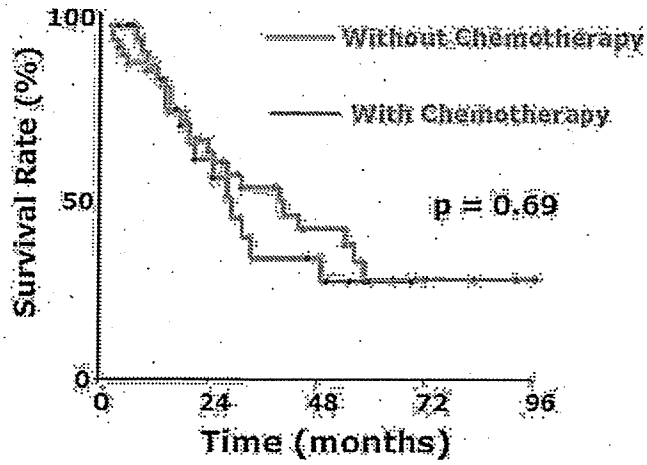

Fig. 2. Overall survival curves with and without chemotherapy were demonstrated; they are almost the same curves ($p = 0.69$).

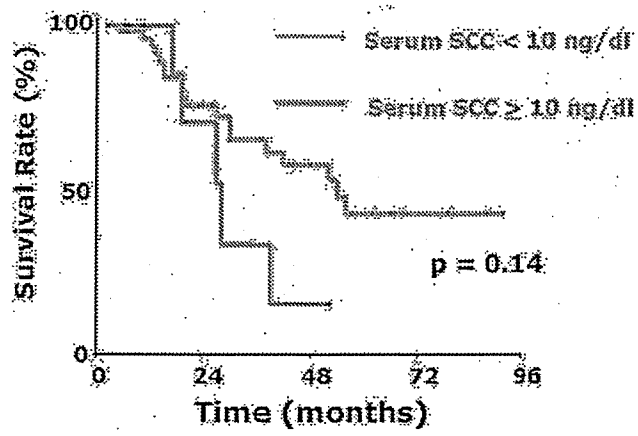

Fig. 4. Overall survival curves by serum squamous cell carcinoma (SCC) level were demonstrated. That of high SCC had a tendency to be superior to that of low SCC ($p = 0.14$).

the initial treatment was 17.8 ng/dL (range, 0.5–100.0). The mean serum SCC antigen level at the isolated para-aortic recurrence was 7.0 ng/dL (range, 0.4–92.8). Eighteen patients had symptoms at the isolated para-aortic recurrence, 12 patients had lumbago, 2 patients had pain of the lower extremities, 4 patients had edema of the lower extremities, and 1 had other symptoms.

As for treatment characteristics (Table 2), the initial treatment was as follows: radiation therapy (the combination of external beam radiation therapy with intracavitary irradiation) was performed in 42 patients. The combination of radiation therapy (the combination of external beam radiation therapy with intracavitary irradiation) with chemotherapy was performed in 16 patients, combination of surgery with radiation therapy was performed in 11 patients, and combination of surgery with chemoradiotherapy was performed in 6 patients. Surgery was performed in 9 patients. As for the isolated para-aortic lymph node recurrence, all patients received external beam radiation therapy. The mean total dose was 50.8 Gy (range, 25–61 Gy). Thirty-two patients received chemotherapy (8 BOMP, 8 UFT, 5 CDDP, 11 other).

As for statistical analysis, survival curves were constructed by Kaplan-Meier method and the log–rank test was performed to compare between clinicopathologic valuables. Statistical significance was assumed for a two-tailed p value less than 0.05.

RESULTS

Median follow-up time of all patients from the initiation of radiation therapy for isolated para-aortic lymph node recurrence was 20 months (2–92 months). Three-year and 5-year overall survival rates of all patients were 49.5% and 31.3%, respectively (Fig. 1).

Stratified by patients with or without chemotherapy, 3-year overall survival rate of patients with chemotherapy group was 37.7% and those without was 56.7% ($p = 0.69$) (Fig. 2).

Moreover, stratified by symptom sign, 3-year overall survival rate of symptom positive group was 27.6% and those in the symptom negative group was 56.1% ($p = 0.018$) (Fig. 3).

Furthermore, stratified by serum SCC antigen level (≥10 ng/dL) at the isolated para-aortic recurrence, 3-year overall

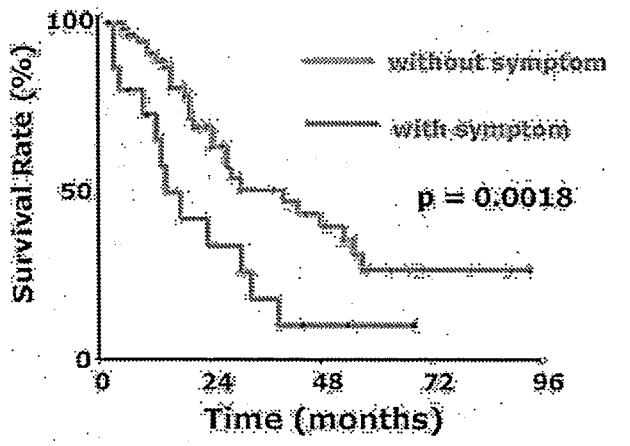

Fig. 3. Overall survival curves by symptom sign were demonstrated. Those without symptoms were significantly superior to those without symptoms ($p = 0.0018$).

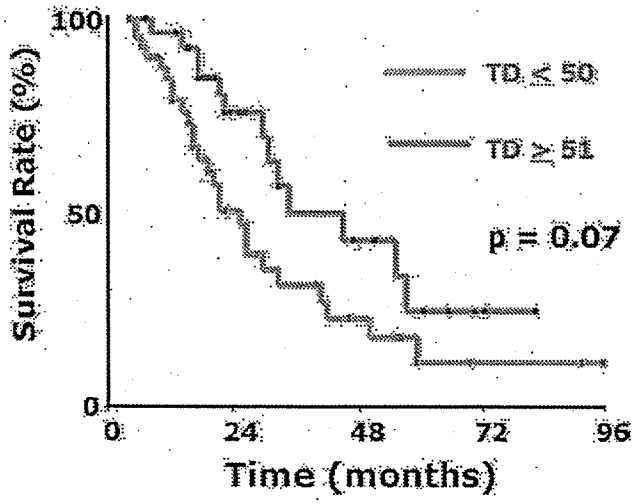

Fig. 5. Overall survival curves by total dose (TD) were demonstrated. That of ≥51 Gy had a tendency to be superior to that ≤50 Gy ($p = 0.07$).

survival rate of high SCC levels was 35.7%, and those with low levels was 66.5% ($p = 0.14$) (Fig. 4).

Three-year overall survival rates of the total dose ≥51 Gy and that of ≤50 Gy were 58.0% and 42.8%, respectively ($p = 0.07$) (Fig. 5).

As for morbidity, no patients received Grade 3 or greater late toxicity (National Cancer Institute-Common Terminology Criteria for Adverse Events version 3.0).

DISCUSSION

We defined one or several sites of recurrence as "oligo-recurrence" in our previous article (1), based on the many published reports on this recurrent pattern. Recently, oligo-recurrence was easily and frequently found owing to the improvements of biochemical markers for malignancies and diagnostic imaging. However, no current strategy, differing from systemic chemotherapy, has been established to cope with oligo-recurrence.

Isolated para-aortic lymph node recurrence in uterine cervical carcinoma is considered to be a regional disease rather than systemic disease of this oligo-recurrence (1). Singh *et al.* recently reported that isolated para-aortic lymph node recurrence in uterine cervical carcinoma treated with chemoradiotherapy achieved 100% of 5-year survival, although their method of chemotherapy did not have sufficient power systemically. Many reports other than Singh *et al.* have been performed on the survival benefit of radiation therapy of isolated para-aortic lymph node recurrence in uterine cervical carcinoma (3–6). Furthermore, 1.7–3.6% of uterine cervical carcinoma treated with curative treatment reportedly resurfaces as isolated para-aortic lymph node recurrence in large population-based studies (1, 3–5).

In the current large population-based study from Japan, 5-year overall survival was 31.3%, which was similar to 38% of 5-year overall survival in a small population-based study also from Japan (6). Survival benefit of chemotherapy in the current multi-institutional retrospective study could not be demonstrated. However, until now no phase III trial comparing radiation therapy alone vs. chemoradiotherapy for the isolated para-aortic lymph node recurrence in uterine cervical carcinoma has been performed. Furthermore, the chemoradiotherapy group in the current study consisted mostly of sequential, nonconcurrent chemoradiotherapy, such as radiation therapy followed by several courses of BOMP. Thus the survival benefit of up-to-date concurrent chemoradiotherapy is a challenge for future study.

In this study, patients with symptoms of recurrent cancer in an isolated para-aortic lymph node had much worse prognoses than those without symptoms. These findings concur with previous small-population studies (3, 7). These facts indicate that early detection of isolated para-aortic lymph node recurrence has great importance. Our previous study on characteristics of isolated para-aortic lymph node recurrence in uterine cervical carcinoma indicated that serum SCC antigen level at the initial curative treatment for pelvic tumors correlated with that at recurrence ($r = 0.492$, $p = 0.01$) (1), which indicated that the monitoring of serum SCC antigen level was useful to detect isolated para-aortic lymph node recurrence regardless of symptoms. Moreover, lower serum SCC antigen level at the detection of recurrence brought better prognosis in the current study. Thus if the primary region has no recurrence when serum SCC antigen level increases, oncologists are strongly recommended to perform abdominal computed tomography to examine whether para-aortic lymph node recurrence exists or not.

As for the total dose, the current study indicated that 51 Gy or more irradiation tended to have a better prognosis than 50 Gy or less. Thus higher irradiation (51 Gy or more) is recommended.

As for morbidity, severe late morbidity was not seen in the current study. Thus 51–60 Gy irradiation to para-aortic lymph node recurrence is considered a feasible dose using a suitable irradiation technique.

In conclusion, radiation therapy for isolated para-aortic lymph node recurrence is safe and effective indicating this method should be strongly recommended for such patients.

