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Clinical Investigation

Identifying Patients Who Are Unsuitable for Accelerated Partial Breast Irradiation Using Three-dimensional External Beam Conformal Techniques

Naoto Shikama, M.D.,* Naoki Nakamura, M.D.,† Naoaki Kunishima, M.D.,† Shogo Hatanaka, M.S.,† and Kenji Sekiguchi, M.D.†

*Department of Radiation Oncology, Saitama Medical University International Medical Center, Saitama, Japan; and †Department of Radiation Oncology, St. Luke's International Hospital, Tokyo, Japan

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Summary

Fifty consecutive patients with Stage 0–II unilateral breast cancer who underwent breast-conserving surgery were subsequently replanned using three-dimensional conformal radiotherapy (3D-CRT) accelerated partial breast irradiation (APBI) techniques. Dose–volume histogram (DVH) constraints were satisfied in 20% of patients with a long cranio-caudal surgical clip distance (CCD; ≥5.5 cm) and 92% of those with a short CCD ($p < 0.0001$). Patients with long CCDs might be unsuitable for 3D-CRT APBI due to nonoptimal DVH constraints.

Purpose: Several recent studies reported that severe late toxicities including soft-tissue fibrosis and fat necrosis are present in patients treated with accelerated partial breast irradiation (APBI) and that these toxicities are associated with the large volume of tissue targeted by high-dose irradiation. The present study was performed to clarify which patients are unsuitable for APBI to avoid late severe toxicities.

Methods and Materials: Study subjects comprised 50 consecutive patients with Stage 0–II unilateral breast cancer who underwent breast-conserving surgery, and in whom five or six surgical clips were placed during surgery. All patients were subsequently replanned using three-dimensional conformal radiotherapy (3D-CRT) APBI techniques according to the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39 and Radiation Therapy Oncology Group (RTOG) 0413 protocol. The beam arrangements included mainly noncoplanar four- or five-field beams using 6-MV photons alone.

Results: Dose–volume histogram (DVH) constraints for normal tissues according to the NSABP/RTOG protocol were satisfied in 39 patients (78%). Multivariate analysis revealed that only long craniocaudal clip distance (CCD) was correlated with nonoptimal DVH constraints ($p = 0.02$), but that pathological T stage, anteroposterior clip distance (APD), site of ipsilateral breast (IB) (right/left), location of the tumor (medial/lateral), and IB reference volume were not. DVH constraints were satisfied in 20% of patients with a long CCD (≥5.5 cm) and 92% of those with a short CCD ($p < 0.0001$). Median IB reference volume receiving ≥50% of the prescribed dose (IB-V_{50}) of all patients was 49.0% (range, 31.4–68.6). Multivariate analysis revealed that only a long CCD was correlated with large IB-V_{50} ($p < 0.0001$), but other factors were not.

Conclusion: Patients with long CCDs (≥5.5 cm) might be unsuitable for 3D-CRT APBI because of nonoptimal DVH constraints and large IB-V_{50}. © 2012 Elsevier Inc.

Keywords: Partial breast irradiation, Breast cancer, Radiotherapy, 3D-conformal radiotherapy, Toxicity

Reprint requests to: Naoto Shikama, M.D., Department of Radiology Oncology, Saitama Medical University International, Medical Center, 1397-1 Yamane, Hidaka-City, Saitama, 350-1298 Japan. Tel: +81-42-984-4111; Fax: +81-42-984-4136; E-mail: nshikama0525@gmail.com

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Introduction

Breast-conserving therapy including partial resection and postoperative whole breast irradiation has constituted standard care for patients with early breast cancer (1). Some Phase III trials of postoperative radiotherapy and systematic reviews have revealed that omission of postoperative radiotherapy increases recurrence in breasts by threefold, and increases absolute breast cancer mortality by more than 5% (1, 2). Several reasons, including the long-term radiation schedule, level of surgeon involvement in the radiation decision, patient refusal, and comorbidity, lead to omission of postoperative radiotherapy. In fact, approximately 25% of patients who underwent conservative surgery did not receive postoperative radiotherapy in the United States (1991–2002) (3).

Approximately 85% of breast recurrences after breast conservative therapy develop in the vicinity of the tumor bed; several percent appear "elsewhere" in the breast, and the absolute number of such failures is very low (4). In the past decade, prospective clinical trials and retrospective studies evaluated the efficacy and safety of accelerated partial breast irradiation (APBI) using small radiation fields and a large fraction size. These studies reported good treatment outcome and minimal late toxicities after a short follow-up duration (4–6). However, two recent studies reported that the large volume of irradiated breast tissue was correlated with higher incidences of late severe toxicities including soft-tissue fibrosis and fat necrosis of the breast, which were clearly associated with marked cosmetic compromise (7, 8). Appropriate eligibility criteria and treatment schedules for APBI should be established to avoid late severe toxicities. The present study aimed to identify patients who are unsuitable for APBI because of the potential risk of late toxicities including soft-tissue fibrosis and fat necrosis after APBI using three-dimensional conformal radiotherapy (3D-CRT).

Methods and Materials

Patients

The study population consisted of 50 consecutive patients with unilateral breast cancer, at Union for International Cancer Control 7th Stage 0–II, who received breast-conserving therapy between April 2009 and September 2009. Median patient age was 49 years (range, 33–73). The right-to-left ratio of the ipsilateral breast (IB) was 25:25, and the medial-to-lateral ratio of the tumor location was 19:31. All patients underwent partial breast resection, and five or six surgical clips were placed at the borders of the surgical bed. Thirty-one patients had pathological T stage 1 (pT1), 7 patients had pT2, and 12 patients had pTis. Sentinel node biopsy and/or axillary node dissection revealed that 47 patients had pathological N stage 0 (pN0), and 2 patients had pN1. pN stage was not evaluated for 1 patient.

Radiation treatment planning

All patients were placed in the supine position and underwent computed tomography (CT) as part of the standard planning for whole breast irradiation. CT scanning was performed using a 2-mm thick-slice and a slice step of 2 mm; slices extended to completely cover the bilateral whole breast, lung, heart, thyroid, and a 5-cm margin in the cranial and caudal directions. No respiratory control was used. The following structures were contoured for the planning of 3D-CRT: surgical clips, clinical target volume (CTV), planning target volume (PTV), ipsilateral whole breast (IB) reference, IB reference excluding PTV (IB-PTV), contralateral breast, heart, bilateral lungs, and thyroid. To keep the probability of comparison consistent with outcomes of other studies, the contouring of IB reference was made up using an automated contouring method applied by the National Surgical Adjuvant Breast and Bowel Project (NSABP B-39) and Radiation Therapy Oncology Group (RTOG 0413) protocol (9). CTV was defined as the volume bound by uniform expansion of surgical clips by 1.5 cm in all dimensions, excluding the pectoralis muscles, chest wall, lung, heart, pericardial fat, and 5 mm beneath the skin (9). PTV was defined as the volume bound by uniform expansion of CTV by 1.0 cm in all dimensions. PTV_EVAL, the volume for dose–volume histogram (DVH) analysis, was defined as the volume of PTV excluding the first 5 mm of tissue under the skin, the posterior breast tissue extent (chest wall and pectoral muscles), lung, heart, and pericardial fat.

All 50 patients were replanned using 3D-CRT planning system software (Pinnacle^3 version 8.0m, Pinnacle Treatment System; Philips, Milpitas, CA). To correctly evaluate heterogeneous tissue density, the convolution algorithm was used. The NSABP B-39/RTOG 0413 protocol dose limitation was used as a guideline for specified normal tissue constraints (9). Beam arrangements included noncoplanar mainly four- or five-field beams using 6-MV photons referring to the method reported by Vicini *et al.* (10). No electron beam was used. The exertion of simulation planning was for minimizing doses to organs at risk, and improving a homogeneous dose to the target volume. Beam weights, beam angle, and wedge angles were manually optimized, such that the targeted goal was to cover ≥90% of the PTV_EVAL by a dose ≥90% of the prescribed dose (9). The DVH constraints adopted for plan optimization are shown in Table 1.

