high ligation is often combined with lateral pelvic lymphadenectomy, which makes interpretation of the results difficult. The 40 % 5-year survival rate reported for patients with Dukes C2 tumors [64, 66] has been replicated in two European series [58, 68], but it is unknown whether this can be widely matched. While there is no solid evidence of improved survival directly attributable to IMA high ligation, the majority of published studies report that patients who underwent this procedure had better survival rates [5, 7, 59], but the difference was not significant.

Ligation level of the IMA and staging

Although there may be no survival advantage, ligating the IMA at its origin from the aorta seems to increase the number of nodes harvested significantly [55], considering that as many as ten nodes have been found along the segment of the IMA between the aorta and the origin of the left colic artery [5]. In all published series disclosing node retrieval rates, high IMA ligation retrieved more than 12 nodes; [8, 60, 61, 66, 71, 75] thought to be the minimum necessary for accurate tumor staging [50] (Table 3).

The most important aspect of node staging is the presence or absence of apical node involvement [76, 77]. Patients with apical node metastases have 5-year survival rates comparable to those presenting with distant metastases and are 2.5 times more likely to die from their cancer than patients with an uninvolved apical node [78]. This was recently confirmed by Kim et al. [71], who reported that metastases at the root of the IMA were an independent prognostic factor.

That high ligation allows for the sampling of more nodes is inherently logical. Somewhat more debatable is that these additional harvested nodes improve prognostication [79, 80]. The ability to examine these nodes and to increase their yield is dictated only in part by the surgical procedure. Specifically, with more colons harvested and a higher the level of ligation, more nodes will be sent to the pathologist; however, the diligence with which the pathologist searches for nodes will impact greatly on the number of nodes reported. Moormann et al. [81] compared the conventional manual and clearing methods used in surgery for carcinoma of the colon and rectum and reported that the mean number of detected nodes increased from 3.1 to 10.6 per patient when the clearing method was used. Cohen et al. [82] reported that standard histopathologic evaluation revealed a mean of 13 (range 0–43) nodes after segmental colectomy, but a mean additional 4 (range 0–12) nodes were found after xylene clearance. A similar increase, from 10.5 to 23.1 nodes, was reported when the clearing method was used in patients with carcinoma of the rectum [83]. Scott and Grace [84] reported a threefold increase in the number of nodes harvested versus traditional sectioning (6.1 vs. 18.9), respectively, which led to a change of stage in 8.6 % of their patients, from Dukes B to Dukes C. Haboubi et al. [85] reported similar results in their analysis of colorectal specimens from 47 patients, 41 of whom had carcinoma. The mean number of nodes harvested at initial dissection from these 41 patients was 7 (range 1–20), which increased almost sevenfold to a mean of 48 (range 10–295) after xylene clearance. They estimated that 88 % of nodes were not recovered by traditional methods. Subsequently, 3 of the 41 (7 %) patients who had initially been staged as Dukes B were subsequently restaged as Dukes C. We reported increasing the mean number of nodes recovered by the clearing method, from 21.2 nodes/patient to 73.7 nodes/patient; however, the incidence of metastasis also increased from 50 % to 57.1 % in patients with rectal cancers [72]. Furthermore, when the clearing method was used, metastatic nodes smaller than 4 mm in diameter accounted for as many as 32.6 % of the total number of metastatic nodes, but only 14.8 % when the manual

Table 3 Level of ligation of the inferior mesenteric artery and staging

References	Results
Morgan and Griffiths [16]	Routine high tie may result in conversion of one in eight C2 cases into C1 cases
Pezim and Nicholls [7]	Some C2 low tie cases might have been C1 had high tie been done
Surtees et al. [8]	Mean no. of lymph nodes examined (*n*), high tie 14.2 (150) vs. low tie 11.9 (100)
Kawamura et al. [55]	Mean no. of lymph nodes examined (*n*), high tie 23* (132) vs. low tie 16 (379)
Kanemitsu et al. [64]	High tie allowed for the upstaging of cancer
	Of the 20 patients with IMA root node (central node) metastasis, 8 did not have intermediate node metastasis
Uehara et al. [54]	Mean no. of lymph nodes examined (*n*), high tie 39 (133) vs. low tie 31 (78)
	Incidence of Dukes C % (*n*), High tie 71.4 (95/133) vs. Low tie 62.8 (49/78)
Liang et al. [70]	High tie allowed for upstaging of cancer (from Dukes B to C2) in five patients (5.1 %)
	Sixteen patients (18.2 %) had skip lymph node metastases

IMA Inferior mesenteric artery

* Significant

method was used [72]. These results suggest that the clearing method should make it possible to identify a greater number of nodes smaller than 4 mm in diameter, some of which would be undetected by the manual method. This explains the higher incidence of metastasis obtained with the clearing method than with the manual method. Thus, although the technique of high ligation may allow for better node sampling and hence, better prognostication and staging, more diligent screening by the pathologist, including fat clearance techniques may also achieve this goal [72, 81–85].

To allow rigorous prognostic stratification, one must reduce the phenomenon of stage migration, which might occur when comparing cohorts of patients who undergo high versus low ligation of the IMA. Indeed, a significant proportion of patients with Dukes C2 cancer in the low-ligation group would have been staged C1, had a high ligation of the IMA been performed. The greater the extent of resection and the greater the number of nodes examined, the higher the incidence of metastasis and the greater the mean number of metastatic nodes per patient. Moreover, with less extensive resection and fewer recovered nodes, the risk of understaging becomes higher. High ligation provides the pathologist with a larger harvest of nodes, to provide more accurate information for the patient and to allow the clinician to predict the likely prognosis [86].

Incidence of leakage after anterior resection

The low ligation technique preserves adequate blood supply to the colon proximally to the anastomosis, whereas after high ligation, vascularization of the distal colon and sigmoid is completely dependent on the middle colic and marginal arteries [16, 66, 87–89]. The marginal artery arising from the middle colic artery is thought to be adequate for sustaining the viability of the remaining colon [44, 45]. Although most studies support this hypothesis [7, 90, 91], Dworkin and Allen-Mersh [1], and Seike et al. [92] concluded from preoperative measurements that high ligation reduces perfusion of the proximal limb significantly. Apart from ischemia, tension on the anastomosis is thought to increase the risk of anastomotic leakage [66, 87, 93]. High ligation is technically easier to perform than low ligation and allows for easy tension-free anastomosis. According to some investigators, high ligation is indispensable for a tension-free anastomosis in low anterior resection [43, 87, 93]. If one contemplates performing a TME or coloanal anastomosis, perhaps with colonic J-pouch [94], then a high ligation becomes mandatory for a completely different reason. However, Coder et al. [90] reported that a tension-free anastomosis also can be achieved in low-ligation resections by cutting the descending branch of the left colic artery.

The incidence of symptomatic leakage after low anterior resection ranges from 5 to 15 % (Table 4) [60, 64, 66, 94–102]. Read et al. [60] reported a high 5-year disease-free survival rate of 84 % with a low anastomotic leak rate of 1.3 % after the high ligation technique, and recommended high IMA ligation and wide mesenteric resection. Furthermore, there were no significant differences in anastomotic leak rates after high or low ligation techniques [90, 91]. In a randomized trial of high- versus low-ligation techniques, Rouffet et al. [57] reported no significant difference in anastomotic leak rates, being 9.9 vs. 12.0 %, respectively. In our study on high ligation of the IMA, all

Table 4 Level of ligation of the inferior mesenteric artery and incidence of leakage

References	Site of tumor	Ligation level	Incidence of leakage % (*n*)
Morgan and Griffiths [16]	Rectum, sigmoid and descending colon	High tie	1.4 (3/220)
Antonsen et al. [95]	Rectum	Low tie	15.2 (27/178)
Bernard et al. [96]	Rectum	High tie	13.2 (5/38)
Corder et al. [90]	Rectum	High tie	13.2 (12/91)
		Low tie	11.5 (6/52)
Heald and Karanjia [97]	Rectum	High tie	8.9 (15/168)
Mealy et al. [98]	Rectum	High tie	7.9 (9/114)
Hall et al. [91]	Rectum, sigmoid and descending colon	High tie	13.3 (4/30)
		Low tie	6.3 (2/32)
Hida et al. [66]	Rectum, rectosigmoid	High tie	6.3 (7/112)
Law et al. [101]	Rectum	High tie	10.2 (20/196)
Nesbakken et al. [102]	Rectum	Low tie	18.5 (17/92)
Zhon et al. [48]	Rectum	High tie	2.3 (4/171)
Kanemitsu et al. [64]	Rectum, sigmoid colon	High tie	3.3 (39/1188)
Liang et al. [70]	Rectum, sigmoid colon	High tie	2.0 (2/98)
Chin et al. [65]	Rectum, sigmoid colon	High tie	2.3 (1/43)

low anterior resection anastomoses were performed in a tension-free manner [66].

