by Cohen's kappa coefficient, it showed moderate agreement ($\kappa = 0.481$), indicating that they might have relatively similar statistical power for predicting prognosis. However, a significant correlation between the expression of ALDH1 and the DFS was found only in the ALNM (odds ratio 3.79, 95% CI 1.37–12.1), which suggests that evaluation of ALDH1 in the ALNM is more likely to be useful for predicting prognosis in breast cancer patients with ALNM compared to primary tumors.

This study is relatively small and, therefore, some true but weaker prognostic variables may not have been detected as significant in this analysis. Also, protein levels from old samples might not represent the actual biological processes. Nevertheless we believe our findings are generalizable and are consistent with prognostic results observed in separate patients in previous publications [7, 25].

Thus, the results of this study indicate that evaluation of biomarker expression in the ALNM may have clinical significance in terms of prognosis for breast cancer patients with ALNM ($n = 1$–3). We need to conduct a prospective study with a larger sample size to confirm the value and methods of evaluation of biomarker expression in ALNM.

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TOPIC HIGHLIGHT

WJCO 5th Anniversary Special Issues (2): Breast cancer

Resection of the primary tumor in stage Ⅳ breast cancer

Tadahiko Shien, Hiroyoshi Doihara

Tadahiko Shien, Hiroyoshi Doihara, Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, 7008558 Okayama, Japan
Author contributions: Doihara H contributed to this paper; Shien T designed and wrote the introductory editorial for the Highlight Topic: "Resection of the primary tumor in stage Ⅳ breast cancer".
Correspondence to: Tadahiko Shien, MD, PhD, Department of Breast and Endocrine Surgery, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, 7008558 Okayama, Japan. tshien@md.okayama-u.ac.jp
Telephone: +81-86-2357265 Fax: +81-86-2357265
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Abstract

Stage Ⅳ breast cancer refers to breast cancer that has already metastasized to distant regions when initially diagnosed. Treatment for stage Ⅳ is intended to "prolong survival and palliate symptoms". Resection of a primary tumor is considered to be "effective only at alleviating chest symptoms and providing local control" in spite of the advances of imaging examination and medication for breast cancer. Molecular target and endocrine drugs are very effective and useful to tailor-make a treatment strategy according to breast cancer subtypes. Positron emission tomography-computed tomography can detect and diagnose the very small metastases and recurrences which can potentially be cured even if they are distant metastases. Recently, many retrospective studies have reported the survival benefit of surgery for breast cancer patients with metastases and some clinical trials which confirm the surgical prognostic benefit for them have started to enrol patients. The goal of treatment has to be clearly identified: increase the patient's survival time, provide local control or perform histology to determine the cancer's properties. The best evidence is absolutely essential to treat patients who need surgery at the right time. We need to evaluate the treatment strategy, including primary resection for stage Ⅳ breast cancer particularly, and find new evidence by prospective analysis.

Key words: Breast cancer; Metastasis; Surgery; Survival; Stage Ⅳ; Clinical trial

Core tip: Resection of a primary tumor of stage Ⅳ breast cancer was considered to be "effective only at alleviating chest symptoms and providing local control" in spite of the advances of imaging examination and medication for breast cancer. Recently, many retrospective studies have reported the survival benefit of surgery for breast cancer patients with metastases and some clinical trials which confirm the surgical prognostic benefit for them have started to enrol patients. We need to evaluate the treatment strategy, including primary resection for stage Ⅳ breast cancer particularly, and find new evidence by prospective analysis.

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INTRODUCTION

Stage Ⅳ breast cancer refers to breast cancer that has already metastasized to distant regions when initially diagnosed. Even if such cancer were to be treated, complete cure would not be expected. Treatment is intended to "prolong survival and palliate symptoms". Medication has made advances and treatments that are anticipated to be efficacious are administered. This situation has changed little as new drugs are coming out every year. In an increasing number of patients, appropriate use of

those drugs allows long-term control of symptoms and a longer life with disease.

In addition, marked advances in diagnostic imaging equipment have been made. Over the past few years, the prevalence of positron emission tomography-computed tomography has led to the early diagnosis of extremely small metastases that were not previously noted[1]. Stage IV breast cancer with these small metastases is referred to as "minimal stage IV disease[2]" and patients with this more limited form are expected to have a better prognosis than patients with full-blown stage IV breast cancer. Although it has yet to be precisely defined, the concept of "oligometastasis" is being debated[3]. According to this concept, metastases can potentially be cured, even if they are distant metastases, depending on their location and number.

Resection of a primary tumor was previously considered to be "effective only at alleviating chest symptoms and providing local control", but some studies have reported that resection increases survival time[4,5]. Breast-conserving surgery is a widely used form of surgery for breast cancer. Anesthesia has also made advances and is safe. At the current point in time, surgery for breast cancer is extremely simple, depending on tumor size, and minimally invasive. A longer survival time seldom results from drug administration but it can result from surgery. Surgery for stage IV breast cancer is an important topic that may substantially alter future treatment strategies.

SIGNIFICANCE OF RESECTION OF THE PRIMARY TUMOR IN STAGE IV BREAST CANCER: STUDIES REPORTING INCREASED SURVIVAL TIMES AND RELATED ISSUES

As mentioned earlier, a number of recent studies have reported that surgery for stage IV breast cancer affects a patient's survival time. Many of these retrospective studies indicated that surgery prolonged survival time. Several systematic reviews have reported significant differences in survival time (HR of about 0.6)[4,5]. A look at subgroups indicates that factors facilitating surgery include "complete excision of the primary tumor", "metastasis only to bone and/or soft tissue", "few metastases" and "being younger"[6,7]. A study reported differences in the effectiveness of surgery for different subtypes of tumors[8]. However, all of the findings cited were the result of retrospective analysis so they are presumed to be highly biased. "Patients who undergo surgery" are invariably "patients in good enough condition to undergo surgery" while "patients who do not undergo surgery" are possibly "patients who are unable to undergo surgery because of their worsening condition". In addition, medication has not been studied in detail and patients who undergo surgery are likely to include a number of patients whose condition could have been satisfactorily controlled with medication. The timing of surgery is also unclear. There is no clear answer as to whether surgery should be done during initial treatment or whether it should be a final option that is used after medication proves inefficacious.

WHY DOES RESECTION OF ONLY THE PRIMARY TUMOR HELP WHEN CANCER CELLS HAVE SPREAD THROUGHOUT THE BODY?

According to the seed and soil theory by Paget[9], the distant metastasis is not local disease. Cancer cells have already spread to whole body circulation. So, local therapies do not affect overall survival, whereas there are several theories on the basic rationale for resection of the primary tumor increasing the survival time for patients with stage IV breast cancer. The first is a "reduction in total tumor volume". Circulating tumor cells (CTCs) are a major indicator of tumor volume. A reduction in CTCs is reported to be correlated with prognosis[10]. Resection of the primary tumor reduces the tumor volume and thus reactivates autoimmunity and increases the efficacy of medication[11]. A study prospectively demonstrated that resection of the primary tumor is useful when kidney cancer is in stage IV (this is the only other solid tumor besides breast cancer for which this holds true)[12]. According to the study, resection of the primary tumor is a theoretical basis for the effectiveness of surgery.

Another theory as to why resection of the primary tumor increases the survival time concerns the particular action of the primary tumor. "Cancer stem cells" that are prevalent in the primary tumor are resistant to medication[13]. In addition, the concept of "cell seeding" indicates that cells released into the blood by the primary tumor return to the primary tumor, so the primary tumor activates those cancer cells[14]. Both of these mechanisms are based on results of basic experiments and no studies have described results from actual patients. If, however, they are true, then they are sure to be key to devising cancer treatment strategies in the future. These mechanisms should be verified in the future.

