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p53 expression in tumor stromal fibroblasts is associated with the outcome of patients with invasive ductal carcinoma of the breast

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The purpose of this study was to determine whether p53 protein expression in tumor stromal fibroblasts assessed immunohistochemically by the Allred score system is significantly associated with nodal metastasis by invasive ductal carcinoma (IDC), and significantly associated with the outcome of 1042 IDC patients according to adjuvant therapy status, UICC pTNM stage, and triple-negative IDC status, in multivariate analyses with well-known clinicopathological factors. The Allred scores for p53 expression in tumor stromal fibroblasts were significantly associated with the number of nodal metastases, and Allred scores of 4–8 for p53 in tumor stromal fibroblasts significantly increased the hazard rate for distant organ metastasis or for tumor death in the triple-negative IDC patients, and the UICC pTNM stage I, II, and III patients. The results indicated that p53 protein expression in tumor stromal fibroblasts is closely associated with the number of nodal metastases and the outcome of IDC patients. (*Cancer Sci* 2009; 100: 2101–2108)

It has recently been reported that the gene expression and protein expression profiles of the tumor stroma play very important roles in tumor progression in carcinoma,[1–3] and the interaction between tumor and stromal cells also plays a very important role in tumor progression by carcinoma.[4–6] We and others have already reported that a characteristic histological feature of tumor stroma, a fibrotic focus, is a very useful prognostic histological tumor stromal indicator for accurately predicting the outcome of patients with invasive ductal carcinoma (IDC),[7–10] and that growth factors produced by tumor cells and tumor stromal cells play a very important role in tumor progression by IDC.[11] In addition, proliferative activity of tumor stromal fibroblasts plays a very important role in nodal metastasis and distant organ metastasis by IDC.[12,13] These findings strongly suggest a significant role of the tumor stroma in tumor progression by IDC.

p53 is the most commonly mutated gene in human neoplasms,[14] and the p53 tumor suppressor protein is involved in the cell cycle, checkpoint control, repair of DNA damage, and apoptosis.[15,16] Also, besides their well-studied cell-autonomous role in cancer cells, mutations of the *p53* tumor suppressor gene have been described in stromal fibroblasts of breast and prostate carcinoma in humans and experimental animals.[17–20] A high frequency of *p53* mutations in tumor cells and the surrounding stroma has also reported,[17] and *p53* mutations in breast cancer stromal cells have been reported to be closely associated with nodal metastasis.[21] Based on the above findings, the *p53* status of tumor stromal fibroblasts may play a very important role in carcinoma progression by IDC.

The purpose of the present study was to determine whether p53 protein expression in tumor stromal fibroblasts is significantly associated with nodal metastasis by IDC, and significantly associated with the outcome of IDC patients with and without adjuvant therapy according to UICC pTNM stage, and triple-negative IDC status. The results indicated that p53 protein expression in tumor stromal fibroblasts is closely associated with the number of nodal metastases and the outcome of IDC patients.

Materials and Methods

Cases. The subjects of the present study were 1042 consecutive patients with IDC of the breast surgically treated at the National Cancer Center Hospital (Tsukiji, Tokyo) between January 2000 and December 2005. The IDC were diagnosed preoperatively by aspiration cytology, mammography, or ultrasonography. Clinical information was obtained from the patients' medical records after complete histological examination of all IDC. All patients were Japanese women, and they ranged in age from 23 to 77 years (median, 55 years). All had a solitary lesion; 497 patients were premenopausal, and 545 were postmenopausal. Partial mastectomy had been carried out in 462, and modified radical mastectomy in 580. Levels I and II axillary lymph node dissection had been carried out in all patients, and level III axillary lymph node dissection had been carried out in some of the IDC patients.

Of the 1042 patients who did not receive neoadjuvant therapy, 873 had received adjuvant therapy, which consisted of chemotherapy in 209 patients, endocrine therapy in 294 patients, and chemoendocrine therapy in 370 patients. The chemotherapy regimens used were anthracycline-based with or without taxane and non-anthracycline-based, and the endocrine therapy regimens consisted of tamoxifen with or without a gonadotropin-releasing hormone agonist, tamoxifen, with or without an aromatase inhibitor, an aromatase inhibitor alone, or a gonadotropin-releasing hormone agonist alone. There were no cases of inflammatory breast cancer in this series. All tumors were classified according to the pathological UICC-TNM (pTNM) classification.[22] The protocol of this study was reviewed by the institutional review board of the National Cancer Center (20-112), and all patients provided written informed consent.

