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**CLINICAL INVESTIGATION** **Head and Neck**

# RADIOTHERAPY FOR EARLY GLOTTIC CARCINOMA (T1N0M0): RESULTS OF PROSPECTIVE RANDOMIZED STUDY OF RADIATION FRACTION SIZE AND OVERALL TREATMENT TIME

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**Purpose: To investigate in a prospective randomized study the effect of radiation fraction size and overall treatment time on the local control of early glottic carcinoma.**

**Methods and Materials: Between December 1993 and December 2001, 180 patients with early glottic carcinoma (T1N0M0) were treated at our department. The patients were randomly allocated to either treatment arm A (radiation fraction size 2 Gy, $n = 89$) or B (2.25 Gy, $n = 91$). The total radiation dose administered was 60 Gy in 30 fraction within 6 weeks for minimal tumors (two-thirds of the vocal cord or less) or 66 Gy in 33 fractions in 6.6 weeks for larger than minimal tumors (more than two-thirds of the vocal cord) in Arm A and 56.25 Gy in 25 fractions within 5 weeks for minimal tumor or 63 Gy in 28 fractions within 5.6 weeks for larger than minimal tumors in Arm B.**

**Results: The 5-year local control rate was 77% for Arm A and 92% for Arm B ($p = 0.004$). The corresponding 5-year cause-specific survival rates were 97% and 100% (no significant difference). No significant differences were found between these two arms in terms of rates of acute mucosal reaction, skin reactions, or chronic adverse reactions.**

**Conclusion: Use of 2.25-Gy fractions with a shorter overall treatment time for Arm B showed superior local control compared with conventional use of 2-Gy fractions for Arm A without adverse reactions from the greater fraction.** 

**Early glottic carcinoma, Fraction size, Overall treatment time.**

## INTRODUCTION

Glottic carcinoma is a common head-and-neck malignancy and accounts for a small percentage of all cancers. Radiotherapy has the advantage of preserving voice quality in most patients and is, therefore, the treatment of choice for early-stage glottic carcinoma. Highly successful local control rates with radiotherapy ranging from 80% to 95% for T1 lesions have been reported. Several institutes have reported ≥90% local control rates using 2.1–2.25 Gy/fraction with a shorter overall treatment time (1, 2). These results were superior to those previously reported by us when we used 2 Gy/fraction (3). Although the importance of overall treatment time, fraction size, and total dose has been documented at many institutions since the 1970s (1, 2, 4–8), no randomized study has been reported to date. To identify the affect of fraction size and overall treatment time in a randomized prospective manner, we compared local control for two fractionation regimens of 2 Gy and 2.25 Gy.

## METHODS AND MATERIALS

Between December 1993 and December 2001, 189 patients with invasive, previously untreated, T1 squamous cell carcinoma of the true vocal cords were enrolled in this trial with curative intent at the Department of Radiation Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases.

Nine patients were excluded from analysis for several reasons. Three were excluded because of machine trouble when 6-MV instead of 4-MV X-rays were used. Another three were excluded because of treatment interruption (one because of newly diagnosed lung cancer, one because of deterioration of general condition, and one at the patient's insistence). The last three were excluded from analysis because of errors in dose administration. The data of the remaining 180 patients were subjected to additional analysis. Pa-

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Table 1. Patient allocation to Arm A and B

| Arm | Tumor length <2/3 of glottis | Tumor length ≥2/3 of glottis |
|---|---|---|
| Arm A (2 Gy/fr) | | |
| A-1 ($n$ = 31) | 60 Gy/30 fr/6 wk | |
| A-2 ($n$ = 57) | | 66 Gy/33 fr/6.6 wk |
| Arm B (2.25 Gy/fr) | | |
| B-1 ($n$ = 31) | 56.25 Gy/25 fr/5 wk | |
| B-2 ($n$ = 61) | | 63 Gy/28 fr/5.6 wk |

tients were randomly allocated to treatment arm A (2 Gy/fraction) or B (2.25 Gy/fraction). Stage was determined according to the UICC TNM classification (4th edition, 1992). Of the 180 patients (170 men and 10 women), 144 had Stage T1a and 36 had Stage T1b. The mean patient age was 65 years (range, 26–86 years). All patients were treated in the supine position with 4-MV X-rays using bilateral parallel opposed fields and an individualized wedge-filtered technique for better dose distribution. A Styrofoam head holder and a shell made of polyisopropylene for immobilization were used during treatment. Minimal tumor was defined as tumor with a length two-thirds or less that of the ipsilateral or bilateral vocal cords. A tumor with a length more than two-thirds of a vocal cord was classified as a larger than minimal tumor (Table 1).

