Non-surgical Ablation Therapy for Early-stage Breast Cancer

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Chapter 1
Introduction

Takayuki Kinoshita

In the surgical treatment of breast cancer, conservative treatment and sentinel lymph node biopsy have already become the standard of care. In addition to being less invasive, treatments are expected to have good aesthetic outcomes. In Japan, the incidence of breast cancer (Fig. 1.1) and the detection rate for early-stage disease have increased due to widespread use of mammography and advances in diagnostic imaging, as is the case in other developed countries. Given this historical background, nonsurgical ablative therapies, noninvasive surgical therapies, have started to attract attention due to patient demand. The nonsurgical ablative therapies used in clinical practice for breast cancer are cryoablation, high-intensity focused ultrasound (HIFU), and radiofrequency ablation (RFA). In Japan, RFA became widespread quickly because of the prevalence and convenience of the device. In this book, an outline of the research on RFA funded by the Japan Agency for Medical Research and Development (AMED), prospects for RFA, and the current status of cryoablation and HIFU are discussed.

Conservative treatment for breast cancer was introduced in Japan in the 1980s as a local treatment for early-stage disease used under cautiously-developed criteria. Its indications have been gradually expanded by, for example, the addition of concomitant preoperative chemotherapy. More than half of breast cancer patients currently benefit from this treatment. Recently, nonsurgical ablative therapies have been tested as definitive conservative therapy. Clinical studies on HIFU and cryoablation began in 2004 and 2006, respectively. Phase I and Phase II multicentre clinical studies of RFA as treatment for early-stage breast cancer were started in 2006 under the Evaluation System of Investigational Medical Care. A prospective Phase III study was started in 2013 under the Advanced Medical Service System.

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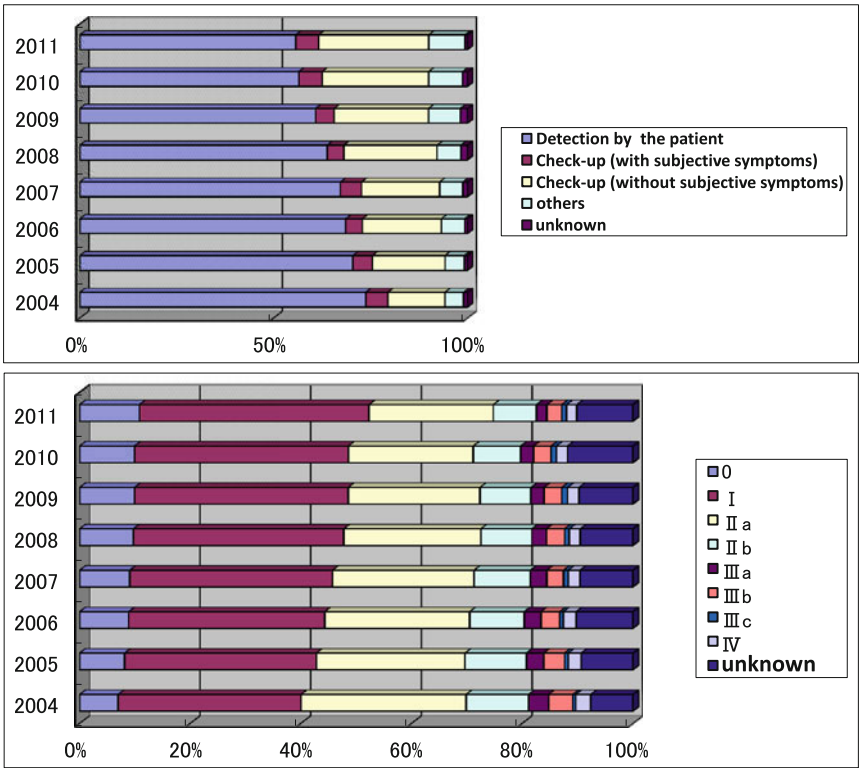

Fig. 1.1 Motives for seeking medical attention and changes in breast cancer stage at diagnosis in Japan

1.1 Current Status of RFA in Japan

In Japan, RFA is used for the treatment of liver cancer. During RFA, alternating electric currents change the ions in the tissue surrounding the electrodes and the heat generated as the result of friction from this change coagulates and necrotises cancer cells. Figure 1.2 illustrates RFA in the liver with the widely used Cool-tip needle (17 G). When the exposure size is 1.5 cm, an area of 3 cm in diameter can be cauterised. This procedure was adopted for the treatment of breast cancer. At first, seven expanding needles were used, as is the case with liver cancer. However, because the tissue of mammary glands is harder than liver tissue and thus it is more difficult to insert needles and control heat propagation to the skin, the Cool-tip FR System (Covidien, Energy-Based Devices, Interventional Oncology, Boulder, CO, USA), which consists of a single needle and allows for easier heat control, is the configuration most commonly used at present for breast cancer.