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Frequency and characteristics of isolated para-aortic lymph node recurrence in patients with uterine cervical carcinoma in Japan: A multi-institutional study

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Abstract

Objective. In most cases of uterine cervical carcinoma recurrence, the first site of distant metastasis or recurrence is reported to be the para-aortic region. Some reports have demonstrated that, in cases of isolated para-aortic lymph node recurrence treated by radiation therapy, patients survived for a long period, which suggests that isolated para-aortic lymph node recurrence in uterine cervical carcinoma is a regional disease rather than systemic disease. Determining the predictive characteristics of isolated para-aortic lymph node recurrence in patients at the time of the initial treatment for primary uterine cervical carcinoma is important, so we conducted the current multi-institutional study.

Patients and methods. Patients (n=3137) with uterine cervical carcinoma of stages Ia to IVa were treated in twelve Japanese hospitals between 1994 and 2003. The current study investigated the frequency and characteristics of patients with isolated para-aortic lymph node recurrence as well as the characteristics of clinical stage, histopathology, serum squamous cell carcinoma antigen level, the treatment method at the initial treatment, the duration between the initial treatment and the recurrence, and the serum squamous cell carcinoma antigen level at the recurrence.

Results. Of the 3137 patients with uterine cervical carcinoma in stages Ia–IVa, 67 (2.1%) experienced recurrence in isolated para-aortic lymph nodes. Stratified by clinical stage, none of the 613 patients with stage Ia experienced recurrence in isolated para-aortic lymph nodes. However, recurrence was experienced by 14 (1.4%) of the 966 patients with stage Ib, 7 (3.5%) of the 199 patients with stage IIa, 14 (2.3%) of the 613 patients with stage IIb, 1 (2.1%) of the 48 patients with stage IIIa, 26 (4.6%) of the 538 patients with stage IIIb, and 5 (5%) of the 100 patients with stage IVa. The mean duration time between the initial treatment and isolated para-aortic recurrence was 20 months (range, 2–49 months). The correlations between duration time and the clinico-pathological factors (clinical stage, histopathology, serum squamous cell carcinoma antigen level, and treatment method) at the initial treatment were investigated. No statistically significant factors have been revealed in the current study.

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Conclusions. The frequency of isolated para-aortic lymph node recurrence was 2.1% and increased with increasing clinical stage at the initial treatment (stage IVa: 5%) in the current study.

Keywords: Isolated para-aortic lymph node recurrence; Uterine cervical carcinoma; Radiation therapy

Introduction

Recently, oligo-metastasis/oligo-recurrence has been one of the most important concerns of oncology, especially in radiation oncology [1]. Advances of diagnostic imaging and biochemical diagnosis for various carcinomas have enabled us to detect isolated metastasis or recurrence, although some decades ago, metastasis and recurrence meant systemic disease in almost all cases. However, no strategy has been established for treating oligo-metastasis/oligo-recurrence in any kind of carcinoma. Most oncologists select systemic chemotherapy for these patients as a community standard. Nonetheless, oligo-metastasis/oligo-recurrence, especially isolated metastasis or recurrence, is considered to not always mean systemic disease. Singh et al. reported that patients with isolated para-aortic lymph node recurrence in uterine cervical carcinoma achieved 100% of 5-year survival when the recurrent site was treated with chemoradiotherapy [2]. Niibe et al. reported that the survival rates of patients with metastatic brain tumors with controlled primary lesions and no other distant metastasis were 88.9% after 1 year and 51.9% after 3 years respectively [3]. These findings suggested that some oligo-metastasis/oligo-recurrence patients could survive for as long a period as the patients with primary carcinoma. Thus, these patients must be treated curatively.

Uterine cervical carcinoma was reported to spread more by the lymphatic route than by the hematogenous route [4]. In most cases, the first site of distant metastasis or recurrence is the para-aortic region. As mentioned above, Singh et al. reported the long-term survival of patients with isolated para-aortic lymph node recurrence, which meant that isolated para-aortic lymph node recurrence in uterine cervical carcinoma is a regional disease rather than a systemic disease. Determining the characteristics of isolated para-aortic lymph node recurrence in patients at the time of the initial treatment for primary uterine cervical carcinoma is important.

Thus, we conducted the current multi-institutional study to reveal the frequency and characteristics of isolated para-aortic lymph node recurrence in uterine cervical carcinoma.

Patients and methods

Patients (n=3137) with uterine cervical carcinoma of stages Ia to IVa were treated in twelve Japanese university hospitals, cancer centers, and major general hospitals between 1994 and 2003. The current study investigated the frequency and characteristics of isolated para-aortic lymph node recurrence as well as the clinical stage, histopathology, serum squamous cell carcinoma (SCC) antigen level, initial treatment method, duration between the initial treatment and the recurrence, and serum SCC antigen level at the time of recurrence (Table 1).

Data were collected on data sheets from these twelve hospitals. Data sheets included patient age, serum SCC antigen level, treatment method, and the date at the initial treatment and patient age, serum SCC antigen level, and the date at the time of detection of isolated para-aortic recurrence. A data center was established at the Department of Radiology, Kitasato University Hospital.

Results

Of the 3137 patients with uterine cervical carcinoma in stages I–IVa, 67 (2.1%) experienced recurrence in isolated para-aortic lymph nodes. Stratified by clinical stage, none of the 613 patients with stage Ia experienced recurrence in isolated para-aortic lymph nodes. However, recurrence was experienced by 14 (1.4%) of the 966 patients with stage Ib, 7 (3.5%) of the 199 patients with stage IIa, 14 (2.3%) of the 613 patients with stage IIb, 1 (2.1%) of the 48 patients with stage IIIa, 26 (4.6%) of the 538 patients with stage IIIb, and 5 (5%) of the 100 patients with stage IVa. These results suggested that patients with more locally advanced stages (IIIb and IVa) were more likely to experience recurrence in isolated para-aortic lymph nodes than patients with early locally invasive stages (I–II).

Other patients characteristics are summarized in Table 2. The mean age was 55.7 years (range, 25–86 years). The mean duration time between the initial treatment and isolated para-aortic recurrence was 20 months (range, 2–49 months) (Fig. 1). As for the initial treatment, 32 patients underwent external radiation therapy combined with intracavity radiation therapy alone; 20 patients underwent surgery combined with external radiation therapy; 12 patients underwent concurrent chemo-radiation therapy (radiation therapy: external radiation therapy combined with intracavity radiation therapy); and 3 patients underwent surgery only. As for histopathology, 56 patients were found to have squamous cell carcinoma; 5 patients had adenocarcinoma; 5 patients had adenosquamous cell carcinoma; and 1 patient had a malignancy that was unclassified. The mean serum SCC antigen level at the start of the initial treatment was 17.3 ng/dl (range, 0.5–100 ng/dl), and the mean serum SCC antigen level at the time of isolated para-aortic lymph node recurrence was 9.5 ng/dl (range, 0–120 ng/dl). These results indicate that the serum SCC antigen level at the time of isolated para-aortic lymph node recurrence tended to be lower than that at the initial treatment. As for symptoms of the isolated para-aortic lymph node recurrence, 20 patients had symptoms with recurrence (Table 3). Lumbago was the most frequent symptom,

Table 1
The frequency of isolated para-aortic lymph node recurrence

Clinical stage	Frequency of isolated para-aortic lymph node recurrence
Ia	0/613 (0%)
Ib	14/966 (1.4%)
IIa	7/199 (3.5%)
IIb	14/613 (2.3%)
IIIa	1/48 (2.1%)
IIIb	26/538 (4.6%)
IVa	5/100 (5%)
Ia–IVa	67/3137 (2.1%)

Table 2
Patients characteristics of isolated para-aortic lymph node recurrence

Mean age	55.7 years (range; 25–86 years)
Histopathology	
Squamous cell carcinoma	56
Adenocarcinoma	5
Adenosquamous cell carcinoma	5
Unclassified	1
Initial treatment	
Radiation therapy alone	32
Chemoradiation therapy	12
Surgery followed by radiation therapy	20
Surgery alone	3
Mean serum SCC level	
Initial treatment	17.3 ng/dl (range; 0.5–100 ng/dl)
Recurrence	9.5 ng/dl (range; 0–120 ng/dl)
Mean DT[a]	20 months (range; 2–49 months)

[a] Mean DT: the mean duration time between the initial treatment and isolated para-aortic recurrence.

Table 3
Symptom at the isolated para-aortic recurrence

Symptom	Number of patients
Lumbago	14
Edema of lower extremities	3
Pain of lower extremities	3

seen in 14 patients. Three patients experienced edema of the lower extremities, and three patients experienced pain in the lower extremities. The correlations between duration time and the clinico-pathological factors (clinical stage, histopathology, serum SCC antigen level, and treatment method) at the initial treatment were investigated. No statistically significant factors have been revealed in the current study.

The correlation between serum SCC antigen level at the initial treatment and that at the time of isolated para-aortic lymph node recurrence was statistically significant ($r = 0.492$, $P = 0.01$) (Fig. 2).

The correlation between higher serum SCC antigen level (>10 ng/dl) at the time of isolated para-aortic lymph node recurrence and coexisting symptoms at the time of recurrence was statistically significant ($P = 0.05$).

Discussion

Some patients with uterine cervical carcinoma and isolated para-aortic lymph node recurrence were reported to survive for a long period and were considered to be cured [2,5–7]. Singh et al. reported that 100% of patients with uterine cervical carcinoma and isolated para-aortic lymph node recurrence treated with concurrent chemoradiotherapy achieved 5-year survival, although patients treated with only chemotherapy died within 1.5 years [2]. Niibe et al. reported that, in cases of advanced uterine cervical carcinoma with isolated para-aortic lymph node recurrence or metastasis treated with radiation therapy, 38% of patients achieved 5-year survival and the authors pointed out that c-erb B-2/HER2 expression in tumor tissues had prognostic significance, suggesting that anti-c-erb B-2/HER2 therapy, molecule-targeting therapy, such as with tratsuximab, might have an influence on survival [5]. These findings indicated that isolated para-aortic lymph node recurrence in uterine cervical carcinoma was not considered to be a systemic disease but to be a loco-regional disease. The detection of isolated para-aortic lymph node recurrence is important, so we investigated the frequency and characteristics of isolated para-aortic lymph node recurrence in patients with uterine cervical carcinoma.