Although approximately one-fifth of the patients experience significant blood flow reduction after IMA clamping, only about 5 % experience ischemia-related anastomotic complications and most of these patients are elderly men [92]. A study comparing tissue oxygenation proximal to the colonic resection margin demonstrated that the marginal artery provides adequate blood supply to the transverse and descending colon [91], explaining the low anastomotic leak rates reported after high-IMA ligation [16, 60, 64, 66]. There is now enough evidence to support that high ligation of the IMA does not increase the risk of anastomotic leaks [5, 7, 64]. Despite the evidence of decreased perfusion of the proximal limb after high ligation, the benefit of low ligation, in relation to perfusion of the anastomosis, has not been proven but might exist in older and more infirm patients with atherosclerotic disease.

High ligation of the IMA with hypogastric nerve preservation

High ligation of the IMA carries a risk of injury to the hypogastric nerve, which may lead to ejaculatory disorders and urinary incontinence [2, 3, 103–106]. The origin of the IMA is surrounded by the inferior mesenteric plexus [107]. Both the IMA and the autonomic plexuses namely, the inferior mesenteric plexus, the preaortic plexus, and the superior hypogastric plexus, lie in the loose connective tissue between the peritoneum and the anterior renal fascia [108, 109]. Bauer et al. [110] and Heald and Leicester [111] reported that hypogastric nerve damage is most frequently encountered over the front of the aorta and below the sacral promontory, where the autonomic plexuses lie on either side of the midline as they enter the sacral hollow during radical high ligation of the IMA. Therefore, special care must be taken not to injure the hypogastric nerve during high ligation of the IMA, preaortic node dissection, and presacral node dissection (Table 5).

In high ligation, the safest point for ligation of the IMA must be identified to avoid autonomous nerve damage during rectal cancer surgery. There is disagreement about the relationship between the origin and the course of the IMA and the autonomous nerve supply. Two anatomic studies concluded that the origin of the IMA is the only safe point for ligation, whereas another found that the inferior mesenteric plexus forms a dense network around the IMA to a distance of 5 cm from the aorta, suggesting that high ligation may damage the sympathetic nerves [48, 87, 112].

Based on the anatomic relationship among the hypogastric nerves, splanchnic nerves, middle rectal artery, and pelvic fascial planes, Havenga et al. [113] reported that the TME following high ligation of the IMA is compatible with autonomic nerve preservation. Furthermore, for TME combined with autonomic nerve preservation, the same authors reported preservation of sexual function in 85 % of men and women, with no loss observed in urinary function [38]. Using the same surgical procedure, similar results were reported [58, 68]. These results match those reported after TME with pelvic nerve preservation and low-IMA ligation [114], indicating that the level of IMA ligation has minimal impact on sexual and bladder function, if precise anatomical plane dissection is employed. On the other hand, Liang et al. [70] reported urogenital dysfunction in the majority of patients who underwent high ligation.

We previously reported a technique of upward node dissection aimed at preserving the hypogastric nerve following high ligation of the IMA [115]. After division of the lateral peritoneal reflection, the sigmoid colon is retracted to the left by the surgeon and the peritoneum is incised to the right border of the inferior vena cava. The incision is extended upward to the lower border of the third part of the duodenum, then made deeper and opened up to expose the front of the right common iliac artery and the aorta. The origin of the IMA and the inferior mesenteric plexus are identified and the IMA is then clamped, divided, and

Table 5 Genitourinary dysfunction after high versus low ligation of the inferior mesenteric artery

References	Ligation level	Urinary dysfunction % (*n*)	Male sexual dysfunction	
			Erectile % (*n*)	Ejaculatory % (*n*)
Cosimelli et al. [68]	High	3.0 (8/266)	27.6 (38/139)	60.6 (84/139)
Leggeri et al. [58]	High	5.9 (7/118)		25.9 (14/54)
Sugihara et al. [2]	High	2.9 (5/172)	28.6 (14/49)	61.2 (30/49)
Masui et al. [3]	High	NA	23.1 (31/134)	32.8 (44/134)
Havenga et al. [38]	High	10.7 (14/131)	19.5 (15/77)	12.5 (10/80)
Mori et al. [105]	Low	2.8 (3/109)	25.8 (17/66)	68.2 (45/66)
Nesbakken et al. [106]	Low	4.1 (2/49)	14.8 (4/27)	7.4 (2/27)
Kim et al. [114]	Low	14.7 (10/68)	19.1 (13/68)	13.2 (9/68)
Kanemitsu et al. [64]	High	Urinary and sexual dysfunction: 8.7 (103/1188)		
Liang et al. [70]	High	14.9 (11/74)	14.3 (12/84)	91.7 (77/84)

NA Not available

doubly ligated on the surface of the inferior mesenteric plexus. The inferior mesenteric vein is ligated at a corresponding level. The root of the mesentery is excised along the surface of the preaortic plexus and the superior hypogastric plexus comprising the presacral nerves, in caudad progression, while those plexuses are confirmed macroscopically to ensure their preservation. At the level of the aortic bifurcation, below the sacral promontory, the superior hypogastric plexus tends to adhere close to the visceral pelvic fascia or the fascia propria of the rectum before the branches separate to run towards the sides of the pelvis. The superior hypogastric plexus and the paired hypogastric nerves should be pushed gently off the visceral pelvic fascia of the rectum under direct vision. Consequently, urinary function was preserved in 93 % of the patients and sexual function was preserved in 81 % of the men. This method of performing high ligation of the IMA enhances radicality of the node dissection surrounding the origin of the IMA, while preserving the hypogastric nerve to prevent sexual and urinary disorders.

Although the superior hypogastric nerves are at risk, ligation of the IMA at its origin is the safest option for avoiding damage to the autonomic nerves [87], while preserving sexual and urinary function in the great majority of the patients [58, 68, 115]. Until now, there has been insufficient evidence about whether low ligation has a better prognosis with regard to sexual and urinary function.

Future direction

Most studies concerning high ligation versus low ligation were carried out before the introduction of TME and neoadjuvant therapy for rectal cancer. Neoadjuvant therapy also has the potential to sterilize microscopic metastasis in nodes more central than those at the origin of IMA, justifying the rationale of high ligation even further. Moreover, preoperative radiotherapy did not seem to prevent distant metastasis in the Dutch TME trial [30]. The technique of high ligation of the IMA prevents the potential intravascular dissemination of cancer cells during tumor manipulation [116, 117]. The possible benefits of high ligation in combination with current surgical techniques and neoadjuvant therapy need to be investigated further. Although the prognosis of patients with metastases to the IMA root nodes is poor, the survival rate of patients with T3 or T4 rectal carcinoma, which carries a higher incidence of metastasis to the IMA root nodes [66], may be improved by performing high ligation of the IMA combined with neoadjuvant and adjuvant chemotherapy and radiotherapy.

