FROM THE DEPARTMENT OF RADIATION ONCOLOGY, CLAIRE ZELLERBACH SARONI TUMOR INSTITUTE, MOUNT ZION HOSPITAL AND MEDICAL CENTER SAN FRANCISCO, CALIFORNIA 941 20, U.S.A.

EVALUATION OF TIME-DOSE FACTORS IN GLOTTIC TUMORS

KENNETH H. LUK and JOSEPH R. CASTRO

Experience has shown excellent tumor control and functional results following radiation therapy for limited squamous carcinoma of the vocal cords (BUSCHKE & VAETH 1963, FLETCHER & KLEIN 1964, GOFFINET et coll. 1973). Most treatment schemes have been based on five or six fractions per week with a range of 6 000 to 7 000 rad (super-voltage) given over a period of five to seven weeks. ARISTIZABAL & CALDWELL (1972) in reviewing a number of reports have recommended a tumor dose biologically equivalent to 1960 ret, utilizing the nominal standard dose formula of ELLIS (1968). The basic dose recommended for ^{60}Co therapy by FLETCHER & KLEIN (1964) is 6 000 rad in five-and-one-half weeks (27 fractions) for minimal disease, plus an additional boost of 500 to 1 000 rad in 2 to 5 fractions for bulky disease. Control rates for T1 and T2 tumors approximate 80 to 90 per cent with a very low rate of severe edema or cartilage necrosis unless a dose biologically equivalent to 2 000 ret is exceeded. Because of a sigmoid curve relationship of tumor control to dose, a control rate of 90 per cent is probably as high as can be obtained in vocal cord carcinoma without an unacceptably high level of necroses.

Despite the very abrupt changes in tumor control rates and necrosis rates with different fractionation schemes in other tumor sites, changes in fractionation from 5 days per week to 3 or 4 days per week do not appear to show similar effects in

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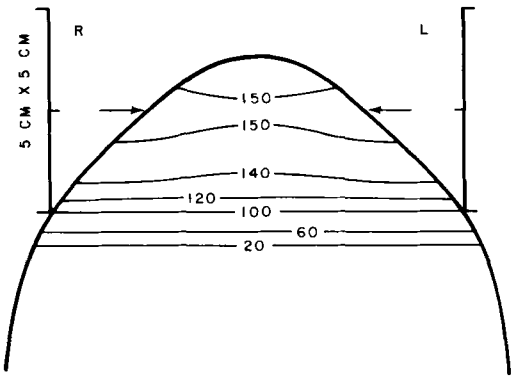

Fig. 1. Opposed lateral fields with compensators. ^{60}Co, 1.25 MeV, SSD 80 cm.

treatment of vocal cord tumors. The reasons for this are unclear but may be related to the small volume of normal tissues included in the treatment field. It has been emphasized by FLETCHER & KLEIN (1964) that partial sparing of the arytenoid cartilages for tumors localized to the anterior part of the vocal cords results in a lower incidence of arytenoid edema and subsequent voice dysfunction. Thus the proportion of the vital structure included in the radiation beam may be more important than the total volume of normal tissues irradiated.

At least one randomized clinical trial is underway to evaluate 3 days per week versus 5 days per week treatment of vocal cord tumors (ELLIS et coll. 1969, WIERNIK et coll. 1972), with no apparent differences in results as yet. Completely erroneous or inadequate localization of vocal cord tumors is rare, so that failure of control or complication ordinarily is a function of the time-dose-volume parameters. Thus vocal cord tumors form a good model for evaluation of time-dose-volume relationships.

Material and Method. Sixty patients with localized squamous cell carcinoma of the vocal cord without nodal or distant metastases were irradiated with 4 fractions per

Table 1

Distribution of patients by T stage. All patients N0, M0

Stage	Vocal cord carcinoma		
	No. of patients	Patients excluded	Patients examined
T1	46	3	43
T2	12	1	11
T3	2	1	1
T4	—	—	—
Total	60	5	55

Table 2

Local control by T stage with minimum 2 years follow-up

Stage	Vocal cord carcinoma	
T1	34/43	80 %
T2	9/11	81.5 %
T3	1/1	—
T4	—	—

week. Five patients were excluded from analysis because of death from intercurrent diseases within 12 months from completion of radiation therapy. At least a 24-month follow-up period was available for 55 patients. All patients were clinically staged according to the TNM system (Table 1).

Dose schedule and treatment technique. The technique ordinarily used was ^{60}Co irradiation through opposed portals, with compensating or wedge filters placed in the radiation beam. An example of a typical dose distribution for such a treatment plan is illustrated in Fig. 1.

