Early Glottic Carcinoma : An Analysis of Dose-time-volume Factors Affecting Radiation Failure and Late Complications

Makoto Kondo, Shozo Hashimoto, Takushi Dokiya, Hiroshi Miyamoto, Yasushi Murakami*, Shigeji Saito* and Hisao Yamashita
From the Departments of Radiology and * Otorhinolaryngology
Keio University School of Medicine

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早期声門癌：放射線治療後の再発と晩発障害に影響を及ぼす因子の解析

慶応義塾大学医学部放射線医学教室
*慶応義塾大学医学部耳鼻咽喉科学教室
近藤　誠　橋本　省三　土器屋卓志　宮本　宏
村上　泰*　斉藤　成司*　山下　久雄

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110例のT1NOMO，T2NOMO声門癌症例を6 MV Linac X線により治療し，2年以上経過観察を行なった．19例に再発を見，4例に喉頭壊死，1例に高度の浮腫が生じた．T stage毎の再発率の差は有意ではなかった．総線量・TDF factorの違いも再発率に影響を与えなかった．T1症例では25cm²以下の照射野で治療された群に再発が多い傾向が見られた．副障害は1回3Gy以上の大分割線量を4回以上照射した群に有意に多かった．本研究結果と文献により，至適治療線量・照射野の大きさについて考察を加えた．

In the previous report (1), we showed that the prognosis of early glottic carcinoma treated with radiation alone in Japan was not different from that in the White. This study provides a detailed analysis of factors affecting the outcome of early glottic carcinoma, including total dose, time-dose-fractionation (TDF) factor and target volume.

Materials and Methods

1969 through 1979, 113 patients with early glottic carcinoma were treated with radiation alone. A minimum follow-up period was two years. All but one patient were not lost to follow-up. The patient who was lost to follow-up after a two-year period of no evidence of disease was excluded from this study. Also excluded were two cases with borderline histology and carcinoma in situ. The remaining 110 patients were staged according to 1978 UICC Cancer Staging System (2) : 65 were Tla, 14 Tlb, and 31 T2. All were NOMO. 106 patients were male and four female. Histological diagnosis was squamous cell carcinoma in all cases.

All patients were treated by 6 MV linear accelerator x-ray with opposing lateral fields. A field size

Table 1　Age vs. relapse

Age	No. of patients	Relapse (%)
≤59	36	8(22)
60≤, ≤69	42	9(21)
70≤	32	2(6)

Table 2　Total dose vs. relapse

Total dose (Gy)	Conventional Fr.#	Large Fr.@
30—39	4(1)	—
40—49	2	—
50—54	7	1
55—59	—	1
60—64	51(9)	11(2)
65—69	8(1)	1
70—79	14(3)	3(1)
80≤	6(1)	1(1)
Total	92(15)	18(4)

Number in parenthesis is of relapses.
#: Treated with a small fraction size of 2 Gy alone.
@: Treated with a large fraction size of 3 Gy or more, with or without conventional fractionation.

Table 3　TDF factor vs. relapse

TDF factor	Conventional Fr.#	Large Fr.@
51— 60	3(1)	—
61— 70	2	—
71— 80	1	—
81— 90	6	—
91—100	23(4)	1
101—110	32(4)	6
111—120	19(5)	5(2)
121—130	—	3(1)
131—140	6(1)	1
141—150	—	1
151—160	—	1(1)
Total	92(15)	18(4)

Number in parenthesis is of relapses.
#: Treated with a small fraction size of 2 Gy alone.
@: Treated with a large fraction size of 3 Gy or more, with or without conventional fractionation.

Table 4　Field size vs. relapse

Area (cm^2)	No. of patients	No. of relapses (%)
T1		
≤25	64	14(22)
26≤	15	1(7)
T2		
≤36	17	2(12)
37≤	14	2(14)

for T1 tumor ranged from 4×4 to 6×6cm in most cases, and was somewhat larger for T2 tumor. One field was treated a day alternatively. For most cases, a 30°wedge filter was used. 2 Gy was delivered 6 times per week for most cases. In order to reduce the number of patient's visits, asked by the patient, a large fraction size of 3 Gy or more was used, 4 to 20 times during treatment, 3 times a week with or without conventional fractionation for 18 patients. Some patients had rest period(s) during treatment due to acute reaction or as initially planned. TDF factor was calculated for each patient (3.4).

Results

Relapse was seen in 19 patients : 11 in T1a cases, four in T1b and four in T2. All but one patient had primary failure with or without nodal and/or distant failures. The other patient had nodal failure at the first echelon of lymph nodes just outside the radiation fields ; since this metastasis might have been prevented by rather larger fields, we handled this case like primary failure one. Since there are no statistically significant differences of the relapse rates according to T stages, all patients are combined for the purpose of analyzing factors affecting relapse and complication.

Age may be a prognostic factor. The patients who were 70 years old or greater showed a lower relapse rate than the younger patients, although the difference is not statistically significant ($0.05<p<0.1$) (Table 1). The mean and median follow-up periods were comparable in both groups.

Total dose, TDF factor and the use of a large fraction size did not influence the relapse rates (Table 2 and 3). Field sizes more than $25cm^2$ showed a lower relapse rate for T1 lesions than field sizes of $25cm^2$ or less, although not statistically significant (Table 4). The relapse rates for T2 lesions were not different according to field size.

