excision of the ablated lesion [8, 10–12]. Burak et al. and Hayashi et al. [1, 9] had an interval of 1–3 weeks before excising the ablated zone. It was hypothesized that due to the effect of local vessel thrombosis and necrosis of surrounding tissue, the ablated zone expands in the period of time and provides a more accurate excision. In the end, the two trials did not have higher percentages of complete tumor ablation compared to the other studies, and it was concluded that an interval time between ablation and excision of the tumor might not be necessary [7, 9].

In cases of tumor diameter less than 2 cm, the NADH viability staining was available for 22 patients, and in 20 (90.9%), there was no evidence of viable malignant cells. The other two viable cases were due to insufficient ablation; the reason for one case was a defective device and for another case that impedance was too high for the tumor to be ablated completely. Breast cancer tissue is usually composed of tumor, normal tissue, fat, vessels, etc., and shows heterogeneity. The fat tissue has one of the highest electrical resistances. High resistance mean less effect from electrical power, such as radiofrequency. Therefore, we suspect that in our cases the component with high impedance against RFA might be fatty.

Up until now, only one pilot study has been performed that tested RFA in three elderly patients with breast cancer without excision of the ablated zone [17]. All three patients completed the treatment without complications, and after 18 months of follow-up, no recurrence had occurred. In the future, if RFA is to be used as a replacement for surgery, CNB might also be an option to confirm successful ablation. Fornage et al. suggested that multiple core-needle biopsies through the ablated lesion and its periphery should be obtained 3–4 weeks after the RFA procedure.

An indication for RFA can be early breast cancer ($T \leq 2$ cm). In 29 cases of tumor diameter ≤ 2 cm, 25 (86%) were confirmed to have complete ablation (Table 3). In 26 cases of tumors without EIC in pathological examination, 22 (85%) were confirmed to have complete ablation. In 23 cases of tumor with EIC, only 9 (39%) were confirmed to have complete ablation. According to MRI detection, tumor diameter and the EIC could be evaluated more accurately. Appropriate cases for RFA should be selected deliberately after enough diagnosing with US and MRI detection concerning the diameter, type, EIC, multiple lesions, etc.

The optimal conditions for RFA correlate to results under the following conditions: (1) tumor diameter <2 cm diagnosed with US and (2) <2 cm except for multiple lesions and extended intraductal spread of lesions of more than 2 cm diagnosed with MRI detection.

Also, in two cases, the tumor body could not be ablated sufficiently. Effects of RFA depend on tissue resistivity, so fatty tissue and tumor components can affect these effects. Components of breast carcinoma are different for each patient, and further studies are needed. In cases in which the initial resistance is too high and rolloff occurs immediately, as our study showed, the target temperature cannot be reached, and procedures should be changed from RFA to lumpectomy for the patients' safety. The reasons for these incidents need to be examined with resected samples.

In Japan, RFA is a popular treatment method for liver cancer.

Half of liver cancer patients are treated by RFA. This system is familiar to many physicians even in local hospitals and clinics.

Although cryoablation and the HIFU have not been approved by the Japanese government, only RFA has been approved and has the possibility to be admitted as an option for local treatment.

RFA seems to be a promising new tool for a minimally invasive procedure for small breast carcinomas. However, follow-up data regarding the local effects on the surrounding breast tissue or recurrence rates are hardly available. Further research will be necessary to establish the optimal technique and to demonstrate the long-term oncological and cosmetic effects of RFA.

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SURGERY TODAY

How to Do It

The Development of New Instruments (NT forceps) for Video-Assisted Thoracoscopic Surgery

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Abstract
A new type of forceps (NT forceps) was developed in November 2007, designed for dividing connective tissues and for holding tissue together. These forceps measure 32 cm in length and are made of stainless steel. The insides of the forceps have atraumatic dispositions because longitudinal notches are placed on them. Therefore, they can grasp important soft organs such as the lung, azygos, and pulmonary vein. In addition, the acral forceps also possess carbide chips with cross notches. They can therefore hold vessel tape, sutures, etc. There are two types of forceps, which are curved at different angles, either a sharp angle or a slight angle. The forceps can be used for dividing and holding tissue while performing basic surgical manipulations, especially during an operation using a video-assisted procedure with a minithoracotomy. These forceps are useful tools for performing technical manipulations for standard operations, such as a lobectomy.

