Table 2 Univariate analysis comparing the patient groups with four or more tumor-positive axillary lymph nodes to those with less than four in the original patient series

	Less than four positive nodes ($n = 545$)	Four or more positive nodes ($n = 130$)	All patients ($n = 675$)	P
Prevalence of four or more positive nodes in each center				
Mean (range)	18.8 % (11.4–25.0)	21.2 % (11.4–25.0)	19.3 % (11.4–25.0)	<0.0001
Standard deviation	6.2	5.6	6.1	
Patient age (years)				0.382
Mean (range)	57.2 (26–87)	58.0 (27–80)	57.4 (26–87)	
Standard deviation	11.6	11.5	11.6	
Histological size of the primary tumor (mm)				0.003
Mean (range)	20.5 (2–160)	25.0 (4–200)	21.4 (2–200)	
Standard deviation	11.7	11.5	13.7	
Multifocality of the primary tumor				0.043
No	438	94	532	
Yes	107	36	143	
Lymphovascular invasion in the primary tumor				0.004
No	375	72	447	
Yes	170	58	228	
Estrogen receptor status				0.189
Negative	88	15	103	
Positive	457	115	572	
Progesterone receptor status				0.751
Negative	133	30	163	
Positive	412	100	512	
HER-2 status				0.356
Negative	479	118	597	
Positive	66	12	78	
Nuclear grade of the primary tumor				0.250
Grade I	51	7	58	
Grade II	257	59	316	
Grade III	237	64	301	
Histological grade of the primary tumor				0.210
Grade I	94	15	109	
Grade II	253	60	313	
Grade III	198	55	253	
Histology of the primary tumor				0.040
Ductal carcinoma	436	95	531	
Lobular carcinoma	51	18	69	
Mixed	24	12	36	
Other	34	5	39	
Detection method of the sentinel node metastasis				<0.0001
Frozen section analysis	256	91	347	
Paraffin standard staining	231	31	262	
Paraffin immunohistochemistry	30	4	34	
Serial sectioning	28	4	32	
Extra-capsular extension				<0.0001
No	381	49	430	
Yes	164	81	245	
Number of negative sentinel nodes harvested				<0.0001
Mean (range)	0.7 (0–8)	0.3 (0–3)	0.6 (0–8)	

Table 2 continued

	Less than four positive nodes ($n = 545$)	Four or more positive nodes ($n = 130$)	All patients ($n = 675$)	P
Standard deviation	1.0	0.7	0.9	
Number of positive sentinel nodes harvested				<0.0001
Mean (range)	1.2 (1–3)	1.6 (1–3)	1.3 (1–3)	
Standard deviation	0.5	0.7	0.6	
Sentinel node ratio				<0.0001
Mean (range)	0.8 (0.1–1.0)	0.9 (0.3–1.0)	0.8 (0.1–1.0)	
Standard deviation	0.3	0.2	0.3	

HER-2 human epidermal growth factor receptor 2, *sentinel node ratio* ratio of tumor-positive sentinel nodes to all harvested sentinel nodes

Table 3 Binary logistic regression analysis using backward stepwise likelihood ratio method in the original patient series

	Coefficient	Standard error	Wald	P	Odds ratio	95 % CI for odds ratio	
						Lower	Upper
Prevalence of four or more tumor-positive nodes	0.049	0.019	6.637	0.010	1.050	1.012	1.090
Number of positive SNs	0.943	0.166	32.147	<0.0001	2.567	1.853	3.556
Number of negative SNs	−0.443	0.150	8.751	0.003	0.642	0.479	0.861
Histological tumor size (mm)	0.018	0.008	5.391	0.020	1.018	1.003	1.034
ECE of SN metastasis	1.036	0.218	22.539	<0.0001	2.818	1.837	4.321
Constant	−4.392	0.516	72.389	<0.0001	0.012		

CI confidence interval, *SN* sentinel node, *ECE* extra-capsular extension

($P < 0.0001$), number of tumor-negative SNs ($P = 0.003$), histological size of the primary tumor ($P = 0.020$) and ECE of SN metastasis ($P < 0.0001$) had statistical significance in the binary logistic regression model and were included in the predictive model (Table 3). The Hosmer–Lemeshow test produced a P value of 0.101 indicating that the model fits and calibrates well for the patient population.

The AUC for the original patient population was 0.769 (95 % confidence interval: 0.721–0.816) suggesting a very good discrimination. The multivariate model predicted 455 (67.4 %) of the 675 patients in the original patient series to have less than four metastatic ALN with a sensitivity of 66.9 % and specificity of 75.6 % at the <20 % cutoff threshold.

A mathematical equation was deduced from the logistic regression analysis to predict a patient specific risk of having four or more tumor-positive ALNs, with p denoting the probability of this risk:

$$\text{logit}(p) = -4.392 + 0.049 \times a + 0.943 \times b - 0.443 \times c + 0.018 \times d + 1.036 \times e.$$

The letters in the equation denote the following variables: a = prevalence of four or more tumor-positive ALNs in patient series (percentage of patients), b = number of tumor-positive SNs, c = number of tumor-negative SNs, d = histological size of primary tumor (mm), e = ECE of SN metastasis (0 if not present, 1 if present). The predictive model is also provided as an excel-based calculator in the online only version of this article and at the website of the Breast Surgery Unit of Helsinki University Central Hospital (www.hus.fi/breastsurgery/predictivemodel).

The predictive model was then validated by insertion of each patient's data from the internal and external validation series into the equation. AUC, sensitivity and specificity for each internal and external validation center are given in Table 4. Receiver operating characteristic curves for the original series and validation series are presented in Fig. 1.

Sensitivity and specificity are given for <20 % risk in the internal and external validation series in Table 4. Sensitivity and specificity of our model in the external validation series for other predicted probabilities are: <5 % risk (sensitivity 99.5 %, specificity 3.4 %), <10 % risk (sensitivity 95.7 %, specificity 22.1 %), <20 % risk (sensitivity 76.1 %, specificity 61.5 %), <30 % risk (sensitivity 54.3 %, specificity 84.6 %), <40 % risk (sensitivity 44.0 %, specificity 91.8 %), <50 % risk (sensitivity 27.3 %, specificity 96.9 %), <60 % risk (sensitivity 23.0 %, specificity 98.7 %). Our model identifies 389 (51.2 %) of the 760 patients in the external

Table 4 Performance of the predictive model in internal and external validation; sensitivity and specificity for <20 % risk of additional metastases

	N	Four or more metastatic ALNs	AUC (95 % CI)	Sensitivity (%)	Specificity (%)
Original patient series	675	130 (19.1 %)	0.769 (0.721–0.816)	66.9	75.6
Internal validation series	367	67 (18.3 %)	0.766 (0.698–0.834)	68.7	70.3
Center A	72	12 (16.7 %)	0.726 (0.559–0.893)	58.3	55.0
Center B	91	19 (20.9 %)	0.767 (0.637–0.897)	68.4	69.4
Center C	33	8 (24.2 %)	0.893 (0.778–1.000)	75.0	76.0
Center D	149	27 (18.1 %)	0.759 (0.647–0.871)	74.1	72.1
Center E	22	1 (4.5 %)	0.667 (0.465–0.868)	–	100
External validation series	760	209 (27.5 %)	0.774 (0.736–0.812)	76.1	61.5
Center F	77	30 (39.0 %)	0.868 (0.782–0.954)	96.7	25.5
Center G	88	20 (22.7 %)	0.775 (0.661–0.889)	75.0	64.7
Center H	42	8 (19.0 %)	0.741 (0.536–0.946)	37.5	85.3
Center I	132	40 (30.3 %)	0.778 (0.693–0.862)	75.0	60.9
Center J	17	3 (17.6 %)	0.750 (0.405–1.000)	66.7	42.9
Center K	79	18 (22.8 %)	0.638 (0.477–0.800)	38.9	85.2
Center L	141	27 (19.1 %)	0.845 (0.772–0.918)	88.9	64.9
Center M	184	63 (34.2 %)	0.736 (0.653–0.818)	77.8	54.5

ALN axillary lymph node, *AUC* area under the receiver operating characteristic curve, *CI* confidence interval

validation series to have a less than 20 % risk of having more than four ALN metastases. Similarly the model identified 73.9 % patients to have a less than 30 % risk and 82.0 % to have a less than 40 % risk. The present model predicts only 20 (2.6 %) patients in the external validation series to have a less than 5 % risk of four or more ALN metastases.

