Table 1. Patient accrual

Institution	RT alone				RT and HT			
	n	Sex (M/F)	Histology (scc/adeno/other)	Age (years)[a]	*n*	Sex (M/F)	Histology (scc/adeno/other)	Age (years)[a]
Kiev City Oncology Centre	14	13/1	5/7/2	66	16	10/6	7/8/1	62
China–Japan Friendship Hospital	13	10/3	13/0/0	62	12	10/2	10/0/2	55
Sun Yat-sen University of Medical Sciences	11	9/2	5/4/2	56	9	9/0	6/2/1	56
Maryknoll Hospital	1	1/0	1/0/0	64	2	2/0	1/0/1	71
St. Mary's Hospital	1	1/0	1/0/0	72	1	1/0	1/0/0	64

RT, Radiation therapy; HT, hyperthermia
[a]Median

In this multi-institutional prospective randomized trial sponsored by the International Atomic Energy Agency (IAEA), radiotherapy in combination with hyperthermia was investigated. The primary purpose was to clarify whether the combination of hyperthermia and radiotherapy improved the rate of local control compared to that obtained by radiotherapy alone.

Patients and methods

Five institutes in three countries participated in this trial. The study was approved by each institution's ethics committee. The eligibility criteria were as follows: (1) patients with stage II, III NSCLC; (2) tumor well defined and measurable; (3) histologically proven malignancy; (4) life expectancy of at least 3 months; (5) performance score (WHO) of 0–2; (6) patient considered a candidate for radical radiotherapy; (7) induction of hyperthermia possible; (8) written informed consent; and (9) age between 20–75 years. Patients were excluded if any of the following were present: (1) cardiac pacemaker; (2) large metal objects within the treatment area; (3) history of radiotherapy for the treatment area; (4) malignant pleural or pericardial effusion; (5) subcutaneous fat thickness more than 3 cm; (6) pregnancy; (7) history of other malignancy within 5 years. Between October 1998 and April 2002, 80 patients with biopsy-proven NSCLC were registered and randomized to treatment by radiotherapy alone (RT) or radiotherapy combined with hyperthermia (RT + HT). The patients were stratified by institution, stage, and histological type. Table 1 shows the results of patient accrual. As shown in Tables 2 and 3, the two arms were well balanced with regard to patient factors and tumor factors. Following randomization, each patient was scheduled to receive external-beam radiation therapy. A total of 66 or 70 Gy was prescribed to the gross tumor volume. Initially, 40 Gy in 2-Gy fractions was given to the gross tumor volume and regional lymph node area. Then the field was reduced to gross tumor volume and an additional 26 to 30 Gy was given, avoiding the spinal cord. Reduction of the daily fraction to 1.8 Gy was acceptable at the presiding physician's discretion if the patient's condition deteriorated. For patients randomized to receive hyperthermia, a minimum of five sessions (60 min each, once per week) was scheduled, employing radio frequency (RF) capacitive heating (Yamamoto Thermotron, Osaka, Japan). Measurement of intraesophageal temperature at the first hyperthermic treatment and at least once more during the course of treatment was planned.

Table 2. Patient characteristics

	RT alone ($n = 40$)	RT and HT ($n = 40$)	*P*-value
Age (years)[a]	62 (38–73)	59 (30–75)	0.14
Sex			
Male	34	32	0.56
Female	6	8	
Performance status			
0	9	16	0.29
1	28	23	
2	2	1	
Unknown	1	0	
Prior treatment			
None	27	30	0.74
Surgery[b]	3	1	
Chemotherapy	9	8	
Chemotherapy + surgery[b]	1	1	

[a]Mean (range)
[b]Includes exploratory thoracotomy

Table 3. Tumor characteristics

	RT alone ($n = 40$)	RT and HT ($n = 40$)	*P*-value
TNM stage[a]			
IIB	10	7	0.70
IIIA	17	18	
IIIB	13	15	
Histologic type			
Squamous	25	25	0.79
Adeno	11	10	
Others	4	4	
Unknown	0	1	
Histologic grade			
GX	20	22	0.70
G1	0	5	
G2	10	4	
G3	9	9	
Unknown	1	0	
Tumor size (cm^3)[b,c]	147.0 (7.3–1539.4)	108.6 (1–785.4)	0.50
Data missing	10	7	

[a]UICC TNM Classification 4th edition (1987)
[b]Mean (range)
[c]$X \times Y \times Z \times \pi/6$

Table 4. Treatment methods

Location	RT dose (Gy)[a] to primary	No. of HT sessions[a]	Duration of HT session (min)[a]	No. of temperature measurements[a]	T_{ave}[a]
Kiev City Oncology Centre	70.0 (70.0–70.0)	6.9 (6–7)	59 (57–60)	1.8 (1–2)	41 (41–42)
China–Japan Friendship Hospital[b]	57.9 (20.0–76.0)	3.2 (0–6)	58 (43–66)	1.5 (0–4)	40 (39–43)
Sun Yat-sen Univ. of Medical Sciences	62.8 (28.0–70.0)	3.3 (1–6)	59 (51–73)	1 (0–2)	40 (37–42)
Maryknoll Hospital	59.3 (48.6–68.2)	3.5 (3–4)	57 (53–60)	0.5 (0–1)	37 (37–37)
St. Mary's Hospital[b]	56.7 (54.0–59.4)	7 (7–7)	35 (30–40)	3 (3–3)	39 (38–39)

RT, Radiation therapy; HT, hyperthermia; T_{ave}, average intratumoral temperature during the treatment seesion
[a]Mean (range)
[b]One of the patients assigned to the RT-alone arm received HT at each of these hospitals

Table 5. Parameters for radiation therapy

	RT alone ($n = 40$)	RT and HT ($n = 40$)	*P*-value
Dose to primary tumor (Gy)[a]	64.5 (54.0–70.0)	61.2 (20.0–76.0)	0.18
Data missing	8	6	
Overall treatment time (days)[a]	52.9 (31–114)	47.2 (11–94)	0.12
Data missing	8	6	

[a]Mean (range)

Table 6. Treatment parameters for hyperthermia

	RT and HT ($n = 40$)
Total number of hyperthermia sessions[a]	4.6 (0–7)
Data missing	6
Number of sessions with thermometry/patient[a]	1.5 (0–4)
Data missing	7
Average of T_{max}[a]	41.3 (37.7–44.0)
Data missing	15
Average of T_{min}[a]	39.5 (35.5–41.7)
Data missing	15
Average of T_{ave}[a]	40.3 (37.0–42.7)
Data missing	14

[a]Mean (range)

Of the 80 patients, 33 could not complete the prescribed radiation therapy mainly due to deterioration of their condition. Of the 40 patients randomized to receive hyperthermia, 39 received at least one session of hyperthermia. Fifteen patients could not receive the designated number of hyperthermia sessions, mainly due to deterioration of their condition. Of note, 2 patients randomized to radiation alone actually received hyperthermia. Twenty-seven patients underwent temperature measurement at least once, and 16 underwent temperature measurement at least twice as required by the protocol. Treatment methods at the participating institutions, the parameters for radiation therapy and the parameters for hyperthermia are summarized in Tables 4, 5, and 6, respectively.

Quality assurance

The equipment, policies, and procedures at each participating institution were personally inspected at least once by the principal investigator (M. H.), to ensure that quality assurance procedures were in place and were followed for treatment according to the protocol guidelines.

Post-treatment evaluation

All patients were followed regularly by physical examination and, when appropriate, by diagnostic imaging such as computed tomography/magnetic resonance imaging (CT/MRI) scans. The evaluation was performed every 3 months for the first 6 months, then at 12 months, followed by at least once/year.