Key words Video-assisted thoracoscopic surgery · New instrument · NT forceps

Introduction

New forceps have been produced by Solve Co. Ltd (Yokohama, Japan), and these instruments (NT forceps) are now commercially available in Japan (Fig. 1).[1] The new instruments were developed in November 2007. NT forceps are designed for dividing connective tissue and for holding tissue together. The forceps measure 32 cm in length and are made of stainless steel. These instruments can therefore be used during a video-assisted thoracoscopic surgery (VATS) operation with a minithoracotomy. The insides of the forceps have atraumatic dispositions because they contain longitudinal notches. Therefore, they can grasp important soft organs such as the lung, azygos, or pulmonary vein. In addition, the acral forceps also possess carbide chips with cross notches that improve their grasping ability. Therefore, they can hold vessel tape, sutures, etc. (Fig. 2). There are two types of forceps curved at different angles, either at a sharp angle or a slight angle.

Technique

A lobectomy for a cancer patient (stage I) is usually performed through a minithoracotomy of the auscultatory triangle with a 5–7-cm skin incision using video-assisted procedures, with two access ports. The forceps can be used for dividing and holding tissue while performing basic surgical manipulations, especially during a lung resection using a thoracoscope. The forceps open automatically and easily with appropriate power because they are powered by a spring in a "pencil-grip" manner. Exfoliation of the tissue can be performed when the closed acral forceps are inserted into soft areas of some tissue. The exfoliating forces result from the restitutive spring power of the forceps. The forceps have been used in combination with other techniques and instruments such as electrocautery, scissors, and new devices (e.g., LigaSure; Valleylab, Boulder, CO, USA, and Harmonic Scalpel; Ethicon Endo-Surgery, Cincinnati, OH, USA). The apex of the forceps should alternately be closed and opened while exfoliations are performed. However, the forceps can be opened naturally at a site of exfoliation, because the forceps utilize the power of the spring. Atraumatic exfoliations can also be performed around blood vessels using the forceps. In addition, the ends of the forceps can also be used to hold and grasp sutures or vessel tape. Cavitation trauma can be avoided when using the Harmonic Scalpel

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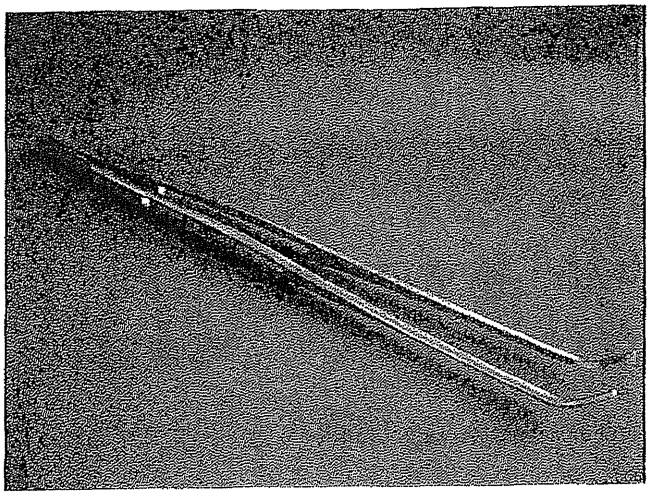

Fig. 1. The NT forceps

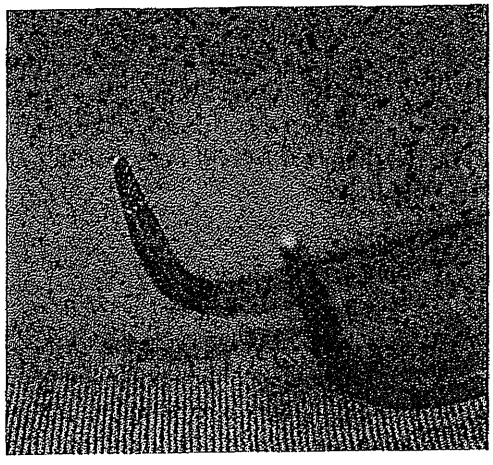

Fig. 2. The insides of the acral forceps have longitudinal notches and possess carbide chips with cross notches

around important organs by applying the forceps to sites beside the organs (Fig. 3). The combination of these new devices might allow useful techniques when cases are complicated with severe adhesions in an intrathoracic space. Exfoliation can easily be performed by repeatedly opening and closing the forceps in a loose tissue area. The forceps and the new devices provide effective approaches for a lymphadenectomy and can spread the mediastinum space using their spring, especially during a VATS procedure. The forceps and new devices are repeatedly used for dividing and cutting connective tissues during such operations. The combination of the forceps and new devices (such as LigaSure and Harmonic Scalpel) can be effectively utilized for the resection of a mediastinum tumor, because the area surrounding the mediastinum includes many important organs and vessels associated with the cardiovascular system (Fig. 4). A tumor resection can be effectively