The past two decades have seen an increasing popularity of laparoscopic surgery for colorectal disorders, including malignant disease. For left colonic and rectal lesions, high ligation of the inferior mesenteric vessels is often performed first, facilitating mobilization of the splenic flexure and laparoscopic dissection in the anatomical planes [116, 118]. This laparoscopic technique is associated with a low perioperative mortality rate and node retrieval, local recurrence, and overall survival rates that at least match those reported for open surgery [119, 120]. Moreover, it allows for autonomic nerve-preserving pelvic dissection, while preserving bladder and sexual function in most patients [121]. Thus, it is conceivable that ligation of the IMA at its origin from the aorta will remain the preferred option in laparoscopic colorectal surgery.

Conclusions

Although no significant survival advantage of high ligation of the IMA has been proven, several points are irrefutable: high ligation allows for en bloc dissection of the node metastases at and around the origin of the IMA; high ligation can be performed safely and does not increase the risk of anastomotic leak after surgery for rectal cancers; high ligation allows for a tension-free low anterior or coloanal anastomosis to be performed more easily, being mandatory for a colonic J-pouch with coloanal anastomosis; high ligation enables both identification and preservation of the sympathetic nerves and is an important component of TME; high ligation is technically easier to perform than low ligation using the avascular windows superior and inferior to the IMA and inferior mesenteric vein; high ligation contributes to improved node retrieval rates and accuracy of tumor staging; the addition of any fat clearance technique will increase the number of nodes harvested. All of these tenets are well recognized. Ultimately, to avoid tumor recurrence, the optimal extent of node dissection should be clarified and adjuvant therapies should be discussed based on the accurate staging. Thus, in rectal cancer surgery high ligation should be the preferred method; however, a rigorous prospective randomized trial comparing high and low IMA ligation is imperative.

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ORIGINAL ARTICLE

Phase II study of neoadjuvant anastrozole and concurrent radiotherapy for postmenopausal breast cancer patients

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Abstract
Backgrounds The aim of this study was to assess the efficacy and safety of neoadjuvant anastrozole and radiation in postmenopausal breast cancer patients with hormone-receptor-positive tumors. In addition, we assessed the predictive factors for clinical and pathological response for concurrent anastrozole and radiotherapy.
Methods Patients with tumors 3 cm or larger were treated with neoadjuvant anastrozole for 24 weeks, and concurrent radiation was administered from 12 weeks after the start of anastrozole. Core biopsies were obtained at baseline and 12 weeks after the start of anastrozole. After completing neoadjuvant treatment, patients underwent definitive surgery. The primary endpoint was the overall objective response. In addition, we assessed the predictive factors for clinical and pathological response for concurrent anastrozole and radiotherapy. This trial is registered with the UMIN Clinical Trials Registry, no. UMIN000002266.
Results The overall objective response rate was 92 %. Toxicity during neoadjuvant therapy was acceptable, with no grade 3 toxicities. After surgery, grade 3 toxicities occurred in 2 of 25 patients (8 %).
Conclusions Our preliminary data suggest that neoadjuvant anastrozole and radiation therapy in postmenopausal breast cancer patients with hormone-receptor-positive tumors has a high potential for clinical response.

Keywords Breast cancer · Endocrine therapy · Neoadjuvant · Radiotherapy · Ki67

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Introduction

Neoadjuvant endocrine therapy is a treatment option for patients with hormone receptor-positive [estrogen receptor (ER)-positive and/or progesterone receptor (PgR)-positive] breast cancer and is being increasingly used in the management of operable breast cancer patients with large tumors with the expectation of breast-conserving surgery [1–3]. For postmenopausal breast cancer, several phase II randomized trials showed that neoadjuvant endocrine therapy with third aromatase inhibitors (AI) has similar efficacy to neoadjuvant chemotherapy and is better than neoadjuvant chemotherapy in terms of toxicities [4, 5]. However, the expected clinical response rate is about 50 %, which is not very high. A new strategy that promotes a higher response rate without increasing toxicity is needed.

Radiotherapy (RT) is standard care for breast cancer patient. After breast-conserving surgery, radiotherapy for the conserved breast halves the rate at which the disease

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recurs and reduces the breast cancer death rate by about a sixth [6]. Breast irradiation is relatively well tolerated. However, data on the interaction of endocrine therapy and RT are less clear [7].

Neoadjuvant concurrent radiotherapy and endocrine therapy have rarely been reported for breast cancer. Bollet et al. [8] retrospectively assessed responses and outcomes following endocrine therapy and RT given concurrently for large, hormone receptor-positive breast cancers in postmenopausal women. Endocrine therapy consisted of tamoxifen for 38 tumors and anastrozole for 4 tumors. Concurrent RT and endocrine therapy demonstrated high efficacy in terms of clinical responses (21 % complete response and 57 % partial response), allowing breast conservation with acceptable tolerance and favorable 5-year local control. Despite these promising results, these findings may not lead to a definitive conclusion because of the retrospective study design and the fact that tamoxifen, used mostly in this study, is thought to be less effective than AI in a neoadjuvant setting [9].

Therefore, we conducted a prospective trial to evaluate the safety and efficacy of concurrent anastrozole and radiotherapy in a neoadjuvant setting for postmenopausal patients with ER-positive breast cancers. In addition, we assessed the predictive factors for clinical and pathological response for concurrent anastrozole and radiotherapy.

Methods

Study design

The purpose of this multicenter, phase II, open-label trial was to assess the efficacy and safety of concurrent anastrozole and RT in a neoadjuvant setting for postmenopausal patients with ER and/or PgR-positive tumors. The study was approved by the institutional ethics committees of the participating centers, and written informed consent was obtained from all patients.

Patients

Eligible patients were postmenopausal women with untreated breast cancer [T (3 cm or larger), N0–2, M0], confirmed by core needle biopsy, with $\geq$10 % nuclear staining for ER and/or PgR, determined by immunohistochemistry (IHC). TNM classifications and stage of disease in all patients were based on the seventh edition of the American Joint Committee on Cancer staging criteria [10]. Women were considered postmenopausal with amenorrhea for at least 1 year, bilateral oophorectomy, or follicle-stimulating hormone and estradiol in the postmenopausal range. Patients had to have a WHO performance status of 0 or 1. Exclusion criteria included prior exposure to AI, tamoxifen, hormone replacement therapy or RT for the affected breast, uncontrolled endocrine or cardiac disease, bilateral breast cancer, distant metastasis, other malignant diseases, and allergy to anastrozole or RT.

Procedure

In this study, postmenopausal patients with ER- and/or PgR-positive tumors were treated with primary anastrozole at 1 mg/day for 24 weeks before definitive surgery. From 12 weeks after the start of the administration of anastrozole, RT for the affected breast was conducted concurrently with anastrozole. A total dose of 50 Gy in 25 fractions was delivered to the breast. For clinical node-positive patients at presentation, 50 Gy in 25 fractions was also delivered to the ipsilateral supraclavicular fossa in the same period of irradiation to the breast. The treatment design is shown in Fig. 1.

Study assessment

Initial evaluation included clinical measurement of the primary breast lesion and regional lymph nodes, pathologic diagnosis by core needle biopsy, and ER, PgR, HER2, and Ki67 analysis by IHC. Ultrasound-based tumor measurements were also obtained. After initiating the study treatment, patients were assessed monthly for clinical response by caliper and ultrasound, adverse events, and concomitant medications/therapies. Core biopsies were also obtained at 12 weeks (before irradiation) for the purpose of assessing in vivo biomarker changes.