Calibration of the predictive model was examined by grouping patients in each series into quartiles according to the predicted probabilities of four or more tumor-positive ALNs. A calibration plot was acquired by plotting the mean predicted probability of each quartile against the actual proportion of patients with four or more tumor-positive ALNs in each quartile (Fig. 2).

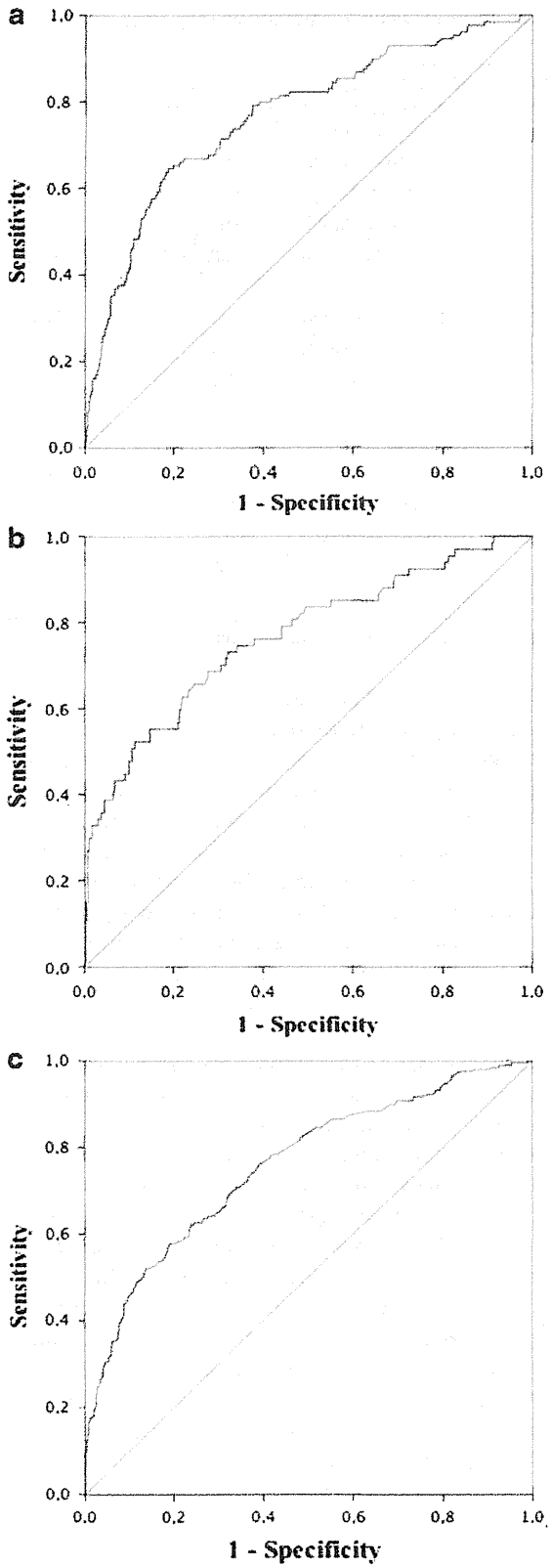
Discussion

The present predictive model

Our predictive model performs very well in the internal and external validation, both having AUC values of >0.75. Our model is also well calibrated as shown by the Hosmer–Lemeshow test and the calibration lines in Fig. 1. As expected, the performance of our model varies between validation centers. The centers at the extremities in terms of AUC values have contributed relatively small numbers of patients and this variation may well be caused by statistical deviation due to the small sample size. The case mix might also differ between centers, for example, in terms of tumor sizes. Growing tumor size increases the prevalence of ALN metastases. The use and sensitivity of preoperative axillary ultrasound affects the prevalence of four or more positive ALNs as well. Patients with a significant axillary tumor burden are more likely to be preoperatively detected by axillary ultrasound compared to patients with only a single ALN metastasis.

We present our predictive model as an equation predicting the probability of an individual patient with macrometastatic SN having four or more tumor-positive ALNs. The three previously published predictive tools are presented in forms of a scoring system [12], a table [13], and a nomogram [14], all of which are approximations of the original logistic regression model. Presenting the predictive model in the form of a nomogram or scoring system allows an easy risk prediction, but such tools work ideally in paper format. At present, most patient records and medical applications display data in electronic format, therefore, entering information into a software-based calculator seems the easiest and certainly most accurate way to proceed with the estimation of patient-specific risks.

Furthermore, by producing a continuous risk percentage our model is not tied up to specific cutoff thresholds as clinical decision-making thresholds may well change in the future. The model's sensitivity and specificity were tested in Table 4 for a cutoff value of less than 20 % risk of having four or more metastatic ALNs. This threshold was chosen as an example and is considerably higher than the <5 % threshold given by the previous predictive models [12–14]. Our model predicts over 50 % of the patients in the external validation series to have a less than 20 % risk



◀ **Fig. 1** Receiver operating characteristic curves for the original patient series (**a**), the internal validation patient series (**b**), and the external validation patient series (**c**)

for four or more ALNs metastases but the proportion of patients understandably changes with the risk level. Because other risk levels may be relevant in various clinical circumstances, we calculated our model's sensitivity and specificity for risk levels ranging from less than 5 % to less than 60 % in the external validation series. At 5 and 10 % cutoff levels, the sensitivity of our model was extremely high, that is over 95 %, but at the cost of the specificity. However, such low cutoff levels will be used when it is important to minimize the risk of missing the diagnosis of pN2–pN3 disease, and then the high sensitivity can be considered as an advantage. Although the risk cutoff level can be altered with changing settings of clinical decision-making, the model needs to be validated for each center's patient population, and sensitivity and specificity need to be calculated for each threshold.

Factors in our model

Our predictive model is based on heterogeneous patient data from five European centers. The exclusion criteria were intentionally kept minimal in order to produce a series closely resembling the normal clinical setting. It is noteworthy that the prevalence of patients with four or more tumor-positive ALNs has not been previously incorporated into any predictive model. This adds an important factor into the model as it facilitates calibration of the model in different centers with varying patient material and surgical and pathological methodology. The importance of such institutional calibrations and validations has been highlighted by

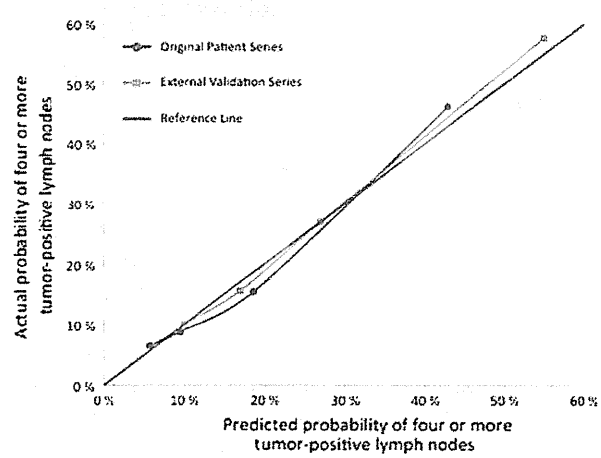


Fig. 2 Calibration plot for the predictive model applied to the original patient series and external validation series split to quartiles

our previous studies demonstrating relevant inter-institutional differences in both the variables used by the predictive models [16] and the best performing predictive tools for patients with low [16] and high [16, 17] risk of NSN involvement [34].

In addition to the prevalence of four or more positive ALNs, four tumor and SN-related variables were found to be statistically significant in the binary logistic regression analysis and were included in our predictive model. Tumor size, number of positive SNs, and SN ratio or number of negative SNs were found to be significant factors also in all of the previous models [12–14]. ECE of SN metastasis was also a significant factor in two of the previous models [13, 14]. Other factors that were found to be significant in previous studies are: lymphovascular invasion of the primary tumor [13, 14], detection method of SN metastasis [12] and tumor histology [14]. As a whole, all of the published predictive models are surprisingly similar regarding factors influencing the prevalence of four or more metastatic ALNs with tumor-positive SNs.

Implications of our predictive model—towards tailored axillary treatment

Completion ALND after tumor-positive SNs has been the gold standard of distinguishing pN1 patients from pN2–pN3 breast cancer patients. Accurate evaluation of the lymph node tumor burden in the axilla has been considered an important prognostic factor influencing adjuvant treatment planning. ALND also reveals the lymph node ratio, i.e., the proportion of metastatic ALNs among all examined nodes. The prognostic value of the lymph node ratio has been considered superior to the number of involved axillary nodes [1, 2].