A total dose of 30 Gy in five fractions was prescribed to the International Commission on Radiation Units and Measurements 50 reference point dose (isocenter) (11). The isocenter was placed in the center of the PTV. This treatment schedule was proposed by the Department of Radiation Oncology at New York University using the prone position and parallel-opposed minitangents external beam therapy (12). The New York University study demonstrated that this abbreviated regimen was well tolerated, with only mild acute adverse events and excellent or good cosmetic outcome. However, given the typical Japanese woman's breast size and shape, we had patients assume a supine position and used a noncoplanar three-, four-, five-, and six-beam technique.

Data analysis

IB volume, target volumes, and distance of surgical clips were measured by CT images on the radiation treatment planning (RTP) system. The craniocaudal surgical clip distance (CCD) was defined as the longitudinal distance along the body axis between head-side clip and foot-side clip, and the anteroposterior surgical clip distance (APD) was defined as the vertical distance between anterior-side clip and posterior-side clip. The IB reference volume receiving 50% of the prescribed dose (IB-V_{50}) was calculated. The homogeneity index (HI) was defined as the ratio of maximum dose

Table 1 DVH constraints for planning

IB reference	≤60%	≥50% of the prescribed dose	IB-V50 ≤60%
	≤35%	≥100% of the prescribed dose	IB-V100 ≤35%
Contralateral breast	Any point	≤3% of the prescribed dose	0.9 Gy
Ipsilateral lung	≤15%	≥30% of the prescribed dose	V30 ≤15%
Contralateral lung	≤15%	≥5% of the prescribed dose	V5 ≤15%
Heart			
Right-sided lesions	≤5%	≥5% of the prescribed dose	V5 ≤5%
Left-sided lesions	≤40%	≥5% of the prescribed dose	V5 ≤40%
Thyroid	Any point	≤3% of the prescribed dose	0.9 Gy

Abbreviations: DVH = dose–volume histogram; IB = ipsilateral breast.

of PTV_EVAL to minimum dose of PTV_EVAL. The conformity index (CI) was defined as the ratio of volume that was covered by the minimal dose of PTV_EVAL to the volume of PTV. The associations between categorical variables (*e.g.*, site of IB) and patient and tumor characteristics at baseline were analyzed using Fisher's two-tailed exact test. Statistically significant differences between two sample means and medians for continuous variables (*e.g.*, IB reference volume) were analyzed using the Student's unpaired *t*-test. A p value of less than 0.05 was considered statistically significant. Multivariate analysis of prognostic factors was performed with the Cox proportional hazards model. Statistical analyses were performed with JMP software, version 5.1 (SAS Institute, Cary, NC).

Results

Outcome of 3D-CRT planning

Median IB reference volume of all patients was 824 cm^3 (range, 425–1868) (Table 2). Median right IB reference volume was 794 cm^3 (range, 463–1556) and the left IB reference volume was 849 cm^3 (range, 425–1868), respectively ($p = 0.63$). Median CCD and APD for all patients were 4.5 cm (range, 2.0–9.5) and 4.2 cm (range, 0.8–7.6), respectively.

Median CTV for all patients was 56.3 cm^3 (range, 11.3–83.6), and median PTV for all patients was 246.9 cm^3 (range, 113.4–370.9) (Table 3). The median ratio between IB-PTV and IB reference volume was 74.9% (range, 54.0–86.9). The number of external beams ranged from three to six; the four-beam technique was mainly used for patients with the right breast region, and the five-beam technique was mainly used for patients with the left breast region. The median value of mean dose of PTV_EVAL was 30.2 Gy (range, 29.5–30.8). The median value of HI for all patients was 1.24 (range, 1.14–1.39), and the median value of CI for all patients was 1.38 (range, 1.01–2.40).

Unsuitable patients for the NSABP B-39/RTOG 0413 protocol

DVH constraints for organs at risk according to the NSABP B-39/RTOG 0413 protocol were satisfied in 39 patients (78%). Seven patients showed nonoptimal DVH for the ipsilateral lung; 5 patients for the contralateral breast; 4 patients for IB-V_{50}; 2 patients for the heart; and 1 patient for the thyroid. Univariate logistic regression analysis revealed that long CCD and medial tumors were correlated with nonoptimal DVH constraints ($p < 0.0001$ and $p = 0.007$, respectively), but pathological T stage excluding pTis (T1a/T1b/T1c/T2), APD, site of IB (right/left), and IB reference volume were not ($p = 0.98$, $p = 0.54$, $p = 0.73$, and

Table 2 Patients characteristics

	All patients ($n = 50$)	Optimal DVH ($n = 39$)	Nonoptimal DVH ($n = 11$)	Univariate analysis p value
Pathological T stage				
pTis/pT1/pT2	12/31/7	10/24/5	2/7/2	0.82
pT1a/pT1b/pT1c/pT2*	5/5/20/7	4/4/15/5	1/1/5/2	0.98
Site of IB				
Right/left	25/25	20/19	5/6	0.73
Location of tumor				
Mediolateral	19/31	11/28	8/3	0.007
IB reference volume (cm^3)				
Median (range)	824 (425–1868)	828 (425–1868)	725 (528–1032)	0.10
CCD (cm)				
Median (range)	4.5 (2.0–9.5)	3.5 (2.0–5.5)	6.0 (4.5–9.5)	<0.0001
APD (cm)				
Median (range)	4.2 (0.8–7.6)	4.2 (0.8–7.6)	4.6 (1.0–7.5)	0.54

Abbreviations: APD = anteroposterior clip distance; CCD = craniocaudal clip distance; DVH = dose–volume histogram; IB = Ipsilateral breast.
* 1 patient was not classified according to subcategory of pathological T stage.

Table 3 Dosimetric characteristics

Dosimetric characteristics	Mean	Median	Range
CTV (cm^3)	55.5	56.3	11.3–83.6
PTV (cm^3)	247.4	246.9	113.4–370.9
IB–PTV/IB reference (%)	74.3	74.9	54.0–86.9
IB-V_{100} (%)	12.7	12.5	5.6–23.4
IB-V_{95} (%)	24.7	24.6	14.6–44.8
IB-V_{50} (%)	48.6	49.0	31.4–68.6
Ipsilateral mean lung dose (Gy)	4.1	4.2	1.2–7.6
Ipsilateral lung-$V_{9\ Gy}$ (%)	12.5	12.6	3.6–23.1
Contralateral lung-$V_{1.5\ Gy}$ (%)	0.3	0	0–10.1
Heart-$V_{15\ Gy}$ (%)	1.0	0	0–7.4
Heart-$V_{6\ Gy}$ (%)	2.7	0	0–17.1
Thyroid-$V_{0.9\ Gy}$ (%)	0.5	0	0–25.5
Contralateral breast-$V_{0.9\ Gy}$ (%)	0.1	0	0–3.6
Mean dose of PTV_EVAL (Gy)	30.2	30.2	29.5–30.8
PTV_EVAL-$V_{27\ Gy}$ (%)	99.4	99.7	96.2–100
Homogeneity index	1.23	1.24	1.14–1.39
Conformity index	1.45	1.38	1.01–2.40

Abbreviations: CTV = clinical target volume; IB = ipsilateral breast; PTV = planning target volume; PTV_EVAL = volume of PTV for evaluation.

$p = 0.10$, respectively). Multivariate analysis revealed that only a long CCD was correlated with nonoptimal DVH constraints ($p = 0.02$). DVH constraints were satisfied in only 20% of patients with a long CCD (≥5.5 cm) and 92% of those with a short CCD (<5.5 cm) ($p < 0.0001$) (Fig. 1). Of the 2 patients with a short CCD (<5.5 cm), 1 patient with a left upper-inner primary tumor and a 5-cm CCD, did not satisfy optimal DVH for the ipsilateral lung and contralateral breast, and the other patient, who had a right upper-outer primary tumor and a 4.5-cm CCD, did not satisfy optimal DVH for the heart and IB-V_{50}. DVH constraints were satisfied in 52% of patients with a long CCD (≥5.0 cm) and 93% of those with a short CCD (<5.0 cm) ($p = 0.0007$). DVH constraints were satisfied in 0% of patients with a long CCD (≥6.0 cm) and in 90% of those with a short CCD (<6.0 cm) ($p < 0.0001$). A long CCD was correlated with not only nonoptimal DVH constraints, but also a large ipsilateral mean lung dose (MLD) ($r = 0.48$, $p = 0.0003$).