Ki67 was stained with an antibody for MIB-1. The Ki67 index was calculated as the ratio of Ki67-positive cells to total cells. Histopathological responses of surgical specimens were classified as grade 0, 1a, 1b, 2, or 3, where grade 0 corresponds to no response; grade 1a to mild changes in cancer cells regardless of the area or marked changes seen in less than a third of cancer cells; grade 1b to marked changes in a third or more of cancer cells but less than two-thirds; grade 2 to marked changes in two-thirds or

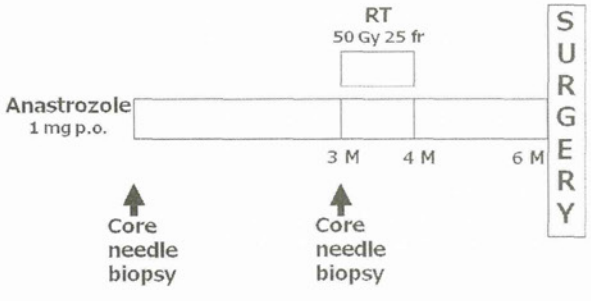

Fig. 1 Trial design

more of cancer cells; grade 3 to necrosis or the disappearance of all cancer cells and replacement of all cancer cells by granuloma-like or fibrous tissue, or both [11]. The pathologist at each individual site assessed histopathological effects by comparing histopathological samples obtained at the baseline and surgery.

The overall objective response after 24 weeks of neoadjuvant therapy was determined based on the clinical response by caliper and ultrasound, and assessed according to response evaluation criteria in solid tumors criteria (RECIST) [12]. Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

The primary endpoint was the overall objective response after 24 weeks of preoperative therapy, determined by caliper. The secondary endpoints were the percentage of patients who underwent breast-conserving surgery, the pathologic response, and toxicity assessment.

Statistical considerations

The target sample size of this study was calculated assuming an overall objective response of 45 % with anastrozole (based on data from prospective trials [2, 3]); 30 patients were required to detect an increase in response with anastrozole and RT to 70 % with 80 % power using the Fisher's exact test and a two-sided 5 % significance level. We expected the addition of RT to anastrozole would lead to a 25 % increase of the response rate. Because there are no data of neoadjuvant endocrine therapy and RT from prospective studies, the 25 % increase was arbitrarily estimated. The association of clinical and pathological response with ER, PgR, HER2, and the Ki67 index at baseline or 12 weeks after the start of the administration of anastrozole was assessed using Fisher's exact test, Spearman's correlation coefficient, or logistic regression analyses. All of the statistical tests and p values were two-sided, and p-values of <0.05 were considered significant. All statistical analyses were performed with StatView 5.0 software (SAS Institute, Cary, NC, USA). This trial is registered with UMIN Clinical Trials Registry, no. UMIN000002266.

Results

Patient characteristics

Twenty-nine patients were enrolled in this study from two institutes in Japan between August 2009 and December 2011. Baseline patient characteristics are described in Table 1.

The flow of patients through the study is outlined in Fig. 2. Before RT, two patients withdrew from the study based on their own decisions. Of the remaining 27 patients, 24 completed preoperative endocrine therapy and RT for the breast and underwent definitive surgery; 1 showed disease progression during anastrozole treatment before RT and proceeded directly to surgery; 2 patients were receiving neoadjuvant anastrozole at the time of this analysis. In three patients with clinically positive nodes at presentation, RT was also delivered to the ipsilateral supraclavicular fossa in the same period as irradiation of the breast. Twenty-four patients were evaluable for the efficacy and toxicity of neoadjuvant endocrine therapy and RT. Twenty-five patients were evaluable for toxicity from neoadjuvant endocrine therapy before RT and postoperative morbidity.

Table 1 Patient characteristics ($N = 29$)

	No. of patients	%
Age (years)[a]	61 (54–81)	
T stage		
2	25	86
3	3	10
4	1	3
N stage		
0	26	90
1	3	10
2	0	0
Stage		
IIa	25	86
IIb	2	7
IIIa	1	3
IIIb	1	3
Tumor diameter (mm)[a]		
Caliper	38 (30–80)	
Ultrasound	28 (19–35)	
ER		
≥10 %	29	100
<10 %	0	0
PgR		
≥10 %	16	55
<10 %	13	45
HER2		
Positive	4	14
Negative	25	86
Ki67 (%)[a]	20 (2–60)	

ER estrogen receptor, *PgR* progesterone receptor

[a] Values are expressed as median (range)

Efficacy

Of the 25 patients evaluable for efficacy by caliper, 23 had a clinical response at 24 weeks. Seven had a complete response, 16 had a partial response, 1 had a stable disease,

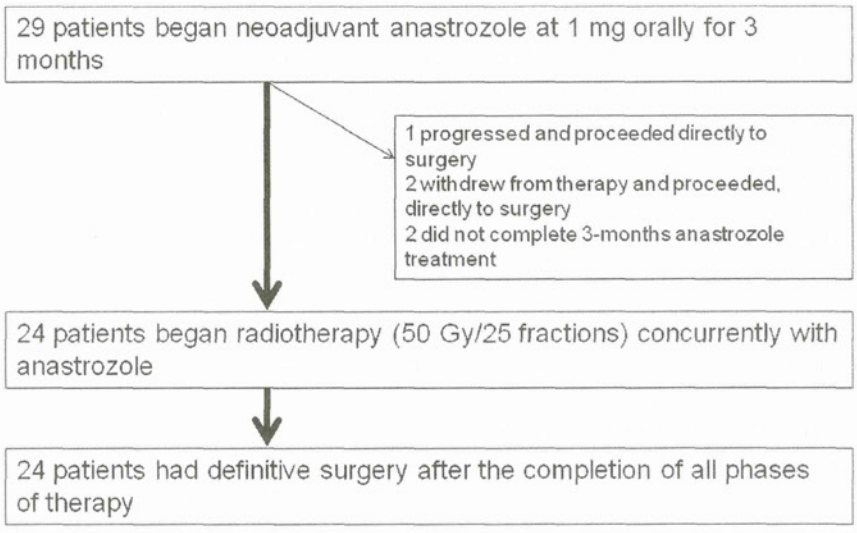

Fig. 2 Patient flow

and 1 had progressive disease. The overall objective response rate was 92 %. Of 25 patients evaluable for efficacy by caliper, 18 patients were also evaluable by ultrasound, and 7 patients were not evaluable because of scale-out by ultrasound at the diagnosis. Of the 18 patients evaluable for efficacy by ultrasound, all patients showed a clinical response at 24 weeks. Waterfall plot analysis of the reduction rates of the tumor size evaluated by caliper and ultrasound is shown in Fig. 3. All 25 patients underwent breast-conserving surgery and axillary lymph node dissection or sentinel lymph node biopsy. Histopathological responses were as follows: grade 1a, 1b, and 2 were seen in 10, 8, and 7 patients, respectively. There was no grade 0 or 3. Because all patients had clear margins in the surgical specimens at the final histopathological analyses, none of the patients underwent subsequent re-excision.

All patients received adjuvant anastrozole except for one patient who showed disease progression during neoadjuvant anastrozole. She received adjuvant tamoxifen. Eight patients received adjuvant chemotherapy, and three patients received adjuvant trastuzumab. With a median follow-up of 18 months (range 4–29), ipsilateral breast tumor recurrence and bone metastases occurred simultaneously in one patient 11 months from the start of anastrozole. Other patients are alive without disease.