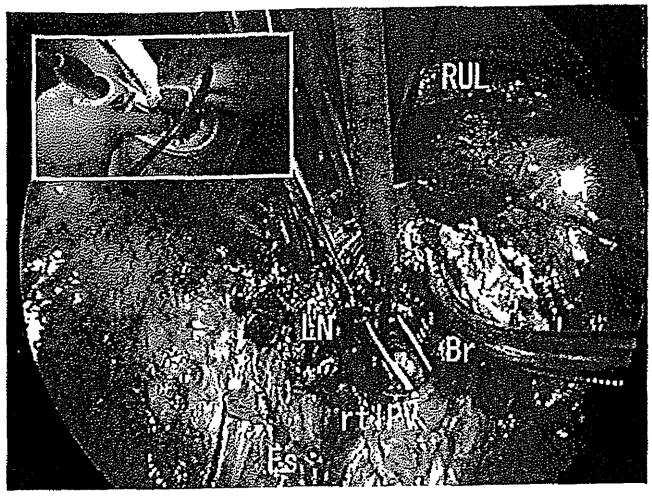

Fig. 3. A combination of the NT forceps and the Harmonic Scalpel is used for dividing and cutting connective tissues during a lymphadenectomy. *RUL*, right upper lobe; *LN*, lymph nodes; *Br*, bronchus; *rtIPV*, right inferior pulmonary vein; *Es*, esophagus

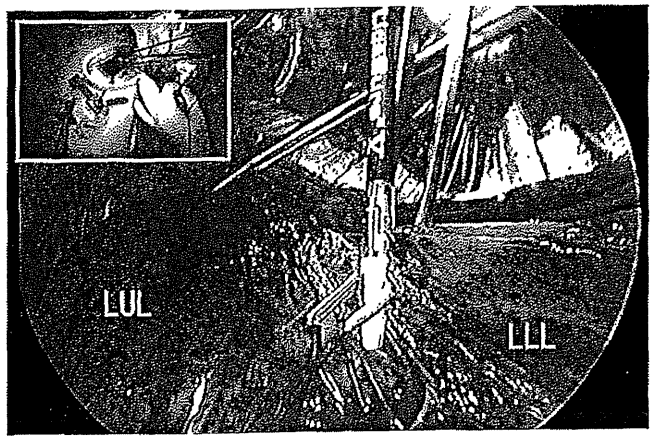

Fig. 4. A combination of the NT forceps and the LigaSure is used for dividing and cutting connective tissues between left upper lobe and lower lobe. *LUL*, left upper lobe; *LLL*, left lower lobe

performed by separating the tumor from those organs in the area of mediastinum. The forceps are useful tools for avoiding important organs surrounding the lesion when there are physical limitations to handling instruments in confined spaces. These forceps have been used for almost all procedures performed at this institute since December 2007, and no complications have occurred as a result of their use.

Discussion

A lobectomy is a standard surgical operation for lung cancer. Recently, the general surgical approach for this

operation has been the use of video-assisted procedures. Almost all thoracoscopic instruments have been developed based on classical instruments such as scissors or forceps. However, thoracoscopic instruments are often limited and difficult to handle, because such procedures demand a comprehensive understanding of the anatomical variations in the intrathoracic space. Therefore, the limitations of classical instruments are often frustrating when performing VATS procedures. In addition, almost all currently commercially available thoracoscopic devices for the use of video-assisted procedures were designed to be held by the operator in a "pistol-grip" manner. When using such pistol-grip forceps, the movements of the device to produce right-and-left or up-and-down motions of the acral forceps are mainly controlled by the senses according to the operator's own experience. Precise and accurate movements of the forceps might therefore often be difficult using the power of the operator's motor control in a two-dimensional view. This drawback motivated the design of a new instrument for performing VATS. In comparison with the pistol-grip forceps, the new pencil-grip forceps are easier to handle and thereby compensate for various limitations, especially when performing video-assisted procedures.

In conclusion, the new forceps are considered to be a useful tool for performing technical manipulations during standard operations such as a lobectomy. In addition, these forceps can also be used with other new devices (such as LigaSure and Harmonic Scalpel) to perform effective combination techniques.

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ORIGINAL ARTICLE

Radiotherapy quality assurance of the Japanese Gynecologic Oncology Group study (JGOG1066): a cooperative phase II study of concurrent chemoradiotherapy for uterine cervical cancer

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Abstract
Background To assess radiotherapy protocol compliance in a multi-institutional phase II study of concurrent chemoradiotherapy for patients with locally advanced cancer of the uterine cervix (JGOG1066).
Methods For study protocol development, various radiotherapy parameters were examined and consensus was reached by Japanese radiation oncologists with cervical cancer treatment expertise. Quality assurance (QA) was also discussed and included in the protocol. A credentialing process was used to select institutions for participation in the study. Individual case reviews referring to 18 QA items were undertaken for each patient. Radiotherapy data were submitted to the Japanese Gynecologic Oncology Group (JGOG) data center and reviewed by the members of the radiotherapy committee. The QA evaluation was classed as per protocol, deviation, and violation.
Results Individual case reviews were performed on 69 of 72 patients entered in the study. In 24 patients (35%), there

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were no deviations for any QA items. There were also no deviations seen for 5 of the 18 items in 69 patients evaluated. Deviations of 64 QA items were seen in 45 cases, and violations were seen in 4 cases (4 items). The most common deviation concerned appropriate application for the external beam radiotherapy (EBRT) boost to involved nodes or parametrium (32 cases). The 4 violations were identified in the QA items regarding high-dose rate intracavitary brachytherapy.

