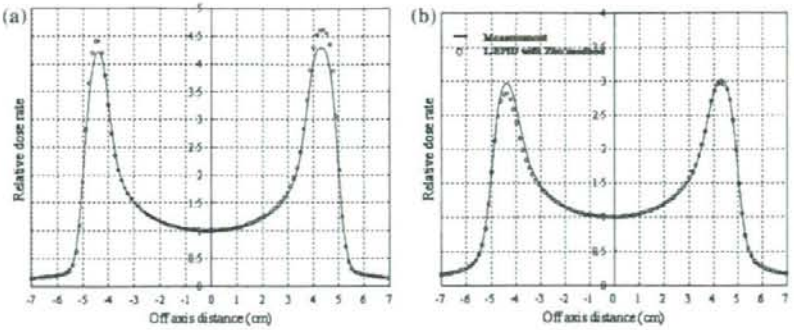

Fig. 6 Comparison of the off-center ratio of the transmission dose of the cylindrical piece of lead between the L-EPID dose rates obtained from Zhu's method [16] and the dose in the RK chamber at an SSD of 100 cm, for a field size of 10 cm × 10 cm, and the maximum depth for 4-MV X-rays (**a**) and 10-MV X-rays (**b**)

because the dose gradient surrounding the central axis is steep. For the 4-MV X-rays (a), the difference between the L-EPID measurement and the measurement with the RK chamber was, at the maximum, less than approximately 1%, and the distributions obtained from the two measurements showed good agreement.

On the other hand, (b) the dose away from the central axis from −1 to −5.5 cm for the 10-MV X-rays was increased approximately 2% over the central dose.

4 Discussion

Throughout the examination and theoretical study of the dosimetric properties of the L-EPID, we have discussed the use of this device as a dosimeter for clinical applications [9]. In this study, on the basis of our previous report, we performed the dose verification in model examples by using the L-EPID. From the results presented, the dose profiles obtained from dosimetry by use of the L-EPID showed good agreement with the conventional measurement that was provided by use of an ionization chamber and a water phantom system (Fig. 2b). In this study, the precision of the dose distribution was improved as compared to the results reported by Zhu et al. [16] and Curtin-Savard and Podgorsak [18], because the FFC in our study was different from that in their reports. In particular, the utility of the FFC was confirmed from the good agreement at the "shoulder" parts of the dose profile curves (Fig. 2b).

For a more objective evaluation, the physical characteristics of a field, such as the symmetry, flatness, and penumbra, were compared, and subsequently good agreement was observed between the L-EPID and the measured doses (Table 1). In the dose verification for an irregular field (Fig. 3), the maximum differences were approximately 8% for 4-MV X-rays and approximately 5% for 10-MV X-rays. These large discrepancies were observed in the steep-dose-gradient regions. The same tendency was observed in the dose verification of Model 1 (Fig. 4). We believed that these discrepancies were affected by the difference of mechanical shape between the L-EPID and the RK chamber.

With respect to the dose distribution in the high-dose-gradient region, Low et al. [19] and Cheng et al. [20] reported that the distance-to-agreement (DTA) is more important than the differences between the measured and the calculated doses obtained from the TPS. The DTA is the distance between measured data points and the nearest point in the calculated dose distribution that exhibits the same dose. In their reports, the measured dose and that calculated from the TPS were used; however, it is believed that the concept of DTA can be adapted in the verification of the measured doses obtained from different measuring instruments. Therefore, we evaluated the DTA between an L-EPID dose and the measured dose with a water phantom-ionization chamber system. The DTA was less than ±1 mm in both the rectangular and irregular fields of this study. Low et al. [19] stated that the permitted value of DTA was less than 3 mm. From their report, it appears that our results are satisfactory. Even for Model 2 (Fig. 5), which is similar to a clinical situation, the DTA evaluation showed good results for both the 4-MV X-rays and 10-MV X-rays.

From these results, it is believed that the L-EPID is very useful for dose evaluation of an irregular field and for verification of the transmission dose. However, the sensitivity of the L-EPID is accompanied by a time sensitivity change. Moreover, approximately 5% of the difference in the calculated dose occurs corresponding to a sensitivity change of 1% in the L-EPID [9]. Although Zhu et al. [16] reported that the sensitivity change of the L-EPID over time showed a maximum value of 3% in the sensitivity during 90-day period and that the change in the daily sensitivity was less than a 1.2% standard deviation, they did not result a corrected method for a sensitivity change. Formula 4 indicated that this study was performed by revising a theory of van Herk [12]. The revision included corrections of the response characteristics of the dose of

each pixel in the L-EPID and a change in the time sensitivity change in each pixel and its daily changes. Therefore, the utility of Formula 4 was verified with a previous process by Zhu et al. [16].

The L-EPID dose in Model 1 determined by the method of Zhu et al. is shown in Fig. 6. The difference between the dose of the L-EPID and the measured dose for 4-MV X-rays (Fig. 5a) increased by approximately 40% at the maximum in the high-dose region at points a distance of ± 4.5 cm from the central axis. On the other hand, a decrease of approximately 20% was observed for 10-MV X-rays (Fig. 5b) at a maximum.

When we calculated the L-EPID dose with Formula 4, the calculated value showed good agreement with that of the measured dose (Fig. 3). From the results, it appeared that good agreement was obtained for the two terms in Formula 4 corresponding to a time sensitivity change of the L-EPID and correction for a daily sensitivity change. By introduction of Formula 4, the correction for the deviation of the L-EPID sensitivity can be executed more accurately and easily. From our results, it is believed that the L-EPID was able to evaluate objectively the physical characteristics of a radiation field. Moreover, L-EPID dosimetry is carried out in a shorter time as compared to the conventional method. Therefore, the use of the L-EPID for daily quality assurance seems to be feasible in clinical applications.

5 Conclusion

We studied dose verification by using the L-EPID. A pixel value in the L-EPID was converted to the dose (L-EPID dose) by use of our formula

$$\overline{P(i,j)} = a \cdot D(i,j) + b \cdot \sqrt{D(i,j)} - k \cdot h.$$

From the results presented here, the verification of physical characteristics such as the degree of symmetry and flatness and the penumbra of the field could be performed objectively by use of the L-EPID. Moreover, the verification can be performed in a shorter time; therefore, we believe that measurements with the L-EPID can be carried out as a substitute for the daily work of quality assurance with a conventional dosimeter and rectangular radiation fields. In addition, the method presented here can be adapted to verification of irregular fields and transmitted doses. L-EPID dosimetry can be useful not only for daily quality assurance but also for application in other clinical fields.

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Brachytherapy for Oral Tongue Cancer: An Analysis of Treatment Results with Various Biological Markers

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Objective: Low-dose-rate (LDR) brachytherapy is an effective treatment for tongue cancer. However, little is known about the biological mechanism underlying this therapy, characterized by delivery of continuous exposures of LDR irradiation. It is reported that lower microvessel density (MVD), lower Ki-67 index or higher expression of endogenous hypoxic markers such as carbonic CA IX and Glut-1 are related to the poor control of tumors treated with external irradiation. To elucidate the biological characteristics of LDR brachytherapy, we analyzed our results in cases of tongue cancer treated with LDR brachytherapy by using immunohistochemical stainings with antibodies against Ki-67 and MVD, Glut-1 and CA IX.
Methods: The prognostic value of Ki-67 index, MVD and the expression of CA IX and Glut-1 was assessed in 68 tongue cancers treated with LDR brachytherapy. The specimens were taken from tongue cancers before radiation therapy and immunohistochemical staining was performed.
Results: The local recurrence-free survival rates were significantly different between T1+T2 and T3 ($P = 0.00067$), but not between low and high Ki-67 indexes ($P = 0.54$), between low and high MVD ($P = 0.071$), low and high CA IX indexes ($P = 0.062$) or low and high Glut-1 indexes ($P = 0.107$). T stage, the size of the tumor was the only significant factor for local control in multivariate analyses ($P = 0.0377$).
Conclusion: LDR could overcome the radioresistence of non-cycling and hypoxic cells; however, we cannot draw firm conclusions due to the limited number of patients.

Key words: tongue cancer – brachytherapy – Ki-67 – microvessel density – CA IX

INTRODUCTION

Low-dose-rate (LDR) brachytherapy with or without external irradiation provides a high local control rate in the treatment of early tongue cancer, comparable to that obtained by surgery (1–3). Recently, LDR brachytherapy has been performed in prostate cancer with excellent results, and the number of patients treated with LDR brachytherapy has been increasing (4).

The good dose distributions delivered by radioactive sources in or near the tumor are a reason for the high local control rate obtained by brachytherapy. In addition, however, LDR brachytherapy is characterized by delivery of continuous exposures of LDR irradiation, which might produce biological advantages that external irradiation does not possess. Although many *in vitro* and *in vivo* researches about the biological effects of continuous LDR have been performed (5), there are no reports on LDR research in which clinical specimens were used for immunohistochemical analysis as far as we are aware.