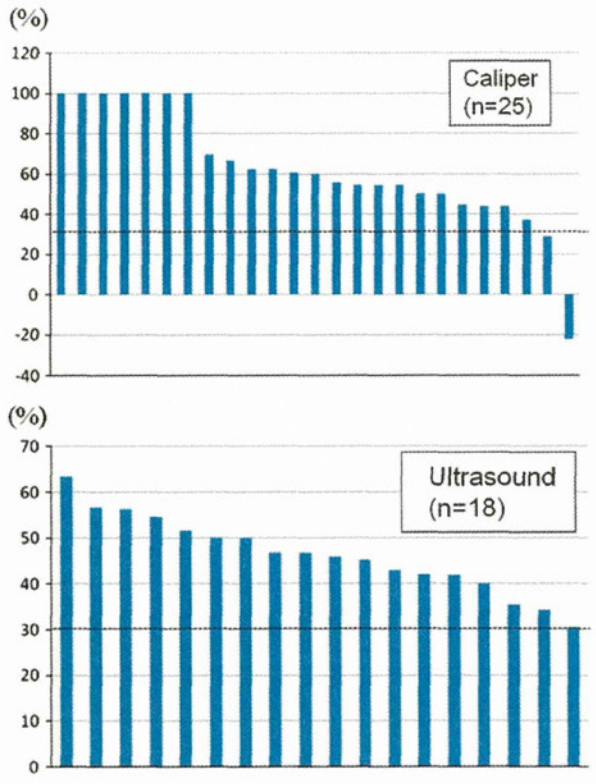

Fig. 3 Waterfall plot analysis of the clinical response at 24 weeks evaluated by caliper and ultrasound. The *horizontal axis* indicates data from each patient and the *vertical axis* the reduction rate of the tumor size evaluated by caliper or ultrasound. A clinical response was defined as 30 % or more (indicated with a *horizontal dotted line*). *Negative values* on the *vertical axis* indicate tumor progression

Toxicity

Patients tolerated neoadjuvant endocrine therapy and RT well, with all patients completing full doses of the planned 24 weeks of anastrozole. All patients completed the planned 50 Gy RT. There was no grade 2 or higher toxicity before RT during neoadjuvant anastrozole. From the start of RT to surgery, grade 2 radiation-dermatitis occurred in three patients, and there was no grade 3 or greater toxicity. After surgery, grade 2 or higher toxicity occurred as follows: grade 2 seroma (5 patients), grade 2 (2 patients) and

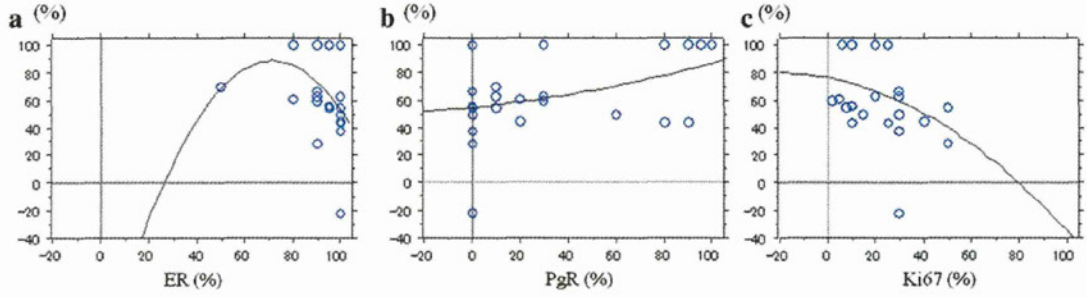

Fig. 4 The correlation between **a** ER, **b** PgR, and **c** Ki67 expression at baseline and clinical response. The *vertical axis* indicates the reduction rate of the tumor size evaluated by caliper

grade 3 (1 patient) wound infection, grade 3 hematoma (1 patient), and grade 2 skin breakdown (1 patient). None of the patients suffered radiation pneumonitis.

Predictive marker

The correlation between ER, PgR, and Ki67 expression at baseline and clinical response is shown in Fig. 4. These markers were not significantly associated with clinical response according to Spearman's correlation coefficient (data not shown).

In Table 2, the correlation between ER, PgR, and Ki67 expression at baseline and clinical and pathological response at 12 weeks and at the time of surgery is presented. Between clinical responders (complete response or partial response) and non-responders (stable disease or progressive disease) at 12 weeks, there was a significant difference in the PgR expression at baseline ($p = 0.0243$ by Fisher's exact test).

We analyzed the correlation between changes in the expression levels of ER, PgR and Ki67 and in clinical and pathological response to treatment. These results are shown in Table 3. Changes in the expression levels of these markers were not significantly associated with clinical or pathological response.

Moreover, we performed the univariate and multivariate analysis of ER, PgR, HER2, and Ki67 with respect to clinical and pathological responses to evaluate predictive factors (Table 4).

Table 2 Correlation between expression levels of ER, PgR, and Ki67 and clinical and pathological response at 12 weeks and at the time of surgery

	ER (%)	PgR (%)	Ki67 (%)
Clinical response			
CR or PR*	95	47***	18
SD or PD*	91	15***	28
CR or PR**	93	33	21
SD or PD**	95	0	40
Pathological response			
Grade 0 or 1a**	93	35	23
Grade 1b, 2 or 3**	93	27	23

ER estrogen receptor, *PgR* progesterone receptor, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

* At 12 weeks, ** at surgery, *** there is significant difference ($p = 0.0243$ by Fisher's exact test)

Table 3 The correlation between changes in the expression levels of ER, PgR and Ki67 and clinical and pathological response at the time of surgery

	ER (%)	PgR (%)	Ki67 (%)
Clinical response			
CR or PR	7	21	4
SD or PD	0	0	35
Pathological response			
Grade 0 or 1a	−2	32	2
Grade 1b, 2 or 3	13	12	9

ER estrogen receptor, *PgR* progesterone receptor, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Discussion

This prospective study of combined neoadjuvant endocrine therapy and RT demonstrated marked efficacy with limited toxicity. To our knowledge, this is the first prospective study of neoadjuvant AI and RT. The overall objective response rate of 92 % in this study is highly encouraging, particularly given the low toxicity of the regimen. As compared with previous studies of neoadjuvant endocrine therapy using AI [1–3] or neoadjuvant hormone (the majority was tamoxifen) and RT [8], the response rate in this study was higher. The combination of anastrozole and RT seems at least to be additive in terms of tumor shrinkage in a neoadjuvant setting. Preclinical data [13] demonstrated the radiosensitization effect of letrozole, one of the third AIs, which is similar to our results. Although

Table 4 Univariate and multivariate analysis with respect to clinical and pathological responses

	Univariate analyses				Multivariate analyses			
	Odds	95 % CI		*p* value	Odds	95 % CI		*p* value
Clinical response								
ER*	0.975	0.812	1.170	0.7849	24.291	0.000	–	0.9962
PgR*	3.898	$1.393e^{-88}$	$1.091e^{89}$	0.9896	0.647	$1.610e^{-126}$	$2.601e^{125}$	0.9976
Ki67*	0.908	0.804	1.027	0.1233	0.158	$1.112e^{-318}$	–	0.9960
HER2**	57045.248	$2.598e^{-309}$	–	0.9763	43.608	0.000	–	0.9998
ER***	0.957	0.822	1.113	0.5673	3.403	0.000	–	0.9978
PgR***	–	–	–	–	0.871	$1.723e^{-213}$	$4.402e^{212}$	0.9996
Ki67***	1.024	0.869	1.206	0.7768	3.343	0.000	–	0.9980
Pathological response								
ER*	1.000	0.928	1.078	>0.9999	0.851	0.569	1.274	0.4331
PgR*	0.994	0.972	1.016	0.5891	1.012	0.961	1.064	0.6593
Ki67*	1.003	0.947	1.063	0.9163	1.135	0.953	1.352	0.1567
HER2**	2.250	0.200	25.374	0.5118	723.911	0.000	–	0.9984
ER***	0.944	0.871	1.024	0.1648	0.724	0.507	1.034	0.0760
PgR***	0.996	0.961	1.032	0.8157	1.042	0.965	1.126	0.2933
Ki67***	0.981	0.926	1.039	0.5194	0.735	0.526	1.029	0.0726

ER estrogen receptor, *PgR* progesterone receptor, *CI* confidence interval

* At baseline, ** at baseline and 12 weeks, *** at 12 weeks

the clinical response in this study was high, the pathological response was low (grade 1a: 10 of 25 patients), which was consistent with the results for neoadjuvant hormone therapy. The reason for the discrepancy between clinical response and histopathological findings is unknown.