Conclusions Radiotherapy protocol compliance was favorable except for the EBRT boost indications. The results of this study validate the quality of radiotherapy in JGOG1066, and indicate that the final analysis will provide meaningful results.

Keywords Carcinoma of the uterine cervix · Radiation therapy · Chemoradiotherapy · Intracavitary brachytherapy · High dose rate

Introduction

Concurrent chemoradiotherapy (CCRT) is a standard treatment for patients with locoregionally advanced uterine cervical cancer [1]. However, some Japanese physicians remain cautious about employing CCRT as a standard treatment, for 2 reasons. The first concerns the feasibility of using the standard chemotherapy of weekly 40 mg/m^2 cisplatin concurrently with radiotherapy. There have been several reports that Japanese cervical cancer patients frequently experienced severe toxicities, and investigators concluded that CCRT using weekly 40 mg/m^2 cisplatin may not be feasible for Japanese patients [2, 3]. The second is that there are limited data on CCRT using high-dose-rate intracavitary brachytherapy (HDR-ICBT) [4, 5]. In addition, total radiation doses to the primary tumor seem to be extremely low compared with doses for definitive radiotherapy or CCRT in the United States [4–7]. A large amount of data concerning excellent outcomes and toxicity have been reported for patients treated with the Japanese standard schedules, but most of this information was derived from retrospective analyses, and CCRT data were limited [8]. Therefore, the 2007 Japanese treatment guidelines for uterine cervical cancer recommended a B grade for CCRT [9]. We undertook a prospective study (JGOG1066) to evaluate toxicities and outcomes in patients treated with CCRT using the standard dose/schedule of cisplatin and the standard Japanese radiotherapy dose schedules for HDR-ICBT.

For scientifically valid CCRT clinical trial results, it is essential to develop an adequate protocol and assure compliance with the radiotherapy protocol. In developing the JGOG1066 protocol, several Japanese radiation oncology experts on cervical cancer undertook extensive deliberations on radiotherapy methods. In addition, effective quality assurance (QA) for radiotherapy was also discussed. In this paper, we describe the process for QA and present results of independent case reviews (ICRs) from the CCRT study.

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Patients and methods

Summary of the JGOG1066

The Japanese Gynecologic Oncology Group (JGOG) conducted a phase II trial (JGOG1066) to evaluate the feasibility, toxicity and efficacy of CCRT using the standard global schedule for cisplatin (40 mg/m^2 weekly, 5 courses) and standard Japanese dose schedules for HDR-ICBT. Table 1 summarizes the trial, listing the criteria for patient eligibility, the endpoints, and treatments.

Protocol development

Radiotherapy parameters were examined and consensus was reached by Japanese radiation oncologists with expertise in the treatment of cervical cancer. A nationwide questionnaire on radiotherapy methods including treatment schedules, delivery of an external beam radiotherapy (EBRT) boost to lymph nodes and the parametria, and bladder/rectum dose calculations (ICRU38) was first distributed to radiation oncologists. Treatment schedule queries included total and fractional doses of whole-pelvis EBRT (with/without midline block) and also total and fractional doses of HDR-ICBT. In developing protocols for radiotherapy methods, data from the questionnaire and from previous published reports were extensively discussed, and a consensus was reached.

To determine location of point A, a rule was established based on the topographical relationships between tandem and ovoid. Basically, a coordinate at the external os (usually equivalent to the position of the tandem flange) was selected as the geographic origin of point A. In cases where the external os was located caudally to the cranial ovoid