For pathological examination, the surgically resected specimens were fixed in 10% formalin, and the size and gross appearance of the tumors were recorded. Their size was confirmed by

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comparison with tumor size on histological slides, and if there was more than one invasive focus, the size of the largest invasive focus was recorded as the invasive tumor size in this study.

Histological examination. Serial sections of each tumor area were cut from paraffin blocks. One section from each tumor was stained with hematoxylin and eosin (HE) and examined histologically to confirm the diagnosis, and another section was subjected to immunohistochemistry. The following 10 histological factors were evaluated: (1) invasive tumor size (≤20, 20–50, >50 mm); (2) histological grade (1–3);[23] (3) tumor necrosis (absent, present);[24] (4) fibrotic focus (FF) (absent, FF diameter ≤ 8 mm, FF diameter > 8 mm);[7,8] (5) lymphatic invasion (absent, present); (6) blood vessel invasion (absent, present); (8) adipose tissue invasion (absent, length ≤ 2 mm, length > 2 mm);[25] (9) skin invasion (absent, present); and (10) muscle invasion (absent, present).

Immunohistochemistry. Immunohistochemical staining for estrogen receptors (ER), progesterone receptors (PR), p53, and HER2 products was carried out with an autoimmunostainer (Optimax Plus; BioGenex, San Ramon, CA, USA). Antigen retrieval device for these antibodies and each specimen was immersed in citrate buffer and incubated at 121°C for 10 min. Immunoperoxidase staining was carried out using a labeled streptavidin–biotin (LSAB) staining kit (BioGenex) according to the manufacturer's instructions. The antibodies used were anti-ER mouse mAb (ER88; BioGenex), an anti-PR mAb (PR88; BioGenex), an anti-HER2 mAb (CB11; BioGnex), and a p53 mAb (DO7; Dako, Glostrup, Denmark). ER88, PR88, and CB11 were already diluted and DO7 was applied at 1:100 dilution. After immunostaining, the sections were counterstained with hematoxylin. Sections of IDC positive for ER, PR, HER2, and p53 were used each time as positive internal or external