LOCAL CONTROL

As mentioned at the very beginning, resection of the primary tumor has been useful in alleviating chest symptoms, such as bleeding and ulceration as well as pain due to invasion of the chest wall. However, no studies or prospective trials have determined whether or not earlier surgery is useful to achieve local control. At the current time, there are absolutely no data corroborating the contention that "earlier surgery is useful since it improves local control, even if it does not increase survival time". When local control alone was envisioned, radiation therapy was considered in addition to surgery. Although sample sizes are small, studies have described an improvement in the prognosis for the primary tumor in stage IV breast cancer as a result of radiation therapy (like the improvement in

Table 1 Ongoing randomized trials testing the worth of local therapy for an intact primary in women with stage Ⅳ breast cancer xvii

Country	Trial number	Accrual period	*n*	Initial therapy	Radiotherapy	Primary endpoint
India	NCT00193778	2005-12	350	Adriamycin-cytoxan	If indicated	Time to progression
Turkey	NCT00557986	2008-12	281	Surgery	For breast conservation	Survival
United States and Canada	NCT01242800	2011-16	368	Appropriate systemic therapy	Per standards for stage Ⅰ-Ⅲ	Survival
Netherlands	NCT01392586	2011-16	516	Surgery	For positive margins or palliation	2-yr survival
Austria	NCT01015625	2010-19	254	Surgery	Per standards for stage Ⅰ-Ⅲ	Survival
Japan	JCOG 1017	2011-16	410	Appropriate systemic therapy	No	Survival

JCOG: Japan Clinical Oncology Group; NCT number: A unique identification code given to each clinical study registered on ClinicalTrials.gov.

prognosis as a result of surgery)[15]. In addition, a study has reported a satisfactory prognosis for asymptomatic rather than symptomatic patients, regardless of whether treatment was administered and regardless of the type of treatment[16]. Results suggest that local control itself may act beneficially on prognosis, irrespective of whether treatment is classified as surgery, radiation, *etc.*

TRIALS CURRENTLY UNDERWAY TO DETERMINE THE USEFULNESS OF RESECTION OF THE PRIMARY TUMOR IN STAGE IV BREAST CANCER

As noted previously, there are absolutely no prospective data at the current time to corroborate the usefulness of resection of the primary tumor in stage Ⅳ breast cancer in terms of increasing survival time or improving local control. At the current time, there is no evidence actively in favor of such a resection. That said, many results of retrospective studies continue to be discussed in various fora. In the absence of robust evidence, this meta-analysis provides an evidence base for primary resection in the setting of stage Ⅳ breast cancer for appropriately selected patients[17]. Resection of the primary tumor could greatly affect breast cancer care so this clinical question needs to be answered in prospective trials. Given this potential, 6 groups are currently enrolling patients[18-20] (Table 1). The first reports of two prospective studies were indicated in the San Antonio Breast Cancer Symposium 2013[21,22]. Both studies did not demonstrate a significant survival benefit of primary surgery. From the Indian trial, the distant disease free survival in the patients with surgery was significantly worse than that of the patients without surgery. One of the reasons was the insufficient systemic chemotherapy after surgery. They did not continue systemic chemotherapy after randomization and appropriate systemic therapies according to breast cancer subtypes were not selected in these protocols. So, the median survival time was shorter than that of retrospective European and American data. In particular, they did not use molecular target therapy for patients with human epidermal growth factor receptor type 2 positive breast cancer. Moreover, the diagnosis of metastasis was uncertain. They only used bone scintigraphy to diagnose a solitary bone metastasis. The Breast Cancer Study Group of the Japan Clinical Oncology Group (1017) and Eastern Clinical Oncology Group (2108) began enrolling patients for a phase 3 trial in June 2011[23]. Patients receive current standard systemic therapy before and after randomization and the latest imaging examination before treatment in these trials. A trial by the current authors is determining the significance of early resection of the primary tumor in stage Ⅳ breast cancer when that tumor can be controlled by medication. Items being assessed include the total survival time as well as the significance of local control; the results of the trial are sure to provide clinically significant evidence.

CONCLUSION

At the current point in time, one cannot say whether or not resection of the primary tumor provides a clear benefit in the management of stage Ⅳ breast cancer. Basic studies have revealed the biology of breast cancer in detail and the role of surgery is changing as treatment is better tailored to the individual in accordance with the individual's biology. The goal of treatment has to be clearly identified: increase the patient's survival time, provide local control or perform histology to determine the cancer's properties. Without a doubt, the best evidence is absolutely essential to treat patients who need surgery at the right time. Announcement of the results of clinical trials that are currently underway and examination of those results in detail are the first steps to obtain that evidence. However, obtaining results takes time and other strategies to treat breast cancer are constantly changing. In addition, the drugs used and patient attributes differ completely in different countries. An effective strategy to treat stage Ⅳ breast cancer must be devised in accordance with medication in light of the patient's symptoms while remaining mindful of the significance of surgery.

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BRIEF REPORT

Estrogen receptor (ER) mRNA expression and molecular subtype distribution in ER-negative/progesterone receptor-positive breast cancers

Mitsuya Itoh · Takayuki Iwamoto · Junji Matsuoka · Tomohiro Nogami · Takayuki Motoki · Tadahiko Shien · Naruto Taira · Naoki Niikura · Naoki Hayashi · Shoichiro Ohtani · Kenji Higaki · Toshiyoshi Fujiwara · Hiroyoshi Doihara · W. Fraser Symmans · Lajos Pusztai

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Abstract We examined estrogen receptor (ER) mRNA expression and molecular subtypes in stage I–III breast cancers that are progesterone receptor (PR) positive but ER and HER2 negative by immunohistochemistry (IHC) or fluorescent in situ hybridization. The ER, PR, and HER2 status was determined by IHC as part of routine clinical assessment ($N = 501$). Gene expression profiling was done with the Affymetrix U133A gene chip. We compared expressions of *ESR1 and MKI67* mRNA, distribution of molecular subtypes by the PAM50 classifier, the sensitivity to endocrine therapy index, and the DLDA30 chemotherapy response predictor signature among ER/PR-positive ($n = 223$), ER-positive/PR-negative ($n = 73$), ER-negative/PR-positive ($n = 20$), and triple-negative ($n = 185$) cancers. All patients received neoadjuvant chemotherapy with an anthracycline and taxane and had adjuvant endocrine therapy only if ER or PR $\geq$ 10 % positive. *ESR1* expression was high in 25 % of ER-negative/PR-positive, in 79 % of ER-positive/PR-negative, in 96 % of ER/PR-positive, and in 12 % of triple-negative cancers by IHC. The average *MKI67* expression was significantly higher in the ER-negative/PR-positive and triple-negative cohorts. Among the ER-negative/PR-positive patients, 15 % were luminal A, 5 % were Luminal B, and 65 % were basal like. The relapse-free survival rate of ER-negative/PR-positive patients was equivalent to ER-positive cancers and better than the triple-negative cohort. Only 20–25 % of the ER-negative/PR-positive tumors show molecular features of ER-positive cancers. In this rare subset of patients (i) a second RNA-based assessment may help identifying the minority of ESR1 mRNA-positive, luminal-type cancers and (ii) the safest clinical approach may be to consider both adjuvant endocrine and chemotherapy.