Patients with T1 and T2 vocal cord lesions commonly received 6 000 rad in six-and-one-half weeks with 4 treatment fractions per week utilizing 5 cm × 5 cm opposed portals as measured by the 50 per cent isodose line. For the few patients with T3 vocal cord lesions the dose was 7 000 rad in 8 weeks, 4 fractions per week, through 7 cm × 8 cm portals.

Results

The interest was directed both to local control (Tables 2, 3) and complication rates (Table 4) in the 4 fraction/week patients. The control rate in T1 lesions is slightly lower than in the best reported series (Table 5) as is the average ret dose calculated directly from Ellis' formula without taking into account the concept of partial tolerance. The control rates for T2 lesions, however, are comparable to other reported series.

Table 3

Analysis of local control according to NSD (ret) of vocal cord carcinoma

Stage	1 600–1 700	1 700–1 800	1 800–1 900	1 900–2 000	Average ret value
T1	4/4	4/6	24/31	2/2	1 800
T2	—	1/1	7/9	1/1	1 850
T3	—	—	—	1/1	1 950
Total	4/4	5/7	31/40	4/4	

Table 4

Evaluation of voice quality after treatment; minimum follow-up time was 24 months

	No. of patients
Good speaking voice	26
Mild or intermittent hoarseness*	16
Persistent hoarseness with necrosis of arytenoid**	1
No data available for analysis	8
Early failure followed by surgery	9
Total	60

*Six of these patients documented to continue to smoke and drink
**The ulceration slowly healed with conservative treatments. Biopsy: No malignancy

Eleven of the 55 patients were radiation therapy failures with recurrence of disease locally. Among the local radiation failures, one patient expired of obstruction by recurrent tumor, three patients had total laryngectomy, five patients had hemilaryngectomy and one patient had stripping of the vocal cord only (Table 6). Four patients had radical neck dissection: one such patient had clinically obvious neck node metastasis, 2 patients had primary recurrence but no palpable nodes, and one was planned for surgery although there was no evidence of primary recurrence or nodal metastasis. Only the patient with clinically palpable neck nodes yielded a positive specimen. Of the 11 patients with local failures, 10 had an attempt at surgical salvage, 9 successfully. The average time of recurrence after radiation therapy was seven-and-one-half months.

Complications. Twenty-six of the 51 patients who had control of their tumors and were available for follow-up examination were documented to have excellent speaking

Table 5

Dose-response of T1N0 vocal cord carcinoma

	Ret value	Patient controlled	Rate
Morris & Deeley (1962	1 700	21/32	66 %
Present material*	1 800	34/43	80 %
Aristizabal & Caldwell (1972)*	1 860	15/20	75 %
Fletcher & Klein (1964)	1 920–2 020	108/118	92 %
Hibbs & Hendrickson (1966)	2 000–2 100	115/125	92 %
Stewart (1966)	1 950–2 130	114/122	94 %

* Treatment schedule of 4 fractions per week

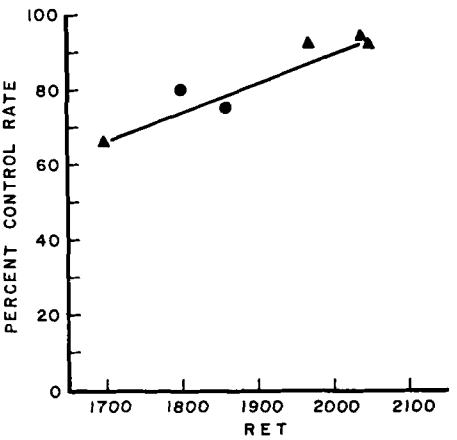

Fig. 2. Dose-response curve for T1N0 vocal cord carcinoma using NSD. Cf. Table 5. ● 4 fractions/week, ▲ 5 fractions/week.

voices. Sixteen patients had mild or intermittent hoarseness, six of whom continued to smoke and drink excessively after the course of radiation therapy. Only one patient developed necrosis of the arytenoid which slowly healed with conservative care.

Twelve patients were followed for more than five years, and no severe late radiation injuries could be demonstrated.

Table 6

Procedures after local irradiation. Failure in true vocal cord tumors

Patient	Stage	Ret	Time after irradiation therapy	Procedure	Comment
1	T1	1 789	8 months	None	Expired 15 months obstruction of larynx
2	T1s	1 821	8 months	Partial laryngectomy	75 month NED
3	T2	1 810	3 months	Total laryngectomy. Neck dissection negative	24 month NED
4	T1	1 810	4½ months	Hemilaryngectomy	48 month NED
5	T2	1 852	5 months	Total laryngectomy. Neck dissection negative	36 month NED
6	T1	1 810	5½ months	Hemilaryngectomy. Neck dissection 6/21 nodes	26 month NED
7	T1	1 859	5 months	Total laryngectomy	50 month NED
8	T1	1 810	6 months	Hemilaryngectomy	45 month NED
9	T1	1 841	28 months	Cord stripping for microinvasive carcinoma	39 month NED
10	T1	1 810	7 months	Hemilaryngectomy	66 month NED
11	T1	1 734	64 months	Tracheostomy Direct laryngoscopy and biopsy	Expired of massive hemorrhage from tracheostomy