In this report, in order to elucidate the biological characteristics of LDR brachytherapy, we analyzed our results in cases of tongue cancer treated with LDR brachytherapy, by using immunohistochemical stainings with antibodies against Ki-67 and microvessel density (MVD), Glut-1 and CA IX.

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MATERIALS AND METHODS

Population

Between 1987 and 2004, 78 patients with Stage I–IV squamous cell carcinoma of the oral tongue, according to the 1997 International Union Against Cancer TNM

Classification, were treated radically with radiotherapy alone. Biopsy samples of four patients were lost or scanty, and six patients who received both external beam irradiation and LDR brachytherapy were excluded from this analysis; 68 patients were, therefore, retrospectively selected.

Patient characteristics are shown in Table 1. The follow-up period ranged from 11 to 146 months (mean 56 months, median 54 months). The minimum follow-up period of the other living patients was 28 months.

Treatment

All 67 patients were treated by LDR brachytherapy alone. The technique of implantation for brachytherapy is same as that in the Manchester system (6,7). Cesium 137 needles were used as radioactive sources. The prescribed dose was 65–70 Gy over a period of 6–7 days when LDR brachytherapy alone was used. No patient had received chemotherapy before or during radiotherapy.

Nine patients had positive neck lymph nodes (N1 or N2). These patients did not hope to be treated with glossectomy. The radical or modified neck lymph node resection was performed after LDR brachytherapy to the primary tumor.

Immunohistochemical Examination

One to three biopsies, 1–5 mm in diameter, were taken from each tumor. All of the biopsies were taken at the initial time of the diagnosis. Immunohistochemical staining was carried out with the methods previously described (8).

Immunohistochemical detection for growth fraction was performed with Ki-67 staining using MIB-1 monoclonal antibody (DAKO, Copenhagen, Denmark) and that for MVD with CD34 monoclonal antibody (Nichirei, Japan).

Rabbit polyclonal antibody to Glut-1 (Chemicon International, USA) and that to CA IX (Novus Biologicals, CO, USA) were also used.

Table 1. Patients and tumor characteristic

	Number of patients
Sex	
Male	40
Female	28
Age	24–88[a] (65)[b]
T classification	
1	19
2	37
3	12
N classification	
0	59
1	5
2	4
Stage (UICC, 1997)	
I	18
II	34
III	12
IV	4

Total number of patients: 68.
[a]Age range.
[b]Median.
UICC, International Union Against Cancer.

Evaluation of Immunostaining

The percentages of Ki-67-positive tumor cells were calculated by counting the number of brown-stained tumor nuclei/total number of cancer cells in the most highly stained area, with a highly magnified view (×400; 0.196 mm^2/field). More than 400 cells were counted in each specimen. The Ki-67 labeling index (Ki-67 index) was estimated by the percentage of Ki-67-positive cancer cells among all the tumor cells counted.

The microvessel count was assessed by light microscopy in three of the most extensive areas of neovascularization (termed 'hot spots') with a highly magnified view (×400; ×40 objective and ×10 ocular; 0.196 mm^2/field), and the average number of vessels was calculated. We counted intratumoral and stromal vessels with actual lumens around the tumor nests, but did not count a single endothelial cell (or cluster) or vessels that existed far from the tumor nests (9,10).

In evaluation of CA IX and Glut-1 positivity, the specimens were scanned at low optical power (×40 and 100), and the percentage of cells with positive Glut-1 or CA IX reactivity was assessed (11).

Measurements of immunostaining of these proteins were performed independently in all cases by two investigators who had no previous knowledge of the clinical outcome. When the evaluation for each antibody differed between investigators, the investigators discussed it, with or without re-evaluation, until an agreement was reached.

Statistical Analysis

Local recurrence-free rates in patients were measured using the Kaplan–Meier method. Differences were analyzed by the log-rank test with significance taken at $P < 0.05$.

Differences in various markers between local control and local failure were analyzed by t-test (two-sided) with significance taken at $P < 0.05$. Patients who died <24 months after LDR brachytherapy were not included in local control, even if they had local control until their death. Multivariate analysis was also performed using Cox's proportional hazard regression model (12).

The date of diagnosis was defined as the date of biopsy confirmation of disease, and survival was calculated from this date to the time of death or last follow-up.

RESULTS

Ki-67 Index and Local Control

Figure 1a shows Ki-67 positive cells immunohistochemically detected using anti-Ki-67 antibody. Table 2 shows the relationship between the Ki-67 index and local control for tongue cancer treated with LDR brachytherapy.

The Ki-67 index ranged from 13 to 75%. The mean Ki-67 index for the local control group was 40% and that for the local failure group was 37%. There was no correlation between Ki-67 index and local control ($P = 0.59$).

In order to clarify whether the Ki-67 index is related with local control rate, tumors were divided into two groups (high Ki-67 index and low Ki-67 index) and the local recurrence survival rates were compared (Fig. 2a). There was no correlation between the Ki-67 index and local control ($P = 0.54$).

MVD and Local Control

Figure 1b shows the microvessels immunohistochemically detected using anti-CD34 antibody. Table 2 shows the relationship between MVD and local control. MVD ranged from 5 to 45 microvessels per field (50.391 mm^2). The mean MVD for the local control group was 21 vessels/field and that for the local failure group was 20 vessels/field. There was no correlation between MVD and local control ($P = 0.52$).

In order to clarify whether MVD is related with local control rate, tumors were divided into two groups (high MVD and low MVD) and the local recurrence survival rates were compared (Fig. 2b). There were no significant

Table 2. Relationship between the expression of various markers and the local control for tongue cancer

Markers	Mean (%)	Range (%)	*P* value*
Ki-67 index			
Local control	40	13–75	0.59
Local failure	37	17–58	
Microvessel density			
Local control	21*	5–45*	0.52
Local failure	20*	5–27*	
CA IX expression			
Local control	10	0–60	0.56
Local failure	12	0–50	
Glut-1 expression			
Local control	30	0–80	0.62
Local failure	18	0–80	

*The *P* value of the statistical difference between local control and local failure.
*The number of microvessels/field.
CA IX, carbonic anhydrase 1%.

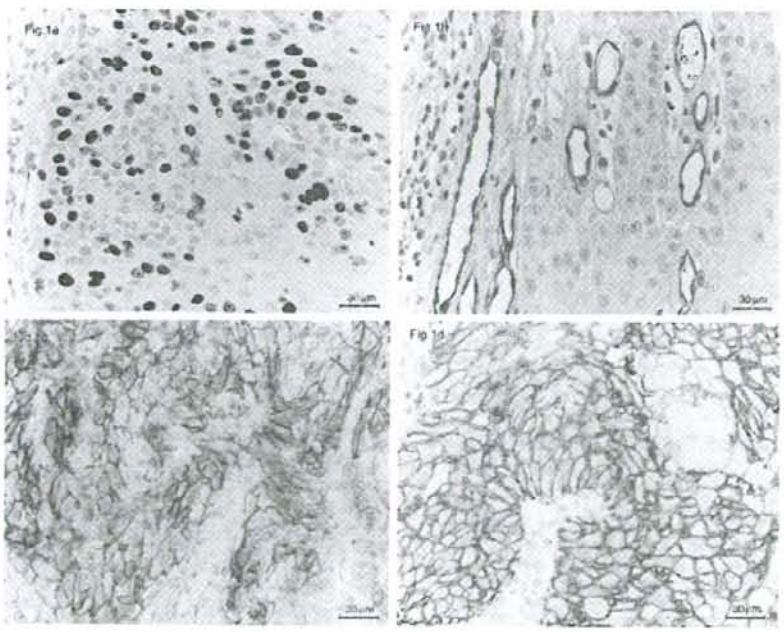

Figure 1. Representative immunohistochemical stainings for Ki-67, CD34, CA IX and Glut-1 in biopsy specimens of patients with tongue cancer. (a) Ki-67, in this case, nuclear staining is scattered in the specimen, ×400. (b) CD34 for microvessels. The microvessels are most numerous at the periphery of the tumor, ×200. (c) CA IX, diffuse membrane expression was noted, ×200. (d) Glut-1, diffuse membrane expression was noted. ×200.