Table 1 Summary of JGOG1066

Eligible patients			
1. FIGO stage III/IVA uterine cervical cancer			
2. Squamous cell carcinoma, adenosquamous cell carcinoma, adenocarcinoma			
3. ECOG performance status 0–1			
4. Age 20–70 years			
5. No para-aortic lymphadenopathy (≥10 mm assessed by CT)			
6. No prior treatment			
7. Adequate organ (bone marrow, hepatic, renal, heart) functions			
8. Written informed consent			
Endpoints			
Primary: 2-year progression-free survival rate			
Secondary: treatment completion rate, toxicity rates (acute and late), complete response rate, 2-year survival rate, 2-year pelvic progression-free rate, 2-year distant metastases-free rate			
Planned sample size and accrual duration:			
70 within 2 years			
Treatment			
Concurrent chemoradiotherapy (CCRT)			
Chemotherapy			
Cisplatin 40 mg/m^2, weekly, 5 courses			
Radiotherapy			
External beam radiotherapy (EBRT) and high-dose-rate intracavitary brachytherapy (HDR-ICBT)			
Radiotherapy schedules			
WP	WP + MB	HDR-ICBT[a]	BED (WP + HDR-ICBT)[a]
30 Gy/15f	20 Gy/10f	24 Gy/4f	$74.5Gy_{10}$
30.6 Gy/17f	19.8 Gy/11f	24 Gy/4f	$74.4Gy_{10}$
40 Gy/20f	10 Gy/5f	18 Gy/3f	$76.8Gy_{10}$
41.4 Gy/23f	9 Gy/5f	18 Gy/3f	$77.8Gy_{10}$

WP whole pelvic radiotherapy, *MB* midline block, *BED* biologically effective dose, *f* fraction

[a] Prescribed at point A

surface (i.e. patients with roomy vaginal vaults), a coordinate at the vaginal vault was selected as the origin of the vertical level with the point A. The concept behind the latter definition is essentially the same as that of point H proposed by the American Brachytherapy Society (ABS) [6]. Four radiotherapy schedules were provided for the protocol (Table 1). Because these schedules have almost biologically equivalent doses, the treating radiation oncologist was allowed to apply one of the schedules at their discretion. The protocol stated that enlarged pelvic node(s) (greater than 10 mm in the shortest diameter) visualized by pretreatment computed tomography (CT)/magnetic resonance imaging (MRI), and palpable nodular parametrium(s) fixed to the wall(s) should received an EBRT boost, with a total dose of 6–10 Gy/3–5 fractions.

To maintain radiotherapy quality, methods for QA were also examined. A credentialing process for participating institutions and independent case reviews (ICRs) of all treated patients were adopted for the QA. A description of the QA process was included in the protocol.

Credentialing

For institutional participation in this study, credentialing was required. The participating institutions had to meet the following 3 criteria:

1. Institution was certified by the Japanese Society for Therapeutic Radiology and Oncology (JASTRO) with JASTRO-certified radiation oncologist(s).
2. All HDR-ICBT procedures (i.e., applicator insertions, calculations, and evaluations) were carried out by JASTRO-certified radiation oncologist(s) or their colleagues.
3. At least 10 cervical cancer cases per year were treated by definitive radiotherapy using HDR-ICBT.

Meeting the first requirement indicated that the institution had a specified accuracy of external beam radiation dose delivery, since JASTRO-certified institutions must regularly undertake output measurements and calibrations of their linear accelerators. The second and third

requirements aid in ensuring that the HDR-ICBT procedure is performed with a reliable degree of skill.

Credentialing was undertaken by the JGOG radiotherapy committee. First, the committee identified JASTRO-certified institutions from 237 JGOG member institutions. Next, the committee asked those institutions if they would like to participate in the study. Institutions responding "yes" were subsequently requested to submit applications providing the following information: name of radiation oncologist(s) performing HDR-ICBT, name of radiologic technician(s) and physicist(s) responsible for HDR-ICBT, number of cervical cancer patients treated by definitive radiotherapy with HDR-ICBT per year, models and manufacturers of the HDR-ICBT machine and planning computer, source strength verification at the time of source replacement, and verification of source positioning in the catheter. With this information, the committee arrived at a consensus on whether or not an institution could participate in the study.

ICR summary

Participating institutions were requested to submit radiotherapy data for all treated patients. Table 2 lists the submitted items. Radiotherapy charts describing daily treatment records and treatment parameters were submitted as hard copies. Other graphical data (including simulation, digitally reconstructed radiography) and figures (including dose distributions) were submitted in digital formats on CD-ROMS. The radiotherapy committee performed ICRs on 18 QA items according to predefined evaluation criteria (Table 3). The QA assessment was classed as per protocol, deviation, and violation. QA evaluation criteria for ICRs were not included in the protocol description, but prepared separately.

Preliminary evaluations were performed by the study chair (T.T.). The preliminary evaluations were reviewed and approved by other JGOG radiotherapy committee members at the time of the QA meetings. The QA meetings were held twice (April 24, 2009, and May 7, 2010).