Toxicity during neoadjuvant therapy was acceptable, with no grade 3 toxicities. The results of this study suggest that anastrozole does not exacerbate radiation-induced acute adverse effects. These results are compatible with other reports of concurrent AI and RT in the adjuvant setting [14, 15]. On the other hand, concurrent RT and chemotherapy in a neoadjuvant therapy will increase skin-related toxicity and lead to a delay in surgery [16, 17]. These reports regarding neoadjuvant chemoradiation consisted of twice weekly paclitaxel and concurrent RT. In both studies, grade 3 skin desquamation occurred.

A major concern on the use of neoadjuvant RT is the development of postoperative complications. In this study 2 of the 25 (8 %) patients had grade 3 toxicity. This complication rate seems relatively higher than that of conventional neoadjuvant treatment. One retrospective study of concurrent endocrine therapy and RT [8] reported that none of the patients had either a wound infection or a voluminous hematoma after tumorectomy. In contrast, studies of neoadjuvant chemoradiotherapy reported several postoperative toxicities. Formenti et al. [16] reported their results of a phase II study of neoadjuvant chemoradiation that consisted of paclitaxel at 30 mg/m^2 delivered intravenously for 1 h twice weekly for a total of 8–10 weeks and concurrent RT (45 Gy at 1.8 Gy/fraction). Modified radical mastectomy was performed at least 2 weeks after the completion of chemoradiation or on recovery from skin toxicity. Postmastectomy complications occurred in 6 (14 %) of 44 patients. These complications included four infections with delayed wound healing, one transverse rectus abdominis myocutaneous flap necrosis that required revision, and one mastitis with grade 3 dermal injury. In another report of neoadjuvant chemoradiation by Chakravarthy et al. [17], of the three patients who underwent transverse rectus abdominis myocutaneous flap reconstruction, two required revisions.

To date, there is limited information regarding the optimal timing of surgery after neoadjuvant RT. However, surgery just after RT seems to be too early in terms of maximizing the radiation effect. In a retrospective study of neoadjuvant hormone administration (the majority was tamoxifen) and RT [8], the median time between the end of RT and surgery was 8 weeks.

There are no reports describing how endocrine therapy and concurrent RT affect biological markers such as ER, PgR, HER2, and Ki67 expression in breast cancer tissue. In this study, these markers were not significantly associated with clinical or pathological response. Further research to predict the response for endocrine therapy and concurrent RT is warranted.

Our study is limited by the small sample size with shorter follow-up. Especially the target sample size ($n = 30$) could not be achieved, and therefore our results

are not confirmed data. In addition, we assessed clinical response by caliper and ultrasound. Using computed tomography or magnetic resonance imaging could improve the accuracy of tumor measurement. Moreover, four patients with HER2-positive tumors were included in this study. Anti-HER2 therapy plus chemotherapy is the standard neoadjuvant treatment for breast cancer patients with HER2-positive tumors worldwide, although patients with HER2-positive tumors were included in other published studies [1–3]. Finally, for clinical node-positive patients at presentation, we performed ipsilateral supraclavicular RT. This procedure may be overtreatment, although there is no consensus on supraclavicular RT for patients who received neoadjuvant therapy.

In conclusion, despite relatively high adverse events and low efficacy in terms of histological response, our preliminary data suggest that neoadjuvant anastrozole and RT have potential for a highly clinical response in postmenopausal women with ER-positive tumors. Further investigations to assess long-term outcomes with this approach are needed.

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ORIGINAL ARTICLE – BREAST ONCOLOGY

Breast Cancer Subtype and Distant Recurrence after Ipsilateral Breast Tumor Recurrence

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ABSTRACT

Background. There is little information about the impact of breast cancer subtype on prognosis after ipsilateral breast tumor recurrence (IBTR).

Methods. One hundred eighty-five patients were classified according to breast cancer subtype, as approximated by estrogen receptor, human epidermal growth factor receptor 2 (HER2), and Ki-67, of IBTR, and we evaluated whether breast cancer subtype was associated with distant recurrence after IBTR.

Results. There was a significant difference in distant disease-free survival (DDFS) after IBTR according to breast cancer subtype defined by a cutoff of the Ki-67 index of 20 % ($p = 0.0074$, log-rank test). The 5-year DDFS rates for patients with luminal A, luminal B, triple-negative, and HER2 types were 86.3, 57.1, 56.6, and 65.9 %, respectively. In addition, breast cancer subtype was significantly associated with distant recurrence after IBTR on adjustment for various clinicopathologic factors ($p = 0.0027$, Cox proportional hazards model).

Conclusions. Our study suggests that breast cancer subtype based on immunohistochemical staining predicts the outcomes of patients with IBTR. Further analyses are needed (UMIN-CTR number UMIN000008136).

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Breast-conserving treatment is the standard treatment for early breast cancer, with similar long-term overall survival to mastectomy.[1,2] Recently, the Early Breast Cancer Trialists' Collaborative Group reported that about 25 % of all first recurrences after breast-conserving surgery and radiotherapy were IBTR (Web Figure 2a in Ref.[3]). IBTR after breast-conserving treatment is associated with an increased risk of distant disease and death.[4–7] However, patients who develop IBTR are a heterogeneous population. Indeed, only a subgroup of patients with IBTR develop systemic recurrence. Therefore, it is clinically useful to verify the risk stratification of patients after IBTR.

Recently, microarray analysis identified breast cancer subtypes with distinct gene expression profiles.[8,9] These subtypes have been shown to divide patients into groups with specific responsiveness to treatments and outcomes. These molecular subtypes can be approximated by immunohistochemical (IHC) staining patterns for estrogen receptor (ER), progesterone receptor, HER2, and Ki-67, providing a clinically useful

differentiation of outcomes.[10–12] More recently, several authors reported that breast cancer subtype was useful in estimating the risk of IBTR.[13–15] At present, however, there is little information about the impact of breast cancer subtype on prognosis after IBTR.

The objective of the current study is to identify the role of breast cancer subtype, as approximated by ER, HER2, and Ki-67, of IBTR in predicting distant recurrence in patients with IBTR.

PATIENTS AND METHODS

A total of 185 consecutive patients with histologically confirmed IBTR without distant metastases who underwent definitive surgery for IBTR between 1989 and 2008 were included in this analysis from eight institutions in Japan. This retrospective study was approved by each institutional review board.

Inclusion criteria were as follows: (1) patients who underwent breast-conserving and axillary surgery (sentinel lymph node biopsy only was allowed if these nodes had no metastases); (2) patients in whom IBTR was confirmed histologically; and (3) patients who underwent definitive surgery for IBTR until 2008.

Exclusion criteria were as follows: (1) synchronous (defined as occurring within 3 months) metastases (at diagnosis of IBTR, bone scan, chest X-ray, liver ultrasonography, or computed tomography scan was performed, and all patients had no evidence of distant metastasis); (2) bilateral breast cancer patients; (3) noninvasive tumor in IBTR specimen; (4) prior malignancy other than breast cancer; (5) patients with tumors located in the skin or muscle only without associated parenchymal disease and (6) patients who received neoadjuvant therapy at the initial treatment.

Questionnaire forms were sent to physicians who participated in this study in December 2011 to collect clinicopathologic patient data. The patient and recurrent disease factors analyzed were age at initial diagnosis and at IBTR, time interval from initial surgery to IBTR, IBTR histological subtype (invasive ductal carcinoma, invasive lobular carcinoma, and other), IBTR lymphovascular invasion status, IBTR estrogen receptor (ER) status, IBTR HER2 status, IBTR grade, and tumor location of IBTR relative to the primary lesion (same quadrant, different quadrant, and unknown). Treatment after IBTR was also examined, including extent of surgery (repeat lumpectomy and mastectomy), surgical margin status (negative and positive), radiotherapy after surgery, and systemic therapy (hormonal therapy, chemotherapy, and trastuzumab).