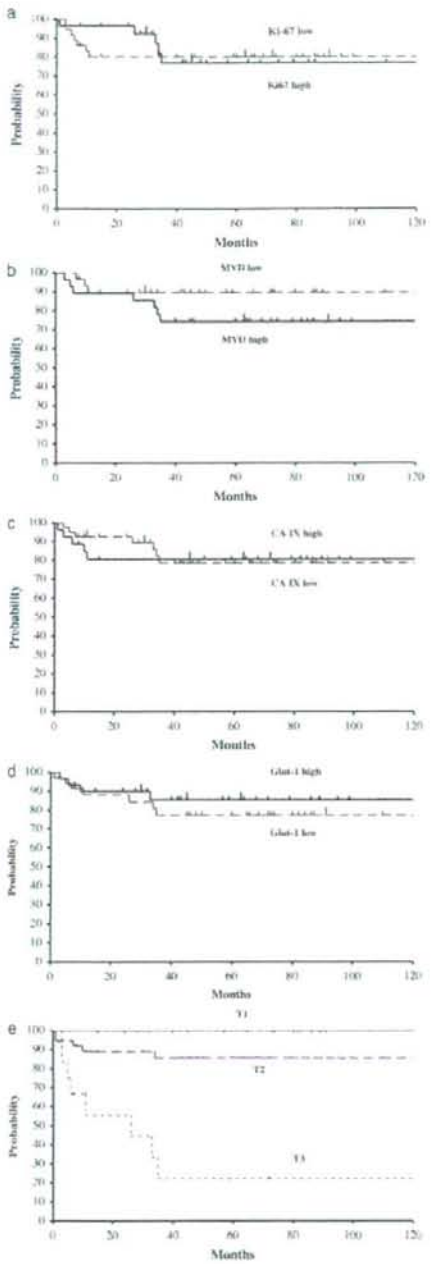

Figure 2. The local recurrence-free survival rates of patients with tongue cancer according to (a) Ki-67 index, (b) microvessel density (MVD), (c) CA IX expression, (d) Glut-1 expression and (e) T stage. The average value of MVD, Ki-67 index and expression of Glut-1 was used to define two groups of tumors with low/negative and high/positive reactivity. Ten percent of cancer cells positive for CA IX were used to define two groups of tumors in CA IX positivity.

differences in local control between tumors with high MVD and those with low MVD ($P = 0.071$).

CA IX Expression and Local Control

Figure 1c shows the immunostaining of CA IX. Table 2 shows the relationship between CA IX expression and local control. The percentage of cells with positive CA IX reactivity ranged from 0 to 60%. The mean CA IX positivity for the local control group was 10% and that for the local failure group was 12%. There was no correlation between CA IX expression and local control ($P = 0.555$).

In order to clarify whether CA IX positivity is related with local control rate, tumors were divided into two groups (low/negative CA IX and high CA IX expression) and the local recurrence survival rates were compared (Fig. 2c). We used the same cutoff point (<10 versus $>10\%$) as Koukourakis et al. (11) to define two groups of tumors with low/negative and high CA IX reactivity. There were no significant differences in local control between patients with negative/low CA IX expression and those with high CA IX expression ($P = 0.062$).

Glut-1 Expression and Local Control

Figure 1d shows the immunostaining of Glut-1. Table 2 shows the relationship between Glut-1 expression and local control. The percentage of cells with positive Glut-1 reactivity ranged from 0 to 80%. The mean Glut-1 positivity for the local control group was 30% and that for the local failure group was 18% (Table 2). There was no correlation between Glut-1 expression and local control ($P = 0.62$).

In order to clarify whether Glut-1 expression is related with local control rate, tumors were divided into two groups (high Glut-1 expression and Glut-1 expression) and the local recurrence survival rates were compared (Fig. 2d). There was no significant correlation between Glut-1 expression and local control ($P = 0.11$).

T Stage and Local Control

The actuarial local recurrence-free rates at 5 years were 100, 85.5 and 22.2% in the patients with T1, T2 and T3 tumors, respectively (Fig. 2e). A significant difference was found in the 5-year local recurrence-free rate between T1+T2 and T3 tumor groups ($P = 0.00067$).

T stage had no significant correlation with Ki-67 ($P = 0.55$), CA IX ($P = 0.63$), Glut-1 ($P = 0.12$) or MVD ($P = 0.051$).

Multivariate Analyses for Local Control

Ki-67 index, MVD, expression of CA IX, expression of Glut-1 and T stage were analyzed for prognostic significance in local control by multivariate analysis. T stage

Table 3. Multivariate analysis of factors prognostic for local recurrence-free survival

Variable	Hazard ratio	95% CI	*P* value	Better prognosis
T stage (T1, T2 versus T3)	0.00133	0.0000026–0.685	0.0377	T1, T2
Ki-67 index (38≥ versus <38)*	0.588	0.0514–6.74	0.7	38≥
CA IX expression (10≥ versus <10)*	1.92	0.222–16.6	0.554	10≥
Glut-1 expression (27≥ versus <27)*	1.11	0.153–8.12	0.914	<27
MVD (21≥ versus <21)*	0.798	0.147–0.685	0.794	21≥

CI, confidence interval.
*This index was divided above or below the average value.

($P = 0.0377$) was the only significant prognostic factor in local control. Ki-67 index, MVD, expression of CA IX or expression of Glut-1 had no significance in local control of tongue cancer (Table 3).

DISCUSSION

In general, radiation kills proliferating tumor cells more efficiently than quiescent tumor cells, resulting in many clonogenic tumor quiescent cells remaining following radiotherapy (13–15). Therefore, it is thought to be harder to control quiescent tumor cells than to control proliferating tumor cells, and many post-radiotherapy recurrent tumors are thought to result partly from the re-growth of quiescent tumor cell populations that were not killed by radiotherapy (16).

Ki-67 is a nuclear protein which is expressed in cycling cells. For patients treated by radiotherapy, the tumors with high Ki-67 labeling index showed good local control in squamous cell carcinomas of the head and neck (17) and esophageal cancer (18), uterine cervical cancer (19) and bladder cancer (20). However, there was no such relationship between the Ki-67 labeling index and local control of tongue cancer treated with LDR brachytherapy in our results. This indicated that LDR brachytherapy may be as effective for tumors that included more non-cycling cells as it was for tumors that included more cycling cells. The accumulated dose over the cell cycle is an appropriate indicator of cell lethality with continuous irradiation (5). A given dose rate of continuous irradiation is more damaging to cells with long cell cycles, because a larger dose is absorbed in each cell cycle. Therefore, non-cycling cells that have much longer cell cycles receive a larger dose over the cell cycle and may be killed more effectively with LDR brachytherapy.

Based on the *in vivo* observations of vascular geometry and blood flow in the tumor microcirculation, oxygen delivery to tumor tissues appears to rely on a network of microvessels indicating that tumor angiogenesis correlates with the oxygenation of tumor tissue. Hulka et al. (21) and Secomb et al. (22) reported that MVD correlates well with blood flow in breast tumors. Tumor MVD was introduced as a representative of O_2 status in laryngeal carcinoma (10) and esophageal cancer (9). In T1- and T2-stage laryngeal carcinoma treated with radiotherapy, multivariate analysis and Kaplan–Meier analysis showed that MVD alone had significant predictive power for radiosensitivity. They concluded that MVD was a useful predictive marker for evaluating radiosensitivity in laryngeal carcinoma (10).

The facilitative glucose transporter 1, Glut-1 is up-regulated via an oxygen-sensing pathway involving the hypoxia-inducible factor-1a (HIF-1a), a transcription factor that is expressed in most cells in response to hypoxia (23,24). CA IX is a novel member of the carbonic anhydrase (CA) family that codes for a transmembrane glycoprotein and is also an HIF-1α-dependent gene (25,26). In head and neck cancer treatment with external irradiation, patients with high expression of Glut-1 or CA IX had significantly poorer results in local control than those with the low/negative expression (11,27,28).

In order to analyze the influence of hypoxia on local control of tongue cancer treated with LDR brachytherapy, we investigated MVD and the expression of endogenous hypoxic markers such as Glut-1 and CA IX in tongue cancer tissues. In contrast with the results of external irradiation, MVD and the expression of hypoxic markers had no relationship with local control. These results indicate that LDR brachytherapy might achieve an equally successful cure of hypoxic tumors as obtained with oxyic tumors. In LDR brachytherapy, the repair of sublethal damage occurs during a long period of radiation exposure. *In vivo* experiments demonstrated that sublethal damage repair is an active process requiring oxygen and nutrients (5). Therefore, hypoxic tumor cells could be killed more effectively than oxyic tumor cells with LDR brachytherapy due to lower sublethal damage repair.

Inoue et al. (29) reported that hyperfractionated high-dose-rate (HDR) brachytherapy for early mobile tongue cancer has the same local control compared with LDR brachytherapy. The good results of HDR brachytherapy in our study may be due to the good dose distributions delivered by radioactive sources in or near the tumor because HDR does not have the biological benefits that LDR has. However, HDR caused bone exposure as an adverse effect. Since the number of patients in the study was small, further study of HDR may be required.