Table 2 Data submitted for ICR

External beam radiotherapy
Treatment charts (beam energy, SAD, gantry angle, field size, MU, plan summary sheets from RTPS, and daily treatment record)
Simulation films or DRRs
Verification portal films or EPIDs
Isodose distributions (central axis plane)
HDR-ICBT
Treatment charts for all sessions (activity, dwell times, dwell positions, and point doses)
AP and lateral orthogonal films or images for all sessions
AP and lateral isodose distributions for all sessions

ICR individual case review, *SAD* source-axis distance, *MU* monitor unit, *RTPS* radiotherapy treatment planning system, *DRR* digitally reconstructed radiographs, *EPID* electronic portal imaging devices, *HDR-ICBT* high dose-rate intracavitary brachytherapy, *AP* anterioposterior

Results

From March 2008 to January 2009, 72 patients from 25 institutions were enrolled. One patient who did not meet the eligibility requirements and 2 patients who stopped protocol treatment because of toxicities were excluded, leaving 69 patients who were considered eligible for the ICRs. Table 4 summarizes the ICR results. In 24 patients (35%), there were no deviations of any of the 18 ICR items. There were also no deviations seen in 5 of the 18 items (i.e., QA-1, -2, -3, -4, -8) in any of the 69 patients evaluated. Deviations were seen in 45 cases, and violations were observed in 4 cases. Table 5 lists the number of cases and number of ICR items assessed with a deviation or violation. Deviations were observed most frequently for QA-7, which evaluated the appropriateness of delivering an EBRT boost.

Details of QA evaluations

QA-1 EBRT beam energy: No deviations were seen. Beam energies included the following: 6 MV in 1 patient, 10 MV in 40 patients, 15 MV in 14 patients, 18 MV in 12 patients, and 20 MV in 2 patients.

QA-2 EBRT method: No deviations were seen. There were 28 patients treated with anteroposterior–posteroanterior (AP–PA) ports, and the remaining 41 patients were treated with the four-field box technique.

QA-3 Daily EBRT dose fraction: No deviations were seen. In 40 patients, 1.8 Gy was used, and in 29 patients, 2 Gy was used.

QA-4 Total EBRT dose of the whole pelvis (WP) with/without midline block (MB): No deviations from the protocol description were seen.

QA-5 MB set-up timing: One patient whose MB was set at 32 Gy received 24 Gy/4 fractions of HDR-ICBT; this was judged as a deviation. The remaining patients were all evaluated as per protocol. The MB was set at 30 Gy in 11 patients, 30.6 Gy in 33 patients, 40 Gy in 15 patients, and 41.4 Gy in 7 patients. There were 2 patients who

Table 3 Radiotherapy quality assurance items and criteria for ICR

Items	Evaluation		
	Per protocol	Deviation	Violation
QA-1: EBRT beam energy	≥6MV	<6MV or cobalt	–
QA-2: EBRT methods	AP–PA or 4-field box	Other methods	All ports not delivered each day
QA-3: EBRT daily fraction dose (prescribed)	1.8 or 2 Gy and 5 fractions/week	Other fraction dose and 5 fractions/week	4 fractions/week
QA-4: EBRT total dose (prescribed)	<±5%	5–10%	>±10%
QA-5: MB set-up timing	1. 30/30.6/40/41.4 Gy	1. 30–41.4 Gy, but not 30/30.6/40/41.4 Gy	Before 30 Gy
	2. after 41.4 Gy with certain clinical validity	2. after 41.4 Gy without certain clinical validity	
QA-6: EBRT treatment portals	WP with proper coverage	WP with improper coverage	Extended fields (covering para-aortic nodes)
QA-7: EBRT boost	Performed properly/not applicable	Not performed even applicable/performed but improperly	–
QA-8: EBRT dose homogeneity within PTV[a]	95–107%	<95 or >107%	–
QA-9: Divergence between simulation and verification	≤5 mm and no difference in shape	≥6 mm or different shape	No verification
QA-10: Timing of the first HDR-ICBT	After 30–41.4 Gy and within 7 days from MB insertion	After 30–41.4 Gy but over 7 days from MB insertion	Before 30 Gy
QA-11: EBRT and HDR-ICBT on same day	No	–	Yes
QA-12: HDR-ICBT planning for each fraction	Yes	–	No
QA-13: HDR-ICBT fraction dose (at point A, prescribed)	6 Gy and once a week	Other than 6 Gy (<7.5 Gy) or ≥twice a week	≥7.5 Gy
QA-14: HDR-ICBT total dose (at point A, prescribed)	18 or 24 Gy	Other than 18 or 24 Gy	≥30 Gy
QA-15: Determination of point A	As stated in protocol	Not as stated in protocol	–
QA-16: Dose calculation at OARs (rectum, bladder; ICRU 38)	Yes	No	–
QA-17: Total EBRT and HDR-ICBT dose (prescribed, BED at point A)	As stated in protocol (74–78 Gy_{10})	Not as stated in protocol but 70–80 Gy_{10}	<70 Gy_{10} or >80 Gy_{10}
QA-18: Overall treatment time	≤8 weeks	8–10 weeks	>10 weeks