The current multi-institutional study revealed that 2.1% of patients with uterine cervical carcinoma treated with curative therapy (including radiation therapy, chemoradiation therapy, surgery, and combined therapy) experienced recurrence in isolated para-aortic lymph nodes. This is the clinical demonstration in the largest population (n=3137). Others report on this theme in a large population as follows. Chou et al. reported in 2001 that 26 out of 867 patients (3%) who received pelvic radiotherapy after the diagnosis of primary cervical carcinoma were found to have isolated para-aortic lymph node recurrence in Taiwan [7]. Hong et al. reported in 2004 that 46 out of 1292 patients (3.6%) with uterine cervical carcinoma who underwent curative intended radiation therapy were found to have para-aortic lymph node recurrence in Taiwan [8]. Tsai et al. reported

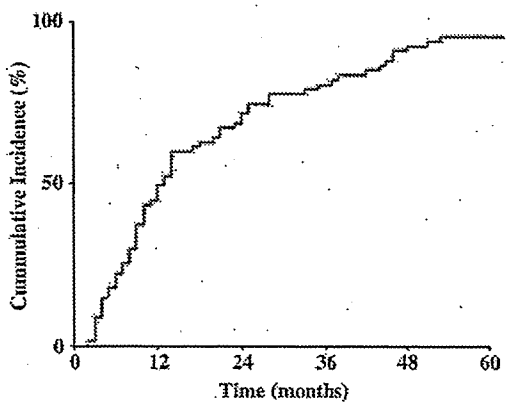

Fig. 1. The cumulative mean duration time between the initial treatment and isolated para-aortic lymph node recurrence was demonstrated. The mean duration was 20 months (range, 2–49 months).

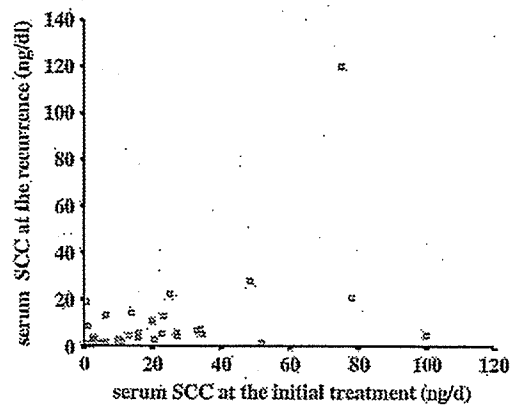

Fig. 2. The correlation between serum SCC antigen level at the start of the initial treatment and serum SCC antigen level at the isolated para-aortic lymph node recurrence. The positive correlation was recognized ($r = 0.492$, $P = 0.01$).

in 2005 that 14 out of 816 patients (1.7%) with uterine cervical carcinoma who received curative intended radiation therapy were found to have para-aortic lymph node recurrence in USA [2]. Furthermore, patients with more locally advanced stages at the initial treatment had a higher frequency of isolated para-aortic lymph node recurrence (stage Ib: 1.4% versus stage IVa: 5%). These results suggested the hypothesis that even locally advanced patients spread with lymphatic rout not with hematogenous systemic rout that existed not in a small number. Ikeda et al. reported that only 8 of 1961 patients with uterine cervical carcinoma experienced recurrence in the brain and that there were no patients with uterine cervical carcinoma that experienced isolated brain recurrence [9]. These results support the above-mentioned hypothesis.

Regarding the characteristics of isolated para-aortic lymph node recurrence in patients with uterine cervical carcinoma, about only one-third of these had symptoms. The others had no symptoms. Even no coexisting serum-SCC antigen elevation was not rare. Thus, routine examination by not only pelvic, but abdominal computed tomography or magnetic resonance imaging of uterine cervical carcinoma patients treated with curative therapy was considered to be required. Furthermore, coexisting symptoms in patients with isolated para-aortic lymph node recurrence were reported to be correlated with a much worse prognosis [2,10]. The mean duration time between isolated para-aortic recurrence and the initial treatment was 20 months (range, 2–49 months) in the current study. However, there were no correlations between duration time and various clinico-pathological factors (clinical stage, histopathology, serum SCC antigen level, and treatment method). These results suggested that long-term routine follow-up was required to detect isolated para-aortic lymph node recurrence. On the other hand, the correlation between the serum SCC antigen level at the time of initial treatment and that at the time of isolated para-aortic lymph node recurrence was statistically significant ($r = 0.492$, $P = 0.01$) (Fig. 2), and the correlation between higher serum SCC antigen level (>10 ng/dl) at the time of isolated para-aortic lymph node recurrence and coexisting symptoms at the time of recurrence was also statistically significant ($P = 0.05$). These suggested that routine follow-up with serum SCC antigen testing is important when the serum SCC antigen level is elevated at the time of initial treatment.

In conclusion, the frequency of isolated para-aortic lymph node recurrence was 2.1% and increased with increasing clinical stage at the initial treatment (stage IVa: 5%) in the current study. Two-thirds of patients with isolated para-aortic lymph node recurrence had no symptoms. Routine follow-up with serum SCC antigen testing and abdominal computed tomography or magnetic resonance imaging is important except stage Ia.

Acknowledgments

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ORIGINAL ARTICLE

Radiation Medicine: Vol. 24 No. 2, 133–138 p.p., 2006

Preliminary Study of Correction of Original Metal Artifacts due to I-125 Seeds in Postimplant Dosimetry for Prostate Permanent Implant Brachytherapy

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Purpose: We investigated a subtraction-based reprojection approach to reduce CT metal artifacts due to I-125 seeds and evaluated the clinical implications in postimplant dosimetry for prostate permanent implant brachytherapy.

Materials and Methods: The raw projection data were used to reduce metal artifacts due to I-125 seeds. CT images of the metal parts only were separated from the original CT images by setting the threshold for pixel value to that of the I-125 seeds. Using these images, sinograms of CT images with and without seeds were obtained by inverse Radon transform (iRT), and the sinogram of the metal image was subtracted from that of the original image. Finally, the image was reconstructed using the sinogram by Radon transform (RT). This technique was applied to a prostate phantom and to a patient undergoing prostate permanent implant brachytherapy.

Results: Metal artifacts from I-125 seeds were reduced in both the phantom and patient studies. This technique decreased the density of the inner region of seeds but enhanced the density of the seed edge, thereby facilitating the identification of seed number, orientation, and location.

Conclusion: This method reduces metal artifacts from I-125 seeds, and has potential for decreasing the time required for and improving the accuracy of postimplant dosimetry.

Key words: I-125 permanent implant brachytherapy, prostate cancer, postimplant dosimetry, seed identification, metal artifact correction

Introduction

I-125 PERMANENT IMPLANT BRACHYTHERAPY FOR PROSTATE cancer was approved by the Ministry of Health, Labor and Welfare of Japan in July 2003, and is now offered by an increasing number of hospitals. According to the American Brachytherapy Society (ABS) recommendation, implant quality should be assessed by CT-based postimplant dosimetry in all patients.[1] This recommendation specifies the recording of dosimetric parameters such as D90 and V100, namely, the minimum dose delivered to 90% of the prostate volume and the prostate volume receiving 100% of the prescription dose, respectively. As these parameters are considered predictable factors of treatment outcome, the accuracy of assessment is important.[2]

The CT images themselves, however, suffer from metal artifacts due to the I-125 seeds, resulting in insufficient visualization of the I-125 seeds and prostate.[3] The accuracy of postimplant dosimetry would be improved by a decrease in these metal artifacts.

Two general approaches to overcoming metal artifacts have been used. Post-processing techniques reduce artifacts by manipulating image window and level.[4,5] This approach is hampered, however, by the need for case-by-case processing in all patients. In contrast, a method using the raw projection data has shown promising effects in reducing metal artifacts,[6-13] but to date has been adapted only to simple situations in which the number of metallic objects is low. This method is thus

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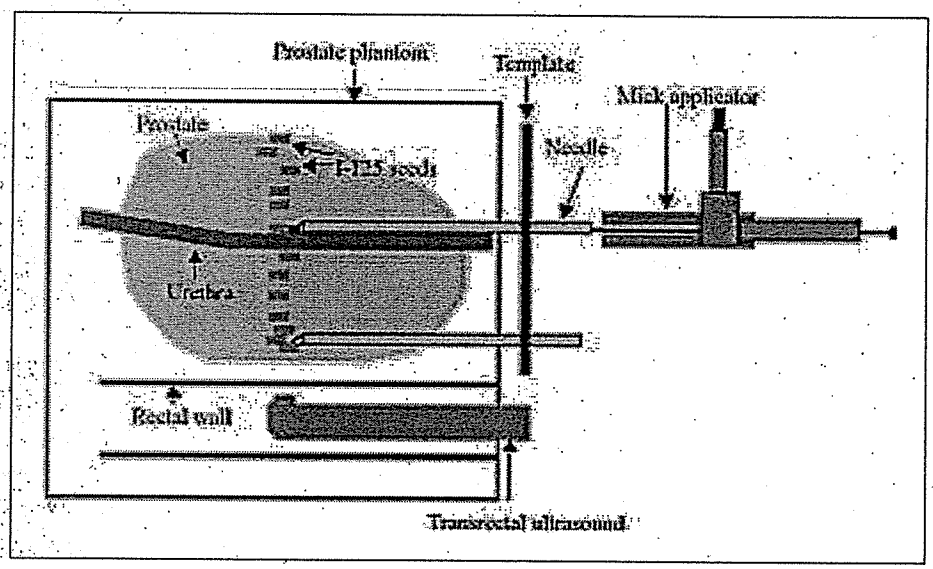

Fig. 1. Scheme of implant technique with a Mick applicator under transrectal ultrasound guidance using the prostate phantom.

unsuitable for use in I-125 prostate permanent brachytherapy, which involves the implantation of about 80 seeds per patient, providing far greater complexity than has been dealt with to date.