One advantage of this therapy is that this device has already been widely used for the treatment of liver cancer. At medical institutions that already have the device,

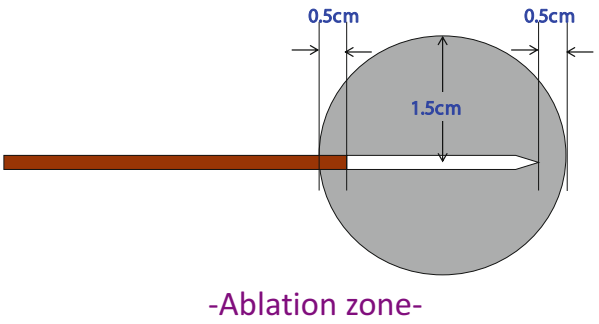

Fig. 1.2 Ablation zone of the cool-tip needle (based on liver tissue data)

only the needles need to be purchased. Therefore, RFA is likely to be prevalent in Japan. The disadvantages of RFA include that general anaesthesia is recommended for the procedure due to severe local pain, observation of the treated area by ultrasonography is difficult due to steam (bubbles) generated in the tissue during the treatment, and the possible development of transient local oedema or induration due to strong local reactions.

According to a survey conducted in fiscal year 2010 by the Japanese Breast Cancer Society, RFA was used to treat breast cancer in 1049 patients at 29 institutions in Japan. However, indications, standard procedures, and management systems varied. At many institutions, RFA was not used within the framework of clinical studies. To respond to this situation, the Japanese Breast Cancer Society requested the use of RFA for breast cancer as a part of clinical studies. Moreover, the Study Group for Minimally Invasive Treatment of Breast Cancer called for examination of the data obtained in the follow-up of patients and their quality of life. It therefore conducted a survey and reported the results at the general meeting of the American Society of Clinical Oncology in 2012. The results confirmed that outcomes for RFA and conservative treatment in Japan were similar for patients with early-stage breast cancer of 2 cm or less in diameter.

1.2 Overseas Studies on RFA

Studies on resection after RFA published from 1999 to date are summarised in Table 1.1 [1–13]. Although there were many studies, all were based at a single institution. The indications and devices used varied. The complete ablation rate ranged from 64% to 100%. The number of subjects in each study was small. None of these studies provided sufficient evidence to support RFA as a standard therapy.

Table 1.1 Studies of RFA followed by surgical excision

Author (year)	No. of Pts.	Disease (T)	Device	Power (W)	Median Treatment Time (min)	Complete Ablation (%)	Complications
Jeffery et al. (1999) [1]	5	T2-3	LeVeen	20–60	30	80	None
Izzo et al. (2001) [2]	26	T1-2	LeVeen	25–80	15	96	Skin burn ×1
Burak et al. (2003) [3]	10	T1	LeVeen	–	13.8	90	None
Singlatary et al. (2003) [4]	29	T1-2	RITA	–	–	86	Skin burn ×1
Hayashi et al. (2003) [5]	22	T1	RITA	–	15	64	Skin burn ×1
							Wound infection ×4
Fornage et al. (2004) [6]	20	T1	RITA	–	15	95	None
Noguchi et al. (2006) [7]	10	T1	RITA	–	15	100	None
Khatri et al. (2007) [8]	15	T1	Cool-tip	7–36	21	93	Skin puckering ×2
							Wound infection ×1
Medina-Franco et al. (2008) [9]	25	T1-2	Elektrotorm	–	11	76	Skin burn ×3
							Wound infection ×1
Garbay et al. (2008) [10]	10	IBTR, ≦3 cm	LeVeen	25–32	11	70	N/A
Imoto et al. (2009) [11]	30	T1	LeVeen	5–42	18	85	Skin burn ×2
							Muscle burn ×7
Kinoshita et al. (2011) [12]	49	T1-2,≦3 cm	Cool-tip	5–118	8.7	63	Skin burn ×2
		T1				89	Muscle burn ×3
Ohtani et al. (2011) [13]	41	T1	Cool-tip	9	9	88	Skin burn ×2