Statistical design

The primary endpoint was the local response rate. The secondary endpoints were local progression-free survival and overall survival. It was assumed that with radiotherapy alone the local response rate was 40%, and in order to detect an improvement of 20% by adding hyperthermia, 108 patients would be required in each arm. However, the study was terminated after 80 patients had been randomized because the slow rate of accrual made it unrealistic to enroll the originally planned number of patients. Local response was evaluated according to WHO criteria.[7] For the evaluation of local-progression-free survival, patients who died without disease progression within the radiation field were censored at the time of death. Observed results were analyzed on an intent-to-treat basis. The Kaplan-Meier method was used for the estimation of survival rates. The χ^2 test was used to compare distribution of the data. A P value of less than 0.05 was regarded as significant.

Table 7. Tumor response

	RT alone ($n = 40$)		RT and HT ($n = 40$)	
Dose of radiation therapy to tumor bed	>65.5 Gy	=< 65.5 Gy	>65.5 Gy	=<65.5 Gy
At the end of treatment				
CR	1	0	0	3
PR	7	7	9	6
NC	3	8	5	2
PD	0	0	0	0
Not evaluable	6	0	2	7
Data missing	8		6	
3 Months after the treatment				
CR	2			2
PR	6	7	11	4
NC	1	5	3	1
PD	1	2	1	
Not evaluable	7	1	1	11
Data missing	8		6	

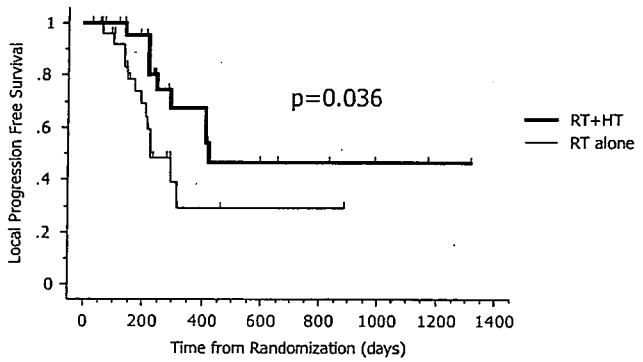

Fig. 1. The local progression-free survival rate analyzed according to the treatment arm. *RT*, radiation therapy; *HT*, hyperthermia

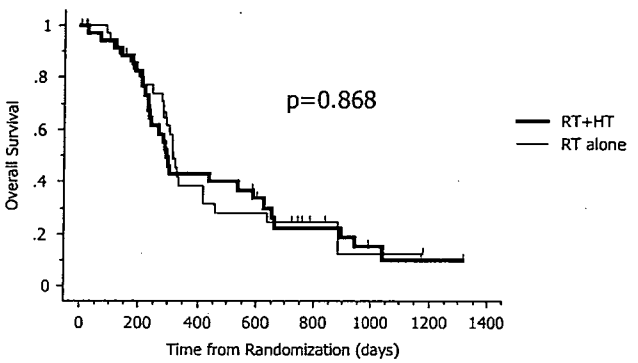

Fig. 2. The overall survival rate analyzed according to the treatment arm

Results

Follow up and response rates

The median follow-up period was 204 days for all patients and 450 days for surviving patients. Fifty-three of the 80 patients were known to have died at final analysis. Tumor responses at the end of treatment and 3 months after the treatment are summarized in Table 7. The response rate (complete response [CR] + partial response [PR]) was 37.5% for the RT arm and 45.0% for the RT + HT arm. There were no significant differences between the two arms ($P = 0.49$).

Survival

The 1-year local progression-free survivals for RT and RT + HT were 29.0% and 67.5%, respectively, and the results were significantly better in the RT+HT arm (Fig. 1; $P = 0.036$). The 1-year overall survivals for RT and RT + HT were 38.1% and 43.0%, respectively, and there was no significant difference between the two arms (Fig. 2; $P = 0.868$).

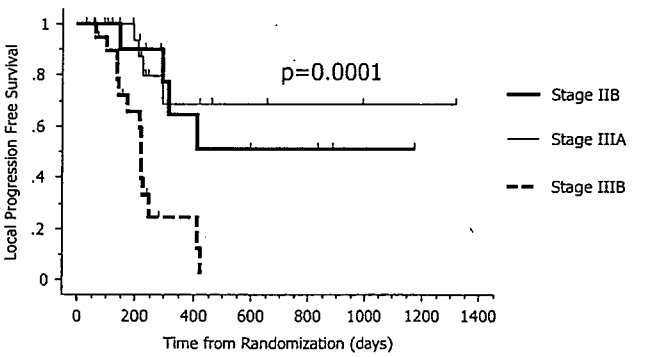

Fig. 3. The local progression-free survival rate analyzed according to clinical stage

Figures 3 and 4 show local progression-free survival analyzed according to the stratification variables: clinical stage of the disease and histological subtype. There were also significant differences according to the stage of the disease (Fig. 3; $P = 0.0001$). There were no significant differences according to histological subtypes (Fig. 4; $P = 0.287$). Figure 5 shows local progression-free survival according to treatment arm and radiation dose. Although

the patients who were assigned to the RT + HT arm and completed the prescribed radiation did better than other groups, there was no significant difference between the groups ($P = 0.26$).

Table 8 shows the first site of disease progression after the treatment for each arm. Of note, the proportion of distant metastasis as the first site of disease progression was higher in the RT + HT arm, but the difference was marginal ($P = 0.07$).

Figures 6 and 7 show overall survival analyzed according to the stratification variables. There were significant differences according to the stage of the disease, as expected (Fig. 6; $P = 0.001$). Of note, there were significant differences according to the histological subtypes; adenocarcinoma showed better outcomes than other histological types (Fig. 7; $P = 0.013$).

Acute and late toxicity

Acute toxicity was generally mild; grade 2 or more toxicity was seen at six sites in five patients treated by hyperthermia and at nine sites of the nine patients treated without hyperthermia. Late toxicity was seen in three patients in each arm. All of these involved radiation pneumonitis/pulmonary fibrosis. The details of the acute grade 2–3 toxicities observed are shown in Table 9.

Discussion and conclusion

Although standard treatment for locally advanced NSCLC has not been well established, combination treatment with radiation and various chemotherapeutic agents seems to be

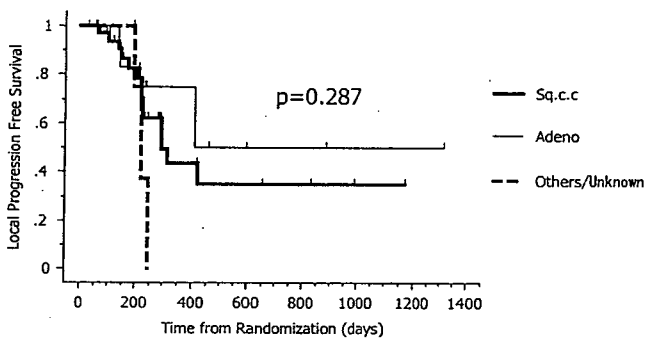

Fig. 4. The local progression-free survival rate analyzed according to the histology of the tumor. *Sq. c.c.*, squamous cell carcinoma; *adeno*, adenocarcinoma

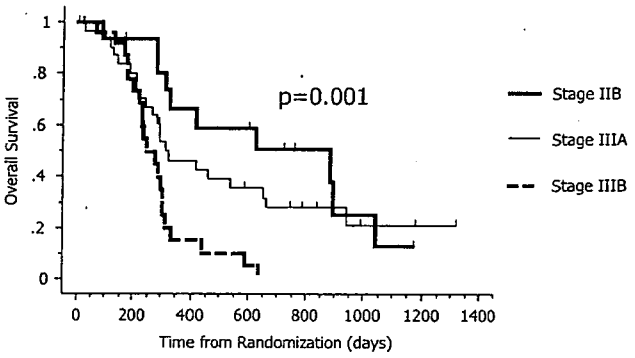

Fig. 6. The overall survival rate analyzed according to clinical stage of the tumor

