Surgery in Practice and Science 17 (2024) 100239

Contents lists available at ScienceDirect

Surgery in Practice and Science

journal homepage: www.sciencedirect.com/journal/surgery-in-practice-and-science

Research Article

Receptor discordance after nipple-sparing mastectomy

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ARTICLE INFO

Keywords:
Breast cancer
Nipple-sparing mastectomy
Local recurrence
Subtype
Nipple–areolar recurrence

ABSTRACT

Background: Recent studies have shown that receptor status of breast cancer change between primary tumor and recurrence, which may influence treatment strategy and prognosis, but there are few reports on receptor discordance between primary tumors and local recurrence (LR) after nipple-sparing mastectomy (NSM).
Patients and methods: We collected 74 patients who had LR after NSM for newly diagnosed stages 0 to 3 breast cancer between 2008 and 2016 at 14 institutions. We classified into 4 subtypes based on hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2). We evaluated clinicopathological factors that correlate with receptor discordance and assessed the impact of receptor discordance on survival.
Results: Discordance rates in estrogen receptor (ER), progesterone receptor (PgR) and HER2 were 9.5, 10.8 and 5.4 %, respectively. The most common change was from HR-/HER2+ to HR+/HER2+, and this pattern of receptor change occurred only in patients with nipple–areolar recurrence. Non-invasive tumors in LR, nipple–areolar recurrence (NAR), HR-/HER2+ primary tumor subtype, and the presence of chemotherapy for primary tumors were significantly associated with receptor discordance. With a median follow-up of 44.5 months (4–153 months), patients in the receptor-discordant group had no disease-free survival (DFS) event after LR resection (5-year DFS; 100 % in the receptor-discordant group vs 85.1 % in the receptor-concordant group; $p = 0.2$).
Conclusion: Our study demonstrates that the presence of chemotherapy for primary tumors, nipple-areolar recurrence, and its related factors (non-invasive tumor in LR, HR-/HER2+ primary tumor subtype) were associated with receptor discordance. However, further studies with longer follow-up periods and larger sample sizes are needed.

Introduction

Change in estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) status between primary tumor and recurrence has been reported frequently in breast cancer [1–3]. Many reports compare ER, PgR, and HER2 status of

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https://doi.org/10.1016/j.sipas.2024.100239
Received 28 February 2024; Accepted 29 February 2024
Available online 5 March 2024

primary tumor with those of distant or regional recurrence, and receptor discordance rates vary widely in the studies. Some believe that receptor changes are the result of the emergence of more aggressive molecular types due to tumor heterogeneity and clonal selection [1,4,5], but receptor changes have also been associated with technical problems, such as poor reproducibility of immunohistochemical techniques [6]. However, there are some points that cannot be explained by technical issues only. It is widely known that there are differences in discordance rates among receptors [1–3] and that changes from positive to negative (receptor loss) are observed more frequently than changes from negative to positive (receptor gain) [1,3,5]. It is difficult to consider that these occurred by chance due to technical problems [1]. In clinical practice, receptor changes lead to coordination of adjuvant therapy, and recent international guidelines recommend biopsy or resection of recurrent disease, if possible, and reevaluate ER, PgR, and HER2 status to determine the treatment plan [5,7]. Local recurrences (LR) can be sampled more easily than distant recurrences, but the receptor status of LR may not be closely examined because the prognostic impact of LR may be considered more limited than that of distant recurrences.

Nipple-sparing mastectomy (NSM) is a surgical technique that preserves the nipple areola and breast skin during mastectomy and has been increasing in recent years in combination with immediate breast reconstruction as a better cosmetic technique. The major difference between NSM and procedures such as conventional mastectomy and skin-sparing mastectomy is that normal breast tissue is preserved in the nipple-areola complex. We previously conducted a multicenter retrospective analysis categorizing LR after NSM into two groups, nipple-areolar recurrence (NAR) and other local recurrence (oLR), based on their recurrence sites. Our findings demonstrated that NAR showed quite different features from oLR, such as the characteristics of the primary and recurrent tumors and the prognostic factors after LR resection [8]. In this study, we examined the receptor discordance rates, the association of the receptor discordance with clinicopathological factors, and its prognostic impact.