We have investigated a method, named the subtraction-based reprojection approach that would allow its use in complex situations such as I-125 prostate permanent brachytherapy. Here, we describe a preliminary evaluation of our metal artifact correction approach to post-implant dosimetry in phantom and patient studies.

Materials and Methods

Implant techniques

In the phantom study, a prostate phantom (Computerized Imaging Reference Systems, Norfolk, VA, USA) was used. We used dummy seeds of the same shape, size, and electron density as OncoSeed Model 6711 seed (GE Health Care, Arlington Heights, IL, USA) with a Mick 200-TPV applicator (Radio-Nuclear Instruments, Bronx, NY, USA) under transrectal ultrasound (Echo Camera SSD1000, Aloka, Tokyo, Japan) guidance. The scheme is shown in Fig. 1. The seeds are 4.5 mm long, 0.8 mm in diameter, and have a 0.05 mm thick titanium wall that is sealed by end welds. This model contains a silver wire of about 3 mm in length with the active materials that produce the metal artifact.[14]

Metal artifact correction

Metal artifact correction was performed using raw projection data (sinogram) obtained with a CT scanner. A sinogram is a 2D visualization of X-ray intensity array before reconstruction, with the vertical and horizontal axes representing the detector channel and a given angle, respectively. The white stripes highlighted by *arrows* in Figs. 2(c) and 2(d) represent the projection data of I-125 seeds that caused the metal artifacts. A decrease in the white stripes is seen after correction (Fig. 2(e)).

The CT images were transferred to the programming package MATLAB (MathWorks, Ver 7.04. Natick, MA, USA). First, the CT number threshold was fixed to separate I-125 seed regions from others, and images that contained only I-125 seeds were obtained (Fig. 2(b)). Using these images, the sinograms of CT images with seeds and those of seeds only were obtained by inverse Radon transform (iRT) (Figs. 2(c) and (d)). The projection data of the metal image was subtracted from that of the original image to provide the sinogram without I-125 seeds (Fig. 2(e)). Finally, the image with metal artifact correction was reconstructed by Radon transform (RT) using the sinogram. This technique was then applied to both a prostate phantom and a patient.

Data acquisition

The phantom, in which 13 seeds were implanted in the same plane, was scanned using dual-detector row CT (HiSpeed-NX/i, GE Health Care, Fairfield, CT, USA) with a 2 mm slice thickness and 2 mm slice intervals by multiple axial scanning.

For clinical study, one of 32 patients who received permanent implants as monotherapy at our institution was randomly selected. Randomization was performed using statistical software (SAS ver. 6, SAS Institute, Cary, NC, USA). The patients were classified according

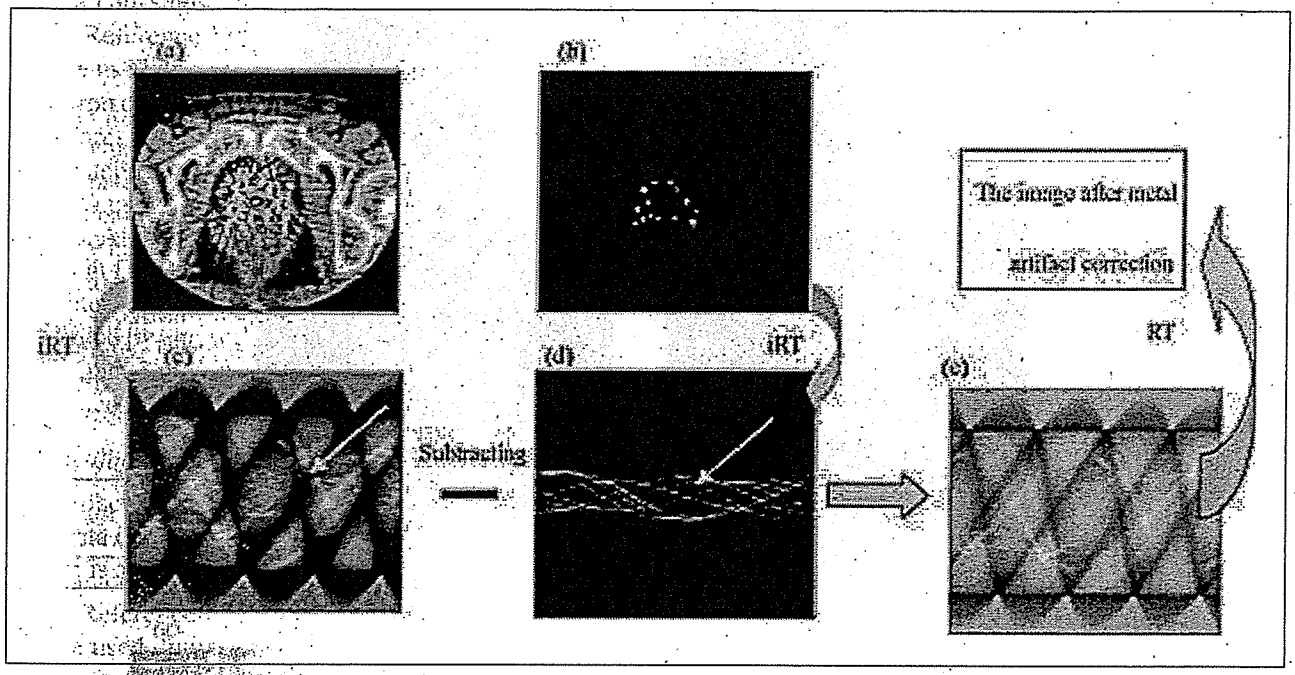

Fig. 2. Scheme of the method for metal artifact reduction.
(a) Original reconstructed CT image of implanted I-125 seeds.
(b) CT image of metal regions separated from (a).
(c) Sinogram of image (a) obtained by inverse Radon transform (iRT).
(d) Sinogram of image (b) obtained by iRT.
(e) Sinogram created by subtracting (d) from (c). Final image after metal artifact correction was obtained by Radon transform (RT). The white stripes highlighted by *arrows* represent the projection data of I-125 seeds that caused metal artifacts.

to the ABS recommendation as having a low-risk grade of prostate cancer (initial PSA <10 ng/ml, clinical stage <T2b, and Gleason score <7).[15] The average number of seeds implanted in these 32 patients was about 80. CT scanning and image import were as described for the phantom study. Written informed consent was obtained from the selected patient after the purpose and procedures of the study had been explained.

Results

Phantom study

Figures 3(a) and 3(b) show the reconstructed CT images of the prostate phantom. Window level and window widths were the same (WL -250, WW 1000). The original image introduced metal artifacts (Fig. 3(a)), and it was difficult to determine whether or not the seeds were separated. In the corrected image, in contrast, the artifacts appeared reduced and the individual seeds were distinguishable (Fig. 3(b)). Furthermore, seed orientation could be determined. Figure 3(b) clearly shows that one of the seeds is turned sideways.

Contrast in these images was not degraded when compared with the pre-correction images. Artifacts remained at the edge of the seeds.

Patient study

We next applied this method to patient data to confirm its suitability in clinical settings using the midgland of the prostate, in which many seeds are inserted in the same plane and the most severe metal artifacts are often seen. The pre-correction image showed a high degree of streaking artifacts (Fig. 4(a)), which prevent the identification of seed condition (number, orientation, and location, etc.) and would likely result in incorrect dosimetry. In the corrected images, in contrast, the artifacts appeared mitigated (Fig. 4(b)). Window level and window widths were the same as in the uncorrected image (WL 50, WW 500). The post-correction image was improved, and the number and orientation of seeds could be clearly determined (Fig. 4(b)).

Discussion

We investigated a subtraction-based reprojection approach to reduce CT metal artifacts caused by I-125 seeds and evaluated the clinical implications in post-implant dosimetry in prostate permanent brachytherapy.

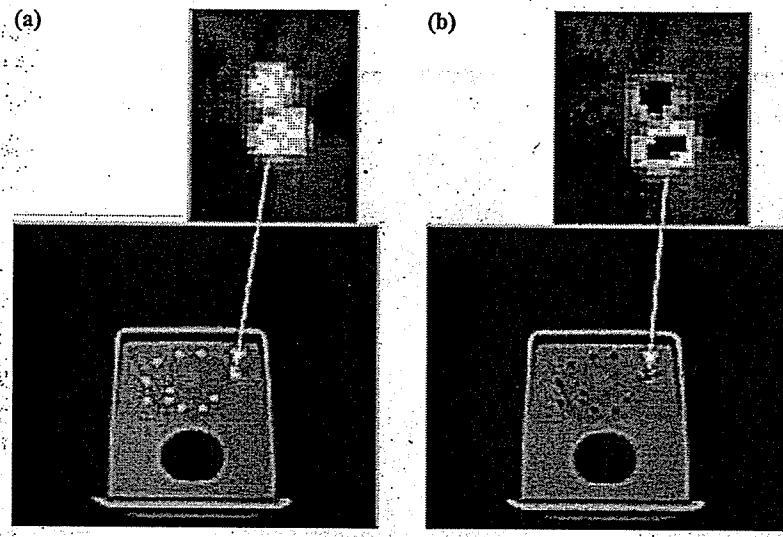

Fig. 3. CT images of the prostate phantom implanted I-125 seeds.
(a) Original image. The region highlighted by the *arrow* is magnified.
(b) Image after metal artifact correction.

