however, preoperative irradiation and laryngectomy seemed to give the best results in T3 and T4 tumors while irradiation alone often was inadequate.

REFERENCES

1. ARISTIZABAL S. A. and CALDWELL W. L.: Radiation tolerance of the normal tissues of the larynx. Its implicaitons in radiotherapy. Radiology 103 (1972), 419.
2. AUBRY M. et BACLESSE F.: Le choix du traitement du

cancer endolaryngé fondé sur les résultats thérapeutiques après 5 ans. Ann. Oto-Laryngol. 76 (1959), 5.
3. BALLANTYNE A. J. and FLETCHER G. H.: Preservation of the larynx in the surgical treatment of cancer recurrent after radiation therapy. Amer. J. Roentgenol. 99 (1967), 336.
4. ELLIS F.: Time, fractionation and dose rate in radiotherapy. *In:* Frontiers in radiation therapy and oncology. Vol. 3, p. 131. Karger, Basel, New York 1968.
5. GOFFINET D. R., ELTRINGHAM J. R., GLATSTEIN E. and BAGSHAW M. A.: Carcinoma of the larynx. Results of radiation therapy in 213 patients. Amer. J. Roentgenol. 117 (1973), 553.
6. HARWOOD A. R. and TIERIE A.: Radiotherapy of early glottic cancer. II. Int. J. Radiat. Oncol. Biol. Phys. 5 (1979), 477.
7. — HAWKINS N. V., RIDER W. D. and BRYCE D. P.: Radiotherapy of early glottic cancer. I. Int. J. Radiat. Oncol. Biol. Phys. 5 (1979), 473.
8. HORIOT J. C., FLETCHER G. H., BALLANTYNE A. J. and LINDBERG R. D.: Analysis of failures in early vocal cord cancer. Radiology 103 (1972), 663.
9. KIM J.-C., ELKIN D. and HENDRICKSON F. R.: Carcinoma of the vocal cord. Results of treatment and time–dose relationships. Cancer 42 (1978), 1114.
10. KIRK J., GRAY W. M. and WATSON E. R.: Cumulative radiation effect. I. Fractionated treatment regimes. Clin. Radiol. 22 (1971), 145.
11. — — — Cumulative radiation effect. IV. Normalisation of fractionated and continuous therapy. Area and volume correction factors. Clin. Radiol. 26 (1975), 77.
12. LEDERMAN M.: Place of radiotherapy of cancer of the larynx. Brit. Med. J. I (1961), 1639.
13. MÅRTENSSON B., FLUUR E. and JACOBSSON F.: Aspects on treatment of cancer of the larynx. Ann. Otol. Rhin. Laryng. 76 (1967), 313.
14. MORRISON R.: Radiation therapy in diseases of the larynx. Brit. J. Radiol. 44 (1971), 489.
15. PETO R., PIKE M. C., ARMITAGE P. et coll.: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Brit. J. Cancer 35 (1977), 1.
16. POWELL R. W., REDD B. L. and WILKINS S. A.: An evaluation of treatment of cancer of the larynx. Amer. J. Surg. 110 (1965), 635.
17. UICC: TNM classification of malignant tumours. Geneva 1978.
18. VAN DEN BOGAERT W., OSTYN F. and VAN DER SCHUEREN E.: Glottic carcinoma limited to the vocal cords. Acta radiol. Oncology 21 (1981), 33.
19. WANG C. C. and SCHULTZ M. D.: Cancer of the larynx. J. Radiol. 80 (1963), 963.