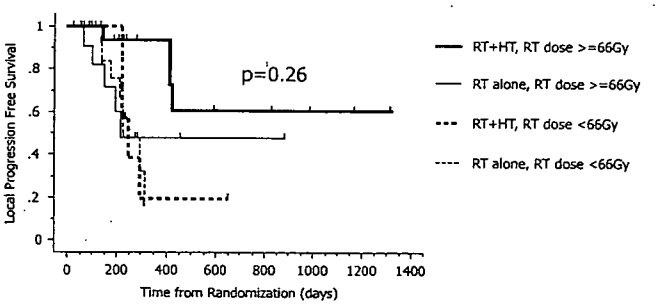

Fig. 5. The local progression-free survival rate analyzed according to the treatment arm and radiation dose

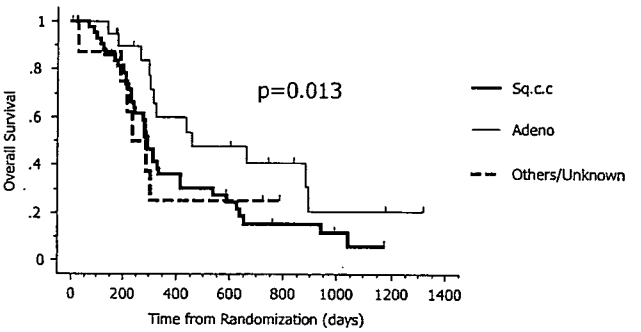

Fig. 7. The overall survival rate analyzed according to the histology of the tumor

Table 8. Initial site of disease progression after treatment

	RT ($n = 40$)	RT + HT ($n = 40$)	P-value
No recurrence	3	4	
Primary tumor and/or regional lymph nodes	15	7	
Distant metastasis	2	10	0.07
Both locoregional and distant[a]	3	4	
Unknown/missing	17	15	

[a]Patients in whom the interval between locoregional disease progression and distant metastasis was less than or equal to 1 month

Table 9. Acute and late toxicity

	RT ($n = 40$)	RT + HT ($n = 40$)	
Acute toxicity			$P = 0.58$
Grade 2			
Dermatitis	4	0	
Fat necrosis	0	1	
Esophagitis	0	2	
Pneumonitis	4	1	
Grade 3			
Dermatitis	0	1	
Fat necrosis	0	0	
Esophagitis	1	1	
Pneumonitis	0	0	
Grade 4	0	0	
Data missing	13	9	
Late toxicity			
Grade 2[a]	3	3	
Grade 3	0	0	
Grade 4	0	0	

[a] Pneumonitis/Pulmonary fibrosis

the trend in research.[5] However, although such combination treatment is not always given in developing countries because the availability of these new agents is limited and the cost is often prohibitive, radiation therapy is well established and available around the world. Theoretically, a combination of radiation and hyperthermia may be advantageous for several reasons.[8–10] Based on these reasons, this trial was conducted to test the hypothesis that adding hyperthermia to radiation therapy is more effective than radiation alone for the treatment of advanced NSCLC.

In a clinical trial of hyperthermia, the selection of heating equipment is particularly important. We employed RF capacitive heating in this trial because of its relatively limited systemic stress and wide applicability to various anatomical sites.[11,12] In addition, the disadvantage of excessive heating of subcutaneous fat is less problematic in thoracic tumors than in abdominal or pelvic tumors. Although the temperature parameter measured in this study was the intraesophageal temperature, which may not accurately reflect the intratumoral temperature, hyperthermia was generally well tolerated and an acceptable temperature was achieved without a significant adverse effect.

Unfortunately, the quality of this trial was reduced by variations in actual treatment and an excessive amount of missing data. We could not reach a consensus regarding the dose of radiation, and both 66 Gy and 70 Gy were accepted as prescription doses to the tumor bed. These problems were mainly due to the poor communication infrastructure in developing countries. Considering these circumstances, this trial is more an aggregation of small institutional randomized trials than a phase III trial with a firm treatment protocol. Still, we believe that the results presented here have clinical relevance, as they are stratified by institutions.

There was no significant difference in the local response rate between the two treatment arms at the end of treatment or 3 months after the treatment. However, local progression-free survival was significantly superior in the RT+HT arm. This might reflect a subtle difference in the local effect between the two treatment methods that was too small to be recognized by the WHO grading system for local response. More precise evaluation of local response will be necessary in future clinical trials to detect such small differences.

In our trial, the 1-year overall survival and median survival time (MST) were almost identical in the two treatment arms, at approximately 40% and 9 months, respectively. These figures correspond well to the existing reports of radiation therapy alone for stage III NSCLC.[13–15] In the present trial, the proportion of distant metastasis as the first site of disease progression was higher in the RT + HT arm, with marginal significance. It is quite logical that the small difference in local control was not reflected in systemic control, because hyperthermia is a local treatment and has no effect on micrometastases outside the treatment volume. Considering that recent trials of chemo-radiation therapy for locally advanced NSCLC have demonstrated a 10% improvement of the 2-year survival rate in sequential settings[13,15] and even greater survival benefit in concurrent settings,[16,17] chemo-radiation should be pursued whenever applicable. Hyperthermia might be a component of treatment in future clinical trials of chemo-radiation for locally advanced NSCLC because locoregional failure remains the biggest issue in this disease.[6,14]

In summary, this prospective randomized study failed to show any significant benefit from the addition of hyperthermia to radiotherapy for the treatment of locally advanced NSCLC. The clinical relevance of the prolonged local progression-free survival observed in the hyperthermia arm should be verified in future trials.

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SPECIAL FEATURE: REVIEW ARTICLE

New trends in radiation therapy as a component of breast conserving therapy

Current status of accelerated partial breast irradiation

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Abstract Accelerated partial breast irradiation (APBI) is a radiotherapy method used in breast-conserving therapy. In APBI, the tumor bed is topically irradiated over a short period after breast-conserving surgery. The fundamental concept underlying APBI is that more than 70% of ipsilateral breast tumor recurrence occurs in the neighborhood of the original tumor, and that hypofractionated radiotherapy can be applied safely when the irradiated volume is small enough. It is expected to reduce the time and cost required for conventional whole breast irradiation while maintaining equivalent local control. Several techniques including multicatheter interstitial brachytherapy, intracavitary brachytherapy, intraoperative radiation therapy, and 3D conformal external beam radiation therapy have been proposed, and each of them has its own advantages and drawbacks. Although APBI is increasingly used in the United States and Europe, and the short-term results are promising, its equivalence with whole breast radiation therapy is not fully established. In addition, because the average breast size in Japan is considerably smaller than in the West world, the application of APBI to Japanese patients is technically more challenging. At this point, APBI is still an investigational treatment in Japan, and the optimal method of radiation delivery as well as its long-term efficacy and safety should be clarified in clinical trials.

Keywords Breast cancer · Breast conserving therapy · Radiation therapy · Accelerated partial breast irradiation

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Abbreviations

APBI	Accelerated partial breast irradiation
BCT	Breast-conserving therapy
IBTR	Ipsilateral breast tumor recurrence
WBRT	Whole breast radiation therapy
BCS	Breast-conserving surgery
TR/MM	True recurrence/marginal miss
EF	Elsewhere failure
EIC	Extensive intraductal component
IORT	Intraoperative radiation therapy
EBRT	External beam radiation therapy
LDR	Low dose rate
HDR	High dose rate

Introduction

Several studies have reported that the survival rate after breast-conserving therapy (BCT) ia similar to that following mastectomy. Thus BCT has been established as a standard treatment for early breast cancer [1–6]. Concerning the role of radiotherapy in BCT, a meta-analysis of seven randomized controlled studies in which lumpectomy alone was compared with the combination of lumpectomy and radiotherapy showed that radiotherapy significantly reduced the incidence of ipsilateral breast tumor recurrence (IBTR) [6–13]. In the NIH consensus statement announced in 1990, the importance of radiotherapy in BCT was emphasized; whole breast radiation therapy (WBRT) at a total dose of 45–50 Gy, a dose of 1.8–2.0 Gy per fraction, and, if necessary, boost irradiation of the tumor bed were recommended.