High-risk patients with large IB-V_{50}

Median IB-V_{50} of all patients was 49.0% (range, 31.4–68.6). Univariate logistic regression analysis revealed that long CCD ($r = 0.72$, $p < 0.0001$) and medial tumors ($p = 0.02$) were correlated with large IB-V_{50} (Fig. 2, 3). The site of the IB (right/left), pathological T stage (T1a/T1b/T1c/T2), IB reference volume, and APD were not correlated with a large IB-V_{50} ($p = 0.47$, $p = 0.92$, $p = 0.13$, $p = 0.10$, respectively). Multivariate analysis revealed that only a long CCD was correlated with large IB-V_{50} ($p < 0.0001$).

Discussion

The Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology Breast Cancer Working Group and the American Society for Radiation Oncology Health

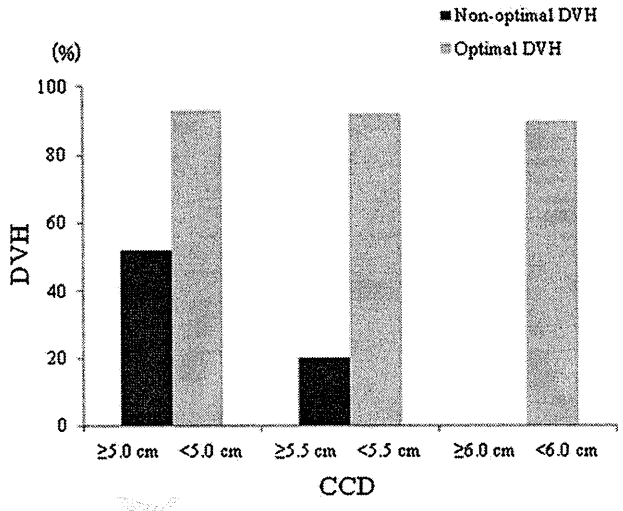

Fig. 1. Frequency of optimal and nonoptimal dose–volume histogram (DVH) constraints according to craniocaudal surgical clip distance (CCD). Left column indicates that 52% of patients with long CCD (≥5 cm) do not satisfy DVH constraints, whereas the center and right columns show that only a few patients with long CCD of ≥5.5 cm and those with long CCD of ≥6.0 cm do not satisfy DVH constraints.

Services Research Committee proposed the patient selection criteria for use of APBI based on available clinical evidence complemented by expert opinion (13, 14). The main eligibility criteria proposed by these task groups included patient age (≥60 years), pathological tumor size (≤3 cm), negative surgical margin, unicentric lesion, and pN0 (13, 14). These recommendations were mainly based on the probability of breast recurrence after APBI. To maintain the efficacy and safety of APBI, potential risk for late severe toxicities should be considered in addition to the probability of breast recurrence. The NSABP B-39/RTOG 0413 protocol requires that the ratio of lumpectomy cavity to IB volume must be <30% based on postoperative/prerandomization CT

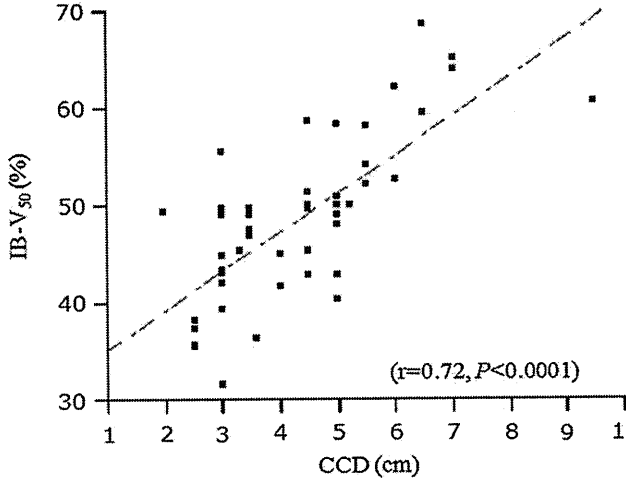

Fig. 2. Scatter plots for craniocaudal surgical clip distance (CCD) and ipsilateral breast reference volume receiving ≥50% of the prescribed dose (IB-V_{50}). Long CCD was strongly correlated with large IB-V_{50} ($r = 0.72$). IB-V_{50}. The dotted line indicates the fitting line.

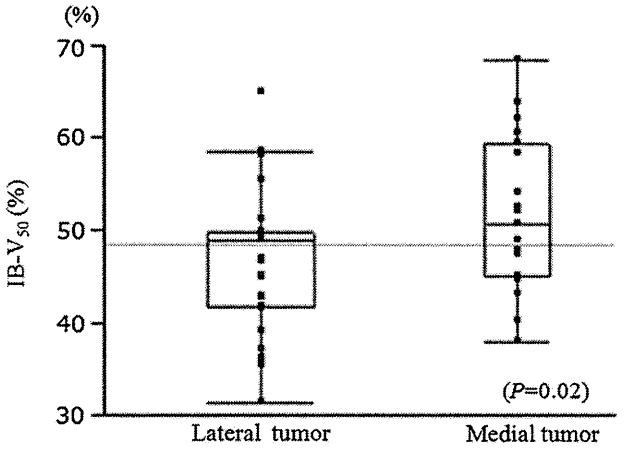

Fig. 3. Box plots for tumor location (lateromedial) and ipsilateral breast reference volume receiving ≥50% of the prescribed dose (IB-V_{50}). The gray line indicates the median value of IB-V_{50}.

imaging (9). Unfortunately, the ratio of lumpectomy cavity to IB volume and that of PTV to IB reference volume are not calculated until the RTP system operation. Thus, eligibility criteria that require complex calculations serve as obstacles toward seamless execution of clinical trials. In the majority of contemporary APBI series, patients for whom the maximal tumor size is less than 3 cm have been eligible (5, 14). In our study, pathological T stage (pT1a/pT1b/pT1c/pT2), which was classified according to pathological maximum diameter of the invasive carcinoma component, was not associated with nonoptimal DVH constraints of the NSABP B-39/RTOG 0413 protocol. Some likely explanations for this are that the pathological T stage does not include the noninvasive carcinoma component and that it does not correlate with specimen shape (*e.g.*, fan shape, slender oval) or the direction of the long axis of the specimen. On the other hand, the distance of surgical clips is directly associated with the size of the resected specimen, and the CCD strongly correlated with the field length in the craniocaudal direction and the breast irradiated volume. Distances between surgical clips are easy to measure with digital chest X-rays rather than the RTP system operation and they serve as tools to help predict which patients are unsuitable for 3D-CRT APBI. However, APD was not closely correlated with either nonoptimal DVH constraints or large IB-V_{50}. We applied the noncoplanar beam technique using tangential beam with a 10–20° steeper gantry angle and couch angles of 0–30°. With this technique, the gantry angle arrangement allows one to reduce the field width in the anteroposterior direction and the irradiated volume, in which case APD does not correlate closely with field size, irradiated volume, or nonoptimal DVH constraints.

Hepel *et al.* reported that high-, intermediate-, and low-dose volumes (IB-V_5–IB-V_{80}) all correlated with incidence of breast fibrosis after 3D-CRT APBI (7). Improved target coverage with external beam techniques comes at the cost of a higher integral dose to the remaining normal breast. With the 3D-CRT APBI technique, the volume of high-dose region (*e.g.*, IB-V_{100}, IB-V_{80}) and that of low-dose region (*e.g.*, IB-V_2, IB-V_{20}) are closely related. Jagsi *et al.* reported on the unacceptable cosmesis that developed in 7 patients among 34 patients after APBI using Intensity-modulated radiotherapy, noting that IB-V_{50} and IB-V_{100} correlated with cosmetic outcome (8). They indicated that there seemed to be a possible threshold at 40%, in which the 5 of 10 patients (50%) with an IB-V_{50} >40% experienced unacceptable cosmesis vs. the 2 of 22 (9%) below that threshold who experienced it ($p = 0.02$). On the other hand, Formenti *et al.* reported good cosmetic outcomes in most patients after performing APBI with the 3D-CRT technique in a prone position with 30 Gy in five fractions, noting that IB-V_{50} ranged from 23 to 75%, and IB-V_{100} ranged from 10 to 45% (12). In our simulation study, median IB-V_{50} of patients with optimal DVH constraints was 46.9% (31.4–58.1), and that for patients with nonoptimal DVH constraints was 59.4% (49.9–68.6) ($p < 0.0001$, data not shown). The appropriate threshold of IB-V_{50} and that of other parameters (*e.g.*, IB-V_{20}, IB-V_{80}, maximum dose) as predictive factors of late soft tissue toxicities has yet to be clarified. Further studies should be conducted to clarify predictive factors for late soft tissue toxicities.