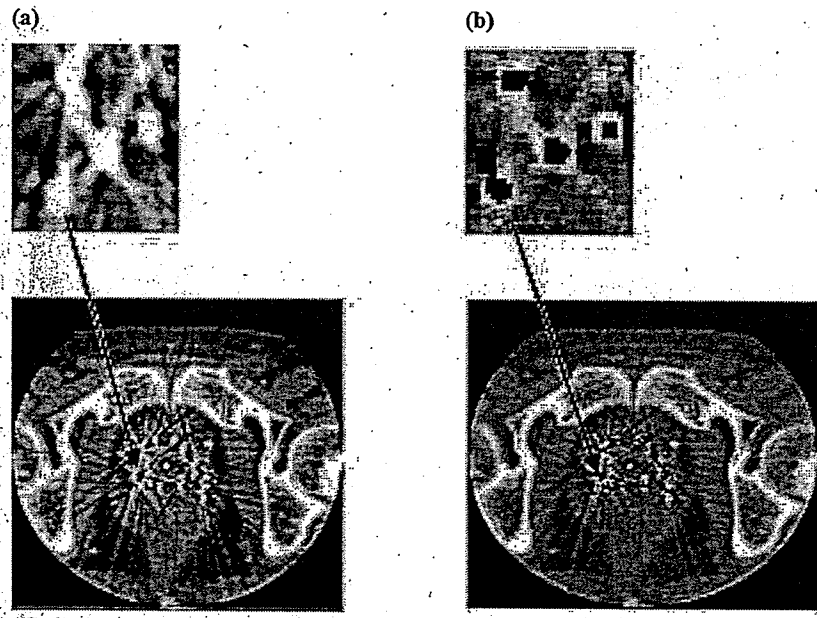

Fig. 4. CT images of a patient who received I-125 permanent implant brachytherapy.
(a) Original image. The region highlighted by the *arrow* is magnified.
(b) Image after metal artifact correction.

Accurate postimplant dosimetry requires correct identification of seeds and prostate.[2] CT-based postimplant dosimetry is hampered, however, by the presence of severe metal artifacts.[3] Many algorithms that identify seeds automatically are available,[16-19] but most require a significant degree of user intervention,[19] which considerably impacts the time required for dosimetry. Our approach is applicable to manual seed identification only, but can accelerate postimplant dosimetry in this use.

Although many authors have attempted to reduce metal artifacts using projection data,[7-11] few reports concerning a reduction in metal artifacts from many high-density objects such as I-125 seeds have appeared. Roeske *et al.* reported that the projection-interpolation method reduced the severe metal artifacts caused by the Fletcher-Suit applicator.[10] Their technique was highly

effective in simple situations, but was unsatisfactory in images that contained complex metal objects.[11] To overcome this, Xia *et al.* reduced CT metal artifacts caused by the Fletcher-Suit applicator using a hybrid approach.[11] They used raw projection data and performed separate reconstructions of metal and non-metal images from their estimated projections. The final image was then formed by appropriately combining the reconstructed metal and non-metal images. Unlike our approach, however, this process can involve the introduction of fusion errors. Although our approach also separates metal and non-metal images, it is performed in the raw projection data rather than the reconstructed image, obviating the possibility of distortion or fusion error.

Previously reported methods for metal artifact reduction have been based mainly on interpolation for missing projection.[6-11] While these methods are generally effective in reducing metal artifacts, permanent implant brachytherapy requires an understanding of seed condition (location, number, orientation, etc.) in terms of both the accurate calculation of dose from seeds as well as the elimination of streaks. For this purpose, we took an approach in which the edge of the seed was kept at high density while the center was kept at low density by direct subtraction of the projection data of the metal image from that of the original image. To our knowledge, this approach has not been reported previously.

In this study, we did not see a significant reduction of streaks (data not shown). However, we confirmed that the standard deviation (SD) of the CT value of post-correction images was lower than that of pre-correction images. When the SD is lower, it means that streaking is reduced.[8] Therefore, the artifact was reduced at least to some extent. Some streaking still remained because the metal region was not completely erased. Determination of individual seed thresholds will enable a more effective reduction in streaking, and thus more accurate identification of the prostate. In addition, this modified method can be adapted to other clinical situations such as imaging of head and neck cancer in patients with gold crown, and other sources of metal artifacts.

In conclusion, this method reduces metal artifacts from I-125 seeds, and has potential for decreasing the time required for and improving the accuracy of post-implant dosimetry. Although further improvements still can be made, this method is helpful for clinical use in prostate permanent implant brachytherapy, specifically in the identification of seeds and prostate. In addition, post-correction images obtained by our method can be suitable for seed identification. Using these images, a novel automatic seed identification system could be developed.

Acknowledgements

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ORIGINAL ARTICLE

CIH-Tokyo Experience with Breast-Conserving Surgery without Radiotherapy: 6.5 Year Follow-Up Results of 1462 Patients

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■ **Abstract:** When breast-conserving therapy was introduced at the Cancer Institute Hospital (CIH) in Tokyo in 1986, we instituted our own strategy as follows: 1) every effort is to be made for complete tumor resection while avoiding deformity of the breast, and 2) radiotherapy (RT) is applied only to the patients with positive surgical margins. This is, in turn, to clarify the group of patients in whom postoperative RT can be safely spared. Among 9670 patients operated on for primary breast cancer during the 16.5 year period from 1986 to 2002 at CIH, there were 2449 patients who underwent breast-conserving surgery (BCS). During the 6.5 years mean follow-up period, ipsilateral intrabreast tumor recurrence (IBTR) developed in 99 of the 2449 patients, with an overall rate of 4.0% and an annual rate of 0.62%. These 2449 patients were categorized into four subgroups according to either negative or positive margins and with or without radiotherapy. The IBTR rates and the number of patients in each subgroup were 5.5% in 1351 margin(–)RT(–) patients, 1.0% in 307 margin(–)RT(+) patients, 2.4% in 680 margin(+)RT(+) patients, and 4.5% in 111 margin(+)RT(–) patients. These results either with or without RT seem to be quite comparable to or even better than the results of BCS with RT reported from Western countries, where less emphasis seems to be placed on completeness of the local tumor resection with BCS, while RT is administered to basically all patients following BCS. IBTR was categorized into true recurrence (TR) and second primary lesion (SP) according to the margin status at the time of BCS, the former being lesions developed in patients with positive margins and the latter being those in patients with negative margins. It was demonstrated that in patients with positive margins, TR was much more common than SP, whereas in patients with negative margins, these incidences were just the opposite (i.e., TR was 60% less common than SP) and postoperative RT was effective in preventing both TR and SP, the effect on the latter being much more striking. With RT, the incidence of developing TR in patients who had positive margins was reduced to almost equal to that in margin(–) patients treated with no RT. Our method of IBTR categorization is based on biological consideration and detailed histopathologic examination, and appears to be the only biologically reasonable means so far that has been proposed for distinction between these two biologically different entities. TR and SP can be further reduced to exceptionally low levels in patients who received RT despite negative margins, though it would not seem reasonable to administer RT to all of these patients because the actual number of patients who would benefit is comparatively small. From these observations, it seems that our imaging, pathologic examination, and surgical approaches for patients who are candidates for BCS have been highly valid, and our criteria for sparing postoperative RT as well as categorization of IBTR into TR and SP are quite appropriate. Although our results with BCS seem to deserve wide recognition, they are not from randomized clinical trials, so the findings must be confirmed by a study in order to investigate whether the results at CIH can be applied generally at other institutions. ■

Key Words: breast cancer extent, breast-conserving surgery, complete surgical excision, local recurrence, postoperative radiotherapy, surgical margin

Breast-conserving surgery (BCS), which has been established as a valid first-line treatment for primary breast cancer (1–3) is now used all over the world, including Japan (4), where BCS replaced mastectomy as the most widely used treatment for breast cancer in 2003 (5). Although postoperative radiation therapy (RT) is generally believed to be mandatory following BCS, that may not be the case for patients in whom complete ablation of local disease by surgical excision has been accomplished.

It is estimated that approximately 20–30% of the breast cancer patients in Japan do not receive postoperative RT to the conserved ipsilateral breast (4), which indicates

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there is a shared understanding among breast specialists in Japan that postoperative RT can be modified or omitted after BCS, at least in some subsets of patients. Since inadequate excision of the primary lesion appears to be one of the most important causes of local failure after BCS (6–9), it is absolutely necessary to have a thorough determination of the extent of complex primary breast cancer lesions by diagnostic imaging in addition to consideration of breast anatomy and breast cancer pathomorphology in each individual case to execute the optimum operative procedure based on the results of such evaluation, and to perform a thorough postoperative histopathologic examination of the resected specimen in order to determine the necessity of postoperative RT to the preserved ipsilateral breast.

Breast-conserving therapy was introduced at Cancer Institute Hospital (CIH), Tokyo, Japan, in 1986, and a policy was adopted not to deliver postoperative RT to those in whom negative surgical margins can be obtained. All the prerequisite conditions required to accomplish our goal of ensuring negative margins have been carefully observed at CIH (10,11).

This report deals with a retrospective analysis of 2449 patients who underwent BCS, and special emphasis is placed on the results with BCS without RT. Although our experience with BCS has been presented at various conferences and in various journals in Japan (4,10,11), this is the first publication in Western literature. It is our great pleasure to present the results of our efforts over the past 20 years at CIH-Tokyo, and we would be more than happy to receive any comments or criticisms about our approach, particularly from abroad.

PATIENTS AND METHODS

The indications for BCS have gradually increased over the years at CIH since its introduction in 1986. During its early years (i.e., 1986–1993), BCS composed less than 20% of all breast cancer operations, and in subsequent years (1994–1997) it became gradually more common (20–40%). Thereafter nearly 50% of patients with operable breast cancer were treated with BCS, and the most recent figure was 51.5% in 2004. In the early years, the majority of BCS patients were those who had T1N0M0 disease, and a gradual expansion of the indications for BCS occurred in the mid- to late-1990s. Some T2 lesions, such as tumors larger than 3 cm, began to be included, nodal status became more or less disregarded, and the tissue volume in relation to breast size that was excised in order to secure negative margins, as well as postoperative esthetic appearance, were considered some of the main determining factors for BCS.

Breast-conserving surgery was largely avoided in cases with intensive lymphatic permeation demonstrated in the biopsy specimen taken by core needle biopsy, Mammotome, or probe (exploratory) lumpectomy, and also in cases with invasive micropapillary carcinoma. Mastectomy was performed in patients who did not wish to have BCS despite their medical suitability.