ER status was determined by immunohistochemistry, and tumors with 10 % or more positively stained tumor cells were classified as positive for ER. HER2 status was considered positive if immunohistochemistry was 3+ or fluorescence in situ hybridization (her-2/*neu* to chromosome 17 ratio) was >2.0. Both ER and HER2 statuses were evaluated by each institution. Proliferation activity was assessed by immunostaining with the Ki-67 antibody (Dako). The Ki-67 index was centrally evaluated by one pathologist (N.A.), from whom all patient data were masked. The proportion of proliferating cells was determined by counting at least 500 tumor cells.

Intrinsic breast cancer subtypes were modified by the criteria recently recommended by the St. Gallen panelists: triple-negative (ER and HER2 negative), HER2 (HER2 positive and ER negative), luminal A (ER positive, Ki-67 low, and HER2 negative), and luminal B (ER positive and Ki-67 high or HER2 positive or both).[16] In this study, three patterns of the cutoff value of the Ki-67 index were defined: (1) 14 % (as recommended by the St. Gallen panelists), (2) 20 % (the median value of prior studies by Nishimura et al.), and (3) 10 %.[17]

Distant disease-free survival (DDFS) was defined as the period from the date of surgery for IBTR to the date of appearance of distant metastases, and was calculated by the Kaplan–Meier method. The log-rank test was used to evaluate differences in DDFS among various patient subgroups. Multivariate analyses for DDFS were performed using the Cox proportional hazards model.

All statistical tests and p values were two-sided, and p values <0.05 were considered significant. All statistical analyses were performed with StatView 5.0 software (SAS Institute, Cary, NC, USA).

RESULTS

A total of 185 patients were registered in this analysis. Patient characteristics are presented in Table 1. The median ages at initial surgery and IBTR were 45 (range 26–84) and 50 (range 29–88) years, respectively. The median time interval from initial surgery to IBTR was 3.8 years (range 0.1–17.1 years). The median follow-up period from surgery for IBTR was 4.5 years (range 0.1–13.2 years). The 5-year DDFS rate was 69.0 %. Among the 101 patients who received breast-conserving surgery for the IBTR, radiotherapy (RT) was omitted at the first diagnosis in 52 patients. Of 37 patients with IBTR who received RT after IBTR surgery, all 37 patients did not receive RT at the initial breast cancer diagnosis.

Various clinical and pathologic factors associated with DDFS are presented in Table 2. The time interval from initial surgery to IBTR, tumor location, lymphovascular invasion of the IBTR, adjuvant chemotherapy, and breast cancer subtype were significantly associated with DDFS by the log-rank test ($p = 0.0074$, defined by a cutoff of the

TABLE 1 Patient characteristics ($n = 185$)

Characteristic	No. of patients	(%)
Age at initial diagnosis (years)		
<40	48	25.9
≥40	137	74.1
Age at IBTR (years)		
<40	26	14.1
≥40	159	85.9
Time interval from initial surgery to IBTR (years)		
≤5	111	60.0
>5	74	40.0
Tumor location		
Same quadrant	106	57.3
Different quadrant	63	34.1
Unknown	16	8.6
Margin of initial surgery		
Negative	153	82.7
Positive	18	9.7
Unknown	14	7.6
Radiotherapy after initial surgery		
Yes	89	48.1
No	92	49.7
Unknown	4	2.2
Hormone therapy after initial surgery		
No	70	37.8
Yes	106	57.3
Unknown	9	4.9
Chemotherapy after initial surgery		
No	110	59.5
Yes	67	36.2
Unknown	8	4.3
Trastuzumab after initial surgery[a]		
No	11	91.7
Yes	1	8.3
Tumor size of IBTR (mm)		
≤20	137	74.1
>20	40	21.6
Unknown	8	4.3
Lymph nodal status of IBTR		
Negative	173	93.5
Positive	12	6.5
Lymphovascular invasion of IBTR		
No	84	45.4
Yes	78	42.2
Unknown	23	12.4
Histologic grade of IBTR		
1	40	21.6
2	45	24.3
3	66	35.7
Unknown	34	18.4
ER of IBTR		
Negative	78	42.2
Positive	107	57.8
HER2 of IBTR		
Negative	142	76.8
Positive	43	23.2
Breast cancer subtype (Ki-67 cutoff: 20 %)		
Luminal A	66	35.7
Luminal B	41	22.2
Triple negative	49	26.5
HER2	29	15.7
Surgery for IBTR		
Breast-conserving surgery	101	54.6
Mastectomy	84	45.4
Radiotherapy after IBTR surgery		
Yes	37	20.0
No	148	80.0
Hormone therapy after IBTR		
No	70	37.8
Yes	112	60.5
Unknown	3	1.6
Chemotherapy after IBTR		
No	131	70.8
Yes	50	27.0
Unknown	4	2.2
Trastuzumab after IBTR[a]		
No	33	76.7
Yes	10	23.3

[a] Including only patients with HER2-positive tumors

IBTR ipsilateral breast tumor recurrence, *ER* estrogen receptor

Ki-67 index of 20 %). The 5-year DDFS rates for patients with luminal A, luminal B, triple-negative, and HER2 types, defined by a cutoff of the Ki-67 index of 20 %, were 86.3, 57.1, 56.6, and 65.9 %, respectively (Fig. 1). When the cutoff of the Ki-67 index was 10 or 14 %, breast cancer subtype was also significantly associated with DDFS by the log-rank test ($p = 0.0336$ and 0.0201, respectively).

Multivariate analyses using the time interval from the initial surgery to IBTR, tumor location, lymphovascular invasion of the IBTR, adjuvant chemotherapy, and breast cancer subtype demonstrated that the breast cancer subtype using a 20 % Ki-67 index as a cutoff was an independent predictive factor of DDFS ($p = 0.0027$, Table 3).

Because HER2 and Ki-67 staining of initial tumors was not routinely recorded, we were unable to assess the impact of breast cancer subtype of initial tumors on prognosis. Of 185 patients, 168 patients had information about the ER

TABLE 2 Five-year distant disease-free survival rates according to various clinicopathologic factors

Characteristic	5-year DDFS (%)	*p* value
Age at initial diagnosis (years)		
<40	68.6	0.2211
≥40	69.1	
Age at IBTR (years)		
<40	69.4	0.3904
≥40	69.0	
Time interval from initial surgery to IBTR (years)		
≤5	61.1	0.0003
>5	80.3	
Tumor location		
Same quadrant	61.3	0.0411
Different quadrant	79.9	
Margin of initial surgery		
Negative	67.6	0.2668
Positive	71.4	
Radiotherapy after initial surgery		
Yes	66.3	0.0981
No	72.3	
Hormone therapy after initial surgery		
No	68.9	0.8803
Yes	66.8	
Chemotherapy after initial surgery		
No	72.4	0.1274
Yes	60.1	
Trastuzumab after initial surgery[a]		
No	63.8	0.0515
Yes	0	
Tumor size of IBTR (mm)		
≤20	71.1	0.0724
>20	56.1	
Lymph nodal status of IBTR		
Negative	70.2	0.3862
Positive	50.0	
Lymphovascular invasion of IBTR		
No	80.0	0.0035
Yes	59.8	
Breast cancer subtype (Ki-67 cutoff: 20 %)		
Luminal A	86.3	0.0074
Luminal B	59.1	
Triple negative	56.6	
HER2	65.9	
Surgery for IBTR		
Breast-conserving surgery	72.7	0.2728
Mastectomy	64.6	
Radiotherapy after IBTR surgery		
Yes	69.8	0.2134
No	68.8	
Hormone therapy after IBTR		
No	66.1	0.3586
Yes	71.1	
Chemotherapy after IBTR		
No	74.8	0.0132
Yes	54.5	
Trastuzumab after IBTR[a]		
No	68.6	0.6999
Yes	77.1	