Table 1.2 Studies of cryoablation followed by surgical excision

Author (year)	No. of pts.	Tumour size (cm)	Complete ablation (%)
Pfleidere et al. (2002) [14]	16	0.9–4.0	31
Sabel et al. (2004) [15]	27	0.6–2.0	78
Pfleidere et al. (2005) [16]	29	0.5–1.5	100
Niu et al. (2007) [17]	27	0.8–2.5	85.2
Morin et al. (2007) [18]	25	1.2–6.0	52
Pusztaszeri et al. (2007) [19]	11	0.5–2.6	20
Manenti et al. (2011) [20]	15	0.4–1.2	93

1.3 Cryoablation

Cryoablation for the purpose of achieving haemostasis for ulcerating breast cancer is covered by the national health insurance system in Japan. However, its use as a radical cure of early-stage breast cancer is not covered. In the United States, cryoablation has been used for the treatment of benign tumours (fibroadenoma) for a long time. Cryoablation requires freezing and thawing for definite tumour destruction. At the same time, control of the ice ball is important. Because cryoablation involves freezing, local pain or reactions are minor and it only requires local anesthesia.

Studies on resection after cryoablation published from 2002 to 2011 are summarised in Table 1.2 [14–20]. The complete resection (freezing) rate ranged from 20% to 100%. The results of Study ACOSOG Z1072, a Phase II study of 87 lesions of early-stage breast cancer (including ductal carcinoma in situ), were reported at the meeting of the American Society of Breast Surgeons in 2014. Complete resection (freezing) was confirmed in 60 patients (69.0%). However, it was 100% effective for the treatment of tumours of 1 cm or less in diameter. Therefore, the investigators concluded that cryoablation was a new promising therapeutic option for early-stage breast cancer.

1.4 High-Intensity Focused Ultrasound (HIFU)

Ultrasound ablation is a truly noninvasive ablative technique because it does not require needle insertion or an incision at the tumour site. When an ultrasound beam is focused at a specific point at a certain distance from the transducer, the acoustic energy is converted to heat, leading to tissue coagulation. Frequencies in the range of 0.5–4 MHz can increase the temperature at the focal point to between 60 °C and 90 °C during a single sonication session.

A single ultrasound beam ablates only a small volume of tissue (approximately the size of a grain of rice), so the skin and surrounding tissue experience minimal temperature changes. Therefore, the entire volume of the tumour and margins need to be covered by overlapping multiple beams, which makes the procedure longer

Table 1.3 Studies of focused ultrasound followed by surgical excision

Author (year)	No. of pts.	Tumour size (cm)	Complete ablation (%)
Gianfekice et al. (2003) [21]	17	<3.5	24
Wu et al. (2003) [22]	23	2.0–4.7	100
Zippel and Papa (2005) [23]	10	<3.0	20
Furusawa et al. (2006) [24]	30	0.5–2.5	53.5
Khiat et al. (2006) [25]	26	0.01–11.2	27

than some of the other ablative techniques. Precise targeting for the procedure can be accomplished with MRI guidance.

There have been several studies examining the efficacy of HIFU at ablating breast cancer. As with other forms of ablation, the initial studies consisted of HIFU followed by resection, which have yielded mixed results (Table 1.3) [21–25].

Although the fact that HIFU is noninvasive, as opposed to cryoablation or RFA, which are minimally invasive, and is in some ways advantageous, it also presents some challenges. For example, there is a risk that if the target lesion moves during treatment, complete ablation might not be achieved. The biggest challenge facing the clinical implementation of HIFU for breast cancer is the heterogeneity of results, with histopathology analysis showing complete tumour necrosis in 20–100% of patients treated.

1.5 Studies on Noninvasive Surgical Treatment Without Subsequent Resection

Studies on nonsurgical ablative therapies without resection are summarised in Table 1.4 [26–32]. The number of subjects and duration of observation are both insufficient and the evidence supporting these therapies as new treatment methods is weak.