For minimal tumors, 60 Gy in 30 fractions within 6 weeks (Arm A-1, biologically effective dose with $\alpha/\beta = 3$ [$BED_3$] of 100) was adopted as the conventional schedule and 56.25 Gy in 25 fractions within 5 weeks (Arm B-1, $BED_3$ of 98.4) for the 2.25-Gy arm. For larger than minimal tumors, 66 Gy in 33 fractions within 6.6 weeks (Arm A-2, $BED_3$ of 110) was used for the 2-Gy/fraction arm and

Table 2. Patient and tumor characteristics by treatment arm

| Characteristic | Arm A (2 Gy/fr; $n$ = 88) | Arm B (2.25 Gy/fr; $n$ = 92) | $p$ |
|---|---|---|---|
| Gender ($n$) | | | NS |
| Male | 85 (97) | 85 (92) | |
| Female | 3 (3) | 7 (8) | |
| Age (y) | 64 ± 9 | 65 ± 10 | NS |
| Smoking ($n$) | | | NS |
| Yes | 82 (93) | 83 (90) | |
| No | 6 (7) | 9 (10) | |
| Stage | | | NS |
| T1a | 71 (81) | 73 (79) | |
| T1b | 17 (19) | 19 (21) | |
| Tumor type ($n$) | | | NS |
| Superficial | 42 (48) | 45 (49) | |
| Exophytic | 45 (51) | 46 (50) | |
| Ulcerative | 1 (1) | 1 (1) | |
| Anterior commissure involvement ($n$) | | | NS |
| Yes | 12 (14) | 14 (15) | |
| No | 76 (86) | 78 (85) | |
| Field size | | | NS |
| 4*5 | (0) | 1 (1) | |
| 5*5 | 67 (76) | 71 (77) | |
| 5*6 | 9 (10) | 5 (5) | |
| 6*5 | 6 (7) | 8 (9) | |
| 6*6 | 6 (7) | 7 (8) | |
| Histologic grade ($n$) | | | NS |
| NOS | 35 (40) | 36 (39) | |
| Well | 35 (40) | 46 (50) | |
| Moderate | 18 (20) | 9 (10) | |
| Undifferentiated | 0 (0) | 1 (1) | |
| Additional fraction | 7 (2)* | 7 (2)* | NS |
| Local control ($n$) | | | 0.02 |
| Yes | 70 (80) | 85 (92) | |
| Failure | 18 (20) | 7 (8) | |
| Salvage surgery ($n$) | | | NS |
| Partial laryngectomy† | 13 (72) | 4 (57) | |
| Total laryngectomy | 4 (22) | 2 (29) | |
| Refusal to further treatment | 1 (6) | 1 (14) | |

Data in parentheses are percentages.

*Abbreviation:* NOS = not otherwise specified.

* Additional fraction: one or two additional fractions were added if physisian thought residual tumor was present at examination; number of local failure after additional fraction depicted in parentheses.

† One patient required trachostomy and 1 patient developed granulation that made clear phonation difficult.

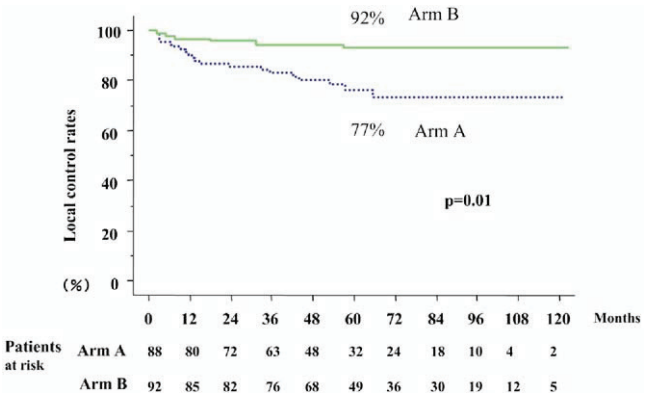


Fig. 1. Local control rates between Arms A and B.

