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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Breast Cancer
DOI 10.1007/s12282-012-0426-2

ORIGINAL ARTICLE

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

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Received: 29 August 2012 / Accepted: 15 October 2012

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

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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Published online: 02 November 2012

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

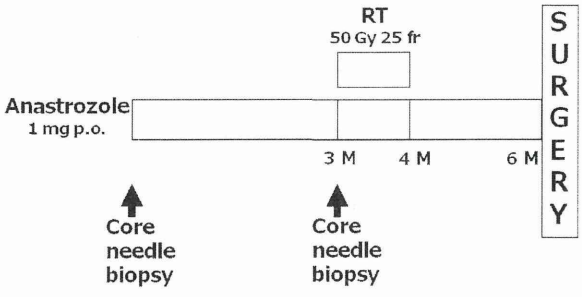

Fig. 1 Trial design

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,

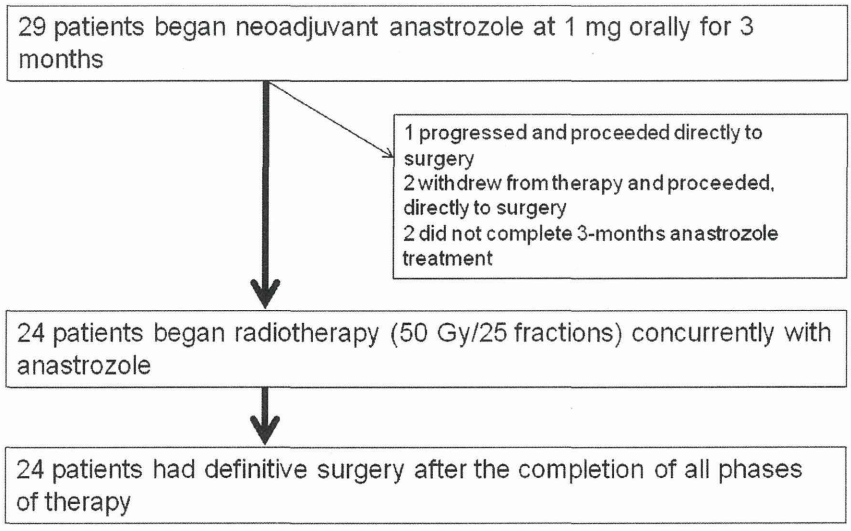

Fig. 2 Patient flow

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.

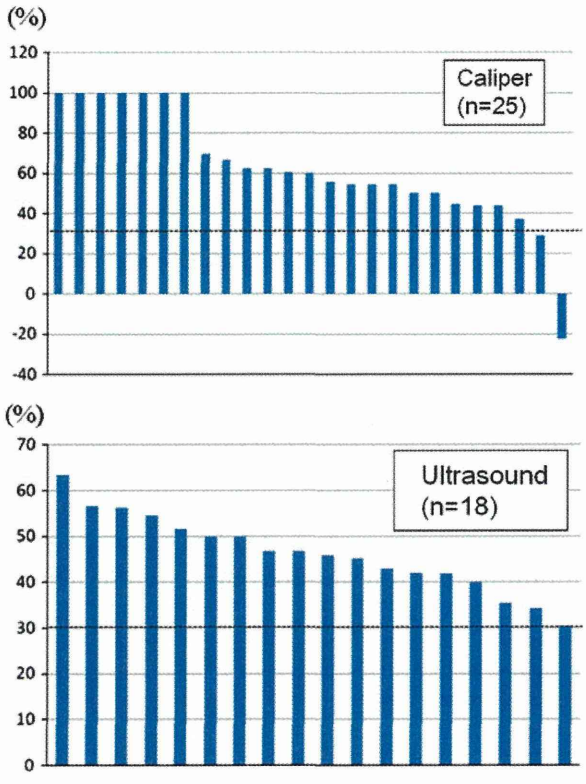

Fig. 3 Waterfall plot analysis of the clinical response at 24 weeks evaluated by caliper and ultrasound. The *horizontal axis* indicates data from each patient and the *vertical axis* the reduction rate of the tumor size evaluated by caliper or ultrasound. A clinical response was defined as 30 % or more (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