Keywords Estrogen receptor · Progesteron receptor · cDNA microarray · Breast cancer · Hormone therapy

M. Itoh · T. Iwamoto (✉) · J. Matsuoka · T. Nogami · T. Motoki · T. Shien · N. Taira · T. Fujiwara · H. Doihara
Okayama University, Okayama, Japan
e-mail: tiwamoto@cc.okayama-u.ac.jp

M. Itoh · S. Ohtani · K. Higaki
Hiroshima City Hospital, Hiroshima, Japan

N. Niikura
Tokai University, Kanagawa, Japan

N. Hayashi
St Luke's International Hospital, Tokyo, Japan

W. F. Symmans
The University of Texas MD Anderson Cancer Center, Houston, TX, USA

L. Pusztai
Yale University Cancer Center, New Haven, CT, USA

Abbreviations

ER	Estrogens receptor
PR	Progesterone receptor
IHC	Immunohistochemistry
HR	Hormone receptor
HER2	Human epidermal growth factor receptor 2
DLDA	Diagonal linear discriminant analysis
SET	Sensitivity to endocrine therapy

Introduction

Estrogen (ER) and progesterone receptor (PR) are routinely assessed in all primary breast cancers by immunohistochemistry (IHC) [1] and adjuvant endocrine therapy is

recommended if either of these receptors is positive (i.e., >1 % by IHC) [2–4]. The expression of PR is activated by ERα via an estrogen-responsive element-containing gene promoter. Therefore, it has been proposed that PR expression indicates the presence of functional ERα [5] and loss of PR expression potentially defines a subpopulation of patients with inferior benefit from tamoxifen compared to PR receptor persisted cancers [6]. In this model, the existence of ER-negative/PR-positive cancers represents an enigma. It has even been suggested that the majority of ER-negative but PR-positive cancers may represent false-negative IHC results for ER [7]. After reevaluation of the tumor slides and control tissues, most cases of ER-negative/PR-positive cases changed their original phenotype [7]. Further, Hefti et al. [8] also reported that ER-negative/PR-positive cases showed no significant reproducibility by integrated gene expression microarray and clinico-pathological data.

The prognostic value of PR expression independent of any endocrine therapy and its interaction with benefit from endocrine therapy in ER-positive cancers has been documented by several studies. In ER-positive cancers, patients with PR-positive disease have lower risks of recurrence and mortality compared to PR-negative cancers both with and without adjuvant endocrine therapy [9]. Prat et al. [10] reported that PR expression adds to the prognostic value of luminal A classification and can further sub-stratify patients among luminal cancers. Viale et al. [11] also showed that PR expression predicts for adjuvant chemotherapy benefit among pre- and peri-menopausal but not post-menopausal patients with ER-positive cancers. The predictive and prognostic value of PR expression in ER-negative cancers is much less understood, mostly because of the rarity of this disease subset.

Approximately 3 % of all breast cancers are ER negative and PR positive [12]. Some data suggest that cancers may not significantly benefit from adjuvant endocrine therapy [9]. In 2010, joint guidelines by the American Society of Clinical Oncology (ASCO) and the American College of Pathologists recommended that hormone receptor (HR) status should be considered positive if 1 % or more tumor cells demonstrate positive nuclear staining of either ER or PR with an IHC assay [1]. Historically, many investigators and clinicians considered 10 % or greater IHC staining as the threshold for defining HR-positive status and, therefore, eligibility for endocrine therapy. We have previously showed that the majority of ER borderline, 1–9 % IHC positive, cases had molecular features similar to ER-negative cancers [13].

In the current study, we examined *ESR1* mRNA expression and molecular subtype distribution among ER-negative but PR-positive cancers and assessed hormone and chemotherapy sensitivity markers in these cancers [14, 15]. The purpose of these analyses was to determine whether ER-negative/PR-positive cancers show the same global gene expression patterns and molecular subtypes as ER-positive cancers do or if they are more similar to ER-negative cancers.

Patients and methods

Five hundred and one patients were included in this study who participated in a prospective Institutional Review Board-approved biomarker discovery study at MD Anderson Cancer Center in Houston, TX and signed informed consent for molecular analysis of their pretreatment cancer biopsy and had routine marker and gene expression data available. The ER, PR, and HER2 status was assessed on diagnostic core needle biopsies in the routine pathology laboratory. Clinical ER status was determined by IHC using the ERalfa antibody 6F11 (Novocastra/Vector Laboratories, Burlingame, CA) and PR status was determined by using the antibody 1A6 (Novacastra Laboratories Ltd., Burlingame, CA). The cut-off for ER or PR positivity for this analysis was ≥1 % tumor cells with nuclear staining. HER2 status had been assessed either by fluorescence in situ hybridization or by IHC (Dako North America, Inc., Carpinteria, CA, USA). HER2 positivity had been defined as either HER2 gene amplification if immunohistochemical score was 2+ or an immunohistochemical score of 3+. Two hundred and twenty-three patients were ER and PR positive, 73 were ER positive but PR negative, 20 were ER negative but PR positive, and 185 were ER and PR negative. All patients received neoadjuvant chemotherapy containing a taxane- and anthracycline-based regimen, and patients with ER- or PR-positive tumors defined as ≥10 % staining also received adjuvant endocrine therapy.

Gene expression profiling with Affymetrix U133 gene chips were performed on fine-needle aspirations obtained before any therapy and independent of the diagnostic core-needle biopsy used for routine ER, PR, and HER2 determination. Gene expression data are available under GEO (Gene Expression Omnibus) accession number GSE 25066 and methods were described in a previous publication [16]. Expression data were normalized with the MAS5 algorithm, mean centered to 600 and log2 transformed. Probe set 205225_at was used as the measure of *ESR1* mRNA expression, and a log2-transformed expression value of ≥10.18 was considered as ER positive by mRNA based on of a threshold established and validated in previous publications [13, 17, 18]. We also assessed PR mRNA expression by probe set 208305_at and Ki67 (*MKI67*) expression by probe set 212021_s_at. An ER metagene was calculated as the average log2 transformed expression values of *ESR1*, *PR*,

Table 1 Patient characteristics

No of Pt (%)	501
Age	
Average	49.8
(min–max)	(24–75)
ER by IHC	
Positive/negative	296 (59.1)/205(40.1)
PR by IHC	
Positive/negative	243(48.5)/258(51.5)
HER2 by IHC and/or FISH	
Positive/negative	6 (1.2)/483(96.4)
NA	12(2.4)
T	
0–2/3–4	284(56.7)/217(43.3)
N	
Positive/negative	155(30.9)/346(69.1)
Grade	
I/II/III	31(6.2)/178(35.5)/256(51.1)
NA	36(7.2)

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *T* clinical tumor size, *N* clinical lymph node status, *NA* not available

BCL2, and *SCUBE2* as measure of endocrine sensitivity (based on OncotypeDX ER score). The PAM50 classifier, the sensitivity to endocrine therapy (SET) index, and the DLDA30 chemotherapy response predictor signature were also applied to the data as previously described [14–16, 19]. The Wilcoxon test was used to determine statistical significance of gene expression differences between IHC subsets. We also plotted survival curves with the log-rank test by ER and PR status based on IHC. Statistical analyses were performed using the BRB-ArrayTools v 4.1.0 (http://linus.nci.nih.gov/BRB-ArrayTools.html) and the R software v 2.7.2 (http://www.r-project.org). Two-sided p values <0.05 were considered statistically significant.

Results

Patients characteristics are shown in Table 1. Sixty-three percent of tumors were hormone receptor (HR) positive (ER and/or PR $\geq$ 1 %[1]) by IHC. Among the IHC ER-negative/PR-positive, ER-positive/PR-negative, ER/PR-positive, and ER/PR-negative patients, 25 % (= 5/20), 79 % (= 58/73), 96 % (= 213/223), and 12 % (= 22/185) were also positive by *ESR1* mRNA expression, respectively (Table 2). Among the ER-negative/PR-positive patients, 15 % were luminal A, 5 % were Luminal B, and 65 % were basal like; among the ER-positive/PR-negative patients, 59 % were luminal type (Table 2). An additional 22 patients who were IHC ER/PR negative (12 % of ER/PR-negative cases) were positive by *ESR1* mRNA gene expression and may be considered as false-negative IHC results (Table 2). The sensitivity to endocrine therapy (SET) index assigned low sensitivity to 90 % of the ER-negative/PR-positive cancers (Table 2). The chemotherapy sensitivity gene score, DLDA30, predicted high chemotherapy sensitivity for 60 % of the ER-negative/PR-positive patients and for 21 % of ER-positive/PR-negative patients (Table 2). Only 5 % (12/233) of the ER/PR-positive patients were assigned to the high chemotherapy sensitivity group.