In conclusion, T stage, the size of the tumor was the only significant factor for local control of tongue cancers treated with LDR brachytherapy. The Ki-67 index, MVD and expression of endogenous hypoxic markers such as CA IX and Glut-1 had no correlation with local control. These results indicate that LDR may overcome the radioresistence of hypoxic cells and non-cycling cells although we cannot draw conclusions due to the limitated number of patients. Such advantages of LDR brachytherapy over external

irradiation might be responsible for the better results of LDR brachytherapy.

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Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

The treatment outcome of patients undergoing breast-conserving therapy: the clinical role of postoperative radiotherapy

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Abstract
Background Treatment outcome was evaluated in patients who underwent breast-conserving therapy and tangential irradiation. After verifying background factors including systemic therapy, the clinical efficacy of postoperative irradiation was investigated.
Method There were 708 study subjects, all of whom had early breast cancer treated between 1992 and 2002. The median follow-up period was 83 months. After breast-conserving surgery, in patients with negative surgical margins, only tangential irradiation at 48 Gy/24 fr was performed. In contrast, in those with positive surgical margins, 10 Gy of radiation boost to the tumor bed with electrons was administered after tangential irradiation with 50 Gy/25 fr. Treatment outcome was analyzed using the Kaplan–Meier method and Cox's proportional hazards regression model.
Results The disease-free survival and no-recurrence rates within the ipsilateral breast after 5 years were 93.4 and 97.2%, respectively. Risk factors for recurrence within the ipsilateral breast included younger age of patient, the number of positive lymph nodes, and no endocrine therapy. However, the surgical margin was not a risk factor. Risk factors for relapse outwith the ipsilateral breast included younger age, the number of positive lymph nodes, and recurrence within the ipsilateral breast.
Conclusions From our analysis of 708 Japanese women who received breast-conserving therapy, which can be regarded as a standard method in Japan, the treatment outcome was compatible with previous reports from other countries.

Keywords Breast cancer · Radiation therapy · Breast-conserving therapy · Radiation boost · Local control

Abbreviations

NRRB	No recurrence rate within ipsilateral breast
DFSR	Disease-free survival rate
y.o	Years old
fr	Fraction
Tm	Tumorectomy

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Bp	Wide excision
Bq	Quadrantectomy
RTP	Radiation treatment planning device
SC-irradiation	Irradiation to the ipsilateral supraclavicular nodal region
ER	Estrogen receptor
PgR	Progesterone receptor
K–M method	The Kaplan–Meier method

Introduction

Breast-conserving surgery is a standard therapeutic procedure for patients with early breast cancer. However, there is a paucity of reports from Japan on treatment outcomes of breast-conserving surgery and, consequently, not enough case numbers and long-term follow-up data are available [1]. In the Sapporo Medical University Hospital, tangential irradiation was started in 1992. Treatment outcome and risk factors for recurrence/relapse in our patients have been analyzed and the clinical efficacy of postoperative irradiation has been studied.

Patients and methods

Patients

The study subjects were those patients with breast cancer who had undergone tangential irradiation between January 1992 and December 2002 (Table 1). There were a total of 708 patients (a total of 716 breasts) with stages I or II breast cancer, excluding those who underwent palliative irradiation for locally advanced breast cancer (such as inflammatory breast cancer) and those who received intravenous chemotherapy or intra-arterial chemotherapy before breast-conserving surgery. Tangential irradiation was administered to bilateral breasts in 8 patients during the study period.

Background of patients

There were 686 surviving patients in the follow-up period, which ranged from 6 to 189 months with a median of 83 months. In total, 22 patients died (of which 16 were breast-cancer related). The patients' ages at irradiation ranged from 24 to 78 years, with a median of 48 years.

Surgery For breast-conserving surgery, tumorectomy (Tm) alone was performed on 57 breasts, and wide excision (Bp) or quadrantectomy (Bq) was carried out on the other 659 breasts. Histologically, the surgical margins were classified as positive when the distance between the cancer and the resection margin was less than 5 mm and as negative when the distance was 5 mm or less. The presence of positive margins in all breasts was 16.3%. The numbers of positive margins according to the type of operation are shown in Table 2. Of the 716 breasts, axillary lymph node dissection was performed in 629, 47 of which underwent sentinel lymph node biopsy. Axillary lymph node metastasis was positive in 135 breasts (18.9%). (In the following analyses, the number of lymph node metastases in 87 patients who were diagnosed as N0 preoperatively and thus

Table 1 Patients' characteristics

No. of patients	708 cases
No. of breasts (rt/lt)	716 (360/356)
Observation period: med/ave.	83/86 mos
Death (patients)	
Of breast cancer	16
Of other disease:	6
Age (years): range 24–78, median/average 48/48.7	
≤35	53
36–50	392
≥51	271
Operation	
Tumorectomy	57
Wide excision or quadrantectomy	659
Margin status	
Negative (≥5 mm)	595
Positive (<5 mm)	116
Not available	5
Pathological type	
I. Noninvasive	58
II. Invasive	658
a. Ductal carcinoma	580
b. Special type	78
Tumor size	
Tis	58
t1 (≤2.0 cm)	541
t2 (2.1–5.0 cm)	98
t3 or Multi-centric	19
Resection of the ipsilateral axillary region	
Yes	629
No	87
Double cancer: 43 patients, 45 sites	
Endocrine receptor	
Positive (estrogen receptor+ and/or progesterone receptor+)	355
Negative	117
Unknown	244 breasts

Table 2 The relationships between type of operation and margin status

Type	No. of breasts	Pathological final margin		
		Positive (%)	Not available	Negative (%)
Tm alone	57	23 (40.4)	0	34 (59.6)
Tm → Bp/Bq	185	20 (10.8)	0	165 (89.2)
Bp alone	179	26 (14.7)	2	151 (85.3)
Bq alone	275	43 (15.3)	3	229 (84.2)
Bp/Bq → more	20	4 (20.0)	0	16 (80.0)
Total	716	116 (16.3)	5	595 (83.7)

Tm tumorectomy, *Bp* wide excision, *Bq* quadrantectomy, *Bp/Bq* Bp or Bq

did not undergo lymph node dissection was regarded as zero.)

Histological classification and t size Histological subtype was determined according to the classification of The Japanese Breast Cancer Society [2]. Non-invasive ductal carcinoma was identified in 58 breasts and invasive ductal carcinoma in 658 breasts. In the cases of invasive ductal carcinoma, the t size of the primary site was 2 cm or less in 541 breasts (t1), 2.1–5 cm in 98 breasts (t2), and 5.1 cm or larger, or with multiple tumors in 19 breasts (t3).

Double cancer At the time of irradiation, multiple primary cancers were identified in 43 cases (45 sites). The sites of multiple primary cancers included the contralateral breast in 18 cases, the uterus in 9, the thyroid in 7, the colorectum in 5, and other sites in 6.

Radiotherapy

Historically, the irradiation performed in our hospital generally corresponded to "The guidelines of breast-conserving treatment (1999) from the Japanese breast cancer society" [3].

Technique of tangential irradiation The patients were irradiated while in a supine position with both elbows bent by our own fixing instrument and with their upper extremities elevated. Prior to 1999, a tele cobalt unit was used for irradiation (in 274 breasts) and, thereafter, a linear accelerator (4MV-X ray) was used (in 442 breasts). In the era of the tele cobalt unit, a MODULEX (Kanematsu electronics inc., Tokyo) was used as a radiation treatment planning (RTP) device to determine dose distribution in the center plane of the radiation field and to select wedge filters properly. Inhomogeneity correction was not performed. In the era of the linear accelerator, opposing portal irradiation was performed in the rectangular field of half beam. FOCUS (CMS-Japan co., Tokyo), a three-dimensional RTP unit that enables radiation treatment planning with multislice CT images, was used. A dose calculation algorithm was used to determine inhomogeneity correction using the Clarkson method. In principle, the prescribed dose of tangential irradiation was 48 Gy/24 fr/4.8 weeks in patients with negative surgical margins and 50 Gy/25 fr/5 weeks in patients with positive margins. The 48 Gy/24 fr was delivered in 605 patients, and 107 patients were irradiated with 50 Gy/25 fr. Among four cases excluded from the protocol above, one received 44 Gy/22 fr for poor pulmonary function, two received 46 Gy/23 fr on the patient's request in one and for arthrosis rheumatism in the other, and one received 48.6 Gy/26 fr for a suspected diagnosis of mixed connective tissue disease. The time interval from breast surgery to breast irradiation was less than 5 weeks in approximately two-thirds of the breasts. The interval was less than 4 weeks in 283 breasts, more than 6 weeks in 245 breasts, and more than 8 weeks in 68 of these 245 breasts (9.5% of all breasts). The duration required for tangential irradiation was less than 43 days in 697 breasts and more than 44 days in the remaining 19 breasts, with an average of 36.5 days (a median of 36 days). In about half of these latter 19 cases (breasts), irradiation was suspended by the year end and new year's holidays.