Recht *et al.* reported that the risk of pneumonitis appeared to be related to the irradiated ipsilateral lung volume treated, and recommended that ipsilateral lung volume receiving 20 Gy or higher should be lower than 3%, and that receiving 5 Gy lower than 20% (6). They indicated that relatively low-dose lung irradiation might better help to determine the risk of pneumonitis after radiotherapy. In our study, a long CCD was correlated with large ipsilateral MLD ($r = 0.48$, $p = 0.0003$), and ipsilateral lung volume receiving 6 Gy or higher (≥20% of the prescribed dose) ($r = 0.63$, $p < 0.0001$).

A limitation of the present study was that we used simulation data rather than clinical outcomes. A prospective clinical trial should be conducted to evaluate the utility of these eligibility criteria and treatment outcomes. In addition, we could not verify the geometric couch and gantry angle limitations for the Varian linear accelerator in all patients. However, before the beginning of this study, we did verify the geometric couch and gantry angle limitations using a human-body phantom placed on a couch.

Conclusions

Patients with a long CCD, especially 5.5 cm or longer, might be unsuitable for 3D-CRT APBI from nonoptimal DVH constraints and large IB-V_{50}. Pathological T stage, APD, site of IB (right/left), tumor location (medial/lateral), and IB reference volume could not predict whether patients were unsuitable for 3D-CRT APBI.

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SPECIAL FEATURE

Strategies of radiotherapy for recurrent and metastatic breast cancer

Management of locoregional recurrence of breast cancer

Naoto Shikama · Kenji Sekiguchi · Naoki Nakamura

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Abstract The locoregional recurrence of breast cancer is not a sign of distant metastases, and a substantial proportion of cases are cured by salvage therapy. Patients with locoregional recurrence should not be treated with palliative intent as if they have visceral metastases. The recommended treatment for ipsilateral breast recurrence after breast conservative therapy is a mastectomy. For patients who suffer from isolated chest wall recurrence after mastectomy, a surgical approach is recommended. Neoadjuvant chemotherapy is considered for patients with unresectable disease in order to render the disease resectable. For patients with isolated chest wall recurrence who have received no prior radiotherapy, postoperative radiotherapy involving the chest wall and regional lymph nodes is recommended. Patients with isolated axillary lymph node recurrence should be treated with axillary dissection or resection. Although the effectiveness of systemic therapy for patients with locoregional recurrence is unclear, there is a trend toward treating patients with supraclavicular lymph node recurrence with radiotherapy plus systemic therapy. Pain relief and the eradication of other distressing symptoms resulting from inoperable disease are achieved in two-thirds to three-quarters of patients by radiotherapy with or without systemic therapy. New anticancer agents and molecular target therapies should be evaluated with the objective of improving the treatment outcome of patients with locoregional recurrence. A combination of approaches is required for treatment of patients with locoregional recurrence, and a multidisciplinary tumor board should be organized at each institute.

Keywords Local recurrence · Lymph node recurrence · Radiotherapy · Chemotherapy · Mastectomy

Introduction

Ten to thirteen percent of patients who receive breast conservative therapy develop locoregional recurrence within 10 years of their initial treatment, and three to eight percent of patients who receive mastectomy plus postoperative radiotherapy will also develop locoregional recurrence [1]. The omission of postoperative radiotherapy increases the risk of ipsilateral breast recurrence or chest wall recurrence threefold. Ipsilateral breast recurrence after breast conservative therapy sometimes occurs after more than 10 years; however, approximately 80% of locoregional recurrences after mastectomy arise within the first 5 years [1–3]. The standard of care for locoregional recurrence has not been clarified because of its heterogeneous biological characteristics and a lack of well-designed prospective clinical trials. The authors have strived to assess the effectiveness of treatment strategies developed in previous studies.

Diagnosis and re-staging

The first step for choosing an appropriate treatment is pathological evaluation of the recurrent disease, and fine needle biopsy, core needle biopsy, and/or open biopsy can

N. Shikama (✉)
Department of Radiation Oncology, Saku General Hospital,
197 Usuda-machi, Saku, Nagano 384-0301, Japan
e-mail: nshikama0525@gmail.com

N. Shikama · K. Sekiguchi · N. Nakamura
Department of Radiation Oncology,
St Luke's International Hospital, Tokyo, Japan

be used for this. The pathological subtype, histological grade, expression of hormonal receptors, and human epidermal growth factor receptor type2 (HER-2) overexpression should be evaluated when choosing appropriate treatment strategies for patients with recurrent disease. Radiation-induced sarcomas in the chest wall appear at a median of 10 years after postoperative treatment, but the latency period varies. The next step is a staging evaluation. Systemic disease can be carefully evaluated by using blood tests, chest computed tomography (CT), abdominal CT, pelvic CT, and radionuclide bone scans. Magnetic resonance imaging (MRI), CT, and color Doppler ultrasonography are useful for evaluating the extent of supraclavicular and infraclavicular lymph node recurrence. Positron emission tomography (PET) scans are performed increasingly in clinical practice and are more sensitive than CT and bone scans; however, meta-analysis of evaluation of breast cancer recurrence demonstrated that the false positive rate of PET scans was relatively high (11%) [4]. The clinical value of PET scans alone is not satisfactory, so addition of other conventional imaging modalities is required.

Prognostic factors

For patients with locoregional recurrence after breast conservative therapy, disease-free interval (DFI) from the initial treatment to recurrence is the most powerful predictive factor. The 5-year survival rate of patients who developed recurrence within 2 years of the initial treatment was 65% and that of the patients who developed recurrence after 2 years was over 80% [5]. Other poor prognostic factors of mortality have been reported, for example age (≥60 years), the number of positive lymph nodes at the initial treatment (four or more), primary tumor size (≥2 cm), histology (invasive cancer), and estrogen receptor expression (negative) [6]. For patients with locoregional recurrence after mastectomy, some tumor characteristics at the diagnosis of recurrence, for example an operable tumor, the absence of tumor necrosis, the recurrent site (chest wall or axillary lymph node), a pT1-2N0 primary tumor, and a long DFI, are associated with a good treatment outcome [7–9].

Schmoor et al. [9] reviewed 337 patients with locoregional recurrence among the 2,746 patients who received conservative therapy or mastectomy in four prospective studies of the German Breast Cancer Study Group. Multivariate analysis demonstrated that number of positive lymph nodes, tumor grade, estrogen receptor, and DFI were independent prognostic factors for progression-free survival after locoregional recurrence. They simplified the risk strata and defined three risk groups:

- low risk: primary node-negative status and a DFI of more than 2 years;
- intermediate risk: primary node-positive status or a DFI of more than 2 years; and
- high risk: primary node-positive status and a DFI of less than 2 years (Table 1).

Although it excludes other prognostic factors, for example age, tumor grade, recurrent site, and estrogen receptor, this simplified prognostic index is a useful tool for choosing treatment strategies in clinical practice and clinical trials.