Another obstacle is that multiple steps are necessary to show equivalency with breast conservation surgery. Most data are from studies of ablation and resection, with strong data for cryoablation, HIFU, and RFA, but there is limited experience with ablation-only trials. The existing data are from small trials with highly selected groups of patients, and in some cases, remain unpublished. Although the completion of the ACOSOG Z1072 trial, a large-scale ablate-and-resect trial of cryoablation, represents a major step forward; a more concerted effort to design and implement multicentre trials is needed for in situ ablation to become a viable alternative to lumpectomy.

For RFA, the results of a large-scale Japanese multicentre clinical study, Radiofrequency Ablation Therapy for Early Breast Cancer as Local Therapy (the RAFAELO study) that began in 2013, are eagerly awaited.

Table 1.4 Studies of in situ ablation without surgical excision

Autor (year)	Type of ablation	No. of pts.	Tumour size (cm)	Posttreatment assessment	Results
Gianfelice et al. (2003) [26]	HIFU	24	0.6–2.5	MRI, CNB	5 (21 %) with residual disease
Wu et al. (2003) [27]	HIFU	22	<5	MRI, CT	5-year recurrence free survival of 89 %
Oura et al. (2007) [28]	RFA	52	<5	FNA, MRI	No local recurrences after median follow/up of 15 months
Furusawa et al. (2007) [29]	HIFU	21	0.5–5	MRI	1 local recurrence (5 %) with a median follow-up of 14 months
Littrup et al. (2009) [30]	Cryo	11	–	MRI	No local recurrences after median follow-up of 18 months
Yamamoto et al. (2011) [31]	RFA	29	Luminal A or DCIS, <1	VAB, MRI	No residual disease in 27/29
					No local recurrences after median follow-up of 17 months
Fukuma et al. (2012) [32]	Cryo	38	Luminal A or DCIS, <1	MRI, CNB	No local recurrences after median follow-up of 43 months

1.6 Conclusion

We expect that nonsurgical ablative therapies including RFA, which are used as minimally invasive local therapies for breast cancer, can achieve outcomes equivalent to surgical resection if the right procedure is carried out for the right indication. We began with evaluating RFA because it has been approved under the Pharmaceutical Affairs Law, thus we believed that it would become prevalent as a therapeutic method of breast cancer in Japan most quickly. In conclusion, we confirmed that cell death can be safely and completely achieved in targeted tumours. However, we identified remaining microscopic intraductal lesions that cannot be detected by diagnostic imaging as a potential problem; this phenomenon also occurs with conservative treatment of breast cancer. The results of long-term observation in prospective studies are awaited to determine whether these microscopic lesions can be controlled in the long term by radiotherapy or medications. Moreover, RFA devices and procedures need continuously to be developed and improved, and medium-to-long term safety, aesthetic outcomes, and capacity for local control need to be evaluated. Although cryoablation, which causes only minor local reactions, and HIFU, which truly does not involve any resection, are promising; given the current state of insufficient evidence, we think they should be used only in clinical studies after obtaining appropriate informed consent under an established monitoring system.

Data on nonsurgical ablative therapies including RFA, cryoablation, and HIFU are steadily accumulating. We believe these therapies can replace lumpectomy, the standard treatment for breast cancer, in the near future. This will trigger further advancement in the field of nonsurgical treatment, because science and technology greatly contribute to the progress of medical technology and diagnostic imaging.

This book was written by experts in nonsurgical ablative therapies for breast cancer and intended for medical professionals whose goal is to treat breast cancer nonsurgically. It is a compilation of their achievements. We hope that the readers will fully utilise this book in order to make future treatment of early-stage breast cancer even less invasive and gentler for patients.

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Takayuki Kinoshita

Chapter 2
Evolution of Operative Methods in Japan

Tadashi Ikeda

2.1 Evolution of Operative Methods in Japan

The first operation for a breast cancer patient was performed in the early nineteenth century in Wakayama (1804.11.14), Japan. This operation was performed by Seishu Hanaoka, a Japanese doctor, using general anesthesia [1]. The general anesthetic agent used was called Tsusen-san, which was an extract of Datura metel. This might have been the first breast cancer operation under general anesthesia in the world. After that, no further descriptions of the operative method for breast cancer patients were given in Japan.