The reported long-term IBTR rates after breast-conserving surgery (BCS) without radiation are between 10

and 40% depending on the extent of local resection and method of pathological evaluation, which in turn means more than half of the patients do not need radiation therapy. Therefore, some trials have been conducted to specify subgroups that do not require radiotherapy. In hormone receptor positive patients over 70 years of age, radiotherapy may be omitted with proper use of hormonal therapy because of relatively small benefit [14]. However, no other subgroup in which radiotherapy can be omitted has been specified [15]. In various treatment guidelines, it is recommended that WBRT should be performed in all patients after BCS.

According to a survey in Japan, radiotherapy is performed in approximately 70% of patients following BCS [16]. In the United States, the percentage is approximately 80% [17]; a relatively large number of patients do not undergo radiotherapy. This is possibly because radiotherapy requires a considerable expenditure and many hours.

The importance of systemic adjuvant therapy in breast cancer treatment has been increasing. Even in patients with early breast cancer for whom BCT is indicated, several months of chemotherapy is increasingly being given early after surgery, raising the issue of the order of chemotherapy and radiotherapy.

Thus, accelerated partial breast irradiation (APBI), in which the tumor bed is topically irradiated over a short period after BCS, was proposed.

Rationale of APBI

APBI was established based on the following rational background:

1. In more than 70% of patients with IBTR after breast-preserving therapy, recurrence is detected at the periphery of the primary tumor (true recurrence/marginal miss [TR/MM]) [18, 19]. The incidence of recurrence elsewhere (elsewhere failure [EF]) is similar to that of contralateral breast cancer; a "second cancer" may develop following treatment.
2. The treated volume is smaller than that of WBRT. Therefore, hypofractionated irradiation, in which the number of fractions is decreased by elevating the dose per fraction, may not cause significant late toxicities.
3. The radiation dose to the normal breast tissue other than the tumor bed is minimized, facilitating additional conservative therapy including radiotherapy, even when IBTR occurs in the future.
4. APBI can be completed within 1 week after surgery. Therefore, radiotherapy can be initially performed even in patients requiring chemotherapy; delayed radiotherapy dose not influence local control.

Indication for APBI

APBI is not indicated for all patients in whom BCT is selected. Previous studies have indicated that the IBTR rate after APBI was high in high-risk patients including those with large tumors, marked intraductal spreading or the presence of an extensive intraductal component (EIC), and young patients. Furthermore, this procedure has some limitations with respect to irradiation techniques; for external beam irradiation, the normal breast tissue including overlying skin, contralateral breast, heart, and lungs other than the tumor bed are exposed to an excessive dose of radiation. For brachytherapy, an excessive dose of radiation to overlying skin may be problematic.

Methods of APBI

APBI methods are mainly classified into three categories: brachytherapy, intraoperative radiation therapy (IORT), and external beam radiation therapy (EBRT). The following five techniques have been reported.

Brachytherapy

Topical irradiation is performed by placing a radioactive source in the tumor bed. Irradiation can be performed immediately after insertion, and takes 4 days to 1 week. The reproducibility of irradiation is favorable. However, the radiation dose in normal tissue, especially the overlying skin, is problematic. When inserting an applicator during surgery, irradiation can be started immediately following surgery. However, it is impossible to examine pathological margin status. Based on the type of applicator, brachytherapy is classified into two subcategories: multicatheter interstitial brachytherapy and intracavitary brachytherapy.

Multicatheter interstitial brachytherapy [20–25]

In the tumor bed, several guide tubes are placed in parallel at an equivalent interval on a single or several planes. Via these guide tubes, irradiation is performed using remote afterloading of ^{192}Ir. Initially, some studies employed a low dose rate (LDR) system [21]. However, recent studies have mainly selected a high dose rate (HDR) system [20, 23, 24]. Prescribed doses are approximately 50 Gy/5 days for LDR and 30–40 Gy/5 days (twice a day) for HDR. Guide tubes can be inserted during or after surgery. When inserting them during surgery, the lumpectomy cavity may be sutured. However, when inserting them following surgery, a removal cavity should be maintained to specify the tumor

bed from the outside. At the end of irradiation, guide tubes are percutaneously removed.

Intracavitary brachytherapy [26, 27]

Following surgery, a balloon-type applicator (Mammosite®) is inserted into a lumpectomy cavity under ultrasound-guidance. For irradiation, a radioactive source (^{192}Ir) is placed at the center of the balloon using the remote afterloading method. The removal cavity cannot be sutured. After balloon insertion/inflation, the distance from the skin cannot be maintained in some cases, or a space between the balloon and the removal cavity may affect dose distribution, making irradiation impossible; therefore, patients should be informed about such conditions prior to the procedure.

IORT [28, 29]

For IORT, the removal cavity is irradiated in the same room immediately after lumpectomy. Electron beam or low-energy X-ray is used. There are no limitations regarding the reproducibility of treatment or excessive radiation of the skin. However, it is impossible to examine pathological findings including the resection margin status prior to irradiation. In Japan, radiation shielding is another issue. Concerning electron beam application, the use of a self-shielding type device (Mobetron®) may minimize any necessary remodeling of an operating room. As a soft X-ray generator has low energy, it is not necessary to perform operating room remodeling.

IORT using electron beam [29]

Using a specially designed instrument for wound opening, an electron beam applicator is applied to the tumor bed, and anterior one-field electron beam irradiation is performed. Veronesi et al. performed single-dose irradiation at 21 Gy based on the results of a dose escalation study. Unnecessary radiation to underlying normal tissue can be avoided by mobilizing the mammary gland during surgery and placing a lead plate for shielding on its dorsal surface. As single-dose irradiation is completed during surgery, a removal cavity can be sutured.

IORT using soft X-ray [28]

Using a special soft X-ray generator with a bulbous applicator, the applicator is inserted into a removal cavity for irradiation before the cavity is sutured after lumpectomy. The dose gradient is steep. Vaidya et al. performed single-dose irradiation at 20 Gy in an area 2 mm distant from the stump and at 5 Gy in an area 1-cm distant from the stump. The device is smaller than an electron beam device (linear accelerator), and easy to manage.

EBRT (3D-conformal radiation therapy) [30–32]

Using the three-dimensional conformal technique, external beam irradiation is performed on the tumor bed. Radiotherapy treatment planning is performed based on CT images. However, to specify the target volume, the removal cavity should not be sutured, or when it is sutured, it must be marked with metal clips. There is enough time to review pathological findings. Various beam arrangements have been proposed [33, 34]. However, there are limitations such as the reproducibility of each fraction of irradiation and the radiation exposure of normal organs in the beam path. Recent studies with proton beams showed that the dose distribution was better than that for photon 3D-CRT or photon/electron 3-port irradiation [32, 35].

The features, merits, and limitations of each procedure are summarized in Table 1. There are differences in the timing of the pathological evaluation of the resected stump, work required for the procedure, and the reproducibility of treatment.

Table 1 Characteristics of modalities used in APBI

	Pathological confirmation before APBI	Work/ resource required for APBI	Conformity of APBI	Reproducibility of APBI
Interstitial (multicatheter)	Δ	Δ	Δ ~ ○	○
Intracavitary irradiation	Δ	○	Δ ~ ○	○
IORT (electron beam)	×	Δ ~ ×	○	○
IORT (soft X-ray)	×	Δ ~ ×	Δ ~ ○	○
3D-CRT	○	×	×	Δ

○ No problem; Δ some problem; × problematic

For IORT, it is impossible to accurately evaluate tumor pathology, especially the state of the resection margin, before irradiation. However, unnecessary irradiation in areas other than the target volume can be reduced. EBRT can be performed after obtaining pathological information. However, the inter-fractional reproducibility is lower than that of brachytherapy and IORT.

Results of APBI

The results of APBI previously reported are shown in Table 2. In some studies, local control was good, but not in others. In studies in which patients with large tumors, young patients, and those with an extensive intraductal component were regarded as eligible, the risk of local recurrence was high, suggesting the importance of patient selection in successful APBI.