Figure 1 shows the relationship between ER/PR protein expression and *ESR1*, *PR*, and *MKI67* mRNA gene

Table 2 Breast cancer subtypes and genomic markers

ER/PR by IHC		Pos/Pos		Pos/Neg		Neg/Pos		Neg/Neg	
No of Pt (%)		223	44.5 %	73	14.6 %	20	4.0 %	185	36.9 %
ER by GE	Positive	213	95.5 %	58	79.5 %	5	25.0 %	22	11.9 %
	Negative	10	4.5 %	15	20.5 %	15	75.0 %	163	88.1 %
Molecular subtypes	LumA	131	58.7 %	21	28.8 %	3	15.0 %	2	1.1 %
	LumB	51	22.9 %	22	30.1 %	1	5.0 %	4	2.2 %
	Her2	12	5.4 %	7	9.6 %	2	10.0 %	15	8.1 %
	Basal	13	5.8 %	13	17.8 %	13	65.0 %	147	79.5 %
	Normal	16	7.2 %	10	13.7 %	1	5.0 %	17	9.2 %
SET index	High	21	9.4 %	0	0.0 %	1	5.0 %	1	0.5 %
	Intermediate	33	14.8 %	3	4.1 %	1	5.0 %	3	1.6 %
	Low	169	75.8 %	70	95.9 %	18	90.0 %	181	97.8 %
DLDA30	pCR	12	5.4 %	15	20.5 %	12	60.0 %	154	83.2 %
	RD	211	94.6 %	58	79.5 %	8	40.0 %	31	16.8 %

ER estrogen receptor, *PR* progesterone receptor, *Pos* positive, *Neg* negative, *GE* gene expression, *SET index*: Symmans et al. 2010 JCO, *DLDA30* Lee et al. 2010 CCR, *pCR* pathological complete response, *RD* residual disease

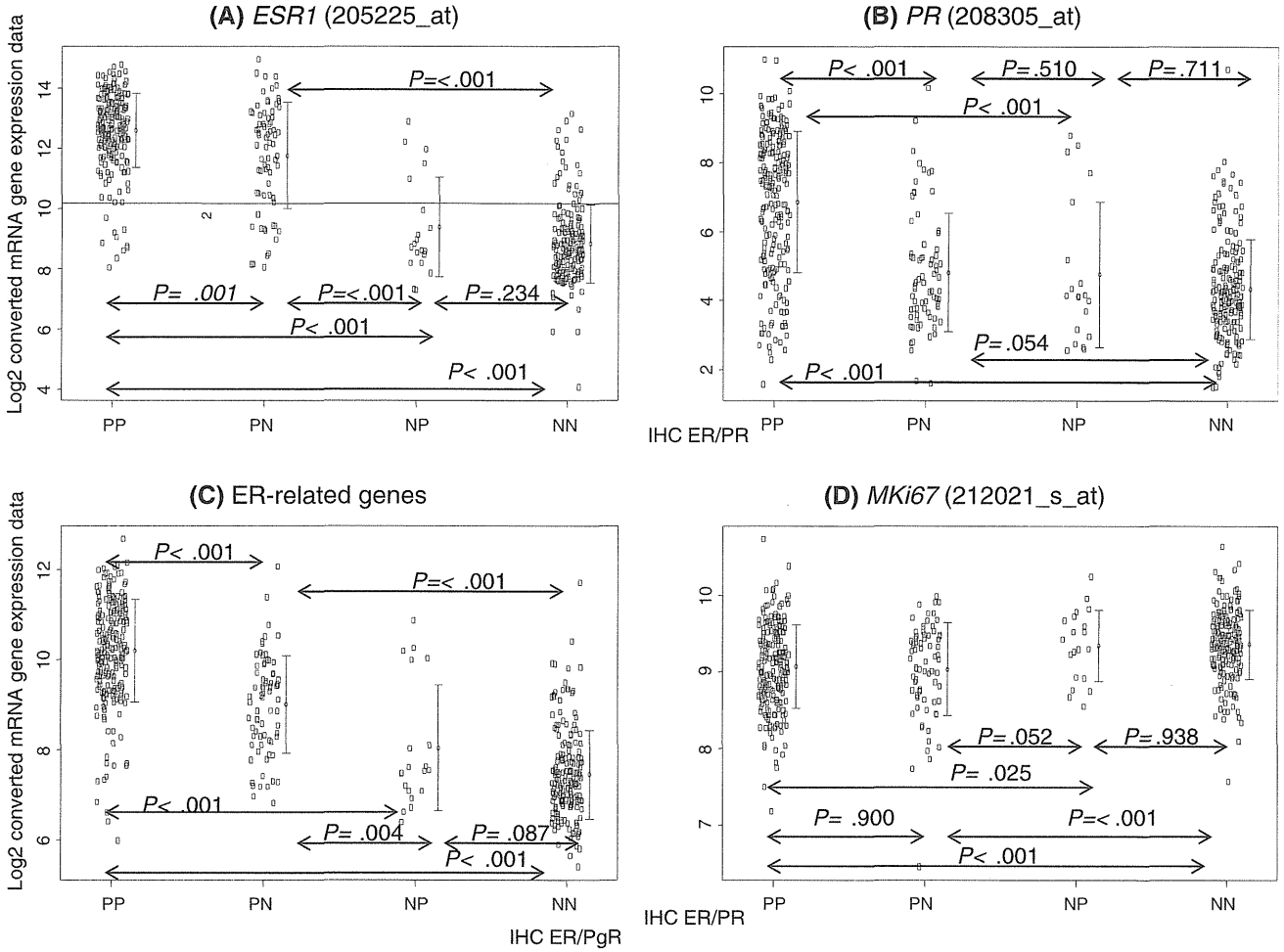

Fig. 1 *ESR1, Progesterone receptor* (PR), ER metagene, and MKI67 mRNA gene expression in four distinct Immunocytochemistry (IHC) groups. IHC groups were defined by the percentage of cells of that were positive of nuclear ER and PR staining. **a** Expression distribution of ESR1 mRNA. **b** Expression distribution of PR mRNA. **c** ER-related genes refers to the average expression of 4 probe sets that are highly coexpressed with ESR1 [25]. **d** Expression distribution of MKI67 mRNA. *P* values were calculated with the Wilcoxon test

expression and the ER metagene. The associations between IHC ER/PR subtypes and the mRNA gene expression level (*ESR1*-, *PR*-, and ER-related genes) were similar and consistent, indicating that they were highly correlated each other. The majority of the ER-negative/PR-positive patients (75 %) showed low *ESR1* mRNA, low PR, and low ER metagene expression, and were assigned to ER-negative status by these metrics. In contrast, the majority of ER-positive/PR-negative cases showed high *ESR1* and ER metagene expression that were consistent with ER-positive status. The average *MKI67* expression was also significantly higher in the ER-negative/PR-positive and ER/PR-negative cancers compared to other subtypes (Fig. 1).

Among the ER negative/PR positive, ER positive/PR negative, ER/PR positive, and ER/PR negative, 40 % (8/20), 16 % (12/73), 8 % (18/223), and 32 % (60/185) achieved pathological complete response that was defined as the absence of any residual invasive cancer in the breast and the absence of any metastatic cells in the regional lymph nodes after neoadjuvant chemotherapy. The relapse-free survival rate of ER-negative/PR-positive patients who received chemotherapy (and nine of them received additional adjuvant endocrine therapy) was equivalent to ER/PR-positive or ER-positive/PR-negative cases that received both endocrine and chemotherapy, and significantly better than the relapse-free survival of ER/PR-negative cancers (Fig. 2).