The results of ACOSOG Z0011 trial were groundbreaking suggesting that omitting ALND in patients with limited number of metastatic SNs may not increase regional recurrence rate nor decrease survival in general [5, 6]. The Z0011 trial had, however, many limitations that reduce its generalizability. The Z0011 trial only included breast cancer patients undergoing breast-conserving surgery followed by whole-breast radiotherapy. The study therefore excluded patients undergoing mastectomy who may benefit from accurate discrimination between pN1 and pN2–pN3 disease in the planning of adjuvant radiotherapy. Moreover, the Z0011 trial included only patients with one or two tumor-positive SNs and a substantial proportion of the patients had micrometastasis as their SN finding (44.8 % in the SNB only arm) [5, 6]. Therefore, the ACOSOG Z0011 trial results do not indicate that every patient with SN metastases can safely avoid ALND.

The forthcoming results of the AMAROS-trial may further increase the need for predictive tools. The AMAROS-trial compares axillary radiotherapy to completion ALND in a randomized setup [35]. If ALND were to be replaced by axillary radiotherapy, the exact extent of the axillary tumor burden would remain unknown. Even if axillary radiotherapy proves equal to completion ALND, a subgroup of patients with extensive axillary tumor burden might benefit from completion ALND either alone or together with axillary radiotherapy.

The trend of omitting routine ALND after tumor-positive SNs increases the importance of statistical models in predicting patients with a risk of significant tumor burden left behind in their axilla. Such patients may benefit from either radiotherapy to regional nodal basins, completion ALND, or even both. The treatment of ALN positive breast cancer patients is undergoing a dramatic change. In the future, these patients may be offered tailored axillary treatment options based on patient-specific risk and need analyses. As clinicians' decisions may be inferior to nomogram-based decisions [36], predictive tools such as the present one will be of major importance in this development.

Conclusion

In this study, we present a novel international multicenter predictive tool to assess patient-specific risk of having four or more tumor-positive ALNs in patients with SN macrometastases. Our model performs very well both in internal and external validation patient series, but needs further validation in each center before application to clinical practice.

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Conflict of interest The authors declare that they have no conflicts of interest.

Ethical standard This study complies with the current law of all the countries in which the patients were treated.

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Original article

Use of the neo-adjuvant exemestane in post-menopausal estrogen receptor-positive breast cancer: A randomized phase II trial (PTEX46) to investigate the optimal duration of preoperative endocrine therapy

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ABSTRACT

Purpose: The optimal treatment duration time and the causal relationship between neoadjuvant endocrine therapy and clinical response are not clear. Therefore, we conducted the present study to investigate the potential benefits of neoadjuvant exemestane therapy with the goal of identifying the optimal treatment duration.

Methods: This study was conducted at three hospitals, as a multicenter, randomized phase II trial(UMIN000005668) of pre-operative exemestane treatment in post-menopausal women with untreated primary breast cancer. Fifty-one post-menopausal women with ER-positive and/or PgR-positive invasive breast cancer were randomly assigned to exemestane for 4 months or 6 months. Clinical response, pathological response, and decisions regarding breast-conserving surgery were the main outcome measures.

Results: Of the 52 patients that enrolled, 51 patients underwent surgery. Of those, 26 and 25 patients had been treated with exemestane for 4 and 6 months, respectively. Treatments were performedat 3 hospitals in Japan between April 2008 and August 2010. The response rates as assessed by clinical examination were 42.3% and 48.0% for 4 and 6 months of treatment, respectively. Pathological responses (minimal response or better) were observed in 19.2% and 32.0% of patients, and breast-conserving surgery was performed on 50.0% and 48.0% of patients from the 4 and 6 month treatment groups, respectively.

Conclusion: The results of this study demonstrate that responses were equal to 4 or 6 months of exemestane treatment. Therefore, we propose that the rates of breast-conserving surgery could be maximized by 4 months of treatment. Furthermore, in addition to using exemestane as a preoperative treatment in post-menopausal women with ER-positive breast cancer, we envision administering the drug over the long term under careful clinical supervision.

Introduction

Since the 1990s, primary endocrine therapy has been considered the gold standard in the adjuvant and metastatic treatment settings for estrogen (ER) and/or progesterone (PR) receptor-positive breast cancer. The NSABP B-18 clinical trial[1] in 1988 demonstrated that neoadjuvant chemotherapy yielded the same survival rate as adjuvant chemotherapy, with an improved rate of breast-conserving surgery, indicating that neoadjuvant therapy could have important clinical ramifications. With that in mind, neoadjuvant endocrine therapy for hormone receptor-positive breast cancer was also assessed, and was shown to be effective in a number of clinical trials (Table 1). Recently, clinical interest has shifted from tamoxifen to third-generation aromatase inhibitors. A few trials[2–8] have indicated that anastrozole led to improved response rates as compared to tamoxifen, but the results were not statistically significant. The PROACT trial reported that anastrozole treatment allowed for breast-conserving surgery in significantly

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Table 1
Neoadjuvant endocrine trials.

Author or trial name	Number of patients	Design	Duration (month)	Clinical ORR[e]
IMPACT[2]	330	ANA[a] vs TAM[b] vs ANA + TAM	3	37%, 36%, 39%
PROACT[3]	451	ANA vs TAM	3	49.7%, 39.7%
PO24 Trial[4]	337	LET[c] vs TAM	4	55%, 36%
GENARI Trial[5]	29	EXE[d]	4	37.0%
French study[6]	45	EXE	14–27 weeks	70.6%
Gil Gil (Spain)[7]	55	EXE	6	50%
Mustacchi[8]	44	EXE	6	66%

[a] ANA = Anastrozole.
[b] TAM = Tamoxifen.
[c] LET = Letrozole.
[d] EXE = Exemestane.
[e] ORR = objective response rates.

more patients than did tamoxifen. The neoadjuvant drug, exemestane, has been evaluated in several small studies. The results have been promising and warrant further evaluation to determine the optimal therapeutic conditions for hormone receptor-positive patients. Specifically, the optimal treatment duration time and the causal relationship between neoadjuvant endocrine therapy and clinical response are not clear (Table 1). In addition, there are studies that have reviewed the optimal duration time of hormone treatments. Here, we investigated the benefits of 4 and 6 month long neoadjuvant exemestane therapy.

Materials and methods

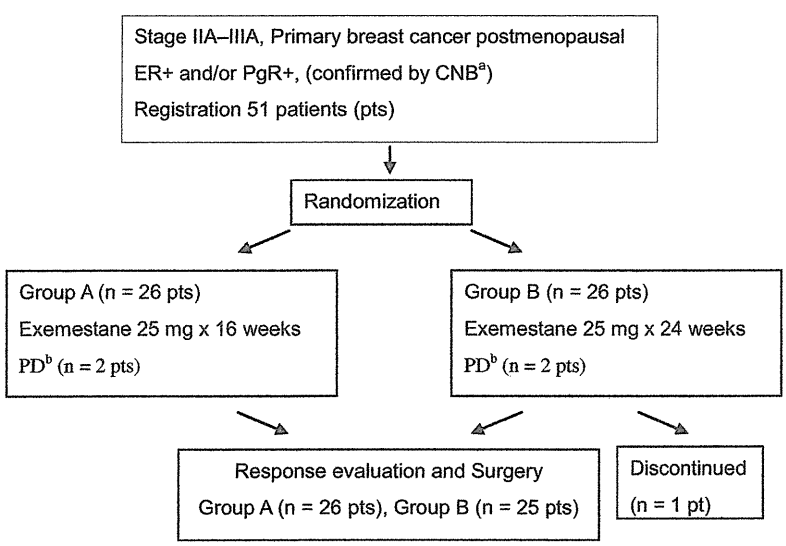
Patients

We enrolled ≥55-year-old post-menopausal women (defined as: no spontaneous menses for > 1 year; LH levels > 30 IU/L; or bilateral oophorectomy prior to breast cancer diagnosis) with stage IIA–IIIA invasive ER- and/or PgR-positive breast carcinoma, as confirmed by immunohistochemical examination of core-needle biopsies (defined as: >10% endocrine receptor + nuclear staining). We further required that tumors be measurable by clinical palpation. Written informed consent was obtained from each patient.