The trends in the operative method for breast cancer in the modern era are about the same in Japan as in Western countries, but in Japan, the changes tend to occur more slowly. Notably, however, Shimada et al. reported the 5-year results of total mastectomy with axillary dissection compared to Halsted's mastectomy as early as 1964 [2]. Their comparison showed no difference between the two methods; however, this method did not become popular in Japan at that time.

According to the breast cancer registry of the Japanese Breast Cancer Society (JBCS) (Fig. 2.1) [3], standard radical mastectomy (Halsted's mastectomy), which consisted of total mastectomy with major and minor pectoral muscle resection and axillary dissection, was the most popular operative method until 1980. About 90 % of the cases underwent standard radical mastectomy. Then, modified radical mastectomy, which consisted of total mastectomy with/without minor pectoral muscle resection and axillary dissection, became the most popular operative method during the 1990s. There were several variations of the modified radical mastectomy, including Patey's modified radical mastectomy, Auchincloss' modified radical

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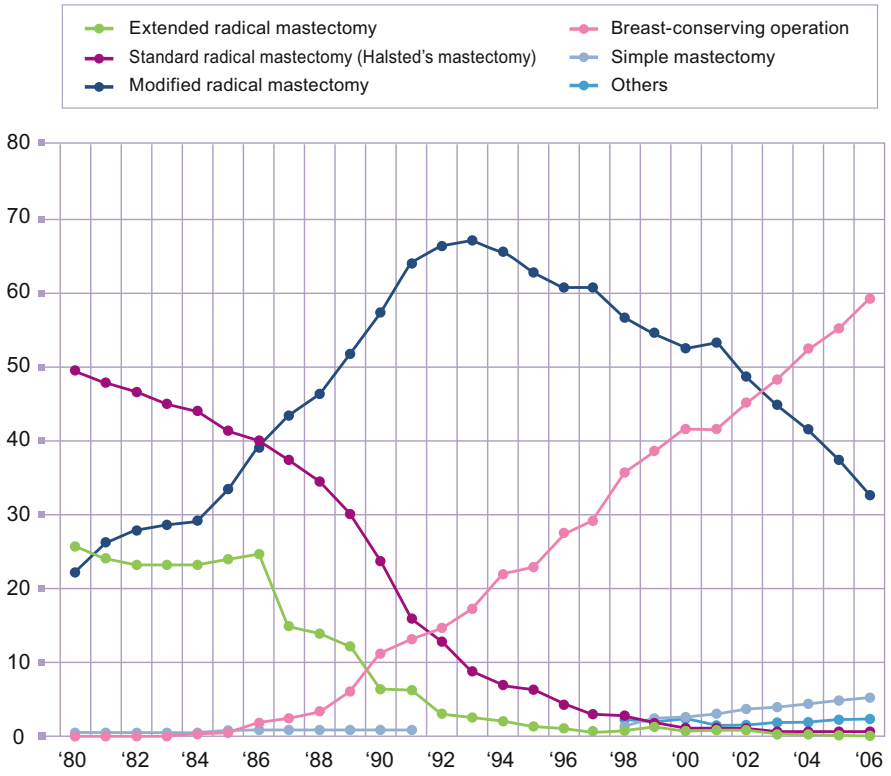

Fig. 2.1 Changing trends in surgical procedures for breast cancer in Japan between 1980 and 2006 (Ref. [3])

mastectomy, and Kodama's method. Patey's modified radical mastectomy was the most popular modified radical mastectomy approach at first, but Auchincloss' method became the most popular during the 1990s. Kodama's method is one type of modified radical mastectomy. High axillary dissection was performed by widening the interpectoral sulcus. With this method, level III axillary lymph nodes could be dissected under direct vision, and the prognosis was comparable to that of radical mastectomy [4].