Discussions

ER-negative/PR-positive breast cancers are rare; this study and previous studies indicate that approximately 3–4 % if all breast cancers fall into this category [12]. Since it represents a rare receptor subtype, it is unlikely that a prospective clinical trial would ever be conducted to

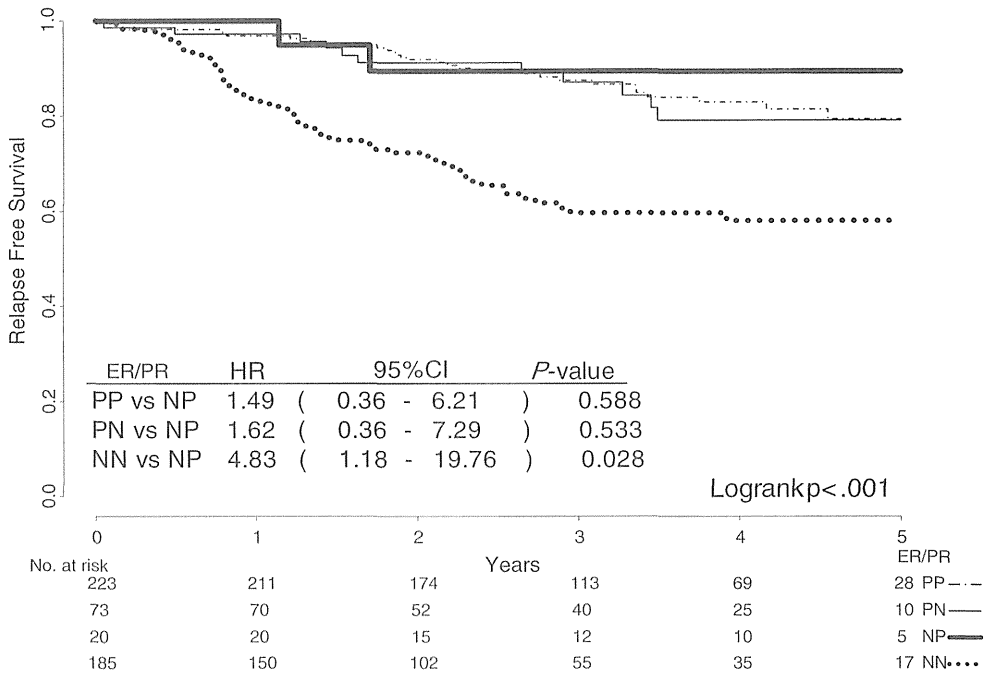

Fig. 2 Kaplan–Meier relapse-free survival curves by estrogen receptor (ER)/progesterone receptor (PR) immunohistochemistry status. Immunohistochemistry groups were defined by the percentage of ER/PR-positive cells. *P* positive, *N* negative, *HR* hazard ratio, *CI* confidential interval

define the optimal adjuvant treatment strategy for this disease. ER-negative/PR-positive status may arise from testing artifacts, including false-positive IHC results in a truly HR-negative tumor [20] or erroneously ER-negative results in a truly ER-positive tumor. It may also indicate the presence of tumor heterogeneity as a small PR positive subpopulation of cells within a larger both ER/PR-negative tumor. In our study, IHC ER/PR status defined by the routine analysis has been done on a fixed core needle biopsy, whereas the molecular profiling has been realized on another frozen samples by fine-needle aspirations. Discordance form the distinct methods of the sampling and the possibilities of false-positive or -negative results may be inevitable [21]. mRNA-based methods to assess hormone receptor status may help resolve some of these uncertainties [22]. We assessed gene expression profiling data in 501 primary breast cancer to find out how often ER-negative/PR-positive patients by IHC showed molecular features of ER-positive disease.

The minority (25 %) of ER-negative/PR-positive tumors and the majority (79 %) of ER-positive/PR-negative tumors showed ER-positive status by *ESR1* mRNA gene expression data and had high expression of ER-related genes. Five of twenty patients with ER-negative/PR-positive cancers by IHC were ER positive by *ESR1* mRNA and ER metagene expression. Four of these five cancers were also classified as luminal subtypes by the PAM50 classifier and, therefore, likely represent false-negative ER IHC results. On the other hand, 15 of the 20 ER negative/PR positive cancers showed low *ESR1* mRNA and ER metagene expression and all of these cancers were classified as non-luminal subtypes by a PAM50. This suggests that the majority of ER-negative but PR-positive cancers may not be endocrine sensitive. However, the mRNA measurements represent bulk expression results for heterogeneous tissue. It is possible that small truly PR-positive and endocrine-sensitive subpopulation of cells may exist within a larger ER/PR-negative tumor and signal from these cells is not apparent in the global expression data from the whole tissue [11, 23, 24].

In these series, twenty ER-negative/PR-positive patients who received chemotherapy (and about half of them received additional adjuvant hormone therapy) have equivalent prognosis to ER/PR positive or ER positive/PR negative that received both chemo and hormone therapies. Overall, the expected benefit from hormone therapy is small in ER-negative/PR-positive tumors because majority of these tumors tend to be ER negative by *ESR1* mRNA (75 %), show low predicted hormone sensitivity by the SET gene signature (90 %), and are predominantly non-luminal class (85 %). On the other hand, 60 % of the ER-negative/PR-positive cancers were predicted to have high chemotherapy sensitivity by the DLDA30 predictor.

This study has limitations. The number of ER-negative/PR-positive patients in this analysis is low. No prior study examined the molecular features of this rare disease subset

and this study has the advantage of using centrally reviewed IHC results and a uniformly performed gene expression analysis. The molecular analysis yielded generally consistent results for different RNA-based methods to assess ER status, and hormone and chemotherapy sensitivities. Another limitation should be that gene expression analysis does not necessarily imply protein expression. Elevated mRNA may not be indicative of elevated protein expression. Therefore, for the potential false positive that can be obtained through IHC, there is equaling uncertainty on whether the mRNA levels in these samples translates to protein expression. The uneven samples size for the four ER/PR subgroups, different types of adjuvant hormone therapy used, and different TNM stages across cohorts limit the interpretation of the survival analysis.

In summary, only 20–25 % of the ER-negative/PR-positive tumors show molecular features of ER-positive cancers (i.e., high ER mRNA expression and luminal molecular class). These cancers also have higher proliferation rate than ER-positive cancers, higher predicted chemotherapy sensitivity, and lower predicted hormone sensitivity. We concluded that in this rare subset of patients (i) a second RNA-based assessment may help identifying the minority of *ESR1* mRNA-positive, luminal-type cancers and (ii) due to the substantial uncertainty about endocrine sensitivity and high chemotherapy sensitivity in this IHC ER-negative/PR-positive cancer population, the safest clinical approach may be to consider both adjuvant endocrine and chemotherapy.

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Disclosures None.

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ORIGINAL ARTICLE

The discordance between primary breast cancer lesions and pulmonary metastatic lesions in expression of aldehyde dehydrogenase 1-positive cancer cells

Tomohiro Nogami · Tadahiko Shien · Takehiro Tanaka · Hiroyoshi Doihara · Naruto Taira · Daisuke Takabatake · Rieko Nishimura · Keiko Nishiyama · Taeko Mizoo · Shozo Ohsumi

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Abstract
Background We evaluated the expression of aldehyde dehydrogenase 1 (ALDH1) between primary breast lesions and pulmonary metastatic (PM) lesions in breast cancer patients.
Methods We retrospectively analyzed the clinicopathological features and the expression statuses of ER, PR, HER2, Ki-67 and ALDH-1 in both primary and metastatic breast cancer lesions and evaluated the discordance rates in the expressions of these markers between the primary and metastatic lesions, and also the prognostic value of these factors.
Results None of the PM patients had metastases at any other sites, and all had undergone curative breast cancer surgery. The pulmonary operation was partial resection in 15 (88 %) patients and lobectomy in 2 (12 %) patients. The median overall survival (OS) after resection of the PNs (OS) was 48 months. The discordance rates in the expressions of ER, PR, HER2, Ki67 and ALDH-1 between the primary and metastatic lesions were 0, 29, 21, 43 and 50 %, respectively.
Conclusion There was significant discordance in the biomarkers between the primary tumors and the metastatic lesions.