Patients were ineligible if they had any severe coincident medical disease that would prevent them from receiving surgery, place them at unusual risk, or confound the study results; were unwilling or unable to discontinue using drugs affecting sex hormones (including hormone replacement therapy); had suffered from any invasive malignancy within the previous 5 years (other than carcinoma of the skin or carcinoma in situ of the cervix, adequately cone biopsied); had received any previous breast cancer treatment or tamoxifen as part of a breast cancer prevention study; or, had received treatment with non-approved drugs during the 3 months prior to randomization. Criteria for withdrawal from the study included patients who had completed the 5-year treatment course; did not begin randomized therapy; withdrew informed consent; had confirmed clinically significant disease before surgery or confirmed recurrence after surgery; had an adverse event; or, were withdrawn at the investigator's discretion.

Study design and setting

This study was conducted at three hospitals in Japan as a multicenter, open-label, double-arm, randomized, phase II clinical trial of pre-operative exemestane treatment in post-menopausal women with primary breast cancer. In order to optimally balance the patients in the two treatment arms with respect to prognostic factors, the patients were stratified by tumor factor, node factor, and age. The neoadjuvant endocrine treatment regimen consisted of one 25 mg exemestane tablet daily for 4 or 6 months. Fifty-one post-menopausal women with ER-positive and/or PgR-positive invasive breast cancer were randomly assigned to exemestane (25 mg/day) for 4 months (Group A) or exemestane



Setting: Multicenter study involving 3 hospitals in Japan

[a]CNB = core needle biopsy

[b]PD = Progressive Disease

The patient with PD canceled treatment and underwent immediate surgery.

Fig. 1. Study design.

(25 mg/day) for 6 months (Group B; Fig. 1). When antitumor effects were observed with progressive disease (PD), the treatment was canceled and patients underwent surgery immediately. All patient data was collected by UMIN (UMIN000005668) and analyzed at the National Cancer Center in Japan. Tumors were measured by caliper before exemestane treatment began, and again in the eighth week of therapy. Tumor regression by clinical examination, pathological response, decisions regarding breast-conserving surgery, and safety assessments were the main outcome measures. All patients provided written informed consent. This investigational registration period was planned three years from May 2008. The trial was conducted in accordance with the principles of Good Clinical Practice as specified in the Declaration of Helsinki (Edinburgh, 2000). The study protocol was guided by the current regulations governing clinical trials, and was approved by the Ethics Committees of the individual hospitals involved. All patients gave written informed consent before study enrollment.

Study endpoints

The primary endpoints were objective response rates (ORR) by caliper at 4 and 6 months of treatment using an intention to treat analysis. Secondary endpoints were the rates of breast-conserving surgery or mastectomy, and the pathological response rates.

Clinical assessments

The primary study objective was to compare the differences between exemestane treatment for 4 and 6 months, using objective complete responses (CRs) and partial responses (PRs) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST),[9] which is based on caliper measurements of tumor size. Clinical response was assessed by comparing the longest diameter of the target lesions with the baseline measurement based on RECIST criteria. Every 4 weeks, patients underwent a physical examination, toxicity assessment, and tumor assessment using WHO criteria. If tumor progression was suspected, the tumor was further assessed by ultrasound or mammography. At baseline and immediately before surgery, the investigator recorded the extent of the least invasive feasible breast surgery option at that particular time: whether breast-conserving surgery or mastectomy was needed, or whether the tumor was inoperable.

Histological assessments

Histopathological therapeutic response was classified according to the General Rules for the Clinical and Pathological Recording of Breast Cancer 2005.[10] For Grade 0, no response was observed; Grade 1a comprised those tumors with mild changes in cancer cells regardless of the area, or marked changes seen in less than one-third of cancer cells; Grade 1b comprised tumors with marked changes seen in more than one-third but less than two-thirds of tumor cells; Grade 2 tumors contained marked changes in more than two-thirds of tumor cells; and Grade 3 tumors demonstrated a complete response, with no cancerous cells remaining. Mild changes included slight degenerative changes in cancer cells not suggestive of cell death (including cancer cells with vacuolation of the cytoplasm, eosinophilic cytoplasm, swelling of the nucleus, *etc.*). Marked changes include noticeable degenerative changes in cancer cells suggestive of cell death (including liquefaction, necrosis, and disappearance). The pathological response group was defined as tumors with Grade 1b and 2 responses. The non-response group was defined as tumors with Grade 0 and 1a responses.

Statistics

Based upon previous results, we assumed the response rate to be 40% and 60% after 4 and 6 months of exemestane, respectively (Table 1). To achieve an 80% statistical power, 46 examples were required to detect differences in both response rates with a 5% level of significance.[1] To account for attrition, we enrolled 50 patients.[11] Analysis was on an intention to treat (ITT) basis. The chi-squared test was used to compare tumor characteristics and responses, and rates of breast-conserving surgery between groups. Results with $p < 0.05$ were considered to be significant.

Results

Patient baseline characteristics

The study enrolled 52 post-menopausal women at 3 hospitals in Japan between April 25, 2008 and August 12, 2010. Of these, 26 patients were allocated to Group A, and 26 to Group B. One patient withdrew and did not complete the study (Group B). The main characteristics of the eligible patients are described in Table 2. The baseline characteristics were well balanced between the two treatment arms (Table 2).

Efficacy results

Evaluation of the primary efficacy endpoint (overall objective response as determined by clinical palpation) revealed that there was no statistically significant difference in the overall objective response (CR + PR) between the two treatment groups: Group A, 42.3%; Group B, 48.0%; $p = 0.89$ (Table 3). Clinically, 7.7% of Group A and 8.0% of Group B patients progressed while 50.0% and 44.0% of Group A and B patients, respectively, remained stable (not significant). As for the anti-tumor effect assessed by caliper at the eighth week, there were no differences between the two cohorts (Table 3). The pathological response rates of Groups A and B were 19.2% and 32.0%, respectively, a difference that was not statistically significant (Table 4, $p = 0.47$). Pathological CR in the primary breast lesion was only observed in one patient in Group B. Withdrawals from the trial due to side effects did not occur in either Group.

Table 2
Patients' baseline characteristics.

		Group A (4 months)	Group B (6 months)
Age, median (range)		66 (51–80)	64 (57–80)
Tumor stage, number (%)	T2	24 (92.3%)	24 (92.0%)
	T3	2 (7.7%)	2 (8.0%)
Nodal stage, number (%)	N0	21 (80.8%)	24 (92.0%)
	N1	5 (19.2%)	2 (8.0%)
Clinical stage, number (%)	IIA	19 (73.1%)	22 (84.0%)
	IIB	7 (26.9%)	4 (16.0%)
BMI[a]		23.9 (18.5–31.5)	24.5 (17.5–32.3)
Tumor diameter (caliper) Median (range) mm		30.5 (20–60)	30.0 (13–55)
Receptor status			
ER[b] positive/HER2[c] negative		25	22
ER[b] positive/HER2 positive		1	3
PgR[d]	Positive	20	18
	Negative	6	8

There were no differences between Groups A and B in these characteristics.
[a] BMI = body mass index.
[b] ER = estrogen receptor.
[c] HER2 = human epidermal growth factor receptor type 2.
[d] PgR = progesterone receptor.

Table 3
Clinical response (caliper).

Response[a]	Group A (4 months) number (26)		Group B (6 months) number (25)	
	8 weeks	16 weeks	8 weeks	24 weeks
CR	0	1	0	2
PR	7	10	5	10
SD	17	13	20	11
PD	2	2	0	2
Clinical ORR (CR or PR)	26.9%	42.3%	20.0%	48.0%

$p = 0.89$.
Complete Response: CR, Partial Response: PR, Stable Disease: SD, Progressive Disease: PD.
ORR: objective response rates.
[a] The RECIST methodology was used to assess response (Therasse et al., 2000).

Table 4
Clinical response (pathological response).

Pathological response[a]	Group A (4 months) number	Group B (6 months) number
3	0	1
2	0	1
1b	5	6
1a	15	13
0	6	4
Response rate (1b or 2 or 3)	19.2%	32.0%

$p = 0.47$.
0 no response, 1a mild response, 1b moderate response, 2 marked response, 3 complete response.
[a] Pathological response was defined as a Grade 1b, 2, or 3 lesion according to the following criteria.