Table 7

Radiation therapy for vocal cord carcinoma. Local control at 24 months

Authors	Stage T1N0		T2N0		T3N0	
ARISTIZABAL & CALDWELL (1972)	15/20	75%	—		—	
BABLESSE (1967)	17/18	94%	34/59	58%	13/36	36%
MORRISON & DEELEY (1962)	21/32	66%	—		—	
FLETCHER & KLEIN (1964)	108/118	92%	24/30	80%	1/3	33%
HIBBS & HENDRICKSON (1966)	115/125	92%	30/39	76%	—	
STEWART (1969)	114/122	94%	66/90	73%	—	
PRESENT material	34/43	80%	9/11	81%	1/1	—

Discussion

An important test of an altered treatment fractionation schedule is the tumor response to radiation and local control of disease by such treatment technique. Such a treatment schedule cannot be justified because of convenience alone; rather it must promise an equal rate of control as well as an acceptable degree of normal tissue reaction and complication rate.

In Tables 5 and 7 several series of reported results are summarized for vocal cord tumors. A dose-response curve can be constructed from the data derived from these series of patients. Fig. 2 demonstrates a linear relationship between dose and local control of T1N0 vocal cord carcinomas treated by different techniques. The ret value for patients treated at 4 fractions per week falls along this dose-response curve at a lower level of control. It appears, despite the decreased fractionation schedule, that the control rate in this current group is somewhat low for patients with T1 tumors. The complication rate, however, is within the acceptable range. Voice quality was also satisfactorily preserved in these patients.

SUMMARY

Sixty patients with localized squamous cell carcinoma of the vocal cord without nodal or metastatic disease were treated with four fractions per week. No serious complications occurred with the dose and fractionation schedule as outlined. Voice quality after treatment has been satisfactory. After a minimum of two years follow-up the control rates for T1 and T2 tumors are 80% and 81.5%, respectively. All radiation therapy failures were cured surgically. A dose-response curve was constructed for T1 lesions, utilizing the Ellis' formula to derive the NSD, from data from different therapy centers. There appears to be no differences in the parameters studied between four and five fractions per week treatment schedules. A ret dose of approximately 1800 appears somewhat low for optimal control rates in T1 and T2 tumors.

ZUSAMMENFASSUNG

Sechzig Patienten mit einem lokalisierten Schuppenzellkarzinom des Stimmbands ohne Metastasen wurden mit vier Fraktionen wöchentlich behandelt. Es traten keine schwerwiegenden Komplikationen bei dem verwendeten Dosierungs- und Fraktionierungsschema auf. Die Qualität der Stimme war nach der Bestrahlung zufriedenstellend. Nach einer Nachuntersuchungsperiode von wenigstens zwei Jahren waren die Kontrollraten für T1 and T2 Tumoren 80% bzw. 81,5%. Alle Versager bei der Strahlentherapie wurden chirurgisch geheilt. Es wurde eine Dosisresponskurve für T1 Schäden unter Verwendung der Ellis'schen Formel aufgestellt, um die NSD von Daten der verschiedenen therapeutischen Zentra herzuleiten. Keine Unterschiede für die untersuchten Parameter zwischen dem vier-mal und fünf-mal wöchentlichen Behandlungsschema scheinen vorzuliegen. Eine ret-Dosis von etwa 1 800 erscheint etwas niedrig für optimale Kontrollraten bei T1 und T2 Tumoren.

RÉSUMÉ

Soixante malades atteints de carcinome épidermoïde localisé de la corde vocale sans atteinte lymphatique ou métastatique ont été traités par quatre fractions par semaine. La dose et le fractionnement décrits n'ont pas entraînés de complications sérieuses. La qualité de la voix après traitement a été satisfaisante. Après un minimum d'observations de deux ans, les taux de guérison pour les tumeurs T1 et T2 sont respectivement de 80 et 81,5%. Tous les échecs du traitement par les radiations ont été guéris chirurgicalement. Les auteurs ont établi une courbe de réponses en fonction de la dose pour les lésions T1 utilisant la formule d'Ellis pour en déduire la NSD, à partir de données provenant de différents centres de traitement. Ils concluent qu'il n'y a pas de différences dans les paramètres étudiés entre les schémas de traitement hebdomadaire par quatre et cinq fractions. Une dose ret d'environ 1 800 parait un peu faible pour un taux de guérison optimale des tumeurs T1 et T2.

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