63 Gy in 28 fractions within 5.6 weeks (Arm B-2, $BED_3$ of 110) for the 2.25-Gy/fraction arm. The dose was prescribed at the isocenter, and all patients received the scheduled dose. The BED was calculated using $\alpha/\beta = 3$ for chronic reaction $BED_3$ in the equation: BED = total dose × [1 + fraction dose/($\alpha/\beta$)]. In addition, the BED corrected for overall treatment time (cBED) was determined by the equation: cBED = $BED_{2\ Gy} - 0.6 \times$ (overall time − $T_{lag}$), where $T_{lag}$ is the assumed lag period of 28 days for a burst of accelerated repopulation of tumor clonogenic cells to occur, 0.6 is the rate of dosage loss in 2-Gy fractions, and $BED_{2\ Gy}$ is the (number of fractions) × (fraction doses) × ($\alpha/\beta$ + fraction doses)/($\alpha/\beta$ + 2). An $\alpha/\beta$ of 10 Gy for each tumor was used in the cBED calculation.

Tumor types were classified into three categories: superficial, exophytic, and ulcerative. Patients were followed for at least 24 months or until death, with a median follow-up of 64 months (range, 24–122 months). The patient characteristics are shown in Table 2. No significant differences were found between Arms A and B.

All patients provided written informed consent. The departmental review board approved concept of this treatment because no institutional review board had been established at our institution in 1993. Local control and survival probability were calculated using the Kaplan-Meier method and compared using the log–rank test. Multivariate analysis was performed using Cox's proportional hazard model. Age (≤64 vs. ≥65 years), gender, hemoglobin level (≤13.9 vs. ≥14 g/dL), treatment arm (A vs. B), tumor type (superficial vs. exophytic and ulcerative), anterior commissure involvement (yes vs. no), and T stage (T1a vs. T1b) were included as covariables. Because of the very close correlation between overall treatment time and treatment arm, we excluded the covariant overall treatment time from the multivariate analysis. Statistical significance was tested by Student's *t* test, log–rank test, or chi-square test. All analyses used the conventional $p < 0.05$ level of significance.

## RESULTS

### *Local control and voice preservation*

The 5-year local control rate for the entire group was 86% (T1a, 83%; T1b, 91%; difference not significant), and the 5-year local control rates after radiotherapy were 76% for Arm A-1, 78% for Arm A-2, 91% for Arm B-1, and 92% for Arm B-2 ($p = 0.02$). A significant difference was found in local control between Arm A (77% at 5 years; 95% confidence interval, 67–87%) and Arm B (92%; 95% confidence interval, 86–98%; $p = 0.004$; Fig. 1). Of the 180 patients, 25 had local treatment failure (Table 2), but no regional or distant metastasis was detected before local failure. Of these 25 patients, 23 were salvaged by surgery, 17 of them by partial laryngectomy and 6 by total laryngectomy; 2 patients refused further treatment. One patient developed recurrence after total laryngectomy, not only at the primary site, but also lymph node and lung metastases that resulted in death; thus, resulting in an ultimate local control rate of 98% (177 of 180). After partial laryngectomy, 1 patient required tracheotomy, and another showed granulation that made clear phonation difficult, so that tumor control with voice preservation was attained for 170 patients (94%). Univariate analysis showed that only the treatment arm had a significant influence on local control (Table 3).