During the 16.5 year period from July 1986 to December 2002, there were 2449 patients who underwent BCS, which consisted of approximately 25% of 9670 breast cancer patients operated on at CIH during the same period. The original number of patients who were planned to have BCS was 2686, and among them there were 237 patients (9%) in whom the breast could not be saved because of strongly positive surgical margins. Of these 2449 patients, 1462 patients (60%) did not receive postoperative RT, whereas 987 patients (40%) received it. The 2449 patients who underwent BCS at CIH were subjected to a retrospective analysis (Fig. 1).

Preoperative Multimodal Imaging Diagnosis

In order to accomplish our goal (i.e., complete surgical eradication of the tumor in the breast), it is essential to examine the extent of the tumor by taking full advantage of various imaging modalities currently available (mammography [MMG], ultrasound (US), magnetic resonance imaging [MRI], computed tomography [CT], etc.). Contrast-enhanced MRI and CT (12) have been particularly useful in depicting the extent of breast tumors, as their images often show wider tumor involvement than that shown by routinely used imaging techniques such as MMG and US. For patients with pathologic nipple discharge,

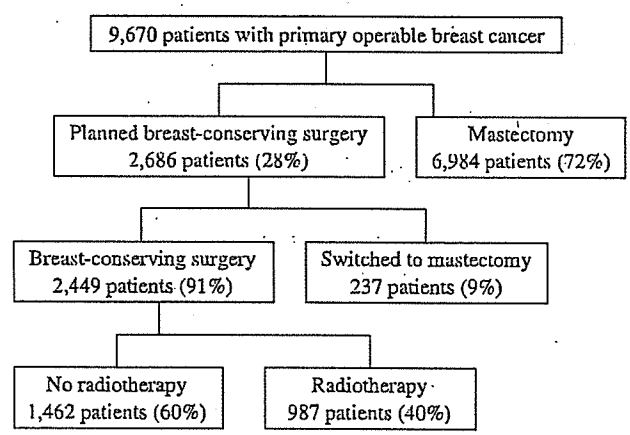

Figure 1. Treatment profile of patients with operable breast cancer at CIH (1986–2002).

ductography and mammary ductoscopy were also employed as indicated (13).

Surgical Resection Strategy

During surgery, every effort is made to completely remove the cancer while taking adequate care to avoid deformity of the breast (10,14). The skin overlying the tumor is resected, thin skin flaps are prepared, staying superficial to the superficial fascia, and the breast parenchymal resection is done along a line at a distance of 1.5–2.0 cm from the tumor edge, which is marked with indigo carmine solution mixed with xylocaine jelly prior to making the skin incision. The breast parenchymal resection is carried vertically down to the pectoral fascia, which is removed. As a rule, the margins are liberally evaluated on the specimen taken from the margin of the remaining breast. If the margin is rated as positive, in cases of reresection, or in cases with intensely involved margins, mastectomy is performed as indicated.

Serial Pathologic Examination on Surgical Specimens

Pathologic examination of 5 mm wide serial sections of the surgical specimen serves as the core of BCS at CIH. Meticulous care is taken to be certain as to the status of the surgical margin, as described in previous reports from CIH (10,14) (Fig. 2). If the tumor cells are found 5 mm or more away from the cut plane, the margin is rated as

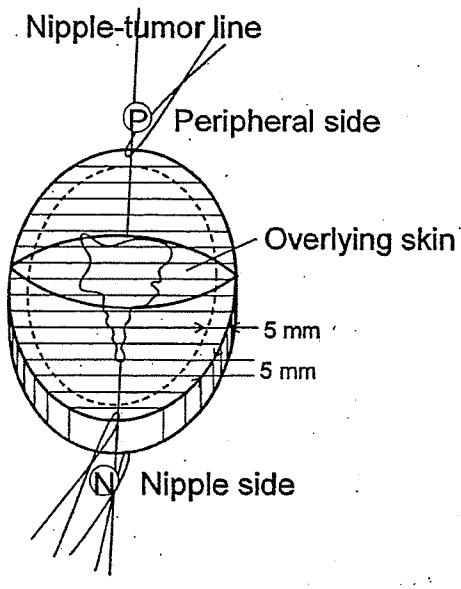

Figure 2. Rigorous pathologic examination of a surgical specimen of BCS. Sutures are placed for orientation and 5 mm wide serial sections at right angles to the nipple-tumor line are made for pathologic examination.

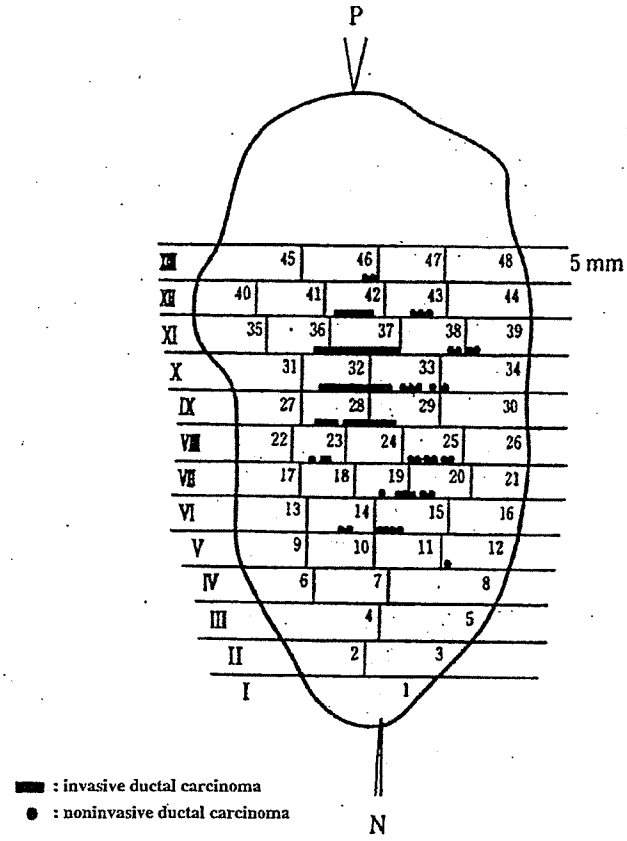

Figure 3. Cancer mapping shows histologically delineated tumor extent in the surgical specimen. Postoperative radiotherapy is not given in this case because of the negative margins.

negative (Fig. 3). If tumor cells are found within 5 mm of the cut plane, the margin is rated as positive (Fig. 4). Positive margin status of the surgical specimen was further categorized according to the type and the amount of tumor at the margin, as well as the presence or absence of lymphatic vessel invasion.

Radiotherapy

The need for postoperative RT was determined by the margin status, in that it was given to patients with positive margins (i.e., presence of tumor cells within 5 mm of the resection line) and it was spared in patients with negative margins. There were some exceptions to this rule, and various factors (lack of surgical biopsy data with uncertainty of margin status, risk relating to multiplicity of the disease and family history, the patient's wishes, and concomitant medical as well as other relevant conditions) were taken into consideration as to the actual application of RT. In general, it was given to patients who were expected to benefit from RT.

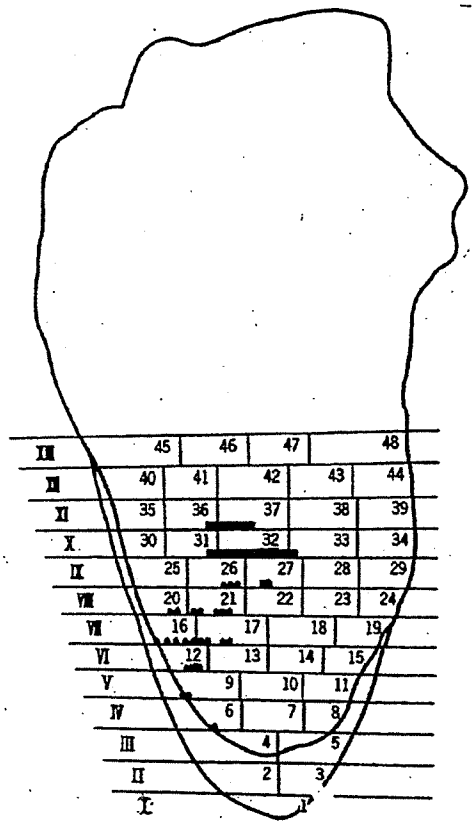

Figure 4. Cancer mapping shows histologically delineated tumor extent in the surgical specimen. Postoperative radiotherapy is given in this case because of positive margins.

Radiation therapy following BCS is given in 4–6 MV linac, CT-simulated, opposing tangential fields, with 50 Gy/25f plus boost (electron) 16 Gy/8f for margin(+) cases, and 50 Gy plus 10 Gy for margin(–) cases.

Adjuvant Chemoendocrine Therapy

Postoperative adjuvant chemoendocrine therapy was applied according to the standard regimens of the time, regardless of whether the patient was treated with RT or not, and was not different from that for mastectomy patients. In general, until the latter half of the 1990s, cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) was used for node-positive patients, which was gradually replaced by cyclophosphamide, Adriamycin, and 5-fluorouracil (CAF). For estrogen receptor (ER)-positive patients, tamoxifen was administered for 2 years in earlier years and 5 years in more recent years.

Ipsilateral Intrabreast Tumor Recurrence

Ipsilateral intrabreast tumor recurrence (IBTR) can be divided into two categories: true recurrence (TR) of previously treated breast cancer and progression of a second primary (SP) breast cancer. This categorization is made as follows: IBTR in patients with positive surgical margins is defined as TR, and that in patients with negative margins is defined as SP, which, by definition, should principally be accompanied by an in situ component in the lesion (15) (Fig. 5).

Data Collection and Analysis

All patient data including demographic, imaging, clinical, as well as pathologic staging, modes of treatment, and outcome parameters that were included in a computerized database at CIH were utilized, and patients' individual medical records were reviewed when necessary.