Criticism of APBI

The rapid widespread use of APBI in clinical practice in the United States has contributed to advances in BCT. However, not all radiation oncologists agree with this strategy [36, 37]. The first goal of APBI is tumor control in the breast on the affected side. However, a consensus regarding the long-term results in comparison with WBRT has not been reached, although some studies have indicated that the short-term results obtained were similar to those of WBRT. APBI is effective at a 2 cm distance from the resected stump. Some researchers are skeptical about the difference between wider resection and APBI. In a randomized controlled trial of BCS, with or without WBRT, in which wider resection (quadrantectomy) was used as protocol treatment, the addition of WBRT still decreased the ipsilateral breast recurrence rate [38]. This suggests that WBRT is more advantageous than APBI.

In APBI, cancer recurrence in areas other than the periphery of the primary tumor bed is not considered. However, it is controversial whether such recurrence, which has been reported in a specific number of patients, may be ignored.

In addition, recent studies reported that WBRT improved the survival rate in patients undergoing BCT [39, 40]. The theoretical background of this benefit remains to be clarified. However, some investigators suggested that WBRT improves survival in a similar fashion to post-mastectomy radiation therapy (PMRT); it improves tumor control not only in breast tissue but also in lower axilla, skin, and subcutaneous tissue in the radiation field, which prevents subsequent secondary dissemination [40]. It should be investigated whether APBI achieves ipsilateral breast control as well as all the benefits of WBRT in a large number of patients over a prolonged period.

NSABP B-39/RTOG 0413 trial

In 2005, a phase III NSABP B-39/RTOG 0413 collaborative comparative study was started to compare WBRT with APBI. According to an RTOG announcement, more than 150 patients per month were registered (as of May 2006). More than 70% of them underwent APBI by external irradiation. Initially a study of 3,000 patients was planned, but this was increased to 4,300. The eligibility criteria were disadvantageous for APBI in that young patients (18 years or older), those with T2 tumors (3 cm or less), those with EIC/DCIS, and those with lymph node metastasis (three or less positive nodes) were eligible, in whom the results of previous studies have suggested an increase in the local recurrence rate. If this clinical study shows that APBI is as effective as WBRT, APBI may become the main irradiation procedure after BCS.

Limitations of APBI in Japanese patients

The most important issues are breast size-related differences in the technique and the relationship between the removal cavity and the skin.

In Europe and the United States, a cavity after extirpation of the main tumor is maintained in many patients. However, in Japan, the cavity is sutured for cosmetic reasons. In this case, it is impossible to insert a device for intracavitary irradiation. For external irradiation, the target of irradiation can be visually confirmed when the margin of the removal cavity is marked with metal clips. However, the entire resected stump cannot always be accurately identified.

In Europe and America, the breast size is generally large, and lumpectomy, in which the extent of resection is about 1 cm from the gross tumor, is frequently performed. Therefore, the mammary gland tissue remains on the lateral, dermal, and pectoralis muscle sides of the removal cavity. In such cases, all-direction irradiation using a Mammosite® device is useful.

In Japan, the breasts are generally smaller, and wide excision involving a 2-cm free margin from the tumor is most commonly performed. In many cases, mammary gland tissue does not remain on the dermal or pectoralis muscle sides of the tumor. The target of irradiation is only the lateral stump. However, the dose distribution in the dorso-ventral direction cannot be controlled with a Mammosite® device; therefore, an excessive dose of irradiation to the skin may be a treatment-limiting factor.

Recently, a new device (SAVI™, BioLucent, Inc., California, USA), in which multi-channel guide tubes at

Table 2 Results of APBI in Western countries

Series	*N*	Age	Size	Surgery	Margin status	EIC/DCIS allowed	Axillary LN
Guy's Hospital [21]	27	<70	≤4 cm	Tumorectomy	Incomplete excision accepted	Eligible	Dissection in all pts.
Guy's Hospital [20]	50	<70	≤4 cm	Tumorectomy	Incomplete excision accepted	Eligible	Level 3 dissection performed
NCI Budapest [24]	45	NR 38–78	<2 cm	Wide excision	Negative microscopically	Not allowed	Single nodal involvement allowed
WBH [25]	199	>40	<3 cm	Lumpectomy	≥2 mm	Not allowed	12% 1–3 positive node
					2 pts. 0–2 mm	21 pts. in-situ	
London Regional [23]	39	NR 39–84	<5 cm	Lumpectomy	Negative	Eligible	15% positive
Osaka Medical Center [22]	20	>20 32–72	<3 cm	Wide excision	1.5–2 cm macroscopically	Eligible	Level 1–2 dissection performed
					3/20 positive in final pathology		Positive in 3/20
WBH [26]	80	>40	≤3 cm	Local resection	≥2 mm	Eligible	≤3 positive nodes
NCI Milan [29]	101	NR 33–80	≤2.5 cm	Quadrantectomy	>1 cm macroscopically	No data	SNB or dissection in 96/101
Christie Hospital [30]	353	<70	≤4 cm	Tumorectomy	Incomplete excision accepted	Eligible	Clinically negative
							No dissection
NYU [31]	40	Post menopausal	<2 cm non-palpable	Lumpectomy	≥5 mm	Not allowed	No data
MGH [32]	20	NR 46–75	≤2 cm	Lumpectomy	≥2 mm	Not allowed	Pathologically negative

Series	RT Technique	RT dose	F/U	Local relapse	Survival	Toxicity	Good to excellent cosmesis
Guy's Hospital	LDR ^{192}Ir multicatheter	55 Gy/5–6 days	6 years	37% crude	70% actuarial read from figure	No data	83%
Guy's Hospital	MDR ^{137}Caesium	45 Gy/4 fr./4 days	6.3 years	18% crude	No data	No data	81%
NCI Budapest	HDR ^{192}Ir multicatheter	30.3–36.4 Gy/7 fr./4 days	81 mo. median	6.7% crude	93.3% actuarial cancer specific survival	Grade 3 fibrosis 2.2%	84.4%
						Symptomatic fat necrosis 2.2%	
WBH	120 pts.: LDR	LDR: 50 Gy/4 days	65 mo. median	1% actuarial	87% actuarial OS	0%	99%
	79 pts.: HDR	HDR: 32 Gy/ 8 fr./ or 34 Gy/10 fr.					
London Regional	HDR ^{192}Ir multicatheter	HDR: 37.2 Gy/ 10 fr./5–7 days	91 mo. median	16.2% actuarial at 5 years	86% actuarial OS	No data	Median subjective score 90/100
Osaka Medical Center	HDR ^{192}Ir multicatheter	HDR: 36–42 Gy/6–7fr./3–4 days	52 mo. median	5% crude	89% actuarial OS	Grade 3:5%	75%
WBH	Intracavitary (Mammosite)	34 Gy/10 fr./5 days	22.1 mo. median	2.9% 3 year actuarial	91.3% 3 year OS	No data	88% 3 year
NCI Milan	IORT (electron)	10–21 Gy Single dose	42 mo. median	2% crude	98% crude	Grade1–2 22%	No data
		10–15 Gy with EBRT				Grade 3:1%	

Table 2 continued

Series	RT Technique	RT dose	F/U	Local relapse	Survival	Toxicity	Good to excellent cosmesis
Christie Hospital	EBRT (electron)	40–42.5 Gy/8 fr./10 days	8 years	25% actuarial	73% actuarial[a]	Marked telangiectasis 33% Marked fibrosis 14%	No data
NYU	EBRT (photon)	30 Gy/5 fr./10 days	12 mo.	0%	0%	No data	No data
MGH	EBRT (proton)	32 CGE/8 fr./4 days	12 mo.	0%	100%	Telangiectasia 3pts. Rib fracture 1 pt	100%

WBH William Beaumont hospital, *MGH* Massachusetts general hospital, *NYU* New York University, *NR* not restricted, *SNB* sentinel node biopsy, *LDR* low dose rate, *HDR* high dose rate, *CGE* cobalt gray equivalent, *F/U* follow-up, *OS* overall survival

[a] Read from survival curve

the circumferential region facilitate the fine control of dose distribution on the inner wall of the resected cavity, was developed. However, treatment results have not been published yet.