Breast conservation

Of the 52 randomized patients, 32 would have required a mastectomy at baseline (17 in Group A and 15 in Group B; Table 5). For one of these patients, an operation was not performed. Surgery outcomes with respect to breast conservation improved in 4 of 26 patients in Group A (15.4%), as compared to 1 of 25 patients in Group B (4.0%). As compared to the intent-to-treat population, the increase in patients eligible for breast conserving surgery was numerically higher in Group A than Group B, although this difference did not reach statistical significance.

Discussion

ER-positive tumors are generally less sensitive to chemotherapy than ER-negative tumors.[12,13] Some trials have shown that tamoxifen is an effective primary endocrine agent for the treatment of locally advanced[14] and operable ER-positive breast cancers, especially in the elderly population.[15,16] A combined analysis of the IMPACT and PROACT clinical trials showed a trend toward better objective response rates when patients received aromatase inhibitors, but no statistically significant difference was observed between treatments with aromatase inhibitors or tamoxifen.[2,3] However, in the P024 trial, the objective response rate for treatment with aromatase inhibitors was significantly greater than that for tamoxifen.[4] At present, the optimum duration of treatment for neoadjuvant endocrine treatment is not known. Ideally, the timing would be based on individual patient response. Clinical trials report a common duration period of preoperative endocrine therapy as 4–6 months. Likewise, the duration of many neoadjuvant chemotherapy treatments is 6 months. Therefore, we carried out this study to compare the use of exemestane for 4 and 6 months prior to surgery. We found no significant differences in outcomes between patients who received the drug for 4 or 6 months; however, the latter group tended to have higher anti-tumor responses. It is thought that this observation did not reach statistical significance because we set the significant difference of both groups at 20%.Our study results show that the maximum response of neoadjuvant hormone therapy by exemestane is around four months. These data are consistent with the study by Antonio Llombart-Cussac et al.,[18] in which the maximum response to therapy with letrozole was at 4.2 months. In addition, a randomized phase II study[17] compared 4–8 months of letrozole in a single arm; there tended to have higher anti-tumor responses. We think that these results indicate that the maximum response to neoadjuvant hormone therapy is also around four months. ER- and/or PgR-positive tumors are biologically heterogeneous. It is thought that biologically heterogeneous groups require detailed statistical adjustment. Krainick-Strobel UE et al.[17] found that 4 months of neoadjuvant exemestane therapy improved the rate of breast-conserving surgery. There was not a large difference in response rates for treatments of 3–6 month duration; however, the anti-tumor effects tended to be greater after 6 months of treatment as compared to shorter time points. In our study, neither treatment group experienced severe side effects as a result of the therapy. However, Group B tended to have a higher pathological response rate. It seems that the maximum anti-tumor effect may be reached at different time points for each patient over the course of 24 weeks of treatment. Therefore, we cannot expect a large antitumor effect by treating for longer than 4 months; however, we could extend the treatment period until the time of operation. Furthermore, in addition to using exemestane as preoperative treatment in post-menopausal women with ER-positive breast cancer, due to the mild side effects observed during the 6 month course of treatment, we envision administering the drug over the long term under careful clinical supervision.

Table 5
Rate of breast-conserving surgery.

Group A (4 months)			Group B (6 months)		
	Estimation (pre treatment)	Post treatment		Estimation (pre treatment)	Post treatment
Mastectomy	17	13	Mastectomy	14	13
BCS[a]	9	13	BCS	11	12
Rate of BCS	34.6%	50%	Rate of BCS	44.0%	48.0%

[a] BCS = Breast-conserving surgery.

Ethical approval

The present work has been approved by the ethical committee of each institutional.

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Conflict of interest statement

All authors declare that they have no conflict of interest.

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None.

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特集／エビデンスに基づく乳癌診療の最前線

患者に優しい乳癌の新しい治療

ラジオ波焼灼治療の現状

井　本　滋

はじめに

ラジオ波焼灼治療（radiofrequency ablation, RFA）は肝細胞癌に対する標準治療の一つである。肝細胞癌の大半は肝炎ウィルスに起因する固形癌であることから切除後の再発率は50%以上と高い。従ってRFAは侵襲を伴う開腹手術に比べて負担が少なく，繰り返し治療できる点が優れている。現在，腎癌，肺癌，甲状腺癌，悪性腫瘍の骨転移などさまざまな領域でRFAの有効性について検証が進められている。では，乳癌におけるRFAはどのような位置付けにあるのか？　残念ながら，現時点でのエビデンスレベルはレベル4ないし5相当である。本稿では乳癌治療におけるRFAの現状と臨床試験について述べる。

Ⅰ．乳癌の特性と集学的治療におけるRFA

乳癌は乳管癌と小葉癌に大別されるが，小葉癌は比較的広範囲に広がる傾向がある。乳管癌も浸潤・非浸潤を問わず乳管内に進展することが多い。Hollandらは浸潤性乳管癌の乳房切除標本の連続切片を作成し，乳管内進展（extensive intraductal components, EIC）のある群とない群を対象に，浸潤性乳管癌の辺縁からどこまで乳管内癌（intraductal carcinoma）が存在するか検討した（図1）[1]。その結果，辺縁から2cmの距離においてEICあり群では33%の症例で乳管内癌が存在したのに対しEICなし群では2%のみであった。臨床試験のメタアナリシスでは，n0乳癌における乳房部分切除では乳房照射の有無によって10年乳房内再発率は19%の差があった[2]。乳癌は腫瘍周囲乳管内癌の広がりを認めることが多いため乳房照射を伴う乳房部分切除が標準治療である。一方，RFAは乳房部分切除の代替治療であるから，乳房部分切除と同等の予後が期待されなければならない。

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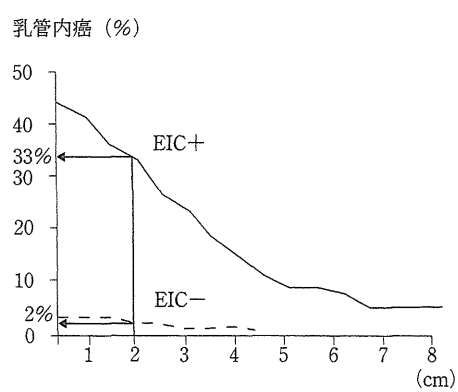
Ⅱ．乳癌におけるRFAの基礎

1．適　応

まずRFAによる焼灼範囲の側面から検討すると，MRIによるEICの治療前評価は必須である。腫瘍径が小さくてもEICが認められる場合は焼灼範囲を超えて癌が遺残する。マンモグラム上で観察される乳癌に伴う広範な石灰病変を伴う症例はRFAの適応外である。乳腺は容量の大きい肝臓と異なり皮膚あるいは大胸筋に囲まれており，周囲臓器への熱傷を防ぐには自ずと焼灼範囲が限定される。以上から，乳癌のRFAは，EICを含めて2cm以下の腫瘍径で，乳頭乳輪の近傍になく皮膚に引きつれを認めず大胸筋膜に接しない腫瘍が適応である[3]。

次に腫瘍の性状に伴う集学的治療の側面から検討すると，RFA前の組織生検は必須である。その結果，Ki67高値やHER2陽性など増殖能の



(Holland, R., J Clin Oncol, 8: 113-118, 1990. より改変)

図1　乳管内進展（EIC）の有無と腫瘍縁からの乳管内癌の存在

表 1　切除を伴うRFA

著者（報告年）	症例数	T	電極針	焼灼率	合併症（症例数）
Jeffrey (1999)	5	T2-3	LeVeen	80%	None
Izzo (2001)	26	T1-2	LeVeen	96%	Skin burn (1)
Burak (2002)	10	T1	LeVeen	90%	None
Singletary (2003)	29	T1-2	RITA	86%	Skin burn (1)
Hayashi (2003)	22	T1	RITA	64%	Skin burn (1)
Noguchi (2006)	10	T1	RITA	100%	None
Khatri (2007)	15	T1	Cool-tip	93%	Skin puckering (2) Wound infection (1)
Medina-Franco (2008)	25	T1-2	Elektrotom	76%	Skin burn (3) Wound infection (1)
Imoto (2009)	30	T1	LeVeen	87%	Skin burn (2) Muscle burn (7)
Hung (2009)	20	T1	LeVeen or Cool-Tip	90%	None
Kinoshita (2010)	49	T1-2	Cool-tip	61%	Skin burn (2) Muscle burn (3)
Ohtani (2011)	41	T1	Cool-tip	88%	Skin burn (1)
Total	282	T1-3	Various	83%	Skin burn (11) Miscellaneous (18)
		T1		86%	(152/177)