Materials and methods

We previously collected patient data with LR after NSM from 14 institutions in Japan between 2008 and 2016 and studied the clinicopathological characteristics of LR according to the locations of LR (NAR or oLR) [8]. The inclusion criteria were patients who underwent NSM and axillary surgery (sentinel lymph node biopsy only was allowed if these nodes had no metastases) for newly diagnosed stages 0 to 3 breast cancer between 2008 and 2016, had LR as a first recurrence and were resected for definitive diagnosis. NSM was performed at the discretion of each physician at each institution, without limitation based on tumor diameter, tumor-to-nipple distance, or other factors. LR was defined as any epithelial breast cancer or ductal carcinoma in situ in the ipsilateral breast or the skin and subcutaneous tissue on the ipsilateral thoracic wall [9]. The study excluded patients with unresected LR, first recurrence that was not LR, and synchronous metastasis (metastasis occurring within 3 months of LR diagnosis). 99 patients were collected from 14 institutions in Japan, and finally 74 cases in which both the receptor of the primary tumor and LR were known were included in this analysis.

Pathological evaluation

Pathological evaluation was performed at the pathology department of each institution, and ER, PgR, and HER2 of the primary tumor and LR were evaluated. ER and PgR were determined by immunohistochemistry (IHC), and tumor cells with >1 % positive staining were classified as positive. HER2 was classified as positive if the IHC diagnosis was 3+ (>10 % of tumor cells had strong, complete and circumferential membrane staining) or if the HER2/CEP ratio was ≥2.0 by fluorescence in situ hybridization (ISH). For both primary and recurrent tumors, receptors status were assessed according to the invasive component in invasive cancer specimens and the intraductal component in ductal carcinoma in situ specimens.

Definition of receptor change and subtype

Receptor status in which either or both ER and PgR are positive (ER+/PgR+, ER+/PgR-, ER-/PgR+) was defined as hormone receptor positive (HR+) and status in which both ER and PgR are negative (ER-/PgR-) as HR negative (HR-). Subtypes were classified into four based on HR and HER2 status (HR+/HER2-, HR+/HER2+, HR-/HER2+, HR-/HER2-). Cases in which both HR and HER2 matched were defined as receptor-concordant group, and cases in which HR and/or HER2 were mismatched were defined as receptor-discordant group.

Statistical analysis

The clinical and pathologic factors were compared using Mann-Whitney's U test and Fisher's exact test. Disease-free survival (DFS) was defined as the time from the definitive surgery for LR to any recurrence (LR, regional, or distant), death or the date of last contact, calculated by the Kaplan-Meier method and compared by the log-rank test. All statistical analysis was performed using EZR (ver. 2.8.2) [10], and a p value < 0.05 was considered statistically significant.

Results

In this study, 74 patients with LR after NSM and known ER, PgR, and HER2 status of both the primary tumor and LR were examined. The clinicopathologic characteristics of the 74 patients are shown in Table 1. Primary tumor subtype was HR+/HER2- in 58 patients, HR+/HER2+ in 6 patients, HR-/HER2+ in 8 patients, and HR-/HER2- in 2 patients. Of the 74 patients, 12 (16.2 %) changed receptor status and 62 (83.8 %) didn't. Discordance rates in HR, ER, PgR and HER2 were 10.8, 9.5, 10.8 and 5.4 %, respectively. According to primary tumor subtype, the receptor discordance rate was highest in patients with HR-/HER2+ primary tumor (62.5 %) and the most common changes were from HR-/HER2+ to HR+/HER2+ (Table 2, 3). Furthermore, this pattern of receptor change occurred only in patients with NAR. (Table 3). When the receptor-discordant cases were divided according to the location of LR (NAR vs oLR), the receptor change rate from HR-/HER2+ to HR+/HER2+ was 83.3 % (5 of 6 cases) in NAR and 0 % (0 of 6 cases) in oLR.