Keywords Breast cancer · Pulmonary metastases · ALDH1

T. Nogami (✉) · T. Shien · H. Doihara · N. Taira · K. Nishiyama · T. Mizoo
Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan
e-mail: imagon12000@yahoo.co.jp

T. Tanaka
Department of Pathology, Okayama University Hospital, Okayama, Japan

D. Takabatake · S. Ohsumi
Department of Breast Oncology, Shikoku Cancer Center, Matsuyama, Japan

R. Nishimura
Department of Pathology, Shikoku Cancer Center, Matsuyama, Japan

Introduction

Recurrent breast cancer involves the spread of cancer cells to the whole body, and complete cure is difficult to achieve. For this reason, in the treatment of patients with recurrent breast cancer, emphasis is laid on prolongation of the survival period and palliative care. Primarily drug therapy is used for patients with recurrent breast cancer, and drugs that elicit some response in the patients are used for as long as possible. New drugs such as molecule-targeted drugs and aromatase inhibitors have been shown to provide good control rates, although complete disappearance of the tumors cannot be expected by treatment with these drugs, resulting in prolongation of the duration of the drug therapy as well as in the effectiveness of the therapy. The treatment for metastatic breast cancer (MBC) is usually systemic therapy, selected on the basis of the hormone and HER2 expression statuses in the primary breast cancer lesion. However, recently, there have been some reports about discrepancies in the hormone and HER2 expression statuses between the primary and metastatic lesions in breast cancer [1–4]. One of the reasons why it is difficult to achieve complete disappearance of metastatic lesions is illustrated by the cancer stem cell (CSC) theory. According to this theory, tumors have CSCs, which (1) make them

resistant to ordinary drugs, (2) are capable of forming new tumor cells and (3) survive in the tumors even after the other tumor cells have been purged by effective drugs, resulting subsequently in the growth of new tumors. To date, several reports have shown the existence of correlations between the presence/absence/amount of CSC in tumors and the tumor responses to treatment [5, 6]. Ginestier et al. reported that ALDH1 is a better marker of breast CSCs, based on the finding that fewer ALDH1-positive than CD44+/CD24− tumor cells were required to form tumors in NOD/SCID mice. Moreover, they documented that immunohistochemically identified ALDH1 expression is associated with a poor prognosis in human breast cancer patients. ALDH1 in CSCs may be a significant enzyme involved in stem cell differentiation, regulating the conversion of retinoic acid to oxidizing retinol [5, 7]. We have previously reported that the expression of ALDH1 in axillary lymph node metastases is often different from that in the primary lesion in breast cancer patients [8]. These findings suggest that surgical resection of MBC lesions may yield information useful for selecting the optimum drug therapy; these possibilities therefore deserve further detailed evaluation. In this study, we evaluated the expression of aldehyde dehydrogenase 1 (ALDH1) between primary breast lesions and pulmonary metastatic (PM) lesions in breast cancer patients.

Patients and methods

Between 1990 and 2006, 17 patients (PM) with the pulmonary nodules that were diagnosed as breast cancer metastases underwent complete resection of the nodules.

All of the patients had undergone curative surgery for the primary breast cancer tumors. Adjuvant endocrine therapy for estrogen receptor (ER)-positive patients and adjuvant chemotherapy for node-positive or ER-negative patients had been administered. Trastuzumab was not used as an adjuvant drug in HER2-positive patients.

We retrospectively analyzed the clinicopathological features and the expression statuses of ER, PR, HER2, Ki-67 and ALDH-1 in both the primary and MBC lesions and evaluated the concordance/discordance rates in the expressions between the primary and metastatic lesions. All patients were administered chemotherapy and/or endocrine therapy and were followed up after the pulmonary operation at our hospital.

Tumor tissues obtained at surgery were fixed in 10 % buffered formalin and embedded in paraffin. A routine histological examination was performed of sections stained with hematoxylin and eosin (H&E). Deparaffinization in xylene and rehydration in a series of decreasing concentrations of ethanol were done. Antigen retrieval using the Bond Epitope Retrieval Solution 1 (pH 6) at 98 °C for 30 min was performed. The slides were treated with ALDH1 (BD Biosciences) at a dilution of 1:200 and Ki-67 (Dako, Japan) at a dilution of 1:250 separately. Immunostaining was performed on a Leica Bond-MAXTM autostainer (Leica Microsystems), and we used peroxidase/DAB BondTM Polymer [the IHCFP H1 (30) protocol]. Specificity of staining was confirmed by liver as positive control, and negative controls consisted of replacement of the primary antibody by either PBS or isotype-specific IgG controls. The sections were counterstained with hematoxylin. The histological grade was determined according to the Scarff-Bloom-Richardson grading system. ER expression (Ventana Japan) and PR expression (Ventana Japan) were defined as positive when $\geq$10 % of the tumor cells showed positive staining. HER-2 expression was determined by immunohistochemical staining using the HercepTest kit (DAKO Japan). A score of 3+ was considered as representing HER-2 positivity. Ki-67 and ALDH1 expressions were considered positive when $\geq$15 and $\geq$5 %, respectively, of the tumor cells showed positive staining. Image analysis of the primary tumors (ALDH1) was performed in one selected area (on 400× high-power field) in each case (Fig. 1).

Results

Table 1 summarizes the background variables of the patients. The median age at the time of recurrence was 53.5 years (range 37–80). The tumor stage at the time of the first examination was I in 5 cases (36 %), II in 7 cases (50 %) and III in 2 cases (14 %). The histological type of primary breast tumor was invasive ductal carcinoma in 12 cases (86 %) and other/special types in 2 cases (14 %). The histological grade of the primary tumor was grade 3 in 7 cases (50 %) and grade 2 in 7 cases (50 %). The adjuvant therapy employed was chemotherapy in 6 cases (43 %) and endocrine therapy in 8 cases (57 %). The 2 cases (14 %) with the special types of primary breast tumors received no adjuvant therapy. The average size of the pulmonary metastases (PM) was 1.3 cm (range 0.5–3.4). The number of PMs was 2 in 1 case and 1 in the other cases. The operative procedure adopted for surgical treatment of the PM was wedge resection in 13 cases (93 %) and lobectomy in 1 case (7 %). No other metastasis other than the PM was identified by diagnostic imaging in any of the cases. The median survival after surgery for the pulmonary metastases was 40 months (survival curve is shown in Fig. 2). The median follow-up period after the first operation was 108 months (range 41–323 months).

Table 2 shows the results of immunohistochemical examinations of the primary tumors as well as of the