After multivariate analysis using Cox's proportional hazard model, the difference in favor of Arm B remained

Table 3. Univariate analysis of prognostic factors for local control

| Variable | Local control | |
|---|---|---|
| | Yes ($n$ = 155) | No ($n$ = 25) |
| Age (y) | 64 ± 9 | 65 ± 8 |
| Gender ($n$) | | |
| Male | 146 (86) | 24 |
| Female | 9 (90) | 1 |
| Hemoglobin (g/dL) | 14.2 ± 1.3 | 14.2 ± 1.0 |
| Arm A-1 + B-1 vs. A-2 + B-2 ($n$) | | |
| A-1 + B-1 | 53 (85) | 9 |
| A-2 + B-2 | 102 (86) | 16 |
| Fields | | |
| 4*5 | 1 (100) | |
| 5*5 | 120 (87) | 18 |
| 5*6 | 9 (64) | 5 |
| 6*5 | 13 (93) | 1 |
| 6*6 | 12 (92) | 1 |
| Tumor type | | |
| Superficial | 75 (86) | 12 |
| Exophytic | 79 (87) | 12 |
| Ulcerative | 1 (50) | 1 |
| Tobacco smoking | | |
| Yes | 143 (87) | 22 |
| No | 12 (80) | 3 |
| Differentiation | | |
| NOS | 59 (83) | 12 |
| Well | 70 (86) | 11 |
| Moderate | 25 (93) | 2 |
| Undifferentiated | 1 (100) | |
| Anterior commissure imvolvement | | |
| No | 135 (86) | 22 |
| Yes | 22 (85) | 4 |
| T stage | | |
| T1a | 122 (85) | 22 |
| T1b | 33 (92) | 3 |

*Abbreviation*: NOS = not otherwise specified.
Data in parentheses are percentages with local control.
No differences were statistically significant.

Table 4. Multivariate analysis of prognostic factors for local control

| Variable | Strata | Odds ratio | 95% CI | *p* |
|---|---|---|---|---|
| Arm | A vs. B | 3.38 | 1.31–8.66 | 0.003 |
| Age (y) | ≤64 vs. ≥65 | 0.62 | 0.26–1.47 | 0.61 |
| Gender | Male vs. female | 0.65 | 0.06–6.92 | 0.72 |
| Hemoglobin (g/dL) | ≤14 vs. ≥14.1 | 0.97 | 0.41–2.36 | 0.97 |
| Type of tumor | Superficial vs. exophytic + ulcerative | 0.77 | 0.34–1.79 | 0.77 |
| Tobacco smoking | Yes vs. no | 2.25 | 0.55–8.87 | 0.26 |
| Anterior commissure involvement | Yes vs. no | 0.25 | 0.04–1.29 | 0.25 |
| T stage | T1a vs. T1b | 5.02 | 0.84–30.1 | 0.07 |

*Abbreviation:* CI = confidence interval.

significant ($p = 0.003$), with an odds ratio of 3.38 (95% confidence interval, 1.31 to 8.66; Table 4).

The calculated cBED was 53.4 ± 3.05 Gy (average ± standard deviation) for Arm A and 55.9 ± 3.4 Gy for Arm B ($p < 0.0001$).

*Survival and second primary cancers*

The 5-year overall survival rate was 88%, without any significant difference between the two arms (87% for Arm A, 88% for Arm B). Two patients died of laryngeal caner (Arms A-1 and A-2), and 1 patient survived with recurrent tumor (Arm B-2). Of these 3 patients, 2 refused salvage surgery, and the disease of 1 patient could not be controlled owing to lymph node and lung metastases, as mentioned previously. The 5-year cause-specific survival rates were 98% for Arm A and 100% for Arm B (no significant difference). Of the 180 patients, 45 (25%) developed 54 second or third malignancies (Table 5). Nineteen patients died of either intercurrent disease ($n = 9$) or a second primary tumor ($n = 10$).

*Complications*

Acute complications were assessed in terms of skin and mucosal reactions (Table 6). Skin complications such as moist desquamation were not observed in either arm. Diffuse coating and/or edema of the vocal cords was recognized in 10 patients (11%) in Arm A and 9 (10%) in Arm B. Minor chronic complications such as persistent arytenoid edema lasting >6 months or benign polypoid lesions of the vocal cords were detected in 9 patients (10%) in Arm A and 6 patients (7%) in Arm B (Table 6). No severe late complications were observed. The differences in complication rates between Arms A and B were not significant.