Radiation boost to the tumor bed Considering both local control and cosmetic effects, irradiation with moderate to high doses is generally recommended for cases with positive surgical margins. In addition, radiation boost has been regarded as desirable by "The guidelines of breast conserving treatment (1999)" from the Japanese breast cancer society [3]. Because the cosmetic aspect has been one great important issue, we decided that radiation boost was added to the tumor bed only in those cases with positive surgical margins. The electron beam was delivered by the rectangular field or the circular field with a size of 5–10 cm. The radiation field was set in consultation with the pathological mapping of resected specimens, the nipple tumor distance, and by small metal markers placed in the breast during surgery. Electron energy was determined according to the distance from the skin surface to the tumor bed and, in many cases, 9 or 6 MeV was chosen. The dosage of radiation boost was set at 10 Gy/5 fr. In fact, radiation boost was given to 108 (89.3%) of 121 breasts with pathologically positive or unknown surgical margins and, in contrast, also in 8 (1.3%) of 595 breasts with negative surgical margins.

Axillary lymph node metastasis and prophylactic irradiation to the ipsilateral supraclavicular nodal region In principle, supraclavicular nodal region (SC) irradiation was

performed on the ipsilateral side of the affected breasts in which axillary lymph node dissection had revealed pathological metastasis. The relationship between the number of axillary lymph node metastases and the use of SC irradiation is shown in Table 3.

Hormone receptor and adjuvant therapy

Positive rate of hormone receptor For the analysis, the state of hormone receptors was classified as positive when either estrogen (ER) or progesterone (PgR) receptors were detected in the resected specimens. The hormone receptor was positive in almost half of the cases, negative in 16.3%, and unknown or suspended in 34.1% (Table 1).

Endocrine therapy and chemotherapy Endocrine therapy was performed in 572 cases and chemotherapy in 214 cases. According to hormone receptor, the number of patients who received adjuvant therapies is shown in Table 4.

Statistical analysis Disease-free survival rate (DFSR) and no-recurrence rate within the ipsilateral breast (NRRB) were analyzed by means of univariate analysis using the Kaplan–Meier method (K–M method). In evaluating DFSR, recurrence in the breast was also regarded as an event, and 43 patients were excluded who had other primary cancers at the start of tangential irradiation. Recurrence within the ipsilateral breast was defined as a recurrence within the treated breast as the first site of relapse/failure with or without a simultaneous regional lymph node recurrence but without a distant metastasis. For both DFSR and NRRB, case of death was censored at that point. Multiple factors were analyzed for significance of association with breast recurrence using the log-rank test. Risk factors associated with recurrence within the ipsilateral breast and those with relapse without the ipsilateral breast were analyzed by means of multivariate analysis using Cox's proportional hazard model. Statistical analysis was done using Dr SPSS II (SPSS inc., Tokyo).

Table 3 Relationship between radiation treatment to supraclavicular nodal region and number of positive axillary nodes

No. of nodes	No. of breasts	Executed rate (%)	
0	3/581		0.5
1–3	100/113	88.5	90.4
≥4	22/22	100.0	
Total	125/716		17.5

Table 4 Adjuvant therapy and receptor groups

Receptor group	No. of breasts	Endocrine therapy (%)	Chemotherapy (%)
Positive	355	305 (86.4)	77 (21.7)
Negative	117	52 (45.2)	63 (53.8)
Unknown	244	215 (88.5)	74 (30.7)
Total	716	572 (80.5)	214 (30.1)

Results

Disease free survival rate and no-recurrence rate within the ipsilateral breast

The 5- and 10-year DFSR values in 673 cases were 93.4 and 86.9%, respectively (Fig. 1). Likewise, the 5- and 10-year NRRBs in all cases were 97.2 and 94.2%, respectively (Fig. 2).

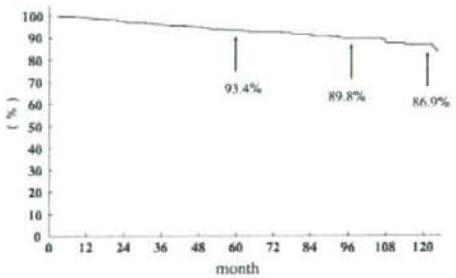

Fig. 1 Disease-free survival rate (DFSR) of 673 patients at 5, 8, and 10 years. *Number of patients at risk: 586 at 5 years, 208 at 8 years, and 76 at 10 years

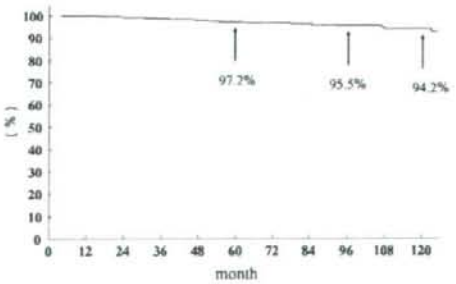

Fig. 2 No-recurrence rate within the ipsilateral breast (NRRB) of all cases at 5, 8, and 10 years. *Number of patients at risk: 626 at 5 years, 225 at 8 years, and 81 at 10 years

Table 5 Treatment outcome according to the age of the patient

Categories	Age (years)	No. of breasts (%)	NRRB at 5 years (%)	No. of breasts	DFSR at 5 years (%)
1	≤35	53 (7.4)	91.9[a]	52	82.4[b]
2	36–40	82 (11.5)	96.2[a]	77	90.9[b]
3	41–50	310 (43.3)	98.0[a]	294	95.4[b]
4	51–60	163 (22.8)	96.7[a]	152	92.6[b]
5	≥61	108 (15.1)	99.1[a]	98	96.9[b]

[a] 1 Versus 3 $P < 0.05$, 1 versus 4 $P < 0.05$, 1 versus 5 $P < 0.005$

[b] 1 Versus 3 $P < 0.005$, 1 versus 4 $P < 0.05$, 2 versus 3 $P < 0.01$, 2 versus 4 $P < 0.05$, 2 versus 5 $P < 0.01$, 1 versus 5 $P < 0.005$

Univariate analysis for each factor

Age

The 5-year NRRB and DFSR according to different age categories are shown in Table 5. A significant difference or tendency was seen among each category, suggesting that younger age could be a risk factor.

t Size, histological type, and pathological resection margin

A comparison among four groups of t size revealed a significant difference in DFSR between t1 and t2, with a P value of 0.01 but no significant difference in NRRB. Among the three groups of histological types (non-invasive carcinoma, invasive ductal carcinoma, and special types), there was no significant difference in NRRB and DFSR. With respect to the surgical resection margin, there was a significant difference between the group with pathologically negative and those with positive margin by a P value of 0.03 in NRRB, but no significant difference in DFSR. With regard to the type of operation, there was a significant difference in preliminary NRRB using the K–M method. However, the type of operation is one of the factors determining the status of the resection margin and also Noh et al. reported that if the surgical margin is appropriate there is no difference in the local control between Bq and Tm [4]. Consequently, we chose the state of resection margin instead of "the type of operation" as a covariate for multivariate analysis.

Axillary lymph node metastasis

When three groups were compared according to the number of pathological positive lymph nodes (0, 1–3, and more than 4), there was a significant association or trend between an increasing number of positive nodes and lowered rates for both NRRB and DFSR (Table 6).

Table 6 Treatment outcome according to number of pathological positive lymph nodes

Categories	No. of nodes	No. of breasts (%)	NRRB at 5 years (%)	No. of breasts	DFSR at 5 years (%)
1	0	581 (81.1)	97.8*	544	95.8+,++
2	1–3	113 (15.8)	96.2**	108	82.9+
3	4	22 (3.1)	85.6*,**	21	85.7++

* 1 Versus 3 $P < 0.05$

** 2 Versus 3 $P < 0.05$

\+ 1 Versus 2 $P < 0.0005$

++ 1 Versus 3 $P < 0.005$

Adjuvant therapy and hormone receptor

A comparison of those patients treated with and those without endocrine therapy revealed a significant difference in the 5-year NRRB at a significance level of 5%, although there was no significant difference in DFSR. In addition, the use of chemotherapy showed no significant difference in either NRRB or DFSR, and hormone receptor status did not correlate with these two survival rates (Table 7).

Radiotherapy

No significant difference in NRRB or DFSR was observed using the different irradiation devices (tele cobalt unit, linear accelerator). With regard to radiation boost, subgroup analysis between patients 40 years or younger and those of 41 years or older revealed no significant difference in either NRRB or DFSR (Table 8). In this analysis, five patients whose surgical margins were unknown or unevaluated were not included. Also excluded were the violated irradiation cases against our protocol for boost therapy according to the surgical margin status. When three groups were separated and compared according to the time interval from definitive breast surgery to breast irradiation (28 days or less, 29 to 35 days, and 36 days or more), there was no significant difference in NRRB (data not shown).