External irradiation also has a similar limitation. When irradiation is performed in the supine position, flat extension of the breast reduces the distance between the target of irradiation and the skin, leading to excessive radiation exposure of the skin.

For external irradiation, the conformity of dose distribution is less favorable than that for other procedures. As reported by Kosaka et al., the radiation dose administered to the normal mammary gland may be excessive when the resected cavity is relatively large compared with the breast.

When the breast size is large to some degree, these limitations may be overcome by suspending the breast in the prone position for irradiation. However, no study has investigated this issue in Japanese women.

Conclusion

Currently, we cannot recommend APBI as a standard option for BCT. However, in Europe and the United States, this procedure is being increasingly employed in clinical practice. If the results of clinical studies are good, it may accelerate this tendency. BCT in Japan markedly differs from that in Europe and the United States with respect to the surgical procedures and the average body habitus. In introducing APBI, unique strategies must be established and inspected.

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Postoperative radiotherapy for non-small-cell lung cancer: Results of the 1999–2001 patterns of care study nationwide process survey in Japan

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KEYWORDS
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Summary To investigate the practice process of postoperative radiation therapy for non-small-cell lung cancer (NSCLC) in Japan. Between April 2002 and March 2004, the Patterns of Care Study conducted an extramural audit survey for 76 of 556 institutions using a stratified two-stage cluster sampling. Data on treatment process of 627 patients with NSCLC who received radiation therapy were collected. Ninety-nine (16%) patients received postoperative radiation therapy between 1999 and 2001 (median age, 65 years). Pathological stage was stage I in 8%, II in 17%, IIIA in 44%, and IIIB in 20%. The median field size was 9 cm × 11 cm, and median total dose was 50 Gy. Photon energies of 6 MV or higher were used for 64 patients, whereas a cobalt-60 unit was used for five patients. Three-dimensional conformal treatment was used infrequently. Institutional stratification influenced several radiotherapy parameters such as photon energy and planning target volume. Smaller non-academic institutions provided worse quality of care. The study confirmed continuing variation in the practice of radiotherapy according to stratified institutions. Outdated equipment such as Cobalt-60 units was used, especially in non-academic institutions treating only a small number of patients per year.

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1. Introduction

Postoperative radiation therapy (PORT) decreases the risk of local–regional recurrence in patients with resected non-small-cell lung cancer (NSCLC) [1–3]. However, reduction in the frequency of local recurrence has not translated into a survival benefit in most studies. In 1998, the impact of PORT for NSCLC was analyzed in a meta-analysis of phase III trials [4]. After publication of the PORT meta-analysis, which emphasized deleterious effects in patients receiving PORT for completely resected N0-1 cases, much of the clinical focus on adjuvant therapy shifted to chemotherapy [5,6]. Thus, the role of PORT for patients at high risk for locoregional failure such as those with N2 disease remains unclear. Adjuvant chemotherapy trials have often permitted use of PORT as an option for patients with N2 disease [5,7]. One clinical study reported promising results for combined PORT and chemotherapy for patients with pathologic stage II or IIIA disease [8]. The results of these trials imply that PORT delivered using modern radiotherapy techniques may potentially provide a survival advantage for selected high-risk patients.

The Patterns of Care Study (PCS) is a retrospective study designed to investigate the national practice for cancer patients during a specific period [9,10]. In April 2002, the PCS started a nationwide survey for patients with NSCLC treated with radiation therapy in Japan. In the present report, we provide results of analyses focused on patients who received PORT for NSCLC during the study period. The objectives of this study were to reveal clinical practice patterns regarding PORT after publication of the PORT meta-analysis and to assess variation in clinical practice according to stratified institutions.

2. Materials and methods

Between April 2002 and March 2004, the PCS conducted a national survey of radiation therapy for patients with lung cancer in Japan. The Japanese PCS developed an original data format and performed an extramural audit survey for 76 of 556 institutions using a stratified two-stage cluster sampling. Data collection consisted of two steps of random sampling. Prior to random sampling, all institutions were classified into one of four groups. Criteria for stratification have been described elsewhere [10]. Briefly, the PCS stratified Japanese institutions as follows: A1, academic institutions such as university hospitals or national/regional cancer center hospitals treating $\geqq 430$ patients per year; A2, academic institutions treating <430 patients; B1, non-academic institutions treating $\geqq 130$ patients per year; and B2, <130 patients. The cut-off values in number of patients treated per year between A1 and A2 institutions and B1 and B2 institutions, respectively, were increased from those used in the previous PCS study because of the increase in the number of patients treated by radiation therapy in Japan [10]. Eligible patients had 1997 International Union Against Cancer (UICC) stage I–III NSCLC that was treated with PORT between 1999 and 2001, a Karnofsky Performance Status (KPS) >50 prior to start of treatment, and no evidence of other malignancies within 5 years. The current PCS collected specific information on 627 patients (A1:157, A2:117, B1:214, B2:139) who were treated with radiation therapy between 1999 and 2001. Of those, 99 (16%) patients (A1:15, A2:17, B1:45, B2:22) who received PORT constitute the subjects of the present analysis. The practice of PORT was investigated by reviewing items in each medical chart such as demographics, symptoms, history, work-up examinations, pathology, clinical stage, treatment course including radiation therapy, surgery and chemotherapy, and radiotherapy parameters. In addition, simulation films and linacgraphy of each patient were also reviewed by surveyors.

The PCS surveyors consisted of 20 board-certified radiation oncologists. For each institution, one radiation oncologist visited and surveyed data by reviewing patient charts. In order to validate the quality of collected data, the PCS utilized an internet mailing-list among all surveyors. In situ real-time check and adjustment of data input were available between each surveyor and the PCS committee. In tables, "missing" indicates that the item in the data format was left empty, whereas "unknown" means that the item in the format was completed with data "unknown". We combined "missing" and "unknown" in tables because their meanings were the same in most cases; no valid data were obtained in the given resources. Cases with missing or unknown values were included when both the percentage and significance value were calculated. Statistical significance was tested by the χ^2 test. A p-value less than 0.05 was considered statistically significant. Overall survival was assessed from the day of surgery and was estimated by the Kaplan–Meier product limit method using the Statistical Analysis System, Version 6.12.

3. Results

3.1. Patient and tumor characteristics

Patient and clinical tumor characteristics are shown in Table 1. Of the 99 patients who received PORT, 32 were treated at academic institutions and 67 at non-academic institutions. The proportion of patients with NSCLC who received PORT was significantly higher in non-academic institutions than in academic institutions (19% versus 12%, $p=0.013$). Overall, median age was 65 years (range, 39–82), and the male to female ratio was 4:1. Ninety-three percent of patients had a KPS greater than or equal to 80%. Preoperative examinations included chest computed tomography (CT) in 97% of patients, bronchoscopy in 87%, brain CT or magnetic resonance imaging (MRI) in 75%, abdominal CT in 75%, bone scintigraphy in 83%, and mediastinoscopy in 4%. The primary tumor site was the upper lobe in 62 patients, middle lobe in 7, and lower lobe in 27. The remaining 2 patients had a primary tumor near the border of the upper and middle lobes that involved both lobes, and they were allocated to "others". Peripheral tumors were twice as common as central tumors. When tumors were analyzed by laterality, the ratio of right to left side primary site was 1.5. Clinical T- and N-classifications were T1 in 28 patients, T2 in 35, T3 in 24, T4 in 11, and N0 in 33, N1 in 19, N2 in 40, and N3 in 6, resulting in clinical stage I in 27 patients, II in 14, IIIA in 41, and IIIB in 16. The numbers less than 99 are due to missing or unknown data.