Patient characteristics according to the receptor change are shown in Table 1. Factors associated with receptor discordance were the presence or absence of LR invasion (non-invasive tumor), the location of LR (NAR), primary tumor subtype (HR-/HER2+), and (neo)adjuvant chemotherapy for primary tumor (yes).

During the median follow-up period of 44.5 months (4–153 months) after LR resection, 9 patients (12.2 %) had a DFS event. The median time from LR as the first event to a second recurrence was 17.5 months (range,14–40 months). The receptor-discordant group tended to have a better prognosis than the receptor-concordant group although there was no significant difference in DFS after LR resection between the receptor-concordant and discordant groups (5-year DFS, 85.1 % vs 100 %; $p = 0.2$, Fig. 1).

Discussion

Most reports of the receptor discordance in breast cancer compare primary tumors with mixed sites of recurrent tumors (local, regional and distant), and the receptor discordance rates varied largely between studies. Aurilio et al. performed a meta-analysis and evaluated receptor change in 4200, 2739, and 2987 tumors for ER, PgR, and HER2, respectively. They reported receptor discordance rate in ER, PgR and HER2 were 20 %, 33 % and 8 %, respectively [1]. There are few reports of receptor discordance limited to LR after NSM. The receptor discordance rates in our study (ER: 9.5 %, PgR: 10.8 %, HER2: 5.4 %) were

Table 1
Patient characteristics according to receptor change.

Variables		Total (n = 74)	Receptor- concordant (n = 62)		Receptor- discordant (n = 12)		p value
		n	n	%	n	%	
Age at primary surgery (years)	Median	42	42		45		0.5
	(range)	(28–71)	(28–71)		(34–58)		
	<40	24	19	79.2	5	20.8	0.5
	≥40	50	43	86.0	7	14.0	
Pathological T stage (primary)	Tis	10	7	70.0	3	30.0	0.6
	T1	45	39	86.7	6	13.3	
	T2	14	12	85.7	2	14.3	
	T3	4	3	75.0	1	25.0	
	Unknown	1	1	100	0	0	
Invasiveness (primary)	Noninvasive	9	7	77.8	2	22.2	0.7
	Invasive	64	54	84.4	10	15.6	
	Unknown	1	1	100	0	0	
Pathological N status (primary)	N0	53	45	84.9	8	15.1	0.8
	N+	20	16	80.0	4	20.0	
	Unknown	1	1	100	0	0	
Lymphovascular invasion (primary)	Positive	25	21	84.0	4	16.0	1
	Negative	48	40	83.3	8	16.7	
	Unknown	1	1	100	0	0	
ER (primary)	Positive	63	57	90.5	6	9.5	0.002
	Negative	11	5	45.5	6	54.5	
PgR (primary)	Positive	58	51	87.9	7	12.1	0.1
	Negative	16	11	68.8	5	31.3	
HER2 (primary)	Positive	14	7	50.0	7	50.0	< 0.001
	Negative	60	55	91.7	5	8.3	
HR/HER2 (primary)	HR-/HER2-	2	2	100	0	0	0.002
	HR-/HER2+	8	3	37.5	5	62.5	
	HR+/HER2-	58	53	91.4	5	8.6	
	HR+/HER2+	6	4	66.7	2	33.3	
(Neo) adjuvant endcrine therapy (primary)[a]	Yes	50	46	92.0	4	8.0	1
	No	4	4	100	0	0	
(Neo) adjuvant chemotherapy (primary)	Yes	28	19	67.9	9	32.1	0.007
	No	46	43	93.5	3	6.5	
(Neo) adjuvant trastuzumab (primary)[b]	Yes	7	3	42.9	4	57.1	1
	No	2	1	50.0	1	50.0	
Postmastectomy radiotherapy (primary)	Yes	0	0	0	0	0	1
	No	72	60	83.3	12	16.7	
	Unknown	2	2	100	0	0	
Nipple margin status (primary)	Positive	2	2	100	0	0	1
	Negative	72	60	83.3	12	16.7	
Anterior, posterior, or lateral margin status (primary) [c]	Positive	11	9	81.8	2	18.2	1
	Negative	63	53	84.1	10	15.9	
Time to recurrence, mo	Median	38	36		42.5		0.2
	(range)	(2–136)	(2–110)		(6–136)		
	36 or less	35	32	91.4	3	8.6	0.1
	More than 36	39	30	76.9	9	23.1	
Age at diagnosis of LR (years)	Median	46	45		50		0.2
	(range)	(29–72)	(29–72)		(39–61)		
	45 or less	36	32	88.9	4	11.1	0.3
	More than 45	38	30	78.9	8	21.1	
Invasiveness (LR)	Noninvasive	6	3	50.0	3	50.0	0.03
	Invasive	65	57	87.7	8	12.3	
	Unknown	3	2	66.7	1	33.3	
Change of invasiveness	Yes	7	4	57.1	3	42.9	0.07
	No	64	56	87.5	8	12.5	
	Unknown	3	2	66.7	1	33.3	
Location of local recurrence	NAR	14	8	57.1	6	42.9	0.008
	oLR	60	54	90.0	6	10.0	