Multivariate analysis

Factors affecting recurrence within the ipsilateral breast

We set NRRB (months) as the survival variable and the presence or absence of breast recurrence as the state variable. The covariates included the patient's age at irradiation (years), t size, number of positive axillary lymph node, surgical margin (negative, positive, or unknown), radiation boost (yes, no), endocrine therapy (yes, no), chemotherapy (yes, no), total number of days required for tangential irradiation, number of days from

Table 7 Treatment outcome according to systemic therapy and receptor

	No. of breasts (%)	NRRB at 5 years (%)		No. of breasts	DFSR at 5 years (%)	
Endocrine therapy						
Yes	572 (79.9)	98.9*	$P < 0.0001$	540	94.9	$P = 0.11$
No	139 (19.4)	90.3*		130	87.5	
Chemotherapy						
Yes	214 (29.9)	96.6	$P = 0.74$	205	90.9	$P = 0.17$
No	498 (69.6)	97.5		465	94.5	
Hormonal receptor						
Positive group	355 (49.6)	97.7*	$P < 0.05$	335	93.9	$P = 0.34$
Negative group	117 (16.3)	92.7*		110	88.0	

Table 8 Subgroup analysis according to age of patient and radiation boost

Age (years)	Boost	No. of breasts	NRRB at 5 years (%)		No. of breasts	DFSR at 5 years (%)	
<40	No	102	93.8	$P = 0.21$	98	87.6	$P = 0.37$
<40	Yes	26	95.8		25	88.0	
>41	No	485	98.3	$P = 0.10$	455	94.8	$P = 0.89$
>41	Yes	81	94.9		75	94.5	

Table 9 Multivariable analysis risk factors of recurrence within ipsilateral breast

Variable	*P* value	Hazard rate exp (B)	S.I 95%
Age	0.013	0.949	0.910–0.989
No. of positive L/N	0.032	1.162	1.013–1.333
Endocrine therapy	0.001	0.189	0.088–0.407

breast surgery to the beginning of tangential irradiation, and radiation devices used (liniac, cobalt). Stepwise selection with backward elimination was used to select these covariates. The results showed the age of the patient, the number of positive axillary lymph nodes, and endocrine therapy to be significant factors (Table 9).

Factors affecting recurrence without the ipsilateral breast

In the same way, risk factors associated with recurrence without the ipsilateral breast were analyzed, including axillary regional recurrence and distant metastasis. The covariates included age of patient, number of positive axillary lymph nodes, surgical margin, endocrine therapy, chemotherapy, and the presence or absence of recurrence within the ipsilateral breast. Stepwise selection with backward elimination was used in the same way to select these covariates. The results showed the age of the patient

Table 10 Multivariable analysis risk factors of relapse without ipsilateral breast

Variable	*P* value	Hazard rate exp (B)	S.I 95%
Age	0.042	0.967	0.936–0.999
No. of positive L/N	0.031	1.138	1.012–1.281
Ipsilateral breast tumorectomy recurrence	0.024	2.790	1.143–6.811

at irradiation, the number of positive axillary lymph nodes, and recurrence within the ipsilateral breast to be significant factors (Table 10).

Discussion

No recurrence rate within the ipsilateral breast and disease-free survival rate

The 5-year NRRB was 97.2%, which is similar to that in many previously published reports. However, this long-term NRRB slightly decreased at 8 and 10 years. We thought that the significant decrease of long-term DFSR over 5 years, shown in Fig. 1, suggests a necessity to re-evaluate the data after a longer follow-up period. If the long-term DFSR was low, one explanation may be a discontinuation of the effects of systemic therapy, especially endocrine therapy. Endocrine therapy was performed in almost 80% of all cases, many of which received medical treatment for 3–5 years.

Factors affecting recurrence within the ipsilateral breast (before irradiation)

Age of patient

Our finding that younger age is an independent risk factor for recurrence within the ipsilateral breast is compatible

with many other reports [5–8]. In particular, our subgroup analysis revealed that NRRB of the group of patients 35 years old or younger (53 cases) and that of those 36 years or older (663 cases) constituted 91.9 and 97.6%, respectively, with a significant difference between the groups at a level of significance of <0.01 (data not shown). In the future, we would like to evaluate results after an increased dose of irradiation to the younger patients.

Pathological resection margin and radiation boost to tumor bed

Although many studies have identified the surgical resection margin as a prognostic factor affecting recurrence within the ipsilateral breast [9–13], our present analysis demonstrated that the resection margin was not a significant risk factor. Joben et al. showed that the resection margin was a risk factor for local control, especially in younger patients [8], and Bartelink et al. [14] reported an efficacy of radiation boost for younger patients. Although their studies were of non-invasive carcinoma, Jhingran et al. [15] reported that younger age is not a risk factor if the surgical margins are negative. In our protocol, radiation boost is almost always performed in patients with positive margins. From the data in Table 8, we supposed that increased radiation dose by boost therapy contributed in some degree to local control in our patients with positive resection margins despite their age.

We briefly describe two randomized studies comparing the treatments with and without radiation boost. Bartelink et al. investigated the efficacy of radiation boost in cases with macroscopically negative surgical margins in a total of 5,318 patients with stages I or II breast cancer who received breast-conserving therapy and reported a 5-year local recurrence rate during a median follow-up period of 5.1 years. The 5-year rate of local recurrence was 7.3% in patients who received 50 Gy of tangential radiation alone and 4.3% in patients who received an additional 16 Gy of radiation boost, showing a significant difference, especially in patients younger than 50 years of age [14]. Similarly, Polgar et al. reported that the 5-year local recurrence rate was 15.5% in patients who received 50 Gy of tangential radiation alone and 6.7% in patients who received an additional 16 Gy electron therapy or equivalent boost irradiation, demonstrating a significant difference [16].

One of the reasons why positive surgical margin was not a risk factor in our present study could be related to the pathological evaluation of the surgical margin and the effect of its stratification. In reports from other countries, the margin status was classified as negative, close, or positive with a cutoff of 1–2 mm [4, 10, 11]; in our study, cases were classified as positive (less than 5 mm) or negative (5 mm or greater) based on the pathological reports. Conceivably, the cases that we classified as positive may have included the aforementioned cases with negative and close margins. Furthermore, Frazier et al. re-studied pathological margins in patients who underwent mastectomy or re-excision following a previous "segmental resection" and reported that residual tumors were found in 32% of patients with close margins and in 26% of those with clear margins, while 48% of patients with involved margins had no residual tumor [17]. It is possible that different definitions of positive/negative surgical margins as well as uncertainty of margin status in individual cases can influence the results of studies on tumor recurrence. However, Horiguchi et al., using a similar approach to ours, classified negative margins as being greater than 5 mm and positive margins as less than 5 mm and performed 50 Gy of tangential irradiation in patients with both negative and positive margins [18]. Their retrospective analysis of 161 patients with breast-conserving surgery included a group of 125 patients with negative margins and 36 patients with positive margins. Their study showed a significant difference in the rate of local control between the two groups, leading to the conclusion that the surgical margin status is a risk factor for local recurrence. These findings led us to consider that our result showing the surgical margin is not a risk factor for local control may not be associated with uncertainties and differences in definitions of margin status.

It is also possible that the influence of surgical margin status was undetectable even by multivariate analysis because of the effects of systemic therapy. However, a randomized study by Fisher et al. [19] showed that the rate of ipsilateral breast tumor recurrence at 8 years after lumpectomy was 16.5% in patients treated with tamoxifen alone, 9.3% in patients with radiation and placebo, and 2.8% in patients with radiation and tamoxifen, clearly indicating that endocrine/chemotherapy cannot supplement radiotherapy. Based on these findings, we considered that our result that showed no significant difference in the rate of recurrence within the ipsilateral breast between cases with positive or negative surgical margins could have been an effect of radiation boost.

Adjuvant therapy (endocrine therapy, chemotherapy)

Using the K–M method of analysis, there was no significant difference in NRRB and DFSR between patients with and those without adjuvant therapy, including endocrine therapy and/or chemotherapy. However, as shown in Table 7, when compared with endocrine therapy alone, there was a significant difference in NRRB ($P < 0.0001$) and a tendency toward DFSR ($P = 0.11$). By multivariate analysis, omission of endocrine therapy was a strong risk factor for recurrence within the ipsilateral breast but not for

recurrence without the ipsilateral breast. This may be a result of determining adjuvant therapy in each patient based on prognostic factors such as the patient's age, tumor size, the presence or absence of hormone receptors, as well as the patient's request.