Table 1 Patient and tumor characteristics

No. of patients	99
Men	79
Women	20
Age (years)	
Median	65
Range	32–89
% KPS ≥ 80	93
Preoperative work-up (%)	
Chest CT	97
Bronchoscopy	87
Brain CT or MRI	75
Abdominal CT	75
Bone scan	83
Mediastinoscopy	4
Primary tumor site	
Upper lobe	62
Middle lobe	7
Lower lobe	27
Other	2
Missing	1
Tumor location	
Central	30
Peripheral	60
Missing	9
Laterality	
Left lung	38
Right lung	59
Missing	2
Clinical T factor	
TX	1
T1	28
T2	35
T3	24
T4	11
Clinical N factor	
NX	1
N0	33
N1	19
N2	40
N3	6
Clinical stage	
IA	14
IB	13
IIA	7
IIB	7
IIIA	41
IIIB	16
Missing	1

KPS, Karnofsky performance status score.

3.2. Surgery and tumor pathology characteristics (Table 2)

The primary surgical procedure was a lobectomy in 78 patients, pneumonectomy in 12, and segmentectomy in 9.

Table 2 Surgical procedure and tumor pathology characteristics

Type of surgery	
Lobectomy	78
Pneumonectomy	12
Segmentectomy	9
Histopathology	
Squamous cell carcinoma	47
Adenocarcinoma	43
Large cell carcinoma	7
Adenosquamous carcinoma	2
Surgical margin status	
Negative	55
Positive	31
Missing	13
Pathological T factor	
T1	22
T2	35
T3	23
T4	18
Missing	1
Pathological N factor	
N0	15
N1	19
N2	56
N3	4
Missing	5
Pathologically involved mediastinal nodes (%)[a]	
No. 1	16
No. 2	23
No. 3	26
No. 4	34
No. 5	28
No. 6	5
No. 7	34
No. 8	12
Pathological stage	
IA	4
IB	5
IIA	9
IIB	8
IIIA	45
IIIB	20
Missing/unknown	8

[a] Nearly half of the data for this item were "missing/unknown".

Among all 99 patients, complete resection was accomplished for 55 patients. Surgical margin status was positive in 31 patients. Histopathology was squamous cell carcinoma in 47 patients, adenocarcinoma in 43, large cell carcinoma in 7, and adenosquamous carcinoma in 2. Predominantly involved mediastinal nodes confirmed pathologically to contain tumor were No. 7 (34%), No. 4 (34%), No. 5 (28%), and No. 3 (26%) according to the lymph node mapping system of the Japan Lung Cancer Society [11], although nearly half of the data for this item were "missing/unknown." The pathological T-

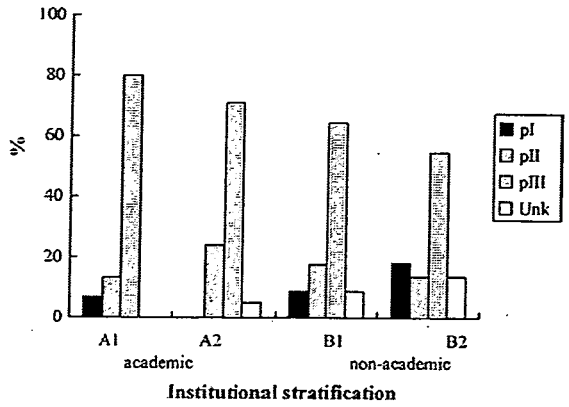

Fig. 1 Proportion of patients with pathologic stage III disease tended to be higher in large academic institutions ($p = 0.13$).

Table 3 Pathological stage in patients with complete surgery according to the stratified institution

Pathological stage	Institutional stratification				Total
	A1	A2	B1	B2	
I–II	2	4	8	4	18
III	5	6	18	8	37
Total	7	10	26	12	55

and N-classifications were pT1 in 22 patients, pT2 in 35, pT3 in 23, and pT4 in 18, and pN0 in 15 patients, pN1 in 19, pN2 in 56, and pN3 in 4. Pathological stage was stage I in 9 patients, II in 17, IIIA in 45, and IIIB in 20, respectively. The proportion of pathological stage III patients tended to be higher in large academic institutions (Fig. 1, $p = 0.13$). Breakdown of pathological stage in 55 patients who underwent complete surgery according to the stratified institution group was shown in Table 3. As for the proportion of pathological stage III patients, no significant difference was observed between institutions.

3.3. Radiotherapy parameters (Table 4)

A CT-simulator was used for planning for 26 patients. Ninety-one patients were treated with opposed AP-PA fields, and field reduction during the course of radiotherapy was done for 48%. Three-dimensional treatment was used in only 2 patients. Photon energies of less than 6 MV were used for 34 patients (34%). Dose prescription by isodose line technique was performed for only 8 patients (8%). The median field size was 9 cm × 11 cm, and the median total dose was 50 Gy. The planning target volume included the ipsilateral hilus in 80%, ipsilateral mediastinum in 86%, contralateral mediastinum in 68%, contralateral hilus in 9%, ipsilateral supraclavicular region in 30%, and contralateral supraclavicular region in 22%. Institutional stratification was found to influence several radiotherapy parameters. A photon energy of 6 MV or higher was used for 73% of patients in A1, 77% in A2, and 80% in B1 institutions, whereas it was used for only 23% of patients in B2 institutions (Fig. 2, $p < 0.0001$). A Cobalt-60 unit was used only in 5 B2 institutions. The planning target volume included the contralateral mediastinum for more than 70% of patients in A1 to B1 institutions, whereas it was included in only 46% of patients treated in B2 institutions ($p = 0.011$).

Table 4 Radiotherapy parameters

Simulation method	
CT-simulator	26
X-ray simulator	38
X-ray simulator + CT	26
Missing	7
Treatment technique	
AP-PA	91
Oblique	2
Three-field	1
Three-dimensional conformal	2
Other	2
Missing	1
Photon energy	
60 Co	5
<6 MV	29
≥6 MV	64
Missing	1
Dose prescription	
Isodose line	8
Point	91
Total dose	
≤3000 cGy	1
3001–4000 cGy	6
4001–5000 cGy	49
5001–6000 cGy	37
6001–7000 cGy	6
Missing	1
Median total dose (cGy)	5000
All fields treated each day (%)	83
Median field size (cm)	
Left-right	9 (range, 5–23)
Cranio-caudal	11 (range, 5–20)
Field reduction during radiotherapy (%)	48
Field included (%)	
Ipsilateral hilus	80
Ipsilateral mediastinum	86
Contralateral mediastinum	68
Contralateral hilus	9
Ipsilateral supraclavicula	30
Contralateral supraclavicula	22

3.4. Use of chemotherapy

Thirty patients (31%) received systemic chemotherapy. For 21 patients, chemotherapy and PORT were administered concurrently, mainly using a platinum-based, two-drug combination. For 9 of the 30 patients, platinum-based chemotherapy was used as induction therapy. Oral fluorouracil was used for 9 patients.

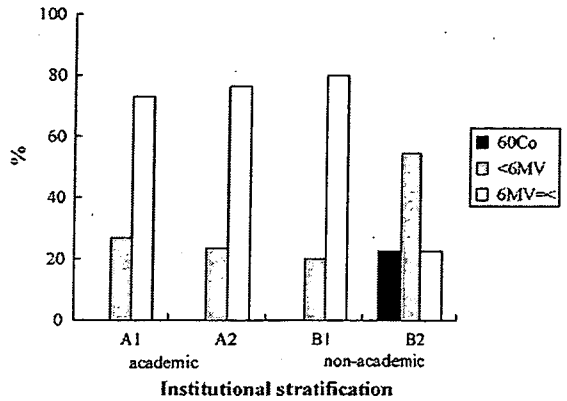

Fig. 2 A photon energy of 6 MV or higher was used for 73% of patients in A1 institutions, 77% in A2, and 80% in B1, whereas only 23% in B2 institutions ($p < 0.0001$). A Cobalt-60 unit was used only in B2 institutions.