高い乳癌では化学療法が初期治療である。腫瘍径の大きな乳癌でも薬物療法によって腫瘍が縮小しRFAが可能となる場合も想定されるが，焼灼することで生物学的特徴に関する情報が失われてしまうことは医学的にも倫理的にも許容されない。以上から，手術先行となる悪性度の低い乳癌，例えばルミナルA相当がRFAの適応である。但し，乳管癌，小葉癌，特殊型など組織型に関する適応の是非は課題である。

2. 基本手技

乳癌RFAではCool-tip型とLeVeen型のRF generatorを用いた報告が多く見られる。電極針は腫瘍中心を貫通するようにエコーガイド下に挿入する。腫瘍径に応じて電極針のサイズを調整し適切な焼灼範囲を確保する。皮膚または大胸筋に近接する場合は，エコーガイド下に皮下あるいは大胸筋膜上に5％ブドウ糖水を注入し焼灼に伴う皮膚熱傷や胸筋熱傷を予防する。RF generatorによる電力の初期設定は10Wから開始し，毎分5～10Wずつ上昇させる。電力上昇に伴いジュール熱が発生し，腫瘍並びに腫瘍周囲組織が焼灼される。完全に焼灼されると，電極針で計測される電気抵抗（impedance）は最大値（Ω）となり急速に電圧が低下するため焼灼終了の目安となる（ロールオフ現象）。焼灼時間は数分から数十分である。焼灼中および焼灼終了後数時間は，氷あるいは保冷剤によって患側乳房の冷却を行う。

3. 熱変性による病理組織診断

RFAによる焼灼温度は70度を超えるため，焼灼領域の細胞は熱変性する。焼灼直後に切除された細胞は，HE染色によって核の膨張や濃染像が認められる。しかし，組織構築自体の変化に乏しく細胞の生死の判断は困難である。熱変性した細胞は時間経過とともに融解しマクロファージに貪食されるが，その時期は不明確であり客観的にcell viabilityを評価する必要がある。Nicotinamide adenine dinucleotide（NADH）diaphorase染色はミトコンドリアに局在し，NADとNADHの2つの状態をとり酸化還元反応に必須の補酵素であり，熱変性による細胞死の評価に適している[3]。生細胞であればミトコンドリアが赤紫色に染色されるが，死細胞では染色されない。抗サイトケラチン抗体や抗ssDNA抗体によるcell viabilityの評価も試みられている[4]。

Ⅲ. 乳癌におけるRFAの治療成績

1. 乳房切除を伴うRFA

RFAによってEICを含めた腫瘍部が完全に焼灼されているかどうか検討することは重要である。表1はRFAを施行した直後あるいは数週間後に乳房切除術を施行した報告である。

表 2　切除を伴わないRFA

著者（報告年）	症例数	T	電極針	観察期間（月）	再発（症例数）
Susini (2006)	3	T1	Cool-tip	18 (mean)	None
Marcy (2007)	5	T1-2	Elektrotom	24～36	IBTR* (1)
Oura (2007)	52	Tis-1	Cool-tip	6～30	None
Nagashima (2009)	17	T1	Cool-tip	12～28	None
Yamamoto (2011)	30	T1	Cool-tip	2～41	None
Yoshinaga (2013)	8	T1	Cool-tip	38 (mean)	None
Noguchi (2013)	19	T1	RITA	37～82	Liver (1)
Imoto (2013)	20	T1	LeVeen	3～45	None
Total	154			2～82	(2)

(*IBTR, ipsilateral breast tumor recurrence)

どれも小規模な研究である。対象の腫瘍径や電極針もさまざまである。さらに，HE染色，NADH diaphorase染色など完全焼灼の判定もさまざまである。282例の検討では焼灼率が64%から100%であり，主な合併症は皮膚熱傷（4%）であった。仮にT1乳癌を対象とした報告のみを集計すると，焼灼率は177例中152例の86%であった。

2. 乳房切除を伴わないRFA

RFAは究極の非切除による乳癌治療である。よって，切除を行わずにRFAのみで経過観察を試みた報告も存在する（表2）。表1と大きく異なる点は，対象の腫瘍径である。ほとんどがT1以下の症例でありRFAの適応基準に合致している。その結果，154例について観察期間は2ヵ月から82ヵ月と幅があるものの，乳房内再発はわずか1例（0.6%）であった。筆者らは20例の検討を行った。その中で，MRIによるRFA後の経過観察が有用であることを報告した[5]。切除を伴うRFAの経験から，MRIによるほぼ無信号な焼灼範囲はRFA後の組織で認められたうっ血した境界（red ring formation）と一致していることが示唆された（図2）。乳癌低侵襲治療研究会では切除を伴わない乳癌RFAの症例について後向き解析を行った[6]。その結果，10施設から497例が集計された。平均腫瘍径は1.6cmでT1乳癌が425例（86%）であった。RFA後の観察期間の中央値は50ヵ月であったが，T1乳癌とT2以上乳癌の5年乳房内非再発率は96%と80%であった。以上から，EICを伴わないT1乳癌であれば，RFAが乳房部分切除の代替治療として容認される可能性は高い。

Ⅳ. 乳癌非切除治療に関する臨床試験

筆者らはCool-tip型の電極針とRF generatorを用いて，切除を伴わない乳癌RFAの多施設共同第Ⅱ相試験を行っている（図3）。対象はEICを含めて2cm以下の0期またはⅠA期乳癌である。Primary endpointは病理学的な完全焼灼率である。RFA後4週目に組織生検を行い，完全焼灼の有無について中央判定を行う。病理学的にも画像診断上も癌の遺残がなければ乳房照射と悪性度に応じた薬物療法を施行し10年間の経過観察を行う。試験は2 step designで検定され，最初の9例が登録された時点で中間解析を行い，試験の継続の有無を決定する。最終的な目標症例数は32例である。

米国ではAmerican College of Surgeons Oncology Group（ACOSOG）Z1072試験が実施された。これは切除を伴う乳癌の凍結治療（cryoablation）に関する第Ⅱ相試験でprimary endpointはRFA同様にcomplete tumor ablationである。99例の登録は本年5月で終了し，現在解析作業とのことである（主研究者であるDuke臨床研究所のDavid. M. Ota教授より私信にて）。

ま　と　め

乳癌におけるRFAあるいはcryoablationはその対象が限定される。以前，筆者がMDアンダーソンがんセンターを訪問した際に，乳腺外科の准教授から小さな腫瘍にRFAをしなくても小さな傷で切除できるのであるから馬鹿馬鹿しいと言われた。確かにその通りである。しかし，RFAはエコーガイド下の組織生検に馴れ