Lymph node metastasis

Many reports have demonstrated that the presence of positive axillary lymph nodes is a factor affecting distant metastasis and overall prognosis. In this study, we found that the number of positive axillary lymph nodes was not only a significant factor for DFSR, but also associated with NRRB/local control. This novel finding is expected to be re-evaluated by other investigators.

Radiotherapy

We found no significant difference in the rate of recurrence within the ipsilateral breast by different radiation devices, suggesting that given radiation dosages and spatial distributions are clinically equivalent by different devices. In addition, the time interval from breast surgery to the beginning of irradiation is regarded as "unfavorable because of accelerated growth of tumor", according to the guidelines from the Japanese Breast Cancer Society [3]. Vujovic et al. reported that delay in the start of breast irradiation of up to 16 weeks from definitive surgery does not increase the risk of recurrence in node-negative (N0) breast cancer patients. The "unfavorable" aspect of the delay is apparently associated with high recurrence rates in patients with positive surgical margins [20, 21]. In our present study, less than 10% of patients had a waiting period of greater than 8 weeks, which is unlikely to be found statistically as a risk factor for recurrence within the breast.

Factors affecting survival rate

Our results confirmed that, even in patients with early breast cancer who can be treated with breast-conserving surgery, risk factors for survival are a younger age of patient and the status of axillary lymph node metastasis. Furthermore, multivariate analysis identified recurrence within the ipsilateral breast to be a significant risk factor for no recurrence without the ipsilateral breast. In Japan, Inaji et al. conducted a national questionnaire survey and identified recurrence within the ipsilateral breast to be a factor associated with distant metastasis. This was from an analysis of 1,901 patients with breast cancer of more than 3 cm in diameter who underwent breast-conserving surgery prior to 1993. However, they have not yet determined whether ipsilateral breast recurrence is a cause of or merely a predictive factor for distant metastasis [22]. Regarding this, Clark et al. used meta-analyses to show that avoidance of a local recurrence in four patients would save the life of one patient, and breast-conserving surgery combined with radiotherapy has reduced 15-year breast cancer mortality risk from 35.9 to 30.5% [23]. In addition, Vinh-Hung and Verschraegen conducted pooled analyses of a total of 15 clinical trials of 9,422 patients, comparing radiotherapy with no radiotherapy after breast-conserving surgery; they reported that postoperative radiotherapy reduced the relative risk of ipsilateral breast tumor recurrence to one-third and also reduced the mortality rate by 8.6% [24].

In conclusion, DFSR and breast control rate at 5 years were 93.4 and 97.2%, respectively, in our analysis of 708 Japanese women with an 83-month median follow-up period. On multivariate analysis, risk factors for local recurrence within the breast were young age, the number of positive axillary nodes, and absence of adjuvant endocrine therapy. However, a positive surgical margin was not a significant predictor.

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Hyperfractionated Accelerated Radiotherapy for T1,2 Glottic Carcinoma

Consideration of Time-Dose Factors

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Background and Purpose: Hyperfractionated accelerated radiotherapy without a split (AF) has been performed to improve the local control probability of early glottic carcinomas since 1990 in the authors' institution. Here, they report their experience treating early glottic cancer patients with AF in a single institution who have a long follow-up period.
Patients and Methods: 131 T1 N0 M0 glottic cancers and 65 T2 N0 M0 glottic cancers were treated with conventional fractionation (CF) from 1984 to 1989 and with AF since 1990. CF consisted of five daily fractions of 2 Gy per week, to a total dose of 64 Gy. AF consisted of 1.72 Gy per fraction, two fractions per day, 5 days a week, to a total dose of 55 or 58.5 Gy.
Results: The 5-year local control probability for T1 tumors was 94% with 58.5 Gy and 87% with 55 Gy of AF, whereas it amounted to 80% with CF. For T2 tumors, it was 56% with 58.5 Gy and 68% with 55 Gy of AF, whereas it amounted to 64% with CF. The data of T2 should be evaluated with caution due to the small number of patients. Patients with AF had more severe mucosal reactions but no severe late reactions.
Conclusion: AF significantly improved the local control rates for T1 glottic cancer.

Key Words: Glottic cancer · Radiation therapy · Hyperfractionated accelerated fractionation · Repopulation

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Akzelerierte hyperfraktionierte Strahlentherapie bei Glottiskarzinomen T1/2. Berücksichtigung von Zeit-Dosis-Faktoren

Hintergrund und Ziel: Die hyperfraktionierte akzelerierte Strahlentherapie ohne Bestrahlungspause (AF) wird durchgeführt, um die lokale Kontrolle früher Glottiskarzinome zu verbessern. In diesem Beitrag geht es um die Erfahrung bei der AF-Behandlung von Patienten mit frühen Glottiskarzinomen in einer einzelnen Institution mit langen Nachuntersuchungszeiträumen.
Patienten und Methodik: 196 Glottiskarzinome (131 T1 N0 M0 und 65 T2 N0 M0) wurden zwischen 1984 und 1989 mit konventioneller Fraktionierung (CF) und seit 1990 mit AF behandelt. Die CF bestand aus fünf täglichen Fraktionen von 2 Gy pro Woche an 5 Tagen pro Woche bis zu einer Gesamtdosis von 64 Gy. Die AF bestand aus 1,72 Gy pro Fraktion, zwei Fraktionen pro Tag, 5 Tage pro Woche, bis zu einer Gesamtdosis von 55 oder 58 Gy.
Ergebnisse: Die lokale 5-Jahres-Kontrollrate für T1-Tumoren betrug mit 58,5 Gy AF 94% und mit 55 Gy AF 87%, während sie mit CF bei 80% lag. Für T2-Tumoren betrug sie mit 58,5 Gy AF 56% und mit 55 Gy AF 68%, während sie mit CF bei 64% lag. Die T2-Daten sollten wegen der geringen Patientenzahl mit Vorsicht beurteilt werden. Patienten mit AF wiesen schwerere mukosale Reaktionen, jedoch keine schweren Spätkomplikationen auf.
Schlussfolgerung: Die AF stellt eine signifikante Verbesserung der lokalen Kontrollrate für T1-Glottiskarzinome dar.

Schlüsselwörter: Glottiskarzinome · Strahlentherapie · Hyperfraktionierte akzelerierte Strahlentherapie · Wiederbesiedelung

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Introduction

Primary radiation therapy with surgical salvage is generally accepted as the modality of choice for treatment of early glottic tumors [7, 23, 29]. We have introduced the hyperfractionated accelerated fractionation (AF) scheme of radiotherapy in 1990 in order to improve the results of radiotherapy for early glottic carcinoma. AF is defined as a radiotherapy scheme with a significant reduction of the overall treatment time compared with conventional fractionation (CF). Consistent radiobiological and clinical data suggest that increasing overall time is detrimental to locoregional control as it enhances tumor repopulation during treatment [2, 13, 20]. It was also reported that overall treatment time is a significant prognostic factor for local control of T1 glottic carcinoma [6, 22]. However, studies of AF in head-and-neck cancer presented so far have excluded early glottic carcinomas [10, 14, 16].

We previously reported our results of AF in a relatively small number of patients with T1 and T2 glottic carcinomas [24]. Since then, we have accumulated patients treated with AF and prolonged follow-up periods. Here, we report the experience treating 131 glottic cancer patients with AF in a single institution who have a long follow-up period.

Patients and Methods

Patient Population

This is an analysis of 196 patients (185 males, eleven females) with untreated squamous cell carcinoma of the glottic larynx which was treated with curative intent by radiotherapy at Sapporo Medical University Hospital, Japan, between 1984 and 2005. Ages ranged from 42 to 91 years with an average of 66 years. There were 131 T1 N0 M0 glottic carcinomas and 65 T2 N0 M0 glottic carcinomas staged according to the 1987 UICC staging system. T-factor staging has been performed mainly by one of the authors (M.Ha.) with nasopharyngeal fiberscopy. None of the patients had lymph node metastases, and all of the tumors were squamous cell carcinomas.

All surviving patients had a minimum follow-up of 2 years, and the median follow-up was 63 months (range, 24–145 months).

Radiotherapy

All patients were irradiated with ^{60}Co γ-ray or 4-MV X-ray and received continuous-course irradiation using once-a-day (56 patients) or twice-a-day fractionation (140 patients). From 1984 to 1989, once-a-day fractionation was used, and since 1990, twice-a-day fractionation has been used. The CF program consisted of five daily fractions of 2 Gy per week, to a total dose of 64–68 Gy. The AF program consisted of 1.72 Gy per fraction, two fractions per day, with a minimum of 6 h between fractions, 5 days a week. The total dose was 55 Gy (104 patients) or 58.5 Gy (36 patients).