ER: estrogen receptor, PgR: progesterone receptor, HER2: human epidermal growth factor receptor 2, LR: local recurrence.
[A] Including only patients with ER-positive invasive tumors.
[B] Including only patients with HER2-positive invasive tumors.
[C] Positive was defined as any of the anterior, posterior, or lateral resection margins were positive. Negative was defined as when all anterior, posterior, and lateral resection margins were negative.

lower than previously reported discordance rates for distant or regional recurrences. Idirisinghe et al. compared the receptor discordance rate between LR and distant recurrence and reported that receptor discordance rate in LR was lower than that in distant recurrence [11]. LR may contain primary tumors that could not be completely resected, and they are likely to have the same receptor expression as the primary tumor. In contrast, distant or regional recurrences may occur from tumor clones that have grown distant from the primary tumor and have acquired receptor change with the acquisition of tumor progression mechanisms.

In previous reports, the receptor loss is more common than receptor gain [1,5,6], and the primary tumor subtype with the highest receptor discordance rate has been reported as HR+/HER2+ [2]. However, the

Table 2
Receptor change between primary tumor and LR.

		LR				Receptor discordance rate (%)
		HR+/ HER2-	HR+/ HER2+	HR-/ HER2+	HR-/ HER2-	
Primary	HR+/ HER2-	53	2	0	3	8.6
	HR+/ HER2+	2	4	0	0	33.3
	HR-/ HER2+	0	5	3	0	62.5
	HR-/ HER2-	0	0	0	2	0

LR: local recurrence, HR: hormone receptor, HER2: human epidermal growth factor receptor 2. HR+: either or both estrogen receptor (ER) and progesterone receptor (PgR) are positive (ER+/PgR+, ER+/PgR-, ER-/PgR+), HR-: both ER and PgR are negative (ER-/PgR-).

primary tumor subtype with the highest receptor discordance rate in this study was HR-/HER2+ (62.5 %, 5 of 8 cases) (Table1), and the most common receptor change was HR-/HER2+ to HR+/HER2+, and this pattern of receptor change occurred only in patients with NAR. (Table 2). When the receptor-discordant cases were divided according to the location of LR (NAR vs oLR), there were no consistent tendencies of the receptor change pattern among oLR, but among NAR, the receptor change from HR-/HER2+ to HR+/HER2+ were more frequently seen (0 % vs 83.3 %). Wu et al. and Shimo et al. reported on the paired status of subtype between primary tumor and NAR among 39 and 10 patients, respectively. However, in both reports, there was no cases with the receptor change from HR-/HER2+ to HR+/HER2+ and no specific tendencies in the receptor changes [12,13]. Previous studies reported that the HR-/HER2+ subtype in primary tumors is the risk factor for NAR after NSM [13,14]. We need more cases to determine which subtype tends to change from HR-/HER2+.