Breast-conserving operations were initiated around 1986 in Japan. They rapidly increased after the reports of prospective, randomized trials from Western countries [5, 6], and over 60 % of the cases underwent breast-conserving operations in 2006. However, the incidence of breast-conserving operations plateaued at about 70 % in 2011 (Fig. 2.2) [7]. Initially, segmental resection was the most popular breast-conserving operation. At first, the breast-conserving operation was performed without postoperative radiation. With this method, ipsilateral intrabreast tumor recurrence (IBTR) developed in 5.5 % of the 1351 patients treated with breast-conserving operation during a mean follow-up period of 6.5 years [8], which is comparable to the results from Western countries. However, it should be noted that, according to the guideline in Japan for treating breast cancer at that time,

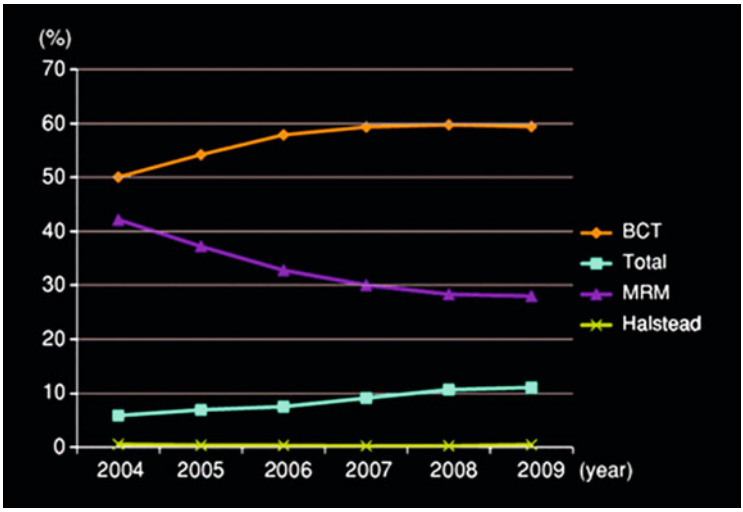

Fig. 2.2 Trends in surgical procedures for breast cancer in Japan from 2004 to 2009 (Ref. [7])

the definition of negative surgical margin was no cancer cells within 5 mm from the cut margin [9], while the definition in Western countries was no cancer cell exposure on the cut surface or within 1 mm [10].

Postoperative radiotherapy is an important component of breast-conserving therapy, and it reduces local recurrence by one-third [11]. Because of this evidence, as well as the operative trend from quadrantectomy (segmental mastectomy) to lumpectomy, lumpectomy with postoperative radiotherapy became the standard procedure for breast-conserving therapy in Japan. The rate of postoperative radiotherapy gradually increased from 60 % in 1992 to 72 % in 2004 and 79 % in 2009 [3, 7].

Because surgical margin status is an important predictive factor for local recurrence, patients with a positive surgical margin for cancer cells are candidates for re-excision. To reduce the reoperation rate, intraoperative frozen section diagnosis and/or print cytology of the surgical margin has been introduced [12]. Since about 27 % of the cases showed pathologically positive surgical margins at the cut end during breast-conserving operations, the evaluation of cut margin status during operation is now commonly performed in Japan.

Preoperative chemotherapy has become more common in Japan, as well as in Western countries, to increase the number of patients eligible for breast-conserving operation. According to the results from the NSABP-B18 trial, the breast-conserving rate increased from 60 % to 68 % after neoadjuvant therapy, while the in-breast recurrence rate increased from 7.6 % to 10.7 % [13]. The surgical margin should be carefully evaluated when performing breast-conserving operations after neoadjuvant chemotherapy, because the intraductal component may be more resistant to chemotherapy and it remains after neoadjuvant chemotherapy. It is important to know the tumor shrinkage pattern, including the concentric, honeycomb pattern, to achieve the appropriate surgical margin. Evaluation of the tumor shrinkage pattern after neoadjuvant chemotherapy by MRI is now commonly performed in Japan [14].

2.2 Surgical Procedures in Axillary Region

With respect to lymph node dissection, axillary dissection was the standard procedure for a lengthy period of time. Parasternal lymph node dissection and/or supraclavicular lymph node sampling were also performed concomitantly with axillary dissection. Level III dissection was also done in the early days, but it was soon abandoned based on the results of a randomized trial. The randomized trial compared level II dissection without minor pectoral muscle resection to level III dissection with minor pectoral muscle resection and showed no difference in terms of both overall and disease-free survival [15]. One other prospective, randomized trial that compared level I dissection to level III dissection also showed no difference in terms of overall survival [16]. Thus, the breast-conserving operation with level I/II dissection became the standard procedure.