## DISCUSSION

Radiotherapy is the standard treatment, with excellent local control rates for early glottic cancer. Several important prognostic factors have been examined, including anterior commissure involvement, beam energy, field size, daily fraction size, total dose, overall treatment time, male gender, poor histologic differentiation, and low pretreatment hemoglobin level (9). Of all these factors, we found that in our study only the treatment arm, which represented both overall treatment time and daily fraction size, was a significant prognostic factor for local control.

Fraction doses and overall treatment time correlated so closely that it was difficult to determine which was the dominant factor. Several previous studies have confirmed the importance of fraction size for local control. Kok (10) treated Stage T1 larynx cancer with 6300 cGy using fraction sizes of 175, 190, and 210 cGy (10). The 175-cGy arm was discontinued when local control was obtained for only 1 of 3 patients compared with 12 (86%) of 14 patients treated with 190-cGy fractions and 4 (100%) of 4 patients treated with 210-cGy fractions. Mendenhall *et al.* (9) reported a local control rate of 100% when carefully selected patients with tumors limited to one vocal cord and measuring 5–15 mm were treated with similar total doses of 6100–6700 cGy in 225-cGy fractions. In contrast, the local control rate was only 80% for patients treated with 200–220-cGy fractions (11).

However, these results were simultaneously affected by the overall treatment time and could thus not reflect the importance of fraction size only. Regarding overall treatment time, several institutions, including ours, have reported that prolongation of the overall treatment time appeared to be an important factor in the reduction of local control (1, 2, 4–9). Rudoltz *et al.* (4) conducted a retrospective analysis and found that for patients treated with <200 cGy/fraction, the local control rate was 62% compared with 87% for those treated with ≥200 cGy/fraction ($p = 0.006$). The local control rate was 100% if treatment was completed within 42 days, 91% if within 43–46 days, 74% if within

Table 5. Second malignancy

| Cancer site | *n* (%) |
|---|---|
| Stomach | 10 (21) |
| Head-neck | 9 (19) |
| Esophagus | 9 (19) |
| Lung | 9 (19) |
| Colon | 7 (15) |
| Urologic cancer | 6 (13) |
| Other | 4 (8) |

Nine patients had triple cancer.

Table 6. Adverse reactions

| Adverse reaction | Arm A ($n$ = 88) | Arm B ($n$ = 92) |
|---|---|---|
| Acute skin reaction | | |
| None | 19 (28) | 13 (14) |
| Erythema | 43 (63) | 76 (83) |
| Dry desquamation | 6 (9) | 3 (3) |
| Moist desquamation | 0 | 0 |
| Confluent moist dequamation with pain | 0 | 0 |
| Acute mucosal reaction | | |
| None | 3 (3) | 2 (2) |
| Hyperemic | 29 (33) | 25 (27) |
| Pathy coating | 46 (52) | 56 (61) |
| Diffuse coating | 8 (9) | 7 (8) |
| Edema | 2 (2) | 2 (2) |
| Chronic reaction | | |
| No | 79 (90) | 86 (93) |
| Yes | 9 (10) | 6 (7) |

Data in parentheses are percentages.
Chronic reactions: persistent arytenoid edema lasting >6 mo or benign polypoid lesion of vocal cord.

47–50 days, 65% if 51–54 days, and 50% if 55–66 days ($p$ = 0.001) (4). Univariate analysis showed that both fraction size and days elapsed had a significant impact on local control. Finally, multivariate analysis indicated that the elapsed treatment time was the only variable affecting local control. These authors, therefore, concluded that the number of treatment days was the most statistically significant factor in local control for patients with Stage T1 squamous cell carcinoma of the glottis. Similar results were obtained in studies by several other institutions (5, 12).