RESULTS

As of October 2004, with a mean follow-up period of 6.5 years, among 2449 patients who had undergone BCS,

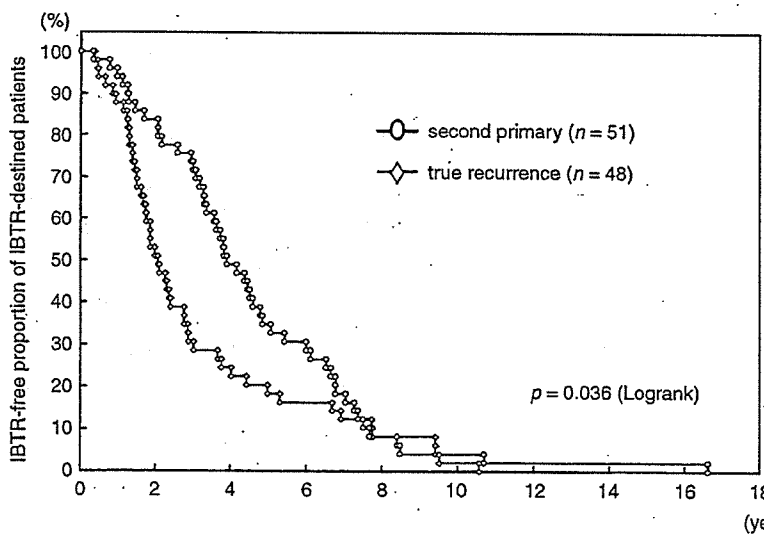

Figure 5. Occurrence of ipsilateral intrabreast recurrence and its timing during the follow-up period. Note that SP tends to occur later as compared to TR, indicating the difference in the amount of tumor cells at the inception.

Table 1. Ipsilateral IBTR Following BCS Categorized According to without or with Radiotherapy

	BCS, total	Without radiotherapy	With radiotherapy
Number of patients	2449	1462	987
Number of IBTR	99 (4.0%)	80 (5.5%)*	19 (1.9%)*
Annual rate, IBTR	0.62%	0.84%	0.30%
True recurrence	51 (2.1%)	35 (2.4%)**	17 (1.7%)**
Second primary	47 (1.9%)	45 (3.1%)***	2 (0.2%)***

*$p < 0.005$; **$p = 0.305$, ***$p < 0.005$.
Subjects: July 1986 to December 2002 at CIH.
Observation period through October 2002; mean observation period 6.5 years.

99 patients (4.0%) developed IBTR with an annual incidence rate of 0.62% (Table 1). Eighty of the 99 patients were among 1462 RT(–) patients and 19 were among 987 RT(+) patients, with IBTR rates of 5.5% and 1.9%, respectively; the difference between these two groups was statistically significant.

Breakdown of the IBTR data into TR and SP showed that TR occurred in 35 patients in the RT(–) group(2.4%) and 17 patients in the RT(+) group (1.7%), whereas SP was observed in 45 patients in the RT(–) group(3.1%) and 2 in the RT(+) group (0.2%). The incidence rate of developing SP in the ipsilateral breast was much lower in the RT(+) group than in the RT(–) group; the difference being statistically significant ($p < 0.005$) (Table 1).

Ipsilateral IBTR was analyzed in relation to margin status, which is shown in Table 2 with its breakdown data. Among 99 patients with IBTR, 78 were in the margin(–) group and 21 were in the margin(+) group, their incidence rates being 4.7% and 2.6%, respectively. Although there was no statistical difference in the occurrence of TR between the margin(–) and margin(+) groups, SP was much more common in the margin(–) group (Table 2).

Indication criteria of postoperative RT were breached at times for various reasons as described earlier. There were 307 patients who received RT even with negative surgical margins—this subgroup of patients being denoted

Table 2. IBTR Following BCS Categorized According to Margin Status

	BCS, total	Margin(–)	Margin(+)
Number of patients	2449	1658	791
Number of IBTR	99 (4.0%)	78 (4.7%)	21 (2.6%)
True recurrence	51 (2.1%)	31 (1.9%)	20 (2.5%)
Second primary	47 (1.9%)	46 (2.8%)*	1 (0.1%)*

*$p < 0.005$.
Subjects: July 1986 to December 2002 at CIH.
Observation period through October 2002; mean observation period 6.5 years.

Table 3. IBTR Following BCS Categorized According to Margin Status and without or with Radiotherapy

	RT(–) ($n = 1462$ patients)		RT(+) ($n = 987$ patients)	
	Margin(–)	Margin(+)	Margin(–)	Margin(+)
No. of patients	1351	111	307	680
Mean age (years)	54.2	61.8	50.4	51.6
Mean tumor size	2.0 cm	2.5 cm	2.2 cm	2.3 cm
No. of IBTR	75 (5.5%)	5 (4.5%)	3 (1.0%)	16 (2.4%)
Annual rate	0.85%	0.69%	0.14%	0.37%
True recurrence	29 (2.1%)	5 (4.5%)	2 (0.7%)	15 (2.2%)
Annual rate	0.32%	0.69%	0.10%	0.34%
Second primary	46 (3.4%)*	0	1 (0.3%)	1 (0.2%)*
Annual rate	0.52%	0	0.05%	0.03%

*$p < 0.005$.
Subjects: July 1986 to December 2002 at CIH.
Observation period through October 2002; mean observation period 6.5 years.

as RT(+)margin(–)—and 111 patients did not receive RT despite documented positive surgical margins—denoted as RT(–)margin(+). Thus 2449 patients who underwent BCS were categorized into four subgroups of patients: RT(–)margin(–), RT(+)margin(+), RT(+)margin(–), and RT(–)margin(+). The first two subgroups were composed of those who were treated in accordance with our criteria for BCS without or with postoperative RT. The mean age and tumor size are also listed in order to show the differences among these subsets of the patients (Table 3).

The subgroup of RT(–)margin(–), with 1351 patients, represents the key element of this study, since it is composed of the patients who were not given RT because of confirmed negative surgical margins. There were 29 patients (2.1%) with TR and 46 patients (3.4%) with SP, the latter being 1.6 times more common than the former. This same observation (i.e., more frequently encountered SP as compared to TR) was also made in the RT(–) group, as previously noted, since the RT(–)margin(–) subgroup was the main component of the RT(–) group.

Among 680 patients in the RT(+)margin(+) subgroup, there were 15 patients (2.2%) with TR and only 1 patient (0.2%) with SP. The rare occurrence of SP as compared to TR was also noted in the RT(+) group, as previously noted, since the RT(+)margin(+) subgroup was the main component of the RT(+) group. As to the incidence of developing SP in the ipsilateral breast, the difference between the RT(–)margin(–) subgroup and the RT(+)margin(+) subgroup was statistically significant ($p < 0.005$), which is consistent with the difference observed between the RT(–) group and RT(+) group.

The TR rate was highest in the RT(–)margin(+) subgroup and lowest in the RT(+)margin(–) subgroup. Among 111 RT(–)margin(+) patients, there were five patients

Table 4. Degree of Positive Margins and Incidence of True Recurrence

Status of positive margins	Total	RT(–)	RT(+)
In situ type	2.0% (5/249)	2.9% (1/35)	1.9% (4/214)
(in one or two specimens)	1.7% (4/240)	2.9% (1/35)	1.5% (3/205)
Invasive type	5.7% (4/70)	16.7% (2/12)	3.4% (2/58)
(in more than two specimens)	6.3% (5/79)	16.7% (2/12)	4.5% (3/67)
Lymphatic vessel invasion(+)	20.0% (3/15)	50.0% (1/2)	50.0% (1/2)

(4.5%) with TR and no patient with SP. Their mean age was 61.7 years, 10 years older than the other subgroups, and they had somewhat larger tumors and had a higher mortality rate (10/111; 9%) than any other subgroup. In the RT(+)margin(–) subgroup, with 307 patients, there were only 2 patients (0.7%) with TR, the incidence being one-third of that in the RT(–)margin(–) subgroup, and there was only 1 patient with SP.

Intrabreast tumor recurrence was then analyzed in relation to the observed amount of tumor cells at the margin and lymphatic vessel invasion; the results are shown in Table 4. It appears that RT reduced the rate of IBTR in each subset of patients with positive margins, and that the effect was more evident in the subsets of patients with the invasive type or multiple positive sites. Furthermore, it should be noted that IBTR became quite common when lymphatic vessel invasion was demonstrated in the surgical specimen. Among 51 patients who developed TR, 20 patients (39.2%) showed lymphatic vessel invasion in the surgical specimen and 17 patients (33.3%) had accompanying distant metastasis.

DISCUSSION

Although Formenti and Green (1) state that five prospective randomized trials consistently confirmed better local control when radiation is added to BCS for T1 invasive breast cancer, it would still be reasonable to raise the question of whether RT is required for every patient undergoing BCS (3,10,11). Originally the Cleveland Clinic reported a local recurrence rate of 10.9% among women undergoing BCS without RT (16). Veronesi et al. (17,18) reported that in 273 cases followed up for 3.3 years after treatment by quadrantectomy alone, the incidence of IBTR was 8.8%, with an annual incidence of 2.7%. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial reported results for BCS without RT, with an unacceptably high local recurrence rate of 39.2% for a mean follow-up period of 20 years with a calculated annual incidence rate of 2.0% (19). In a phase II single-arm trial, the Joint Center of Radiation Therapy (JCRT) selected patients with a very favorable prognosis for BCS alone (20). The rate of local failure was 16% after a median follow-up of 56 months, and this trial was closed prematurely. Several other randomized trials compared BCS alone with BCS and RT, and showed that the IBTR rate was higher without RT, but that the survival rate was not significantly different (3).

It has been repeatedly shown that close or involved margin status is one of the most significant predictors of increased local recurrence (8,9), and reports from many Western institutions as well as from many Japanese facilities clearly suggest the importance of negative surgical margins (3,4,10). Although in the NSABP B-06 trial it was requested that the margin should be tumor negative for recruitment to the study (19), it can be roughly estimated that the percentage of cases with positive margins would have been more than 50% had they been examined by our pathologists. Many of these reports state little about the methods utilized in their studies for pathologic examination (21). The NSABP B-06 trial refers to the method of examining the surgical margins with a rather simplified shaving method (19). Veronesi et al. (18) state that at least five sections of 5 mm width are to be examined. If only several representative strips are examined at the margin, the margin status as well as the extent of cancer cannot be conclusively clarified.