However, after the first successful report of sentinel lymph node biopsy (SLNB) [17, 18], this technique was rapidly introduced to clinical settings. As the results of the sentinel node trials revealed no difference in terms of prognosis between SLNB and that of axillary dissection [19], SLNB has been accepted as a standard procedure for early breast cancer with no nodal involvement clinically [20]. According to the breast cancer registry under the auspices of JBCS, SLNB started in 1996, and about 40 % and 60 % of registered institutions began SLNB in 2006 and 2008, respectively. The most used method for SLNB is the blue dye method, followed by a combination method involving the radioisotope (RI) method and the blue dye method. The RI method alone was seldom performed [21]. Only Tc^{99m}-tin colloid and Tc^{99m}-stannous phytate are permitted as radioisotopes, and indocyanine green (ICG) and indigo carmine are permitted as dyes for SLNB by government health insurance. ICG and indigo carmine are proven to be safe, with grade 1 adverse effects occurring in only 0.06 % of patients [22]. Japanese government health insurance approved SLNB for patients with no clinical nodal involvement for reimbursement in 2012. SLNB has not only been accepted as a standard procedure in early breast cancer patients; it has also been accepted in various situations, including large breast cancer, after neoadjuvant chemotherapy, and in-breast cancer recurrence [23].

Given the results of ACOSOG Z-0011 [24], whether backup axillary dissection is needed in patients with 1–2 positive sentinel nodes remains controversial. There is considered to be insufficient evidence to not perform backup dissection, so omitting backup dissection in a patient with macrometastasis is not considered standard procedure in Japan [25]. However, omitting backup dissection has already begun in carefully selected patients at the time of 2013.

In recent years, molecular diagnosis of sentinel nodal metastases has been developed and is currently entering into clinical use [26, 27]. It is now validated to be as accurate as pathological diagnosis for the diagnosis of sentinel node metastasis.

2.3 Reconstruction

Though breast reconstruction after mastectomy has not been commonly performed in Japan, the rate of postmastectomy reconstruction is increasing. According to a questionnaire survey in 2007, about 60 % of the institutions belonging to JBCS did not perform reconstruction [28]. Reconstruction using a latissimus dorsi flap was the most used method, followed by a rectus abdominis flap, and tissue expander immediately after mastectomy. Because government health insurance started to cover breast reconstruction including tissue expander for patients who underwent mastectomy since 2006 and implants this year (2013), the rate of postmastectomy reconstruction is expected to increase. There are no exact statistics concerning secondary reconstruction, but the number of actual cases is considered small [28].

The number of reconstructions after breast-conserving operations is also not large. But among them, many patients who have undergone breast-conserving operations are looking for breast reconstruction due to deformity. Fat grafting is one of the promising methods to reform the deformed breast [29].

Many breast surgeons have noticed the need for oncoplastic surgical procedures during breast-conserving operations. However, there is as yet no established way to perform such procedures, because no method of evaluating the esthetic outcome has been established. One evaluation method that evaluated several issues, including volume, shape, scar, and firmness of the breasts and size, shape, color, and deviation of the nipples, was proposed by a working group of the JBCS [30]. In addition, the Japanese Society of Breast Oncoplastic Surgery was established in 2012.

2.4 Nonsurgical Ablation

The history and procedures for nonsurgical ablation are presented elsewhere in this book, so only the outline of the evolution of these procedures is presented here.

Radiofrequency (RF) ablation for the treatment of hepatocellular carcinoma (HCC) began in the early 1990s. HCC develops with a background of hepatitis B or C infection; therefore, multicentric development occurs. This means that another HCC could develop after resection of one HCC. With this in mind, less invasive methods have been investigated. One less invasive method is RF ablation, which has been covered by government health insurance since 2004. It has become a common treatment for HCC.

In the field of breast cancer treatment, as the concept that breast cancer is a generalized disease from the beginning has been widely accepted, the operative procedure has become less invasive. In addition, core needle biopsy (CNB) has become popular. By performing CNB, one can easily obtain information about hormone receptor status, Her2 overexpression, and other pathological features, which are essential pieces of information needed to plan the treatment of breast cancer patients in the modern era.