ICR individual case review, *EBRT* external beam radiotherapy, *AP–PA* anteroposterior–posterioanterior, *MB* midline block, *WP* whole pelvis, *PTV* planning target volume, *HDR-ICBT* high-dose-rate intracavitary brachytherapy, *OAR* organ at risk, *BED* biological effective dose

[a] At level of field isocenter

received 50 Gy of whole-pelvis EBRT without MB, in whom the treating radiation oncologists thought that adequate shrinkage of the primary tumor had not been achieved for effective ICBT. This situation had been described as "clinically appropriate" in the protocol, and was judged per protocol.

QA-6 EBRT treatment portals: There were 6 patients with deviations. These were all from a single institution, and planning was based on clinical target volume (CTV) contouring on CT images.

QA-7 EBRT boost: In 32 patients, the EBRT boost was not applied appropriately as stated in the protocol. These were judged as deviations.

QA-8 EBRT dose homogeneity within planning target volume (PTV): No deviations were seen.

QA-9 Geometrical divergence between simulation and verification: There were 3 patients from a single institution for whom a geometrical divergence ≥5 mm was seen. These were judged as deviations.

QA-10 Timing of the first HDR-ICBT. There were 2 patients whose first HDR-ICBT was delayed for ≥7 days, which was judged as a deviation. There

Table 4 Radiotherapy ICR summary: JGOG1066

Items	Evaluation		
	Per protocol	Deviation	Violation
QA-1: EBRT beam energy	69	0	–
QA-2: EBRT method	69	0	0
QA-3: EBRT daily fraction dose (prescribed)	69	0	0
QA-4: EBRT total dose (prescribed)	69	0	0
QA-5: MB set-up timing	68	1	0
QA-6: EBRT treatment portals	63	6	0
QA-7: EBRT boosts	37	32	0
QA-8: EBRT dose homogeneity within PTV	69	0	–
QA-9: Divergence between simulation and verification	66	3	–
QA-10: Timing of the first HDR-ICBT	65	2	2
QA-11: EBRT and HDR-ICBT on same day	68	–	1
QA-12: HDR-ICBT planning for each fraction	68	–	1
QA-13: HDR-ICBT fraction dose (prescribed)	66	3	0
QA-14: HDR-ICBT total dose of (prescribed)	65	4	0
QA-15: Determination of point A	64	5	–
QA-16: Dose calculation of OARs (ICRU38)	66	3	–
QA-17: Total EBRT and HDR-ICBT dose (prescribed)	67	2	0
QA-18: Overall treatment time	66	3	0

ICR individual case review, *EBRT* external beam radiotherapy, *MB* midline block, *PTV* planning target volume, *HDR-ICBT* high-dose-rate intracavitary brachytherapy, *OAR* organ at risk

were 2 patients who received their first HDR-ICBT before 30 Gy of EBRT had been administered, which was judged as a violation.

QA-11 Prohibition against same-day delivery of EBRT and HDR-ICBT: There was 1 patient who received both EBRT and HDR-ICBT on the same day, which was judged as a violation.

QA-12 HDR-ICBT planning for each fraction: The protocol stated that dose calculations should be performed for every HDR-ICBT session. There was 1 patient who received her second and third HDR-ICBT based on planning data from her first application. This was judged as a violation.

QA-13 HDR-ICBT fraction dose: There were 2 patients who received HDR-ICBT with an incorrectly prescribed point A dose, which was judged as a deviation. Another patient received HDR-ICBT using an inappropriate reference point instead of point A, which was also judged as a deviation.

QA-14 HDR-ICBT total dose: The 3 patients with QA-13 deviations and 1 patient who did not receive the last HDR-ICBT because of acute toxicity were judged as deviations.

QA-15 Determination of point A: There were 5 patients who received HDR-ICBT at an incorrectly defined point A. These were judged as deviations. One of those patients also had deviations for QA-13 and -14. In 4 of these patients, the external os was selected as the geometrical origin for point A instead of the vaginal vault level (which was the correct definition), although the external os was located caudally to the cranial ovoid applicator surface.

Table 5 Numbers of cases and quality assurance items with deviations or violations

Number of deviations	Number of cases[a]
0	24
1	36 (2)
2	6 (1)
3	0
4	1 (1)
5	1
6	0
7	1

[a] Parentheses include number of cases also having violations

QA-16 Organs at risk (OAR) dose calculation [10]: Bladder dose calculations were not performed in 3 patients, which were judged as deviations.

QA-17 Total EBRT and HDR-ICBT dose: Two of 3 patients who had deviations in QA-13 were also assessed with deviations for this.