3.5. Failure pattern and preliminary clinical outcome

The site of first failure was local in 6, regional in 5, and distant in 31. Of the patients who developed failure, the median time to first failure was 7 months. Although the current PCS has limitations in terms of outcome analysis due to a short follow-up period and significant variations in follow-up information according to institutional stratification [10,12], overall survival for the entire group was 88% at 1 year and 63% at 3 years, with a median follow-up period after PORT of 1.7 years.

4. Discussion

The results of the present PCS reflect national practices for PORT for NSCLC in Japan. However, when interpreting our data, it is important to note that they were limited to patients who received radiation therapy. We have no information about patients who did not receive radiation therapy after surgery. Thus, we have no data concerning the percentage of patients who underwent radiation therapy after surgery. Analysis of the national practice process for all patients with NSCLC in the adjuvant setting is beyond the scope of this study.

All eligible patients in this study received radiation therapy after publication of the PORT meta-analysis that emphasized deleterious effects in patients receiving PORT, especially for patients with completely resected N0-1 disease [4]. Since then, the clinical focus on adjuvant treatment has largely shifted to chemotherapy, which has become part of the postoperative standard of care for patients with NSCLC [5,6,8]. In the United States, use of PORT has substantially declined due to the lack of proven survival benefit [13]. However, PORT was still incorporated as an option in recent clinical trials that recruited patients with pathological N2 disease [5,7]. The recent analysis of Surveillance, Epidemiology, and End Results (SEER) data in the United States demonstrated that PORT was associated with improved survival for patients with N2 disease [14,15]. In addition, a recent clinical study has reported promising results for combined PORT and chemotherapy using modern radiotherapy techniques [7,8]. Thus, the current clinical question is whether adjuvant chemotherapy combined with PORT improves survival for patients at high risk for locoregional failure compared with adjuvant chemotherapy alone. Taking all of the evidence together, we conclude that PORT still plays an important role in the adjuvant setting. We believe that this PCS study provides basic data of current practice regarding PORT in Japan.

Results of the present study demonstrated that patients who received PORT accounted for 16% of all patients with NSCLC who received radiation therapy in Japan between 1999 and 2001. Of all 99 patients, 65 had pathological stage III disease (45, stage IIIA; 20, stage IIIB). Using a median field size of 9 cm × 11 cm, a median total dose of 50 Gy was delivered mainly through opposed AP-PA fields. Three-dimensional conformal treatment was infrequently used. Field size reduction during the course of radiotherapy was done for almost half of the patients. A dedicated CT-simulator was used for 26 patients. The PORT meta-analysis was criticized because the authors included several old studies in which a cobalt machine was used for radiotherapy. It was pointed out that suboptimal administration of PORT using outdated techniques counterbalanced the beneficial locoregional effects of PORT treatment in the meta-analysis [16]. Because of potential pulmonary/cardiac toxic effects of mediastinal radiotherapy, PORT should be delivered with modern radiotherapy techniques using CT-based three-dimensional conformal treatment planning, a technique with which target volumes and normal tissue constraints are precisely defined. Although the patients included in this PCS survey were treated between 1999 and 2001, the modern radiotherapy era, 34% of all patients were treated using photon energies <6 MV, including five patients who were treated using a cobalt machine. Institutional stratification influenced several radiotherapy parameters in PORT for NSCLC. As shown in the previous report for small-cell lung cancer in Japan [17], smaller non-academic institutions (B2) provided a lower quality of care for their patients. Planning target volume typically included the ipsilateral hilus, ipsilateral mediastinum, and contralateral mediastinum in A1 to B1 institutions, whereas the contralateral mediastinum was included for only 46% of patients treated in B2 institutions. Although there is controversy concerning prophylactic nodal irradiation in the setting of definitive radiation therapy, PORT for patients with pN2 NSCLC should include the contralateral mediastinum. Proportion of patients with pathological stage I–II who underwent complete surgery did not differ between stratified institution groups. Thus, it was considered that omission of treating the contralateral mediastinum in B2 institutions was not caused by unbalance in stage distribution. We speculate that this discrepancy in care was due mainly to the extremely small number of radiation oncologists in B2 institutions. We also found that obsolete equipment such as Cobalt-60 units were still used, especially in non-academic institutions treating only a small number of patients per year. The proportion of patients treated with 6 MV or higher photon energies was significantly higher in A1 to B1 institutions than in B2 institutions. A Cobalt-60 unit was used only in B2 institutions. The present study again confirms differences in the practice of radiotherapy according to institutional stratification status.

We consider that the structure of radiation oncology is a domestic problem specific to each country. The results represent intrinsic problems with the structure of radiation therapy in Japan. Considering the current immaturity of the Japanese structure of radiation oncology, PCS still perform an important role in monitoring structure and process, as well as providing essential information not only to medical staff and their patients but also to administrative policy makers.

5. Conclusions

Through the audit survey and subsequent data analyses, the PCS established nationwide basic information on the practice of PORT for NSCLC in Japan. Even after the publication of the PORT meta-analysis, PORT was used for a considerable proportion of patients receiving radiotherapy. However, this PCS documented that outdated modalities such as cobalt-60 units were still used in small non-academic institutions during the study time frame. Thus, the current PCS confirmed the continuing existence of variation in the practice of radiotherapy according to institution stratification.

Conflict of interest

We have no conflict of interest in connection with this paper.

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Postoperative Radiotherapy for Patients with Prostate Cancer in Japan; Changing Trends in National Practice between 1996–98 and 1999–2001: Patterns of Care Study for Prostate Cancer

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Objective: To evaluate the changing trends of standards and practices for postoperative radiotherapy (RT) for patients with prostate cancer in Japan.
Methods: The Japanese Patterns of Care Study (PCS) conducted a national survey in 84 institutions from 1996 to1998 (PCS96-98) and 76 institutions from 1999 to 2001 (PCS99-01). Detailed information relevant to RT was collected on a total of 169 patients (64 from 1996 to1998 and 105 from 1999 to 2001) with prostate cancer who had undergone radical prostatectomy.
Results: The fraction of clinical T3–4 tumours before prostatectomy decreased from 63% in the period 1996–98 to 26% in the period 1999–2001 ($P = 0.0004$). The pre-RT prostate-specific antigen level was significantly lower in 1999–2001 than in 1996–98 ($P = 0.0002$). We did not find a significant difference in the percentage of patients who received pelvic irradiation in the time periods between PCS96-98 and PCS99-01 ($P = 0.18$). Although the median radiation doses of 60 Gy were not changed between the surveys, various doses (from 20 to 74.6 Gy) were delivered to the prostatic bed. In the 1999–2001 survey, 73 of 105 patients received a median dose of 56 Gy in an adjuvant setting, while the other 32 received a median dose of 60 Gy in a salvage setting ($P = 0.0015$).
Conclusion: These data suggest that consensus has not been reached on the practice and management of postoperative RT for patients with prostate cancer in Japan.

Key words: postoperative radiotherapy – prostate cancer – Patterns of Care Study

INTRODUCTION

The Patterns of Care Study (PCS), which was developed in the United States by the American College of Radiology and has been administered by them for over 25 years, was introduced to Japan to evaluate the current status of radiotherapy (RT) and to improve the quality of radiation oncology (1–3). The PCS in the United States has disclosed the evidences that elementary techniques contribute to improvement of outcome; for example: multiple fields' technique, dose escalation and higher energy beam selection >6 MV for prostate cancer (3). The Japanese PCS Working Group of Prostate Cancer conducted the first nationwide process survey of patients with prostate cancer who received RT between 1996 and 1998 (PCS96-98). Subsequently, a second PCS of patients treated with RT between 1999 and 2001 was conducted (PCS99-01). Nakamura et al. (4,5) presented the preliminary results of these surveys for RT in patients with prostate cancer in Japan. We present here the final analysis of PCS96-98 and PCS99-01 in order to reveal the status of national practices for postoperative RT for prostate cancer and the changing trends seen between 1996–98 and 1999–2001.

SUBJECTS AND METHODS

The standard methods used in data collection for a national process survey have been described previously in detail (1,3). In brief, the PCS survey utilized a stratified two-stage cluster

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