Our scheduled doses were adjusted with $BED_3$, calculated using $\alpha/\beta = 3$, which represents chronic reactions. $BED_{10}$, which represents tumor behavior without taking repopulation of tumor cells into account, was greater for Arm A (Arm A-1, $BED_{10} = 72$; Arm A-2, $BED_{10} = 79.2$) than for Arm B (Arm B-1, $BED_{10} = 68.9$; Arm B-2, $BED_{10} = 77.2$). Our finding that Arm B showed superior results to Arm A could thus not be explained by this $BED_{10}$ equation. This means that the three factors ($\alpha/\beta$, total dose, and fraction dose) did not suffice as determinants of clinical outcome. In view of the findings of several clinical studies (5, 12), we took overall treatment time and repopulation of tumor cells into consideration when calculating the cBED. The cBED was 57.4 ± 2.2 Gy for Arm B-2 and 52.9 ± 3.3 Gy for Arm B-1, greater than the 54.5 ± 3.0 Gy for Arm A-2 and 51.3 ± 1.7 Gy for Arm A-1. Our clinical data could thus be explained with the cBED equations, which take the repopulation of tumor cells after a lag time into account. Therefore, the number of elapsed days is an important and dominant factor that can explain the difference in local control between Arms A and B. However, cBED in its present form does not completely explain our results (i.e., the difference in cBED between 52.9 Gy for Arm B-1 and 51.3 Gy for Arm A-1 does not seem large enough to explain the significant difference in local control).

Although the greater single dose reduced the number of treatment days, it could also lead to an increase in adverse events, especially in the late phase. It became clear that, although the treatment using ≥3-Gy fractionation was successful in terms of local control, because of the shorter overall treatment time, it was accompanied by an unacceptably high level of severe complications. Harwood and Tierie (13) reported greater complication rates for a group of patients treated with a larger dose per fraction (i.e., 62 Gy in 20 fractions within 4 weeks) compared with a group of patients treated with a lower dose per fraction (55 Gy in 24–26 fractions within 5 weeks). Randall *et al.* (14) found 10% of cases developed severe edema and 29% complications after salvage operation followed by a 333-cGy regimen in three weekly fractions to a total dose of 60 Gy in 6 weeks. van der Voet *et al.* (5) reported Grade 3 and 4 complication rates of >10% during a 15-year follow-up period if ≥3 Gy/fraction was used. Therefore, the feasibility of such a comparatively high-dose fractionation using ≥3 Gy should be carefully tested before it can become widely accepted.

The harmful effects of the larger doses per fraction used in hypofractionated schedules can be compensated for by delivering a lower total dose in this situation, and the gain made in reducing the overall time compensates for the small reduction in total dose administered. The experience of the continuous hyperfractionated radiotherapy (CHART) trial deserves mention in this context. Overgaard *et al.* (15) reported an overall 5-year locoregional control rate of 70% and 60% for the six-fraction and five-fraction per week groups, respectively ($p$ = 0.0005). Their median overall treatment time was 39 days in the six-fraction group and 46 days in the five-fraction group. These figures concur with ours: the treatment days numbered 46.2 ± 5.0 days for Arm A and 38.7 ± 4.7 days for Arm B. These results imply that the important threshold of elapsed days was around 40–45 days. Again, with the schedules used in our trial, the gain

from the reduction in overall time exceeded the loss resulting from a reduction in the total dose.

In addition, from the point of view of health economics, the hypofractionated schedule can be expected to win out over the conventional schedule, because the shorter overall treatment time achieved with the hypofractionation scheme reduces the socioeconomic burden, not only for patients but also for radiotherapeutic institutions. Patients benefit from the reduced costs and treatment time. This would enable radiotherapeutic institutions to maintain the mechanical and human resources required to meet the increasing demand for radiotherapy.

Because of the principle of randomized phase III trials known as the "intention to treat," we were tempted to include the 9 patients who were excluded from analysis. However, their treatment did not meet the criteria for this trial in terms of beam energy, fraction dose, or overall treatment time. We considered that their exclusion did not influence our results for either local control or adverse reactions.

The 2.25-Gy fractionation used in our trial has been widely employed and reported by several institutions (1, 2, 8) to be safe and effective. However, because we were unable to find any randomized studies, ours is the first prospective randomized trial to confirm that a greater daily fraction dose and shorter overall treatment time improve local control of Stage T1 glottic carcinoma. For this schedule to be accepted as standard treatment, however, a multiinstitutional prospective randomized trial is essential.

## CONCLUSION

The 2.25-Gy/fraction scheme with a shorter overall treatment time is superior to 2 Gy/fraction for local control of Stage T1 glottic carcinoma.

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