In this study, receptor-discordant group had no DFS event after definitive surgery for LR, although there was no significant difference in DFS compared with receptor-concordant group (100% vs 85.1 %, $p = 0.2$) (Fig. 1). Previous studies reported that HR loss was associated with poor prognosis [2,5,15,16] and ER gain was associated with longer progression-free survival [16]. Furthermore, Wu et al. showed that patients with NAR had better prognosis than those with oLR [17]. In this study, NAR was more common in the receptor-discordant group, which may explain the better prognosis in the receptor-discordant group. In addition, 4 patients (33.3 %) (Table 3, No.2–4,6) in the receptor-discordant group changed treatment based on the receptor discordance, and it is possible that treatment changes based on receptor discordance may have affected prognosis.

The current study had some limitations. First, a central pathology review was not performed, so receptor status of some patients was misclassified. Second, the sample size was relatively small. This made it impossible to analyze in-situ recurrences and invasive recurrences separately, limiting the generalisability of our study's findings. However, despite the small number of patients, to our knowledge, the current study represents one of the largest series in the literature to date. The third limitation was the high frequency of missing data regarding receptor status, mostly arising from patients with noninvasive carcinoma. Patients with noninvasive carcinoma in primary tumors or LR often omit adjuvant therapy and therefore do not often undergo evaluation of receptor status. Fourth, the follow-up period after definitive surgery for LR was relatively short (median, 44.5 months). The possibility that differences in prognosis are being overlooked due to the short observation period cannot be denied. Fifth, the analysis in this study was limited to cases of isolated, resected local recurrence and did not include cases of regional or distant recurrence.

Conclusion

The most common change in NAR was from HR-/HER2+ to HR+/HER2+. The presence of chemotherapy for primary tumor, NAR, noninvasive tumor in LR, and HR-/HER2+ primary tumor subtype were the factors associated with receptor discordance in LR after NSM. There was no difference in prognosis with receptor changes. These may be due to the fact that NAR includes recurrence from residual mammary tissue (new primary).

Author contribution

MI conceived the idea of the study. RK and MI developed the statistical analysis plan, conducted statistical analyses, contributed to the interpretation of the results and drafted the original manuscript. All authors reviewed the manuscript draft and revised it critically on intellectual content. All authors approved the final version of the manuscript to be published.

CRediT authorship contribution statement

Rena Kojima: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Makoto Ishitobi:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Naomi Nagura:** Data curation, Writing – review & editing. **Ayaka Shimo:** Data curation, Writing – review & editing. **Hirohito Seki:** Data curation, Writing – review & editing. **Akiko Ogiya:** Data curation, Writing – review & editing. **Teruhisa Sakurai:** Data curation, Writing – review & editing. **Yukiko Seto:** Data curation, Writing – review &

Table 3
Cases of receptor changes.

	Primary				LR				
No.	Invasiveness	HR	HER2	(Neo)adjuvant therapy	Invasiveness	HR	HER2	Location	Adjuvant therapy
1	Invasive	–	+	–	Unknown	+	+	NAR	–
2	Invasive	+	–	ET	Invasive	–	–	oLR	CT, ET
3	Invasive	–	+	CT, TZB	Invasive	+	+	NAR	ET
4	Invasive	–	+	CT, TZB	Noninvasive	+	+	NAR	ET
5	Invasive	–	+	CT, TZB, ET	Invasive	+	+	NAR	CT, TZB, ET
6	Invasive	–	+	CT, TZB	Invasive	+	+	NAR	ET
7	Invasive	+	+	CT, TZB, ET	Invasive	+	–	oLR	ET
8	Invasive	+	–	CT, ET	Invasive	+	+	oLR	ET
9	Invasive	+	–	CT, ET	Invasive	+	+	oLR	ET
10	Noninvasive	+	+	–	Noninvasive	+	–	NAR	–
11	Invasive	+	–	CT, ET	Noninvasive	–	–	oLR	ET
12	Invasive	+	–	CT	Invasive	–	–	oLR	–