[a] Including only patients with HER2-positive tumors

IBTR ipsilateral breast tumor recurrence

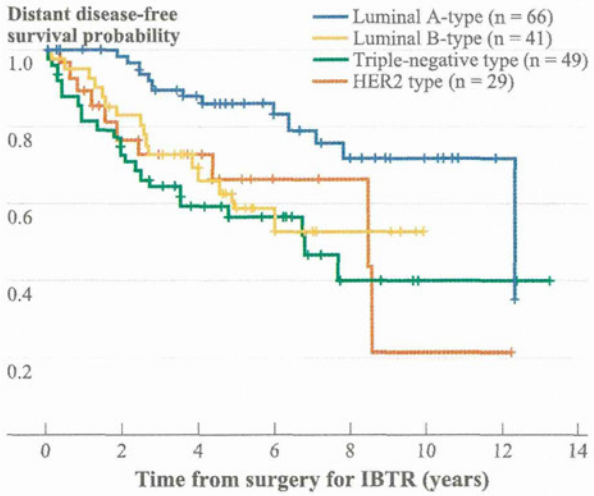

FIG. 1 Distant disease-free survival rates after ipsilateral breast tumor recurrence according to breast cancer subtype

TABLE 3 Multivariate analyses of predictors of distant recurrence after ipsilateral breast tumor recurrence

Characteristic	Hazard ratio	95 % CI	*p* value
Time interval from initial surgery to IBTR (>5 versus ≤5 years)	3.274	1.681–6.379	0.0005
Tumor location (different versus same quadrant)	2.515	1.298–4.874	0.0063
Lymphovascular invasion (no versus yes)	2.247	1.248–4.032	0.0069
Breast cancer subtype (luminal A versus other)	2.865	1.439–5.714	0.0027
Chemotherapy after IBTR (no versus yes)	1.248	0.690–2.257	0.4641

IBTR ipsilateral breast tumor recurrence, *CI* confidence interval

status of both initial and IBTR tumors. We performed statistical analyses to assess the impact of discordance in ER between initial and IBTR tumors on DDFS. The 5-year DDFS rates for patients with discordant ER status were significantly higher (82.1 %; $n = 38$) than those with concordant ER status (62.4 %; $n = 130$; $p = 0.0289$ by log-rank test). Among patients with concordant ER status, the 5-year DDFS rates for patients with ER-positive tumors ($n = 78$) and ER-negative tumors ($n = 52$) were 69.1 and 52.4 %, respectively. Among patients with discordant ER status, the 5-year DDFS rates for patients with ER-positive IBTR tumors ($n = 18$) and ER-negative IBTR tumors ($n = 20$) were 87.8 and 76.5 %, respectively.

DISCUSSION

Although breast cancer subtype based on gene expression or immunohistochemical evaluation can predict the risk of distant recurrences as well as IBTR, there is little information about the impact of breast cancer subtype on prognosis after IBTR.[8–15] To our knowledge, the current study is one of the largest to examine the role of breast cancer subtype in distant metastases of patients after IBTR.

Most studies regarding the risk of distant recurrences after IBTR focused on clinical and pathological factors. Among these studies, the time interval from initial surgery to IBTR, type of recurrence (new primary versus true recurrence), and lymphovascular invasion of IBTR were strong predictors of distant metastases after IBTR, which is consistent with our results.[4,18–21] Furthermore, in our study, breast cancer subtype of IBTR was a predictive factor for distant metastases after IBTR, independent of tumor location, time interval from initial surgery to IBTR, and lymphovascular invasion of the IBTR. In this study, we classified the recurrence type using the tumor location. The tumor location is the most commonly used parameter in new primary versus true recurrence differentiation. However, one of the problems regarding the type of recurrence is the current lack of a standard for classification of new primary versus true recurrence. To exclude confounding findings, we further performed statistical analyses excluding 63 patients with IBTR tumors in a different quadrant from the initial tumor. Multivariate analyses using the time interval from the initial surgery to IBTR, lymphovascular invasion of the IBTR, adjuvant chemotherapy, and breast cancer subtype demonstrated that breast cancer subtype using a 20 % Ki-67 index as a cutoff was an independent predictive factor of DDFS (hazard ratio, 2.500; 95 % confidence interval, 1.168–5.348; $p = 0.0182$).

There are a few reports regarding the prognostic significance of ER and HER2 after IBTR. These studies reported that patients with ER negativity, HER2 overexpression, or triple negativity in their IBTR tumors were associated with poor prognosis.[18,22,23] These results are consistent with ours. However, our analyses using breast cancer subtype defined by ER, HER2, and Ki-67 could predict patient outcomes more accurately than these studies.

As a method using molecular markers other than IHC, several authors reported that classifications by DNA clonality or the DNA breakpoint were useful for prognosis after IBTR.[24,25] However, DNA clonality or the DNA breakpoint seems impractical because of the time and expense required. In contrast, the expressions of ER, HER2, and Ki-67 are routinely assessed clinically to guide adjuvant therapy decisions.

Recently, a retrospective analysis from the European Institute of Oncology demonstrated that breast cancer subtype was associated with prognosis after locoregional recurrence following breast-conserving treatment.[26] However, in this report, the statistical analyses of local recurrence (i.e., IBTR) and regional recurrence were not separated. Because IBTR and regional recurrence have different natural histories and prognoses, it is not possible to make definitive conclusions regarding the impact of breast cancer subtype on prognosis after IBTR from this report.

In this study, patients with discordant ER status had significantly higher 5-year DDFS rates than those with concordant ER status. Interestingly, change to aggressive phenotype (i.e., patients with ER-positive primary tumors who had ER-negative IBTR tumors) was not associated with worse prognosis in this study. Further studies including HER2, Ki-67, and breast cancer subtype are warranted.

One of the limitations of our study is the inaccurate classification of breast cancer subtypes because of the lack of gene profiles. However, the low rate of distant recurrence among patients with luminal A-type IBTR tumors in this study is comparable to the low risk for both local and distant recurrence in luminal A-type primary tumors in other reports.

The second limitation is the relatively short follow-up period (median 4.5 years). It could not be ruled out that our finding that patients with luminal A-type IBTR tumors had better DDFS than those with other subtypes merely reflects the different timing of recurrence.[27,28] It is now well known that triple-negative and HER2-positive disease is most likely to recur within the first 3 years, whereas ER-positive disease may recur many years later.

The third limitation is the high frequency of missing data, especially for HER2 and Ki-67 of initial tumors. This limitation is consistent with a prior study regarding the impact of breast cancer subtype on prognosis after locoregional failure reported by Montagna et al..[26] They reported that, among 279 patients, 148 patients (53.0 %) with a missing value for breast cancer subtype were

observed at primary breast cancer or at locoregional recurrence.

Fourth, because central pathology review of ER and HER2 was not performed, it is possible that ER and HER2 status were misclassified in some patients. However, one of our strengths was central staining and review of Ki-67 index.

Small sample sizes were another limitation. However, despite the small numbers, to our knowledge, the current study represents one of the largest series in the literature to date.

In this study, 37 patients did not receive RT at the first diagnosis and then underwent repeat lumpectomy with RT at the time of their recurrence. These patients did not undergo what would be the standard of care. These patients were older than other patients in this study (data not shown), which is consistent with previous reports.[29,30]

Finally, the frequency of repeat lumpectomy for IBTR seemed to be high in this study (54.6 %) compared with that in other countries, for example, the Surveillance, Epidemiology, and End Results registry data during 1988 and 2004 (24 %).[31] However, the frequency in our study is similar to that reported by Gentilini et al. from Italy (51.3 %).[32]

At present, there is a lack of an ideal cutoff of the Ki-67 index.[33] Many cutoffs have been used, although staining levels of 10–20 % have been the most common.[34] In this study, we used three cutoffs (10, 14, and 20 %) for the Ki-67 index, which were used in previous studies of different patient cohorts.[16,17]

In conclusion, our study suggested that breast cancer subtype by IHC predicts outcomes of patients with IBTR. However, further research and validation studies are needed.

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