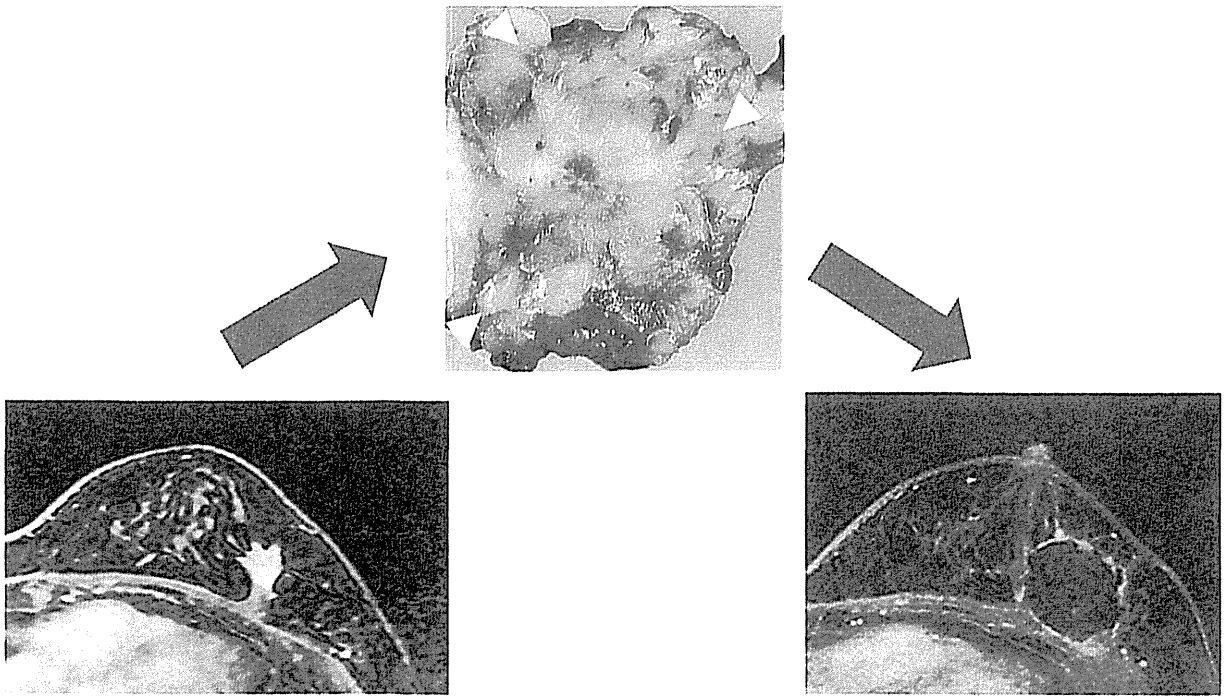


図　2　焼灼による red ring formation（矢尻）と MRI 上の焼灼領域との関係

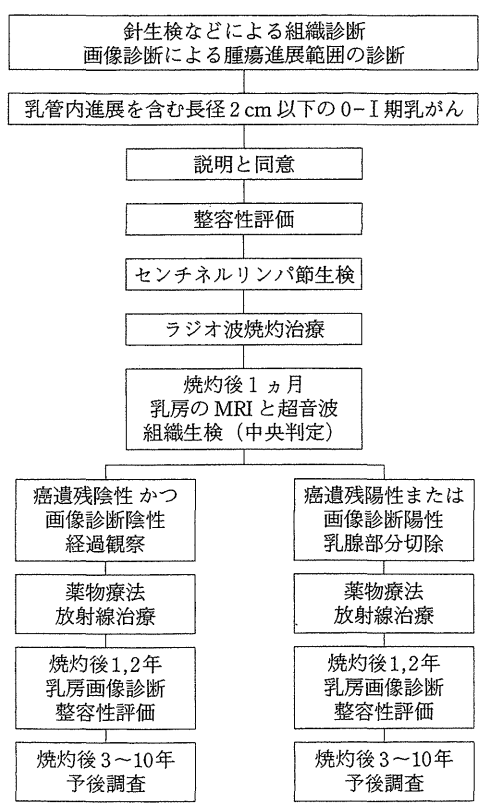


図　3　広範な乳管内進展を伴わない0-Ⅰ期乳がんに対するラジオ波焼灼治療の安全性と有効性に関する第Ⅱ相臨床試験

た外科医あるいは画像診断医であれば，乳房にメスを入れずに行うことができる究極の低侵襲治療である。彼の批判に答えるには，第Ⅲ相試験が必要である。残念ながら，乳房部分切除と比較する第Ⅲ相試験は非現実的である。理由は，対象が全乳癌の数%でかつ予後良好な症例を選別することになるからである。対象は EIC が限局していることから乳房温存療法を施行した場合の乳房内再発率は極めて低いことが予想される。以上から，endpoint の設定にも寄るが，RFA と乳房部分切除の治療効果に関する非劣性を検証する場合，少なくとも千例以上の症例登録が見込まれる。もし千例を 4 年で集積し，かつ適格条件を満たす症例が全乳癌の 5 %と仮定すると，年間 5 千例の乳癌手術を行う施設数が必要である。しかし，同意取得率が半数ならば 1 万例の乳癌手術を行う施設数を要する。そして 5 年以上の経過観察である。では，RFA は乳癌治療としての将来を諦めるべきか？　ACOSOG が cryoablation の試験を行っているように非切除治療への関心は世界的に高まりつつある。現在，国立がん研究センター中央病院が中心となり先進医療における乳癌 RFA の試験が計画されている。少なくともレベル 3 のエビデンスに相当する前向き研究は必須であるが，将来的には RFA が保険診療として，あるいは医療の国際化と規制緩和の潮流を受けて混合診療として行われる日が来ることを期待する。

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CASE REPORT

Rectoseminal vesicle fistula as a rare complication after low anterior resection: a report of three cases

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Abstract A rectoseminal vesicle fistula is a rare complication after a low anterior resection for rectal cancer, usually developing in the outpatient postoperative period with pneumaturia, fever, scrotal swelling or testicular pain. A diagnostic water-soluble contrast enema, cystography and computed tomography reveal a tract from the rectum to the seminal vesicle. Anastomotic leakage is thought to be partially responsible for the formation of such tracts. This report presents three cases of rectoseminal vesicle fistula, and the presumed course of the disease and optimal treatment options are discussed.

Keywords Colon fistula · Seminal vesicle · Urinary fistula

Introduction

The complications of end-to-end anastomosis for lower rectal cancer include anastomotic leakage, rectovaginal fistula, intrapelvic abscess and stenosis. A rectoseminal vesicle fistula is rare. Three patients developed rectoseminal vesicle fistula and were treated over a period of 19 years. This report reviews and summarizes similar previously reported cases, while focusing on the presumed course of the disease, diagnostic procedures and treatment options.

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Patient 1

A 73-year-old male was admitted to the surgical department for treatment of rectal cancer 7 cm from the anal verge. Colonoscopy revealed a type 2 tumor of the rectum and the histopathological examination of a specimen obtained by colonoscopy revealed adenocarcinoma. Laboratory tests were normal. The preoperative staging was T3N0M0. The patient did not receive any neoadjuvant therapy.

A low anterior resection was performed with an end-to-end anastomosis. Microscopic examination of the specimen revealed well-differentiated adenocarcinoma of the rectum with adequate resection margins and no metastases in the 12 resected lymph nodes. This was a T3N0M0 tumor, according to World Health Organization (WHO) classification.

The immediate postoperative course was uneventful. The discharge from the intrapelvic drain was noted to be purulent on postoperative day 7. A water-soluble contrast enema demonstrated minor anastomotic leakage on day 14. The patient was treated conservatively with intrapelvic drainage and antibiotics. Oral diet was resumed on postoperative day 24 and the patient was discharged on day 29. He was readmitted on postoperative day 37 with acute left testicular pain, fever and pneumaturia. A vasogram followed by fistulography demonstrated a fistula from the seminal vesicle to the rectum via the anastomotic site (Fig. 1).

Computed tomography revealed air bubbles located between the rectum and seminal vesicle. Anastomotic leakage followed by coloseminal vesicle fistula after low anterior resection was diagnosed. The leakage was locally restricted, without any sign of generalized peritonitis, and was successfully treated using only urethral catheterization

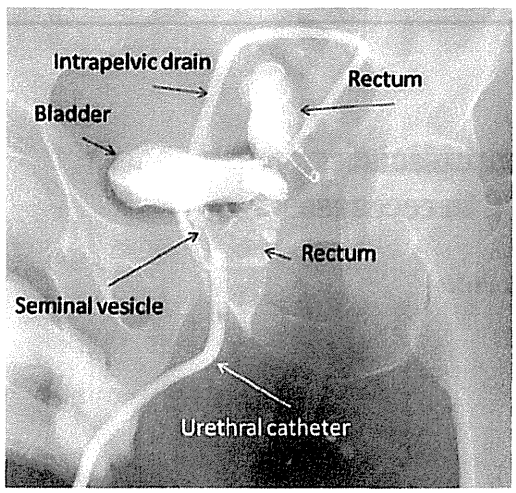

Fig. 1 A vasogram followed by fistelography demonstrating fistula from the seminal vesicle to the rectum via the anastomotic site. 136 × 128 mm (150 × 150 DPI)

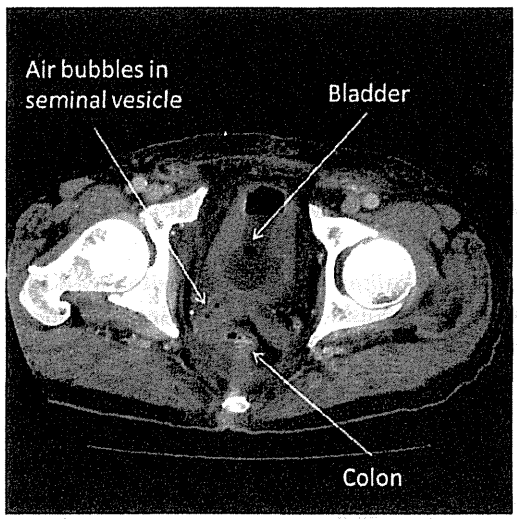

Fig. 2 CT showing air bubbles in and around the seminal vesicle. This slice is 1 cm above the anastomotic site. 125 × 125 mm (150 × 150 DPI)

and antibiotics with oral diet. The fistula had successfully healed by postoperative day 62, or 25 days after readmission.