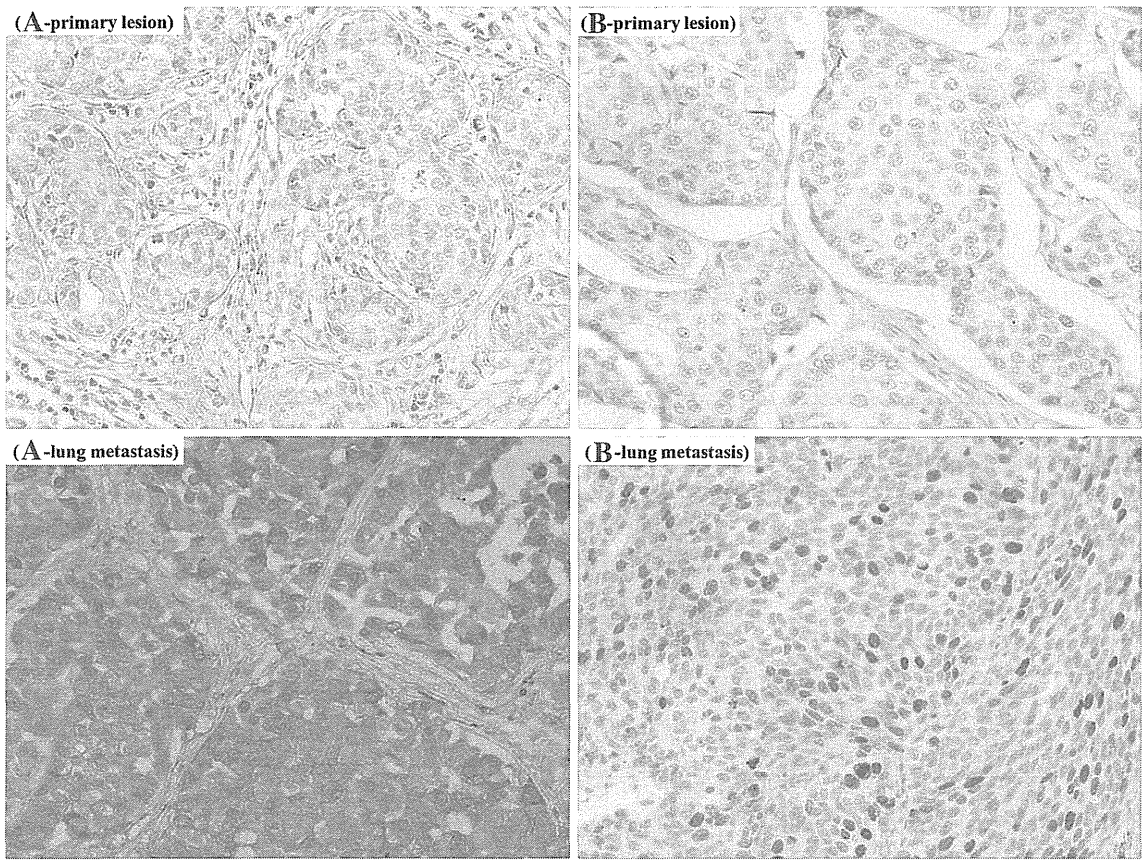

Fig. 1 Results of immunohistological examination for ALDH1 and Ki67 (×200). **a** The primary lesion was negative for ALDH1, while the lung metastasis was positive for this biomarker. **b** The primary lesion was negative for Ki-67, while the lung metastasis was positive for this biomarker

Table 1 Patient characteristics

Characteristics	No. of patients (%)
Total	14
Age (years) median	53.5 range (37–80)
Median follow-up (months)	108 range (41–323)
cStage I/II/III	5 (36 %)/7 (50 %)/2 (14 %)
OS after operation for lung metastases (months)	40 range (5–147)
Histology	
Invasive ductal cancer	12 (86 %)
Others	2 (14 %)
Histological grade I/II/III/unknown	0 (0 %)/7 (50 %)/7 (50 %)
Adjuvant therapy CT/ET/none	6 (43 %)/8 (57 %)/2 (14 %)
Lung tumor size (cm) mean	13 range (0.5–3.4)
Operation of lung metastasis	
Wedge resection/lobectomy	13 (93 %)/1 (7 %)

CT chemotherapy, *ET* endocrine therapy, *OS* overall survival

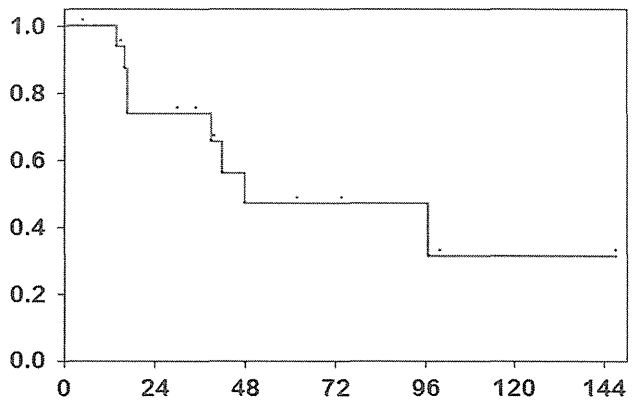

Fig. 2 Overall survival after the lung operation in the MBC patients ($n = 14$)

pulmonary metastatic lesions in the 14 cases of invasive ductal carcinoma after exclusion of the cases with the special types of tumors. The primary tumors were positive for ER, PR, HER2, Ki67 and ALDH1 expression in 11 (79 %), 9 (64 %), 1 (7 %), 6 (43 %) and 5 cases (36 %), respectively, and the PMs were positive for the above

Table 2 Immunohistological examination of the primary lesions and lung metastases

	ER		PR		HER2		Ki-67		ALDH-1	
	+	−	+	−	+	−	>20 %	<20 %	>5 %	<5 %
Primary	11 (79)	3 (21)	9 (64)	5 (36)	1 (7)	13 (93)	6 (43)	8 (57)	5 (36)	9 (64)
Lung meta	11 (79)	3 (21)	5 (36)	9 (64)	4 (29)	10 (71)	10 (71)	4 (29)	6 (43)	8 (57)

Table 3 Concordance rate of biomarker expressions between the primary lesions and the lung metastases

Primary/lung meta	ER		PR		HER2		Ki-67		ALDH-1	
	+/−	−/+	+/−	−/+	+/−	−/+	+/−	−/+	+/−	−/+
No. op pts (%)	0 (0)	0 (0)	4 (29)	0 (0)	0 (0)	3 (21)	1 (7)	5 (36)	3 (21)	4 (29)
Concordance (%)	100 %		71 %		79 %		57 %		50 %	

markers in 11 (79 %), 5 (36 %), 4 (29 %), 10 (71 %) and 6 cases (43 %), respectively.

The concordance rate of the marker expressions between the primary tumors and the PM was 100 % for ER, 71 % for PR, 79 % for HER2, 57 % for Ki67 and 50 % for ALDH1. Thus, the histopathological judgment as to the presence/absence of ER was identical between the primary tumors and the PM in all the cases, while the judgment as to presence/absence of ALDH1 differed between the primary tumors and the PM in about a half of the cases. There were 4 cases (29 %) in which the metastatic lesion was negative but the primary tumor was positive for PR expression, while there was no case in which the metastatic lesion was positive and primary tumor was negative for PR expression. There was no case in which the primary tumor was positive and the metastatic lesion was negative for HER2 expression, while there were three cases (21 %) in which the primary tumor was negative but the metastatic lesion was positive for HER2 expression. In regard to Ki67 expression, the Ki67 expression level tended to be higher in the metastatic lesions than in the primary tumors in 5 cases (36 %). The number of cases in which the primary tumor was negative but the metastatic lesion was positive was equivalent to that of the contrary case (Table 3).

Discussions

Recently, there has been increasing debate on whether breast cancer patients can be divided into several groups depending on their responses to drug therapy and whether the optimal treatment methods may vary markedly among these different groups. There has been an increasing tendency toward tailoring of drug therapy to individual cases, based on the prediction of the responses of individual patients to drugs, made possible by the recent advances in endocrine therapy, molecule-targeted therapy and translational research. Patients with breast cancer with a high ER-positive rate are considered to respond better to endocrine therapy and poorly to anti-cancer drug therapy, while patients with HER2-positive breast cancer or with breast cancer showing high expression levels of Ki67 are considered to respond better to anti-cancer drug therapy, even in the presence of ER positivity, and active use of anti-cancer drugs has begun to be recommended for these cases [9]. This process of selection of the optimal treatment method is adopted not only for adjuvant chemotherapy, but also for the treatment of MBC. There have been several reports on surgical treatment of MBC, although all of these reports are based on retrospective analyses [10–14].

Some investigators have reported that in 7–66 % of all cases in which surgery was performed for solitary pulmonary nodules suspected to be breast cancer metastases after surgery for the primary tumor, the resected tumor was not a metastasis but some other type of tumor (lung cancer, etc.) [15, 16]. Conducting a prospective study is the only means of clarifying the usefulness of surgical treatment for pulmonary metastases from breast cancer and precisely identifying the indications for surgical treatment.

At present, treatment of metastatic lesions developing after curative surgery for the primary breast cancer is selected on the basis of the characteristics of the primary tumor, based on the assumption that the biological features of metastatic lesions are identical to those of the primary tumors. However, several reports have demonstrated discrepancies in the biological features between primary tumors and metastatic lesions [1–4].