LR: local recurrence, HR: hormone receptor, HER2: human epidermal growth factor receptor 2, CT: chemotherapy, ET: endocrine therapy, TZB: Trastuzumab, NAR: nipple–areolar recurrence, oLR: other local recurrence.

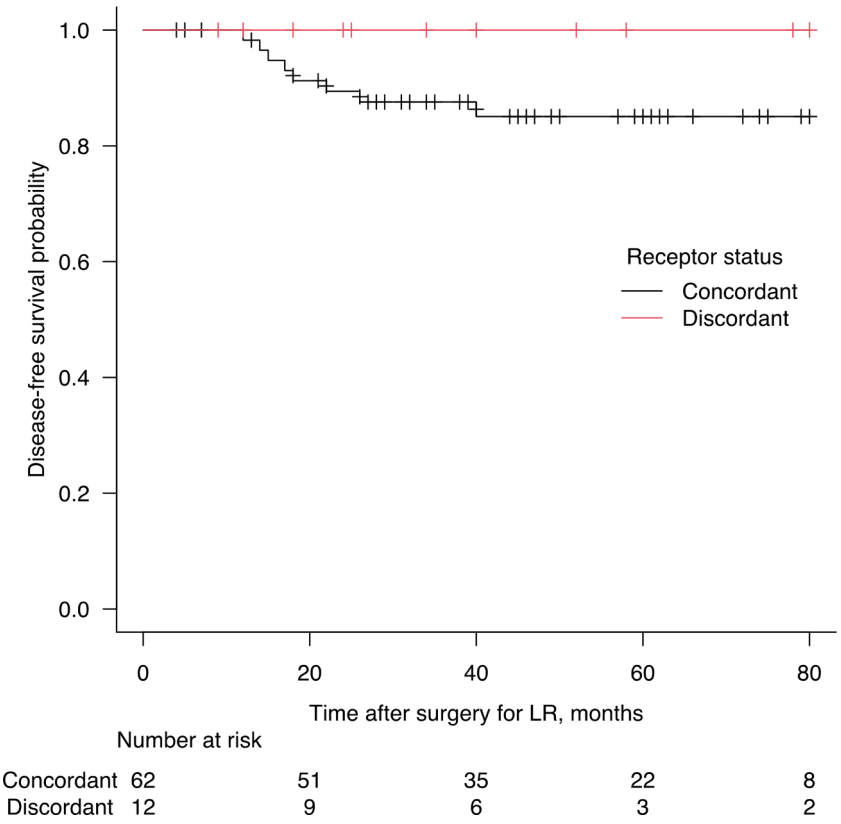

Fig. 1. Disease-free survival curve according to receptor change.
LR: local recurrence.

editing. **Shinsuke Sasada:** Data curation, Writing – review & editing. **Chiya Oshiro:** Data curation, Writing – review & editing. **Michiko Kato:** Data curation, Writing – review & editing. **Takahiko Kawate:** Data curation, Writing – review & editing. **Naoto Kondo:** Data curation, Writing – review & editing. **Tadahiko Shien:** Data curation, Writing – review & editing.

Declaration of competing interest

Tadahiko Shien has received honoraria from Daiichi Sankyo, Chugai, and Lilly. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study was supported in part by grants-in-aid for scientific research from the Japan Oncoplastic Breast Surgery Society (grant no., 2021). The funding source had no involvement in the study design; the collection, analysis, or interpretation of data; the writing of the report; or the decision to submit the article for publication.

We thank Amanda Holland, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

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