Recurrence after breast conservative therapy

Thirteen percent of patients who develop recurrence after conservative therapy have locoregional recurrence alone, 30% have locoregional recurrence with distant metastases, and another 57% have distant metastases alone [2]. Approximately 80% of patients with locoregional recurrence develop ipsilateral breast recurrence as the first site [10, 11]. Recurrence in the ipsilateral breast includes two different types of disease, true recurrence and second primary tumors. True recurrence occurs within the primary tumor site or its vicinity, and second primary tumors occur in other quadrants of the breast or have a different pathological subtype [10, 12, 13]. However, some second primary tumors may occur in the same quadrant, and others will have the same pathological subtype. Strict distinction between true recurrence and second primary tumors is difficult, and some investigators have distinguished between them by using pathological subtype, location, and deoxyribonucleic acid (DNA) flow cytometry [10, 12, 13]. True recurrence is associated with early development (median interval: 3.7 vs. 7.3 years) and poor treatment outcome (10-year overall survival: 55 vs. 75%) compared with second primary tumors [12].

Table 1 Prognostic index for patients with locoregional recurrence of breast cancer [9]

	5-year PFS (95%CI)	5-year OS (95%CI)
Low risk		
Node (−) and DFI ≦2 years	53% (41–64)	66% (55–77)
Intermediate risk		
Node (+) or DFI >2 years	40% (31–49)	53% (44–62)
High risk		
Node (+) and DFI >2 years	17% (9–25)	27% (17–36)

Node (−), primary node-negative status; DFI, disease-free interval from initial treatment to recurrence; Node (+), primary node-positive status; PFS, progression-free survival; OS, overall survival; 95%CI, 95% confidence interval

Ipsilateral breast recurrence after breast conservative therapy

More than 20% of evaluated mastectomy specimens of ipsilateral breast recurrence after conservative therapy revealed substantial residual disease in two or more quadrants of the breast [14]. The generally recommended treatment for ipsilateral breast recurrence after breast conservative therapy is salvage mastectomy with or without axillary dissection [5, 6, 14–17]. Approximately 90% of the patients have operable recurrent tumors, and other patients have inoperative tumors with diffuse infiltration or inflammatory changes [11, 14–16, 18]. Most patients who received salvage mastectomy achieved good local control, and the 5-year overall survival rates after recurrence ranged from 60 to 86% [5, 6, 12, 14, 18]. Patients who have inoperative tumors involving diffuse infiltration or inflammatory changes have a poor prognosis [19].

Less intensive salvage care for locoregional recurrence has also been investigated. Several investigators have reported the outcome of repeated conservative therapy including partial breast resection with or without radiotherapy after ipsilateral breast recurrence [16, 18, 20]. Salvadori et al. [18] reported the same overall survival in patients who underwent re-conservative therapy (85%) and patients who received salvage mastectomy (70%); however, second ipsilateral recurrence was more common in the patients who received re-conservative therapy (19 vs. 4%). Galper et al. [16] reviewed 341 patients with local recurrence after conservative therapy and reported that the time to distant failure, second malignancy, or death of the patients who received re-conservative therapy was worse than that of the patients who received salvage mastectomy (hazard ratio: 2.0, $p = 0.02$). Re-conservative therapy for ipsilateral breast recurrence is not recommended. Sentinel lymph node (SLN) biopsy is a less toxic tool, and the experience of the Memorial Sloan–Kettering Cancer Center demonstrated that SLN were identified in 55% of 117 patients who had undergone prior axillary dissection or biopsy. Although SLN biopsy is available for some patients who have undergone prior axillary dissection, further studies are required [21].

Postoperative radiotherapy after salvage mastectomy is used for patients with a positive surgical margin or macroscopic residual tumor who have no history of breast irradiation. Re-irradiation is associated with late adverse effects such as tissue necrosis, fibrosis, and rib fractures. There are no data supporting prophylactic regional lymph node irradiation after salvage mastectomy for patients with ipsilateral breast recurrence.

Only one randomized clinical trial has evaluated addition of tamoxifen (TAM) for patients who underwent complete resection and postoperative radiotherapy [22]. Although the addition of TAM prolonged relapse-free survival, 9-year overall survival did not improve. Le et al. [23] reported that systemic chemotherapy and hormonal therapy reduced the risk of death for premenopausal patients, but did not reduce it for postmenopausal patients. Cochran's systematic review concluded that there was little evidence to support the addition of systemic therapy for patients with locoregional recurrence of breast cancer [24]. However, the addition of hormonal therapies is considered to be reasonable in selected patients because of their limited toxicities [25].

Regional lymph nodes recurrence after breast conservative therapy

Regional lymph node recurrence after breast conservative therapy is relatively rare (0.5–6.3%) [6, 26, 27]. The most common sites of regional recurrence are the axillary area and supraclavicular fossa [28, 29]. The pooled analyses of the National Surgical Adjuvant Breast and Bowel Project studies demonstrated that the prognosis of patients with isolated axillary lymph node recurrence was more favorable than that of patients with supraclavicular lymph node recurrence, and the 5-year distant metastases-free survival of the former was 31.5% whereas that of the latter was only 12.1% [6].

The experience of the MD Anderson Cancer Center was that surgery for axillary recurrence achieved good local control; however, the absence of radiotherapy or systemic therapy from the multimodality treatment strategy did not correlate with disease control or the frequency of distant metastases [30]. Maximum axillary control is achieved with an axillary dissection whenever feasible. Limited data are available regarding postoperative regional lymph node irradiation [28]. Radiotherapy is indicated for patients who undergo incomplete resection of axillary disease and patients with supraclavicular lymph nodes metastases [29]. Although the role of systemic therapy has not been established, there is a trend towards administering systemic therapy to patients with supraclavicular lymph nodes recurrence [17].

Fowble et al. [27] reported that none of their six patients with isolated axillary recurrence subsequently developed breast recurrence. They also concluded that isolated axillary node recurrence without clinical or mammographic evidence of ipsilateral breast recurrence does not require a prophylactic mastectomy.

Recurrence after mastectomy

According to the pooled analysis of the Easton Cooperative Oncology Group, locoregional recurrence developed in 420

patients among 2,016 patients who received mastectomy and adjuvant systemic therapy without postoperative radiotherapy [31]. Among 254 patients without simultaneous distant metastasis, isolated chest wall recurrence was found in 131 patients (52%), and locoregional recurrence with or without chest wall recurrence was found in 123 patients (48%). One hundred and sixty-six patients had locoregional recurrence and distant metastases simultaneously.

Isolated chest wall recurrence after mastectomy

Maximum local control of isolated chest wall recurrence is achieved with a wide excision whenever feasible [32–37]. Schwaibold et al. [36] reviewed 128 patients with isolated locoregional recurrence and reported that the 5-year overall survival and relapse-free survival rates of patients with a long DFI, surgical resection, and locoregional control were 61 and 59%, respectively. However, this favorable subgroup accounted for fewer than 20% of patients with isolated locoregional recurrence. On the other hand, aggressive surgery including extensive excision and reconstruction using skin grafts leads to a reduced quality of life, and, therefore, optimum treatment is achieved by balancing the potential benefits of local treatment with its adverse effects [38, 39]. If there is no clinical finding of axillary lymph node involvement, a prophylactic axillary dissection is unnecessary for patients who have undergone prior complete axillary dissection. The identification of SLN after prior axillary dissection is unlikely to be as successful as prior SLN biopsy alone (38 vs. 74%, $p = 0.0002$), and so SLN biopsy is not recommended for patients who have undergone prior complete axillary dissection [21].

Dahlstrom et al. [32] reported that 45% of patients had a new local recurrence after wide excision plus a 3-cm margin for isolated chest wall recurrence. In the study by Mallinckrodt, the 5-year freedom from chest wall re-recurrence of patients who received entire chest wall and regional lymph node irradiation was 75%, and that of patients who received small-field irradiation alone was 36% ($p = 0.0001$) [7]. Toonkel et al. [40] demonstrated that postoperative radiotherapy including chest wall and regional lymph node irradiation enhanced 5-year overall survival rates compared with chest wall irradiation alone (54 vs. 27%). The three-field or four-field technique including tangential chest wall fields and an en face supraclavicular area field are usually applied, even if the recurrent disease involves an isolated chest wall recurrence [32, 34, 36, 40–42]. The optimum daily fraction size is 1.8–2.0 Gy, and should be delivered five times weekly. The total dose administered to the initial field ranges from 45 to 50 Gy, with a boost of 10 to 20 Gy administered to areas of residual gross disease and the tumor bed. The biopsy scar should be covered by the bolus in order to obtain the optimum dose distribution [25]. In the MD Anderson Cancer Center, all areas treated prophylactically receive 54 Gy in 27 fractions, and all areas to be boosted because of microscopic disease receive an additional 12 Gy in 6 fractions [43].