It seems that the methods of histopathologic examination used in many of these reports may well be suboptimal, and that the addition of postoperative RT could have compensated for suboptimal pathologic examination and consequently suboptimal surgical management in many of these trials. There might be some discrepancies between Japan and Western countries in regard to diagnostic and therapeutic approaches to breast cancer, which in part may stem from possible differences in breast cancer biology. There was one report dealing with comparative breast pathology nearly 30 years ago (22), and it has been suggested that among Japanese patients, the percentage of cases with differentiated adenocarcinoma is higher and that with undifferentiated or lobular cancer is lower. The present study has yielded no answer to the question pertaining to the incidence or pattern of IBTR in relation to each histopathologic subtype. These issues are quite important to explore in relation to BCS and its subsequent IBTR and must be addressed in the future.

One of the most significant factors responsible for positive margins is the component of intraductal carcinoma (IDC) around an invasive carcinoma, and indeed IDC was found to be responsible in 78% of patients (249 of 319 cases) in our series.

It is believed that all breast cancers begin at one point (from a single cell). The cancer then spreads through the mammary ducts and stroma in a contiguous manner, much like oil spreading on a pan; it does not show any skipping or other spreading patterns. Our pathologic diagnosis of breast cancer is based on the view that breast cancer invading the stroma does not reenter the mammary duct. We have not encountered any event that contradicts this view (15). In light of this biological concept of contiguous spread of tumor cells, it would be quite reasonable to believe that a clearance of 5 mm is quite sufficient to be sure about near-perfect negative margins, on condition that all the detailed histopathologic examinations are undertaken on the surgical specimen, as demonstrated in Figures 2–4. A varying distance of clear surgical margins has been suggested; Silverstein et al. (7) demonstrated that RT did not further reduce local recurrence among those whose tumors were excised with margins of 10 mm or more. For ductal carcinoma in situ (DCIS), the Radiation Therapy Oncology Group (RTOG) study requested that excision margins be at least 3 mm (3), Boyages et al. (8) suggest clear surgical margins of at least 5 mm, but preferably 10 mm for low-grade, small DCIS if RT is to be omitted, and pathologically documented 1 cm negative margins were among the criteria set by the Joint Center for Radiation Therapy (JCRT) (20). By referring to these reports and by counting on reliable, detailed, precise pathologic diagnoses at CIH, a 5 mm clearance was chosen as the critical point.

Pathologic examination of 5 mm width sections serves as the core of BCS at CIH, although we cannot be dogmatic about the desirable distance because we are still uncertain about what constitutes adequate margins. The evaluation of margin widths requires complete tissue processing, without which involved margins and invasive foci may go unrecognized. At CIH, in order to secure definitely negative surgical margins, the holoblastic cleavage technique is used with complete tissue processing of the surgical specimen, which makes the distinction between cancer and benign conditions easier by elucidating their essential features. Thus a judgment as to whether invasive versus noninvasive carcinoma or positive versus negative margins is not very difficult to make since these determinations can be made histopathologically by observing static elements on the slides.

The margin(+) rate, which is the critical point for requirement of RT, has been nearly 50% since 1997, when indications for BCS were further expanded and the actual number of BCS cases increased to nearly half of all breast cancer surgeries; the most recent margin(+) rate was 46% in 2003. In general, a higher positive rate of surgical margins has been reported in Japan than in Western countries, which may be related to the more detailed pathologic examination practiced in Japan. Indeed, it should be noted that the multiple-cancer detection rate rose from 5% to 7% with 5–10 sections to 21% when 11 or more sections were examined (23).

Despite this increase in BCS at CIH, the annual incidence of IBTR has remained unchanged, which is suggestive of the stability of pathologic examination as well as the surgical approach to BCS at CIH. Our results with 6.5 years follow-up, overall and of any subgroup, seem to be comparable to or better than the results reported in Western countries, where less emphasis seems to be placed on complete local resection of tumors with BCS and RT is administered to essentially all the patients following BCS seemingly based upon the belief that lumpectomy is by definition cytoreductive only and that more curative treatment is RT (18).

Age at diagnosis has been shown to be a factor that is predictive of recurrence, and the rate of local recurrence after BCS tends to be higher for younger women (8,18,24). Veronesi et al. (17,18) noticed that IBTR was higher in patients in the less than 55 years of age group than in the more than 55 years group. As observed in this series, the incidence of breast cancer in Japan is slightly higher in premenopausal than in postmenopausal women, with the peak age being between the late 40s and early 50s, although the incidence of postmenopausal breast cancer has been rising steadily. Thus the low incidence of IBTR in this report seems to be noteworthy.

There have been isolated trials to distinguish IBTR into two biologically different entities, namely TR of previously treated breast cancer and SP. Most recurrences occur in the immediate vicinity of the primary surgical site, which suggests that the recurrences arise from tumor cells that remain after incomplete surgical excision rather than from separate areas of DCIS (8). Veronesi et al. (18) drew a distinction between the two on the basis of the 2 cm distance between the previous operative scar and the new lesion, which does not seem to be necessarily rational in light of the biological behavior of breast cancer (15). Our method is based on biological considerations and detailed histopathologic examination, and appears to be the only biologically reasonable method thus proposed to distinguish these two entities.

Intrabreast tumor recurrence categorized into TR and SP was further analyzed in each subgroup. It was demonstrated that in patients with positive margins, TR was much more common than SP, whereas in patients with negative margins, these incidences were just the opposite

(i.e., TR was 60% less common than SP), and postoperative RT was effective in preventing both TR and SP, the effect to the latter being much more striking. Indeed, the occurrence of SP in the RT(+)margin(+) subgroup was 1/17 of that in the RT(–)margin(–) subgroup. With RT, the incidence of developing TR in patients who had a positive margin was reduced to almost equal to that in margin(–) patients treated without RT. A high incidence of both TR and SP would be expected in the RT(–)margin(+) subgroup, since the patients in this subgroup did not receive RT despite positive margins. Their mean age was 61.7 years, 10 years older than the other groups, and they had a higher mortality rate as compared to the other subgroups. Their concomitant medical as well as other relevant conditions largely prevented these patients from receiving RT.

Although there have been many reports demonstrating the effectiveness of RT (1,3,17,18,24–26), there has been not a single study to clarify the targeting component for RT following BCS. Our results suggest that RT is effective in reducing both TR and SP following BCS, the effect being more prominent in preventing SP in the preserved ipsilateral breast. Thus our report may well represent the first one dealing with the targeting component of RT following BCS.

Recurrence seems to depend largely on the amount of residual tumor following BCS. The incidence of IBTR was higher with positive invasive margins than with positive in situ margins, and rose as the number of tumor-positive sections increased, as previously shown in Table 4. Because most patients with strong positive margins are usually treated with mastectomy, the amount of tumor left unresected in patients with positive margins in BCS should not be too large, and it stands to reason that RT should be quite effective. Indeed, the effect of RT was quite pronounced in reducing IBTR in cases with positive margins of invasive type in contrast to cases with positive margins of in situ type. It thus should be noted that RT is essential in cases with positive margins of invasive type, which is in agreement with the observations of Silverstein et al. (6,7), who reported that the incidence of IBTR was more than 15% among the RT(–) cases of invasive carcinoma.

One other significant factor related to recurrence is lymphatic vessel invasion, which is a dynamic factor, and may be difficult to detect, in contrast to finding static tumor cells, which are usually confined within the mammary duct at the margin. It is important to keep in mind that lymphatic vessel invasion can be positive even when the margin shows no lymphatic vessel invasion. The importance of lymphatic vessel invasion has been repeatedly suggested by many investigators. The JCRT noted no lymphatic or vascular invasion as one of the criteria for BCS without RT, in addition to pathologically documented 1 cm negative margins (20), and more recently at the 9th St. Gallen conferences in 2005, the panel accepted peritumoral vessel invasion, especially lymphovascular invasion, as a new adverse prognostic feature (2). In our series, with positive lymphatic vessel invasion, the incidence of TR was 50% (1 of 2) without RT and was 15.4% (2 of 13) with RT. Thus we make it a rule to recommend RT, or mastectomy, if lymphatic vessel invasion is intense in cases where lymphatic vessel invasion is observed inside and outside an invasive carcinoma lesion, particularly cases where the lymphatic lumen is dilated.

Table 5. Incidence of True Recurrence, Lymphatic Vessel Invasion, and Accompanying Distant Metastasis Evaluated Chronologically

Years	No. of BCS	No. of TR	No. with lymphatic vessel invasion	No. with metastasis[a]
1986–1993	312	12 (3.8%)	3 (25%)	3 (25%)
1994–1997	638	14 (2.2%)	6 (43%)	5 (36%)
1998–2002	1449	25 (1.7%)	11 (44%)	9 (36%)
Total	2449	51 (2.1%)	20/51 (39.2%)	17/51 (33.3%)

[a]Distant metastasis.

The relationship between TR, lymphatic vessel invasion, and distant metastasis was evaluated in relation to the percentage of BCS among breast cancer surgeries since 1986 by dividing the 16.5 years into three periods (Table 5). While BCS increased gradually, the TR rate remained quite stable at low levels. There appeared to be a relationship between the percentage of cases showing lymphatic vessel invasion and the accompanying rate of distant metastasis. Thus it can be justifiably speculated that lymphatic vessel invasion serves as a useful risk factor not only for IBTR and TR, but also for distant metastasis.

Among the 51 TR diagnosed cases, 17 patients (33%) had distant metastasis upon detection of TR and 8 (15%) of them succumbed. These data were contrasted to the quite low figures in 48 patients with SP, the corresponding rates of distant metastasis and mortality being 0.8% and 0.2%, respectively. It also can be speculated that the volume of residual tumor would be reflected in the timing of IBTR, and that the volume of SP is minimal compared to the volume of tumor left unresected in margin(+) cases. It also appears that SP can be effectively controlled by RT for quite a long time (Fig. 5). These observations strongly support our categorization of IBTR into TR and SP as biologically adequate and valid.

Margin status with 5 mm clearance has been quite satisfactory in determining the need for RT at CIH. It is