QA-18 Overall treatment time (OTT): There were 3 deviations in OTT. The OTTs of these 3 patients were 56, 57, and 65 days. The longest OTT was

caused by a delayed starting time of the EBRT boost to the parametrium.

Discussion

This study determined that there was favorable radiotherapy compliance with the JGOG1066 protocol. Based on our findings, we expect the final results of this study on long-term outcomes and complications to be scientifically valid.

A credentialing process was used to select the participating institutions in this study. Our credentialing consisted of a review of questionnaires received from institutions and an assessment of radiotherapy QA, especially with regard to HDR-ICBT. The credentialing process has been adopted for some recent clinical trials performed by the Gynecologic Oncology Group (GOG). Lowenstein and colleagues reported that major protocol deviations were more frequently seen in non-certified institutions than in certified institutions [11]. We believe that the credentialing process in this study may be one of the reasons that favorable protocol compliance was achieved.

Favorable radiotherapy compliance was observed for EBRT, especially with regard to parameters defined by numerically prescribed values, such as beam energy and prescribed dose, which had 100% compliance. Regarding EBRT port arrangements, deviations were observed in 6 patients. These were all from a single institution and were based on CTV delineation-based treatment planning. Only 2-dimensional (2D) treatment planning was prescribed in the protocol. Some clinical study groups have published consensus guidelines for CTV delineation of the pelvic node region [12, 13], and the Radiation Therapy Oncology Group (RTOG) has also released a guideline for primary cervical cancer tumors [14]. For future clinical trials, it will be essential to include detailed descriptions of 3-dimensional (3D) treatment planning, including the definition of CTV contouring. In this study, frequent deviations were observed for EBRT boosts. Most deviations were omissions at the discretion of the treating physicians, despite indications for a boost. These physicians might have prioritized their clinical impressions and experiences over the protocol. We believe that there was a discrepancy between the protocol and current daily clinical practice. At present, there is no obvious evidence that an EBRT boost provides therapeutic value [15]. In ongoing Gynecology Oncology Group (GOG) and RTOG trials, EBRT boosts have been optional. Therefore, for trials in the near future, it is reasonable to keep the EBRT boost as an option.

Although protocol compliance was also favorable for HDR-ICBT administration, 4 violations were seen. Two were in patients who received their first HDR-ICBT application before they received 30 Gy of EBRT. Eligible patients in this study all had extensive cervical disease. It is thought that locoregionally advanced disease should receive adequate doses of EBRT before HDR-ICBT application, and it is essential to deliver an adequate HDR-ICBT dose to the entire cervical tumor [16]. There was 1 patient who received EBRT and HDR-ICBT on the same day, which was judged as a violation. In accordance with the ABS guidelines [6], concurrent delivery of EBRT and HDR-ICBT was strictly prohibited in the protocol. In 1 patient, treatment planning for the first HDR-ICBT was also applied during the subsequent HDR-ICBT sessions. We believe that these types of violations should be strictly avoided, because they could cause poor treatment outcomes and decrease safety [6].

Only 4 deviations were observed for the designation of point A. We adopted 2 alternative determination methods for point A from a previous prospective study (JAROG0401/JROSG04-2) [17]. In that study, 10 of 60 patients were assessed with deviations regarding the definition of point A [17]. We think that compliance with this definition has improved over the previous study. To further improve compliance with point A determination, a dummy run may be effective. This would also be effective for CTV delineation on EBRT treatment planning. While image-guided brachytherapy is becoming popular, especially in the United States [18], point A is still widely used for dose prescription along with DVH parameters [19]. We think that our system can provide consistent and clinically appropriate point A determinations [20].

The theoretical weakness of our present QA process is lack of physics QA, including an external dosimetry audit and independent dose calculation of HDR-ICBT. In the GOG and RTOG studies, an independent HDR-ICBT dose calculation was performed and revealed some variation of actual doses compared with prescribed doses [20]. We need to establish an effective QA system for physics by ensuring active participation of medical physicists in the CCRT studies of cervical cancer. Our QA assessments regarding deviations and violations may be considered subjective. We classified the cases into 3 QA categories based on previously decided criteria. Our QA criteria were developed with reference to those used in other clinical study groups, such as GOG [11]. Development of standard QA criteria, including those pertaining to physics which can be used globally, should be encouraged.

In conclusion, compliance with the radiotherapy protocol in JGOG1066 was favorable, except for indications for the EBRT boost. The results of this compliance study validate the quality of radiotherapy in JGOG1066 and indicate that the final analysis will provide meaningful results.

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Conflict of interest No author has any conflict of interest.

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SPECIAL FEATURE

Strategies of radiotherapy for recurrent and metastatic breast cancer

Management of locoregional recurrence of breast cancer

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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

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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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