A higher dose of definitive radiation for macroscopically residual tumors is associated with less in-field failure [7, 25]. It is difficult to obtain long-term local control in patients with diffuse inflammatory disease or unresectable disease. Neoadjuvant chemotherapy is considered for patients with unresectable disease in order to render the disease resectable, and radiotherapy is delivered after surgery. There is little information about re-irradiation after postoperative chest wall irradiation. Limited field re-irradiation using tailored conformal therapy techniques and concurrent chemoradiotherapy and/or twice daily fractionation regimens have been tested for patients with inoperative recurrent disease who had previously received radiotherapy [44, 45]. Re-irradiation of limited volumes with limited radiation doses can result in meaningful palliation for some patients.

Regional lymph nodes recurrence after mastectomy

Willner et al. [34] analyzed 145 patients with first locoregional recurrences after mastectomy and reported that the 5-year survival rate was better for patients with recurrences confined to the axillary lymph nodes (50%) than for those with recurrence confined to the supraclavicular lymph nodes (28%) or combined chest wall and axillary recurrences (28%). The 5-year survival rate of patients with supraclavicular lymph nodes recurrence and chest wall and/or axillary lymph nodes recurrence was only 5%.

Axillary lymph node recurrence after mastectomy

Axillary lymph node recurrence is rare after complete axillary dissection. Regional lymph node control for patients who receive axillary dissection after axillary recurrence is better than that for patients who receive radiotherapy alone [42]. Whenever feasible, a complete axillary dissection (Level I and II) is indicated for patients who have undergone prior SLN biopsy alone, and gross tumor resection is considered for patients who have undergone prior complete axillary dissection. Although the role of postoperative radiotherapy after salvage surgery is unclear, postoperative radiotherapy is used for patients who have not undergone prior axillary irradiation in some institutes [33, 34, 42, 46]. Radiotherapy should be considered for patients with incompletely resected disease or inoperable disease. The risk of symptomatic arm edema

after axillary dissection or axillary irradiation alone ranged from 4 to 8%; that after complete axillary dissection followed by radiotherapy was 36%, however [47].

Supraclavicular lymph node recurrence after mastectomy

Chen et al. [48] reviewed 63 patients with isolated supraclavicular lymph node recurrence among 3,170 breast cancers and reported that their 5-year survival rate was 33.6% and that surgical removal of the supraclavicular lymph nodes was associated with good overall survival after recurrence ($p = 0.03$). Although a surgical approach for supraclavicular lymph node recurrence is feasible, the clinical benefit of a surgical approach is believed to be small, because of the high frequency of local and distant relapse [49].

The clinical complete response rate for radiotherapy with or without chemotherapy ranged from 85 to 94%, the median time to progression was 28 months, and the 5-year overall survival rate after recurrence ranged from 21 to 35% [34, 46, 50]. Pergolizzi [51] compared 18 patients who received six-cycle chemotherapy alone with 19 patients who received initial three-cycle chemotherapy followed by involved-field radiotherapy and demonstrated that the local control of the former patients was worse than that of the latter patients (13 patients vs. 18 patients) and that the 5-year disease-free survival rate of the former was worse than that of the latter (5.5 vs. 21%, $p = 0.01$). Although there are no data supporting the use of systemic therapy for patients with locoregional recurrence, there is a trend toward the application of systemic therapy especially for patients with supraclavicular recurrence [23, 24, 34, 46].

Tumor infiltration of the brachial plexus induces shoulder pain, sensory changes in the fingers, and weakness and atrophy of the upper limbs. Radiation therapy is an effective local therapy for obtaining local control and avoiding distressing symptoms. Doses of 30–50 Gy are applied in 10–25 fractions over 2–5 weeks, and pain relief and the eradication of other distressing symptoms were achieved in more than two-thirds of patients [46, 50, 52]. Doses of 40 Gy or more were better at improving the distressing symptoms caused by supraclavicular lymph node metastases than those of less than 40 Gy (92 vs. 55%) [52].

New challenge

The 5-year overall survival rates of patients with ipsilateral breast or chest wall recurrence with simultaneous regional lymph node recurrence range from 7 to 24% [6, 34, 46]. Although systemic therapy has been commonly applied for patients with locoregional recurrence, the clinical benefit of systemic therapy including anthracycline-based and methotrexate-based regimens is uncertain. The clinical data regarding taxane-based regimens and molecular-targeted therapies, for example trastuzumab and lapatinib, should be evaluated using prospective trials, and a pilot study using hyperfractionated accelerated radiotherapy with or without systemic therapy has been conducted [44]. Additionally, patients with diffuse inflammatory disease and unresectable disease have an unfavorable prognosis. The optimum treatment for unresectable diffuse inflammatory recurrent disease needs to be established.

Locoregional recurrences of breast cancer have heterogeneous biological characteristics, and it is difficult to choose an appropriate treatment for each patient. Prospective clinical trials integrating adequate prognostic indices should therefore be conducted to define standard salvage treatment for patients with locoregional recurrence [9].

Conclusion

The optimum treatment for patients with locoregional recurrence requires a combination of modalities, and a comprehensive multidisciplinary treatment approach is essential. A multidisciplinary tumor board for breast cancer should be organized at each institute in order to propose an appropriate treatment for each patient.

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Original Article

A Long-term Follow-up Study of Prospective 80%-dose CHOP Followed by Involved-field Radiotherapy in Elderly Lymphoma Patients

Naoto Shikama[1,*], Masahiko Oguchi[2], Koichi Isobe[3], Katsumasa Nakamura[4], Yoshio Tamaki[5], Masatoshi Hasegawa[6], Takeshi Kodaira[7], Shigeru Sasaki[8] and Yoshikazu Kagami[9] on behalf of the Japan Radiation Oncology Group (JAROG)

[1]Department of Radiation Oncology, Saku Central Hospital, Nagano, [2]Department of Radiation Oncology, Cancer Institute Hospital, [3]Department of Radiology, Chiba University Hospital, Chiba, [4]Department of Radiology, Kyushu University Hospital, Beppu, [5]Department of Radiology, Gunma Prefectural Cancer Center, Gunma, [6]Department of Radiation Oncology, Nara Medical University, Nara, [7]Department of Radiation Oncology, Aichi Cancer Center Hospital, Aichi, [8]Department of Radiology, Shinshu University School of Medicine, Matsumoto and [9]Department of Radiation Oncology, National Cancer Center, Tokyo, Japan

*For reprints and all correspondence: Naoto Shikama, Department of Radiation Oncology, Saku Central Hospital, 197 Usuda, Saku-City, Nagano 384-0301, Japan. E-mail: nshikama0525@gmail.com

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Objective: The purpose of this study was to clarify the long-term clinical outcome of elderly patients with localized aggressive lymphoma and to explore appropriate treatment strategies for this population.

Methods: Subjects of this multicenter prospective study were untreated patients aged ≥70 years with aggressive Stage IA–IIA lymphoma. Therapy with 80%-dose CHOP (cyclophosphamide 600 mg/m^2, doxorubicin 40 mg/m^2, vincristine 1.1 mg/m^2 and prednisolone 80 mg/day for 5 days) was repeated every 3 weeks. After three cycles of chemotherapy, involved-field radiotherapy was performed with 30–50 Gy in 15–28 fractions.

Results: A total of 24 patients (median age, 75 years; range, 70–84 years) were enrolled. Nineteen patients (79%) had non-bulky tumors <6 cm. The median follow-up period was 7.3 years. The 7-year overall and progression-free survival rates were 78.9% (95% confidence interval, 62.3–95.5) and 65.3% (95% confidence interval, 45.3–85.3), respectively. Six patients developed systemic relapse, two of them after 6 years. The median survival time after relapse was only 5 months (range, 2 weeks–5.2 years). Five patients developed second malignancies, and three other patients died from other causes without lymphoma progression. None of the patients developed local relapse within the radiation field and/or regional relapse in adjacent lymph node areas.