In patients treated with 55 Gy of AF, overall treatment time was 22 days in 84 patients, 23 days in 13, 24 days in two, 25 days in four, and 26 days in one. In patients treated with 58.5 Gy of AF, overall treatment time was 22 days in 13 patients, 23 days in eleven, 24 days in eight, 26 days in two, and 27 days in two. We excluded patients whose overall treatment time was ≥ 24 days from analysis of local control and gross survival in patients treated with 55 Gy of AF. We also excluded patients whose overall treatment time was 27 days from analysis of local control and gross survival in patients treated with 58.5 Gy of AF. In patients subjected to CF, 51 patients were treated with 64 Gy, two with 66 Gy, three with 68 Gy, and two with 70 Gy. In patients treated with 64 Gy of CF, median overall treatment time was 47 days, ranging from 44 to 57 days. For analysis of local control and gross survival, we considered only patients treated with 64 Gy and an overall treatment time of ≤ 53 days. Thus, of the patients treated with 55 Gy of AF, 70 with T1 and 27 with T2 tumors and of the patients treated with 58.5 Gy of AF, 18 with T1 and 16 with T2 tumors were included in the analysis. Of the patients subjected to CF, 31 with T1 and 15 with T2 tumors were considered in the analysis.

Concerning age distribution, the median age was 66 years (range, 44–91 years) for CF and 66 years (range, 42–81 years) for AF patients.

Parallel opposed lateral fields were used. The dose was specified at the isocenter of the field without tissue inhomogeneity corrections. The dose distributions were calculated with a treatment-planning computer, and wedge filters of 15° or 30° were used in most patients to ensure a dose inhomogeneity within the larynx of < 5%. Field size ranged from 36 to 42 cm^2. Most of the patients were treated with a field size of 6 × 6 cm. Combined chemotherapy was not used.

Statistical Analysis

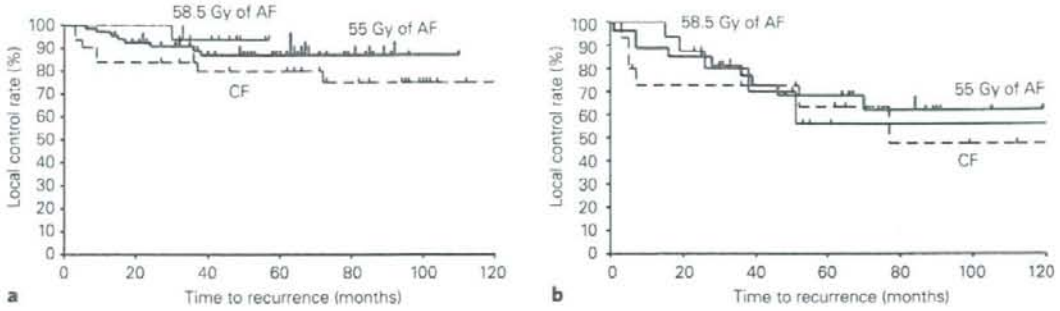
The endpoints analyzed were local control and overall survival, which were calculated from the first date of treatment. All patients whose primary lesions failed either method but were successfully salvaged by surgery were counted as failures of the radiation therapy program. Kaplan-Meier estimates were used for the analysis of local control and survival probabilities. Differences were analyzed by the log-rank test. For evaluation of acute or late effects, the RTOG toxicity criteria were used [9].

Calculation of Biologically Effective Dose E/α

The biologically effective dose E/α is the quantity by which different fractionation regimens are intercompared [15]. The equation corrected for tumor proliferation is

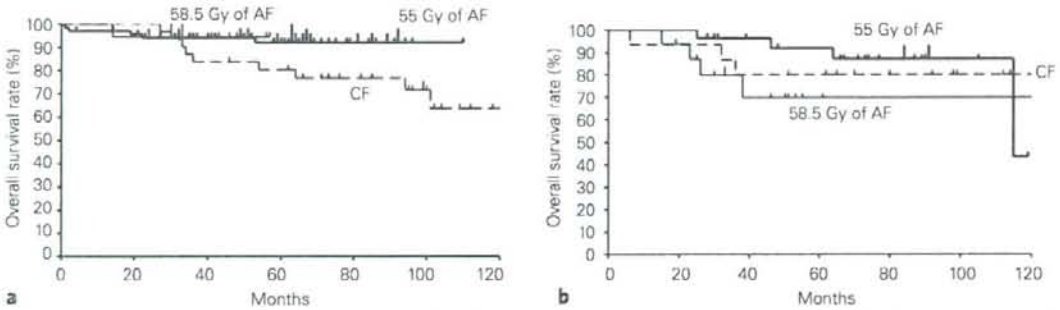
$$\frac{\mathbf{E}}{\alpha} = \mathbf{nd}\left(1 + \frac{\mathbf{d}}{\alpha/\beta}\right) - \frac{0.693}{\alpha}\,\frac{(\mathbf{t})}{\mathbf{T}_{pot}},$$

where d is the dose per fraction, n is the number of fractions, t is the duration of treatment, α/β is a characteristic of the tumor, and T_{pot} is the potential doubling time of the tumor. An α/β of 10 Gy, α of 0.3 Gy, and various values of T_{pot} were adopted in the present analysis.



Figures 1a and 1b. a) Local control curves for patients with T1 tumors according to fractionation schedules: broken line, CF (n = 31); solid black line, 55 Gy of AF (n = 70); fine black line, 58.5 Gy of AF (n = 18). b) Local control curves for patients with T2 tumors according to fractionation schedules: broken line, CF (n = 15); solid black line, 55 Gy of AF (n = 27); fine black line, 58.5 Gy of AF (n = 16).

Abbildungen 1a und 1b. a) Lokale Kontrolle bei Patienten mit T1-Tumoren entsprechend den Fraktionierungsplänen: gestrichelte Linie CF (n = 31); dicke schwarze Linie AF (55 Gy, n = 70); feine schwarze Linie AF (58,5 Gy, n = 18). b) Lokale Kontrolle bei Patienten mit T2-Tumoren entsprechend den Fraktionierungsplänen: gestrichelte Linie CF (n = 15); dicke schwarze Linie AF (55 Gy, n = 27); feine schwarze Linie AF (58,5 Gy, n = 16).



Figures 2a and 2b. a) Overall survival curves for patients with T1 tumors according to fractionation schedules: broken line, CF (n = 31); solid black line, 55 Gy of AF (n = 70); fine black line, 58.5 Gy of AF (n = 18). b) Overall survival curves for patients with T2 tumors according to fractionation schedules: broken line, CF (n = 15); solid black line, 55 Gy of AF (n = 27); fine black line, 58.5 Gy of AF (n = 16).

Abbildungen 2a und 2b. a) Gesamtüberleben bei Patienten mit T1-Tumoren entsprechend den Fraktionierungsplänen: gestrichelte Linie CF (n = 31); dicke schwarze Linie AF (55 Gy, n = 70); feine schwarze Linie AF (58,5 Gy, n = 18). b) Gesamtüberleben bei Patienten mit T2-Tumoren entsprechend den Fraktionierungsplänen: gestrichelte Linie CF (n = 15); dicke schwarze Linie AF (55 Gy, n = 27); feine schwarze Linie AF (58,5 Gy, n = 16).

Results

Local Control

Figure 1 shows the local control probabilities for T1 and T2 tumors treated with CF and AF. The 5-year local control probability for T1 tumors was 94% ± 6.0% with 58.5 Gy of AF treatment and 87% ± 4.3% with 55 Gy of AF, whereas for patients treated with CF it amounted to 80% ± 7.3%. The difference of local control probability between CF and 58.5 Gy of AF in T1 tumors was significant ($p < 0.01$). The 5-year local control probability for T2 tumors was 56% ± 16% with 58.5 Gy of AF treatment and 68% ± 9.3 % with 55 Gy of AF, whereas for patients treated with CF it amounted to 64% ± 13%.

Figure 2 shows the overall survival probabilities for T1 and T2 tumors treated with CF and AF. The 5-year overall survival for T1 tumors was 94% ± 5.4% with 58.5 Gy of AF treatment and 92% ± 3.5% with 55 Gy of AF, whereas for patients treated with CF it amounted to 80% ± 7.2%. The difference of overall survival between CF and 58.5 Gy of AF in T1 tumors was significant ($p < 0.01$). The difference between CF and 55 Gy of AF in T1 tumors was also significant ($p < 0.01$). The 5-year overall survival rate for T2 tumors was 70% ± 13% with 58.5 Gy of AF treatment and 92% ± 5.5% with 55 Gy of AF, whereas for patients treated with CF it amounted to 80% ± 10%.

Reactions (Table 1)

The peak mucosal reactions at the larynx and/or hypopharynx were much more severe and appeared at smaller doses and