Also in the present study, the ER expression status in the primary tumors coincided with that in the metastatic lesions in all cases, whereas a discrepancy in HER2 (negative in the primary tumor but the metastatic tumor is positive) expression was noted in 21 % of all cases. For cases with HER2-positive tumors, trastuzumab is often used, and very good responses have come to be expected.

This 21 % of cases was found to show discrepant results for HER2 expression even before trastuzumab began to be used commonly in clinical practice, and this drug was not used for any of these cases. However, such a discrepancy in HER2 expression between the primary tumors can be of clinical significance.

In regard to Ki67, the importance of the criteria for judgment has attracted close attention in recent years. Although there is no widely accepted cutoff level yet for the judgment of Ki67 expression in the world, we applied the cutoff level recommended in 2009 in St. Gallen [9] in the present study and considered cases with 15 % or more positively stained cells as being Ki67-positive.

When judged using this criterion, the metastatic lesion became Ki67-positive in 36 % of all cases with Ki67-negative primary tumors. Although the method of evaluation of Ki67 in metastatic lesions is still controversial, it has been shown that high Ki67 expression levels in the primary tumors of patients with breast cancer are associated with a poor prognosis; Ki67 has thus begun to be used as an indicator to decide on the active use of anti-cancer drugs. In this sense, the discordance in the Ki67 expression status between the primary and metastatic tumors may be of significance in the selection of the treatment method.

CSCs have conventionally been reported to be more resistant to drug therapies than other cancer cells [6]. In the present study, ALDH1-positive lesions were found in 43 % of all pulmonary metastases, and no correlation was found with the expression of ALDH1 between the metastatic lesions and the primary tumors.

When CSC expression in tumors was examined before and after preoperative chemotherapy, their expression was found to be higher after preoperative chemotherapy. This would seem to reflect the increase in the density of CSC remaining after eradication of all other cells by effective drug therapy rather than to an absolute increase in the CSC count. It is highly probable that existing anti-cancer drugs fail to exert activity against CSC.

Conclusions

Considering the results of the present study, it may be useful to evaluate the biomarkers in pulmonary metastatic lesions in cases of MBC. However, there are many unresolved questions about the usefulness of evaluating CSC using ALDH1 as an indicator. It would be desirable to conduct further studies on this subject for a clearer elucidation.

Conflict of interest All authors have no employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, or grants or other funding to disclose.

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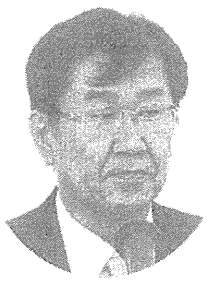
会議　県医

平成26年度第２回　乳がん検診講習会

標記研修会が６月14日（土）午後２時から午後３時30分の間、岡山衛生会館５階中ホールにて開催された。今回は岡山大学病院乳腺・内分泌外科　土井原博義教授が「乳がん検診の現状－受診率の向上に向けて－」と題してご講演された。本会より松山理事、大原理事が出席した。出席者115人。

「乳がん検診の現状 －受診率の向上に向けて－」



岡山大学病院　乳腺・内分泌外科　土井原　博義

乳がんは年間約68,000人の女性が罹患し（女性12人に１人）、12,500人が死亡するといわれており、罹患率は1990年代前半より女性の第１位で死亡率は現在第５位である（http://ganjoho.jp /public index.html）。ただ年齢別にみると30歳～69歳までの壮年期女性においては死因の第一位である。このように年々増加している乳がんの死亡を減少させるには３つのポイント、すなわち乳がんの予防（一次予防）、乳がん検診による早期発見（二次予防）、治療（主に薬物療法）の進歩が重要である。

【乳がんの予防】日本乳癌学会のガイドラインによれば罹患リスクを上昇させる因子はアルコール、喫煙、閉経後の肥満、ホルモン補充療法、乳がんの家族歴などが挙げられ、一方リスクを低下させる因子は大豆、イソフラボンの摂取、運動、出産、授乳などが確実あるいは可能性のある因子として

取り上げられている。乳がん家族歴以外は個人の努力により達成可能な因子であり、個々の頑張りにより、罹患率は低下させることができるものと思われる。乳がん家族歴に関しては最近、遺伝性乳がん・卵巣がん症候群（Hereditary breast and ovarian cancer：HBOC）として注目を浴びている。すなわち乳がんを発症する遺伝子であるBRCA1（17q21）、BRCA2（13q12）が同定されるとともに変異があるかどうかの検査が可能となった。これらの遺伝子は常染色体優性遺伝で若年発症や両側乳がん、多発乳がんが多いことが特徴である。浸透率（発症率）はBRCA 1で47～66％、BRCA2で40～57％と報告されているが、年齢の上昇とともに発症率は高くなる。ガイドラインによれば乳房切除では乳がんの発症を90％抑えることができ、内分泌療法では62％、また卵巣卵管切除では卵巣がんの発症は80％減少させ、さらに乳がんの発症を50％抑制することができると報告されているが、検査費用も含めていずれも自費診療となり、今後の費用面での対策が必要である。

【乳がん検診】検診の第一の目的は乳がんによる死亡率の減少であるが、早期発見により機能温存やQOLの維持が可能となる。すなわち乳房温存療法の施行や腋窩リンパ節郭清の省略、化学療法の回避などである。受診率は欧米の70～80％に比べて本邦では25％前後でマンモグラフィ検診が施行された2000年以降ほとんど受診率は向上していない。その理由は忙しいから、面倒くさい、痛いから、恥ずかしいから、健康に自信があるから（日本乳癌検診学会2013）などの個人的な理由であることも多いが、どこで受けたらいいかわからない、夜間、休日に行けないなど医療、行政側の啓発不足や努力不足も一因となっている。その対策として厚生労働省健康局がん対策推進室（http://www.mhlw.go.jp/）はがん検診受診のための普及啓発アプローチを示している。すなわち国・都道府県、市区町村、地域ボランティア、医療関係者（かかりつけ医を含む）、学会、企業などが連携し、乳がん検診の啓蒙、普及活動を行い、検診受診率の向上に繋げようとするものである。市区町村の無料クーポン事業、かかりつけ医のための検診ハンドブックの作成、企業に対するがん企業アクションなどを通じて地域住民あるいは住民個々に対して普及啓発活動、勧奨、再勧奨を勧める事業を展開しているところである。

また最近乳がん検診の利益と不利益に関する論文が多くみられる。利益は死亡率の減少であることは明らかであるが、一方不利益に関しては放射線被爆、疼痛、精神的不安、偽陽性による追加画像診断や組織検査、偽陰性、過剰診断などがあげられる。特にUSPSTF（米国予防医療研究班）が報告した「40歳代のマンモグラフィは不要ではないか？」というコメントに関しては偽陽性による追加画像診断は40歳代に多く、40歳代に検診を開始しても死亡率減少効果は３％に過ぎないというのが主な理由であった。本邦でも乳がん検診に強くかかわっている５県からのデータで検証されたが、欧米に比較して偽陽性率は同等であるが、追加画像診断、組織生検施行率は明らかに低く、また偽陰性率（見逃し）も低いという結果であった。従って現状では日本乳癌学会診療ガイドラインに沿って〈40歳以下：推奨グレードC1〉若年者に対する診療マンモグラフィは、いまだ十分な科学的根拠はないが、細心の注意のもと行うことを考慮してもよい、〈40歳代：推奨グレードB〉40歳代女性に対して行われるマンモグラフィによる乳がん検診は勧められる、

〈50歳以上：推奨グレードA〉50歳以上の女性に対して行われるマンモグラフィによる乳がん検診は強く勧められる、に従うべきであると考える。

本邦のがん検診はがん対策推進基本計画の個別目標である「がん検診受診率50％以上」という目標からはほど遠い状況であり、行政、医療者、ボランティア、企業が一致団結して取り組み、早急に個々が何らかのアクションを起こす必要があろう。

御津医師会：山中慶人