Conclusions: Although systemic relapses, short survival time after relapse and death from other causes occurred, no loco-regional relapses were observed. Less intensive radiotherapy such as low-dose and small field might not compromise the treatment outcome for this population.

Key words: aggressive lymphoma – chemotherapy – geriatric oncology – dose intensity – radiotherapy

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is a disease with high incidence in the elderly. The incidence rate of aggressive NHL increases with age (1). Nearly one-half of all newly diagnosed cases occur in patients older than 60 years (2), and the outcome of elderly patients is poor due to aggressive disease subtype and diminished organ function (2,3). Many clinical trials have demonstrated the benefits of systemic chemotherapy in patients with aggressive NHL, and standard treatment schedules, which can be applied to the majority of elderly patients, have been investigated (2,4). Some investigators have reported unacceptable toxicity due to aggressive therapy in elderly patients, and Balducci and Lyman (5) emphasized that patients older than 70 years are at high risk for neutropenic infection (6). In general, elderly patients have been considered too frail to receive the standard treatment and have instead received low-intensity treatment schedules. The US National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program demonstrated that even in 1999, nearly 50% of elderly patients were still not receiving doxorubicin-based chemotherapy, which has gained general acceptance for use among the elderly (7). Older age, congestive heart failure and other co-morbidities are associated with treatment without doxorubicin.

On the other hand, the Groupe d'Etude des Lymphomes de l'Adulte (GELA) conducted a prospective randomized trial to evaluate the administration of full-dose CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), with or without rituximab (Rituxan; Roche), in elderly patients (60–80 years old), and showed that these two full-dose regimens were safe for elderly patients aged $\leq$80 years (8). In general, patients participating in prospective clinical trials do not have severe co-morbidities and have good performance status, and thus full-dose chemotherapy is safe for such elderly patients. The gap between prospective clinical trials and clinical practice should be reduced to improve the level of clinical practice for elderly patients with NHL. To this end, we previously conducted a multicenter prospective study to evaluate the efficacy and safety of 80%-dose three-course CHOP followed by involved-field radiotherapy for elderly patients with localized aggressive NHL and reported that this regimen was safe for patients aged over 70 years (9).

The purpose of the present study was to clarify the clinical status of elderly patients after long-term follow-up and explore appropriate treatment strategies for elderly patients with localized aggressive NHL.

PATIENTS AND METHODS

Patients

Elderly patients aged $\geq$70 years with localized aggressive NHL were recruited between December 2000 and February 2004. Eligibility criteria were reported in detail previously (9). Histological subtypes were diffuse large B-cell, peripheral T-cell or anaplastic large cell lymphoma according to the World Health Organization classification, and localized diseases included Stage IA or IIA (10). All patients had good performance status (0–2) according to the Eastern Cooperative Oncology Group (ECOG) classification. Patients were excluded from the trial if they had a history of active cancer during the previous 5 years, co-morbidity with other serious medical conditions including severe ischemic heart disease or cardiomyopathy, positive serology for human immunodeficiency virus, or the presence of hepatitis B virus antigen or anti-hepatitis C virus antibody. All patients were required to have sufficient hematological, renal and hepatic function. Minimal staging procedures included clinical examination; chest radiography; gallium scintigraphy; computed tomography (CT) of the neck, chest, abdomen and pelvis; bone marrow biopsy; and blood studies. The staging procedure did not require positron emission tomography (PET).

This study complied fully with all provisions of the Declaration of Helsinki. All participating hospitals obtained the permission of their institutional review boards and all patients gave their written informed consent prior to entry into the study.

Treatment

The detailed treatment schedule and stopping rules were reported previously (9). Reduced-dose chemotherapy (80%-dose CHOP) included cyclophosphamide 600 mg/m^2 (day 1), doxorubicin 40 mg/m^2 (day 1), vincristine 1.1 mg/m^2 (day 1) and oral prednisolone 80 mg/day (days 1–5). Chemotherapy was repeated at 21-day intervals. If a patient developed Grade 4 neutropenia or febrile neutropenia, all subsequent cycles were administered with granulocyte colony-stimulating factor support.

Involved-field radiotherapy was performed after three cycles of chemotherapy. The involved field was defined as the regional area including the primary lesion and involved nodes determined by pre-chemotherapy evaluations, as well as adjacent uninvolved nodes. Examples include the full Waldeyer's ring and prophylactic bilateral whole-neck fields for Stage I tonsil lymphoma, and the ipsilateral neck field between the mastoid process below the tumor and the infraclavicular lymph node for Stage I lymphoma. The radiation dose was 30–30.6 Gy given in fractions of 15–20 Gy over 3–4 weeks in patients who achieved a complete response (CR) and 40–50 Gy in 20–28 fractions over 4–6 weeks for those who did not achieve CR. Response was assessed using Cheson's criteria, which did not include PET examination (11). Clinical examination was performed every 6 months for the first 5 years, and then at the discretion of the attending physician. Neck, chest and abdominal CT scans were performed after 6 months, and every 6 months thereafter during the first 5 years. After 5 years, clinical examination

was performed annually and continued for as long as possible.

Outcome Measures

Endpoints included overall survival (OS), progression-free survival (PFS) and relapse pattern. Survival was measured from the date of study registration. The last follow-up date of OS was the date of death, and that of PFS was the date of death or the date of disease progression (whichever came first). Data from patients who were alive at the last follow-up were censored. OS rate was calculated using death from any cause as an event, and PFS rate was calculated using disease progression or death from any cause as an event. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria grading system, version 2.0. OS and PFS rates were calculated using the Kaplan–Meier method. All patients were included in analyses of efficacy and safety. The log-rank test was used to compare survival distributions of different groups using a significance level of 0.05. Statistical analyses were performed with JMP software version 5.1 (SAS Institute, Cary, NC, USA). Tumor responses were classified as CR, CR unconfirmed (CRu), partial response (PR), stable disease or progressive disease according to the proposed International Workshop criteria (11).

RESULTS

Treatment Compliance and Toxicity

A total of 24 patients from eight Japanese institutions were enrolled in the study between December 2000 and February 2004. Patient characteristics are shown in Table 1. The most popular primary sites were Waldeyer's ring and other head and neck extranodal regions. The median age was 75 years (range, 70–84); four patients (16%) were >80 years. Three patients did not complete the study protocol; these patients received only two cycles of chemotherapy. The physician stopped the protocol in one patient, and another patient refused administration of the third round of chemotherapy. Another patient developed pancreatic cancer during chemotherapy, and the protocol was stopped. The compliance rate of the protocol was 87.5%. The administration of chemotherapy was delayed due to hematological toxicity in six patients, and the dose of chemotherapy was reduced due to hematological toxicity in one 84-year-old patient.

Severe non-hematological toxicity (Grades 3–4) during chemotherapy occurred in four patients (infection in three patients and diabetes mellitus in one patient). Non-hematological severe toxicity (Grade 3) during radiotherapy occurred in one patient (mucositis). None of the patients died from treatment-related toxicity.

Of the 22 patients who received radiotherapy at the head and neck area, we observed mild dry mouth in 10 patients at the last follow-up. None of the patients ate soft food due to the dry mouth and thus were administered a feeding tube.

Table 1. Patient characteristics

	No. of patients (%)
Age (years)	
Median	75
Range	70–84
70–75	15 (62)
76+	9 (38)
Gender	
Male	13 (54)
Female	11 (46)
Performance status (ECOG[a])	
0	18 (75)
1	6 (25)
Location	
Waldeyer's ring	11 (46)
Neck node	6 (25)
Maxillary sinus	3 (13)
Thyroid	2 (8)
Other sites	2 (8)
Stage	
I	16 (67)
II	8 (33)
LDH	
≤ULN[b]	20 (83)
>ULN, <1.5× ULN	4 (17)
≥1.5× ULN	0 (0)
Stage-modified International Prognostic Index[c]	
1	14 (59)
2	8
3	2 (8)
Tumor size	
<6 cm	19 (79)
>6 cm, <10 cm	4 (17)
≥10 cm	1 (4)

ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of the institutional normal range.
[a]Stage-modified International Prognostic Index; age (≥60 vs. >60), stage (I vs. II), serum LDH (normal vs. increased), performance status (0–1 vs. 2) [from ref. (17)].