Distant metastases were found 17 months after the first operation. The patient underwent partial hepatectomy and pulmonary resection for metastases from rectal cancer. He is doing well without local recurrence at 4 years after the first operation.

Patient 2

A 76-year-old male was admitted to the surgical department for treatment of rectal cancer 7 cm from the anal verge. Colonoscopy revealed a type 2 tumor of the rectum and the histopathological examination of a colonoscopic specimen led to a diagnosis of adenocarcinoma. Laboratory tests yielded normal results. The preoperative stage was T3N1M0. The patient's medical history included diabetes mellitus, hypertension, angina pectoris and pulmonary hypertension. The patient did not receive any neoadjuvant therapy.

A low anterior resection was performed with end-to-end anastomosis. A microscopic examination of the specimen revealed moderately differentiated adenocarcinoma of the rectum with adequate resection margins and lymph node metastasis in one of the 12 resected nodes. This was a T3N1M0 tumor.

The patient accidentally removed the urethral catheter while the balloon was still inflated on postoperative day 7. No apparent damage was observed in the urethra at that time. He was discharged on postoperative day 11. He presented to the emergency department 1 month after first discharge with acute testicular pain, pneumaturia and a swollen scrotum. A water-soluble contrast enema demonstrated a fistula between the anastomotic site and a seminal vesicle. CT revealed air bubbles around the seminal vesicle and a series of abscesses from the seminal vesicle to the scrotum (Fig. 2). Conservative therapy with antibiotics and urethral catheterization was attempted which failed, so diverting transverse colostomy was performed on postoperative day 50 (day 39 after readmission). Healing of the fistula was confirmed at another hospital and stoma closure was eventually performed, about 14 months after the first operation.

The patient was treated for pulmonary metastases with oral tegafur-uracil. He has survived 3 years and 10 months since the first operation without local recurrence.

Patient 3

A 49-year-old male was admitted to the surgical department for treatment of a huge rectal cancer. Colonoscopy revealed a type 3 tumor of the rectum and a histopathological examination led to a diagnosis of adenocarcinoma. Computed tomography (CT) and magnetic resonance imaging demonstrated the tumor and adjacent abscess forming a mass 10 cm in diameter, with infiltration into the right seminal vesicle. The C-reactive protein level was elevated to 7.1 mg/dl. Pelvic incisional drainage was performed prior to the radical operation. Preoperative staging was T4N2M0.

A low anterior resection of the tumor with the bilateral seminal vesicles and diverting ileostomy were performed with end-to-end anastomosis. A microscopic examination of the specimen revealed moderately differentiated

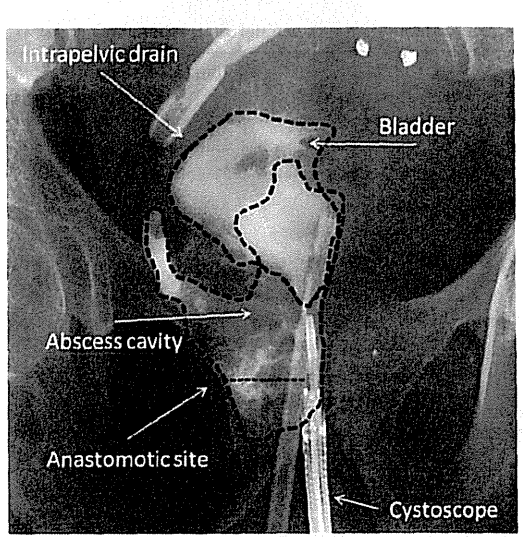

Fig. 3 A vasogram under cystoscope control demonstrates fistula from the ejaculatory duct to the anastomotic site via an abscess cavity. 137 × 137 mm (150 × 150 DPI)

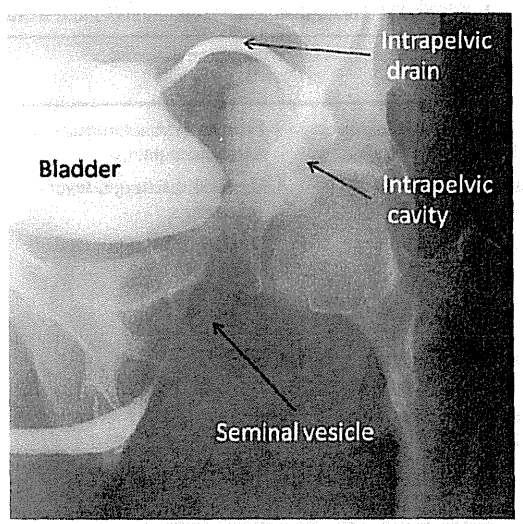

Fig. 4 Retrograde cystourethrography shows fistulous communication between the seminal vesicle and intrapelvic cavity. This represents seminal vesicle fistula after concomitant resection of rectum and seminal vesicle. 125 × 125 mm (150 × 150 DPI)

adenocarcinoma of the rectum with adequate resection margins and no metastases in any of the 44 resected lymph nodes. This was a T3N0M0 tumor.

The patient displayed fever and fecaluria on postoperative day 10. CT revealed anastomotic leakage surrounded by a cavity filled with pus and an increased air–water level. A vasogram under cystoscopic control demonstrated a fistula from the ejaculatory duct to the anastomotic site via an abscess cavity (Fig. 3). He was diagnosed with anastomotic leakage followed by creation of a fistula between the anastomotic site and the excision site of the seminal vesicles. The patient was effectively treated using lavage from an intrapelvic drainage tube and urethral catheterization with a saline flush. The abscess cavity gradually contracted and disappeared, but the fistula remained refractory. Gracilis muscle flap closure was attempted but proved unsuccessful. Additional abdominal rectus muscle flap closure achieved an improvement of the fistula.

The patient finally underwent total pelvic exenteration for intrapelvic recurrence along with intention to treat urinary division after 2 years and 6 months. He has survived 3 years since the first operation.

Discussion

Abscess formation around the seminal vesicle is infrequently encountered in patients without apparent anastomotic leakage that have undergone concomitant resection of the rectum and seminal vesicle (Fig. 4). The usual clinical course is cloudy discharge from the pelvic drain, fever, and relatively normal results of laboratory tests, other organ function and general status. A water enema of the anastomotic site subsequently reveals no leakage. Cutting off the root of the seminal vesicle without ligation causes a seminal vesicle fistula and local collection of pus. Simply leaving the fistula open may be adequate as long as the fever is controlled by antibiotics. The patient usually recovers from the fistula within several weeks. The prophylactic approach includes a ligation of the base of the resected seminal vesicle.

This report presented three cases of rectoseminal vesicle fistula after low anterior resection. Low anterior resection has been performed at this institution since 1992, with more than 1100 patients treated. Three patients developed rectoseminal vesicle fistula and were treated over a 19 years period. Coloseminal vesicle fistula is particularly uncommon. The causes or origin of such fistulae include inflammatory bowel disease, low anterior resection, prostatectomy, radiation proctitis, and sigmoid colon diverticula [1–3]. Only 10 cases of seminal vesicle fistula were found among the reported postsurgical intervention cases [3–9] (Table 1).

Minor leakage was demonstrated on postoperative day 14 in the first case, and was conservatively treated using only a drainage tube. Mild residual inflammation might have adversely influenced the fragile seminal vesicle wall. Outpatient follow-up on postoperative day 37 revealed a fistula to the seminal vesicle. Denonvilliers' fascia, which is located between the rectal anterior wall and the seminal vesicle beneath the level of the peritoneal reflection, may be removed when performing total mesorectum excision [10]. Denonvilliers' fascia is a very strong tissue that divides the urinary tract and rectum. Infectious material