Table 5 A list of those having large fraction sizes of 3 Gy or more during their treatment

No.	T stage	Total dose (Gy)	Large fractions (3x/w) Size (Gy)	No.	No. of fractions of 2 Gy (6x/w)	Overall time (days)	TDF factor	Area (cm^2)	Follow-up
1	1a	61.5	3.5	5	22	38	110	26	Necrosis, Laryngectomy
2	1a	71	3.5	14	11	45	138	22	NED@
3	1a	60	3	20	—	46	113	24	Relapse, Salvaged
4	1a	60	3.5	16	2	49	120	18	NED
5	1a	56	3.5	16	—	37	115	19	Edema
6	1a	60	3	4	24	48	102	33	NED
7	1a	60	3	4	24	43	104	25	NED
8	1a	60	3	6	21	40	104	26	Necrosis, Laryngectomy
9	1a	60	3	12	12	58	104	27	NED
10	1a	84	3	20	12	51	154	48	Relapse, Dead
11	1a	52.5	3.5	7	14	31	97	15	NED
12	1b	60	3.5	12	—	41	120	23	Relapse, Salvaged
			3	6					
13	1b	60	3	20	—	47	113	23	NED
14	1b	70	3	6	26	48	122	23	DOI#
15	2	69.2	3.4	8	5	42	143	29	Necrosis, Laryngectomy
			4	8					
16	2	63	3	5	24	54	109	48	NED
17	2	70	3.5	8	21	61	125	33	Relapse, Dead
18	2	61.5	3.5	13	8	39	125	23	DOI

@ No evidence of disease. # Dead of intercurrent disease.

Table 6 Major chronic complications vs. field size

Area (cm^2)	Conventional Fr.	Large Fr.
≤25	64(1)@	10(1)#
26≤, ≤36	15	6(3)@
37≤	13	2
Total	92(1)	17(4)

Edema
@ Laryngeal necrosis

There were five cases with major chronic complications. Four patients had laryngeal necrosis: three patients eventually needed total laryngectomy, and the other patient underwent arytenoidectomy. One patient had persistent edema of the arytenoids, and received biopsy twice in order to rule out recurrence. Of the five cases with complications, four were in the group which had large fraction sizes during the treatment (Table 5). The other patient with arytenoidectomy received 52 Gy in 26 fractions over 32 days for Tlb disease. The difference of the complication rates between the group with conventional fractionation (1/92) and the group with large fractionation (4/18) is highly statistically significant ($p<0.001$). The difference is also statistically significant ($p<0.025$), when comparing only the incidence of laryngeal necrosis (1/92 vs. 3/18). Field size may be a factor affecting the complication rates (Table 6).

Discussion

Radiotherapy alone has been accepted as the treatment of choice for TINOMO and T2NOMO glottic carcinoma. Our results showed several important points for planning radiotherapy schedules. Firstly, total doses and TDF factors used in this study did not affect tumor control probability for T1 and T2 lesions. One of two T1 lesions, and one T2 lesion were controlled by only 30 Gy, while even 84 Gy failed to control one T1 lesion. Probably, the plateau of the sigmoid response curve has been

reached at the relatively low dose, and the tumor control probabilities of 85-90% for T1 lesions and about 70% for T2 lesions may not be raised by increasing doses (5-7). Most authors recommend doses of 60-70 Gy for early glottic carcinoma. We feel that even lower doses are sufficient for T1 lesions. However, since the shape of the dose response curve at the lower dose level are not fully elicited, and considering almost no existence of chronic major complications with conventaional fractination schemes, the use of 60 Gy or more for T1 lesions may be justified (507).

An optimal dose level for T2 lesions needs to be evaluated further. The tumor control probability for T2 lesions with normal mobility was higher than for T2 lesions with imparied mobility (7). Our results(1) showed the same tendency with no statistically significant difference which may be due to the small number of the patients. Harwood et al. found that the tumor control probability for T2 lesions with or without normal mobility was higher in the group receiving a nominal standard dose (NSD) of 1650 ret or more than in the group receiving less than 1650 ret (7). The tumor control probability for T2 lesions with normal mobility is almost identical with that for T1 lesions (1,7,8), suggesting that the superficial tumor spread is not a poor prognostic factor. For T2 lesions with or without normal mobility, 60-70 Gy in 30-35 fractions seems sufficient.

Field size is probably a more critical factor than dose for controlling early glottic carcinoma. For T1 lesions, field sizes of 26cm² or greater yielded a higher local control rate than those of 25cm² or less (6). Similarly, for T2 lesions with normal mobility, field sizes of 36cm² or greater produced a higher local control rate than those of 35cm² or less (7). For T1 lesions, we found the similar tendency that field sizes of 26cm² or more had the lower local recurrence rate than those of 25cm² or less. Since only one of 21 T2 lesions with normal mobility had local recurrence in this study, the influence of field size for these lesions could not be ascertained. We recommend, however, a field size of 5×5cm or more for T1 lesions ; and a field size of 6×6 to 6×8cm for T2 lesions which will inculude the first echelon of lymph nodes as well, for up to 45-50 Gy may be advantageous.

Major chronic complications can be avoided. Most of the patients with major chronic complications were treated with excessive doses, too rapid a dose rate and/or overly large irradiated portals (5, 8,9). From our results, the usage of large fraction sizes may be added to the list of the causative factors of major chronic complications. Host factors may also be important, since one patient developed cartilage necrosis after receiving only 52 Gy in 26 fractions with a field size of 18cm² although he retained a voice after resection of the cartilage. The presence of diabetes mellitus and/or hypertention produces a significant risk of major chronic complications (9).

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