Treatment Response and Survival Rates

Nineteen patients (79%) had a non-bulky tumor <6 cm in size. The response rate after chemotherapy and that after combined treatment were 79% (19 patients) and 88% (21 patients) for CR or CRu, respectively.

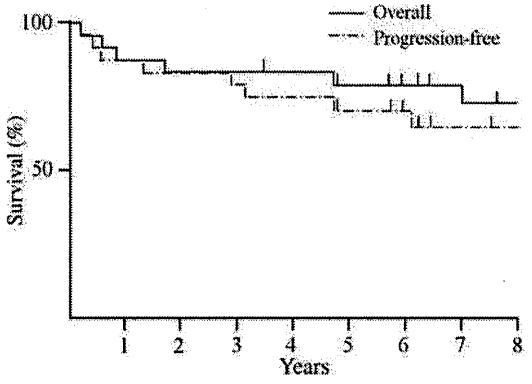

Figure 1. Overall and progression-free survival curves of the 24 patients.

The median follow-up period was 7.3 years (range, 0.3–9.3). The 7-year OS and PFS rates were 78.9% [95% confidence interval (CI), 62.3–95.5] and 65.3% (95% CI, 45.3–85.3), respectively (Fig. 1). All four patients aged >80 years survived longer than 4 years (4.8–8.9). The 7-year OS and PFS rates did not differ significantly with age (70–74 and 75+) ($P = 0.36$ and 0.79), stage (I and II) ($P = 0.77$ and 0.41) or stage-modified International Prognostic Index (1–3) ($P = 0.55$ and 0.59).

Relapse and Late Adverse Events

Six patients developed systemic relapse at distant sites: lung, heart, mediastinal lymph nodes, liver, adrenal gland, kidney, abdominal lymph nodes or bone marrow. Among these six patients, four had undergone the planned treatment schedule and had achieved CR or CRu after initial treatment, and two had undergone incomplete treatment and had achieved PR or stable disease. The median relapse interval from the start of initial treatment was 3 years (range, 5 months–8 years), and two patients developed systemic relapses after 6–8 years. After systemic relapses, these patients were treated with systemic chemotherapy and/or supportive care. The median survival time after relapse was only 5 months (range, 2 weeks–5.2 years). None of the patients developed local relapse within the radiation field and/or regional relapse in the adjacent lymph node areas during the follow-up period.

Five patients developed second malignancies: colon cancer in two patients, and gastric cancer, bladder cancer and pancreatic cancer in one patient each. The former four patients underwent curative surgery or endoscopic intervention. In the fifth patient, pancreatic cancer developed during initial lymphoma treatment, and he died 3 months after the present study registration. Three patients died due to other causes—cardiac failure, deterioration of general condition and sepsis without lymphoma progression—at 7 months, 4.8 and 9.3 years after registration.

DISCUSSION

More than half of all new cancer cases occur in patients aged ≥60 years. Despite the high frequency of cancer in this population, elderly patients have been underrepresented in clinical trials evaluating the standard of care for cancer, and few guidelines specifically address the evaluation and treatment of this population. Clinical trials have tended to exclude patients with co-morbid medical conditions, and physicians and patients prefer less toxic treatments in clinical practice. Among patients in the older age group, there is a large degree of heterogeneity in the ability to tolerate aggressive therapy, such as full-dose chemotherapy and/or definitive radiotherapy. Despite evidence that chronological age does not meaningfully influence the efficacy or toxicity of cancer treatment, elderly patients tend to receive less comprehensive cancer therapy compared with younger patients (12). This may be due to concerns of increased toxicity, coexistence of co-morbid medical conditions, and physician or patient preference. Predicting severe toxicity due to aggressive therapy plays a large part in treatment strategy decisions for elderly individuals. The treatment strategy for elderly patients should take into account the balance between harm and benefit. The Vulnerable Elders-13 Survey (VES-13) and comprehensive geriatric assessment (CGA) are useful tools for a geriatrician's baseline evaluation of an elderly individual (13). These programs are helpful for predicting toxicity due to treatment, estimating survival, identifying new problems during follow-up and improving general well-being (14–16). A weak point of our study was that we did not evaluate our study participants with VES-13 or CGA. In the future, these programs and other useful tools should be included in clinical trials to set the standard care for elderly patients with NHL.

The Southwest Oncology Group (SWOG) reported the effectiveness of three-course CHOP followed by involved-field radiotherapy in comparison with eight-course CHOP in patients with localized NHL (17). Three-cycle CHOP followed by involved-field radiotherapy was considered the standard care for patients with localized aggressive disease (18,19). Full-course chemotherapy is another standard type of care for patients with NHL. It was reported that elderly patients with NHL who had good performance status and minimal co-morbid illness could tolerate full-course chemotherapy without increased toxicity (20–22). However, in clinical practice, elderly patients have been considered too frail to receive the standard treatment and have been treated with low-intensity schedules (7). We performed a prospective study to evaluate the tolerability and effectiveness of short-course 80%-dose CHOP followed by radiotherapy and reported satisfactory tolerability and survival rates in the elderly (9). The addition of rituximab, a chimeric human/murine immunoglobulin G1 monoclonal antibody that binds specifically to the B-cell surface antigen CD20, to the full-course CHOP regimen was shown to improve treatment outcome in elderly patients with advanced disease with no accompanying increase in toxicity (8,23). The MabThera International Trial (MInT) Group demonstrated that the addition of rituximab improved treatment outcome in patients aged <60 years with low risk (24). However, the

clinical benefit of rituximab addition has not been clarified in patients with localized disease (25). SWOG conducted a Phase II study (SWOG0014) that evaluated four doses of rituximab plus three-course CHOP followed by radiotherapy in patients with localized aggressive NHL and reported 4-year PFS and OS of 88 and 92%, respectively (25). The SWOG8736 study applied short-course CHOP without rituximab in the same population and reported 4-year PFS and OS of 78 and 88%, respectively (17). These two different Phase II studies could not be compared using statistical analysis, and thus further studies are required. Given that the median survival time following relapse in the current study was only 5 months, initial effective treatment should be applied. Rituximab and other target therapies should be evaluated to develop a more effective and less toxic therapeutic strategy for elderly patients with aggressive localized NHL.

The SWOG studies applied relatively high radiation doses of 40 Gy or more. However, no prospective randomized trials have evaluated adequate radiation doses following chemotherapy in patients with NHL (26,27). Wilder et al. (26) conducted a retrospective analysis and reported that the local control rate in patients with tumors larger than 3.5 cm who received a radiation dose of $\leq$39.1 Gy was only 40%. However, this analysis included only a very small number of patients, which is problematic with regard to statistical analysis. Kamath et al. (27) reported that a radiation dose of $<$40 Gy led to a poor local control rate in patients with large tumors. However, in this study, the local control rate of good responders who achieved CR after chemotherapy was excellent even if they received low-dose radiotherapy (i.e. $<$30–40 Gy). Isobe et al. (28) reported a sufficient control rate in patients who received an intermediate radiation dose of 30–40 Gy following brief chemotherapy. Yu et al. (29) analyzed 86 patients with head and neck localized aggressive NHL who received short-course chemotherapy followed by irradiation of the involved node areas and reported that whole-neck irradiation including prophylactic irradiation of the contralateral neck area was not necessary. Our study included 19 patients (79%) with non-bulky tumor $<$6 cm and 16 patients (67%) with clinical Stage I lymphoma, and the response rate after chemotherapy was 79% (19 patients) for CR or CRu. Our study showed that none of the patients developed local relapse within the radiation field and/or regional relapse in the adjacent lymph node areas. Less intensive radiotherapy, such as low-dose radiation and the use of a small radiation field, should be investigated for the elderly population.

Our study indicated that late systemic relapses, short survival time after relapse, second malignancies and death from other causes occurred, and these adverse events were associated with failure to thrive, physical frailty and cognitive impairment. However, no loco-regional relapse was observed. Less intensive radiotherapy might not compromise treatment outcome for elderly patients with non-bulky and chemotherapy-responsive lymphoma.

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Conflict of interest statement

None declared.

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