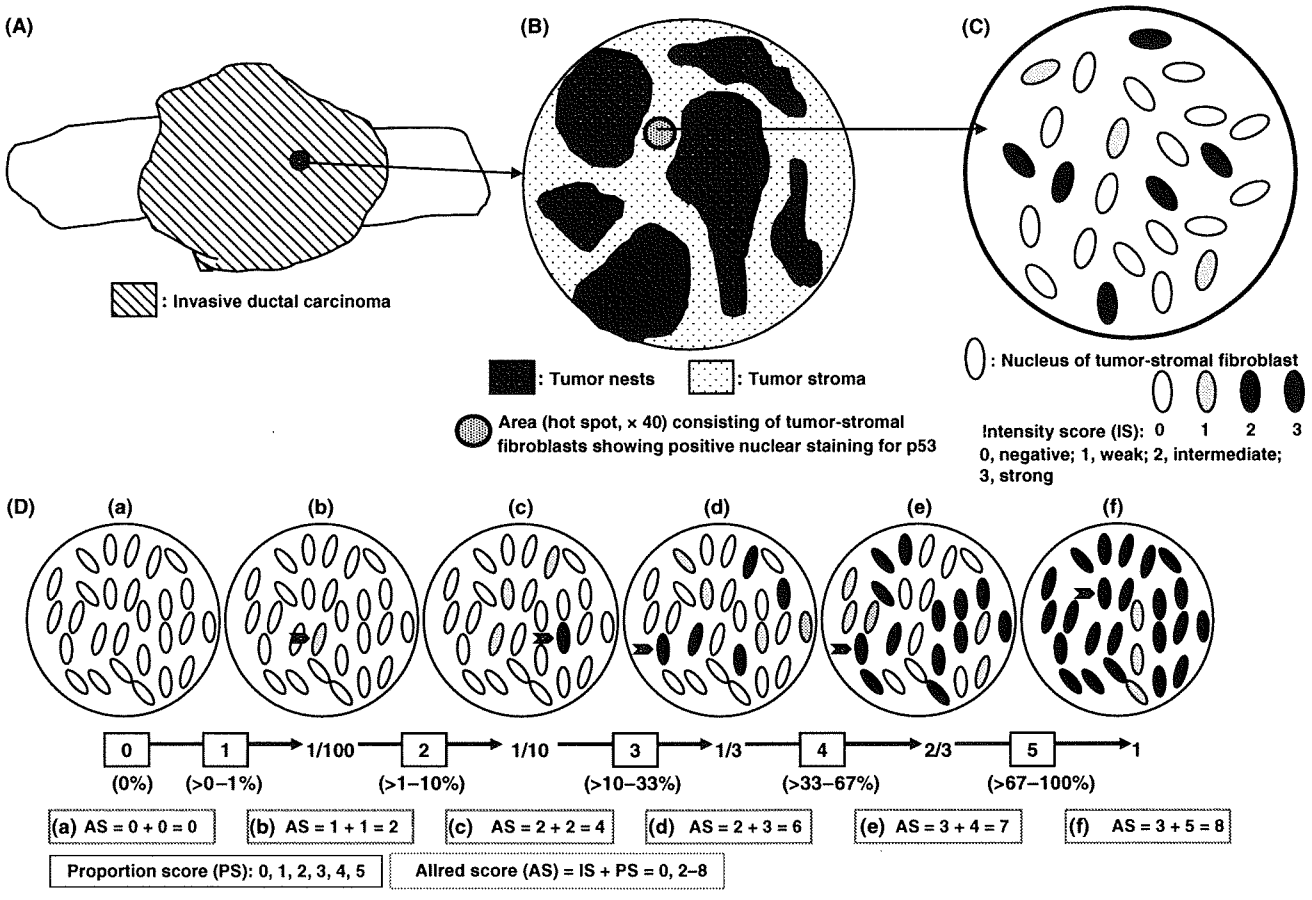

Fig. 1. Method for immunohistochemical assessment of tumor stromal fibroblasts in invasive ductal carcinoma (IDC). (A–D) First, sections on slides were examined for the presence or absence of p53 expression in tumor stromal fibroblasts in a medium-power field (×10 objective and ×10 ocular or ×20 objective and ×10 ocular), and areas in which tumor stromal fibroblasts showed p53 expression were found. Intensity score (IS) and proportion score (PS) were then assigned for p53 expression in tumor stromal fibroblasts in one high-power field in each medium-power field in which staining was found (×40 objective and ×10 ocular). The high-power field with the highest Allred score (IS + PS) for p53 expression was selected as the hot spot in the tumor. (C) Negative and positive tumor stromal fibroblasts for p53 expression were observed in the same high-power field, the hot spot in this tumor (×40 objective and ×10 ocular). Of the tumor stromal fibroblasts that showed positive nuclear staining for p53, two had a strong IS of 3 for p53, four had an IS of 2, and three had an IS of 1. The IS of tumor stromal fibroblasts for p53 expression in this case was 3. (D) PS for p53 expression. PS ranged from 0 to 5, and the highest PS was recorded as the PS of the case. The IS and PS for p53 expression in tumor stromal fibroblasts were then added to obtain a total score, the Allred score (AS), with total scores of 0 and 2–8. There was a hot spot in the tumor in each of the six IDC cases (a–f). The IDC case with hot spot a had an AS of 0, and the AS of the IDC case with hot spot b was 2. The IDC cases having hot spots c, d, e, and f had AS of 4, 6, 7, and 8, respectively. The IS for p53 in tumor stromal fibroblasts in each case were based on the tumor stromal fibroblasts with the highest IS for p53 expression (arrowheads).

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controls. As a negative control, the primary antibody was replaced with normal mouse immunoglobulin.

Assessment of ER, PR, p53, and HER2 expression. Slides immunostained for ER, PR, and p53 in tumor cells were scored by the Allred scoring system as described previously.[26–30] Although the validity of the Allred scoring system for assessing expression of ER, PR, and p53 in tumor cells has been demonstrated,[26–30] the number of tumor stromal fibroblasts that express p53 in tumors is relatively small, and the distribution of tumor stromal fibroblasts expressing p53 is scattered even in IDC with tumor stromal fibroblasts having Allred scores of 4–8. We therefore modified the Allred scoring system to assess expression of p53 in tumor stromal fibroblasts by identifying the field with the highest proportion score (PS) and intensity score (IS) for p53 expression in the tumor area (hot spot) by scanning the entire tumor section stained for p53 at medium power (×10 objective and ×10 ocular) (Fig. 1A,B). The highest IS (0, none; 1, weak; 2, intermediate; 3, strong) for expression of p53, not the average IS in the original,[26–30] was assigned for tumor stromal fibroblasts (Figs 1C,D,2A–F), and the highest p53

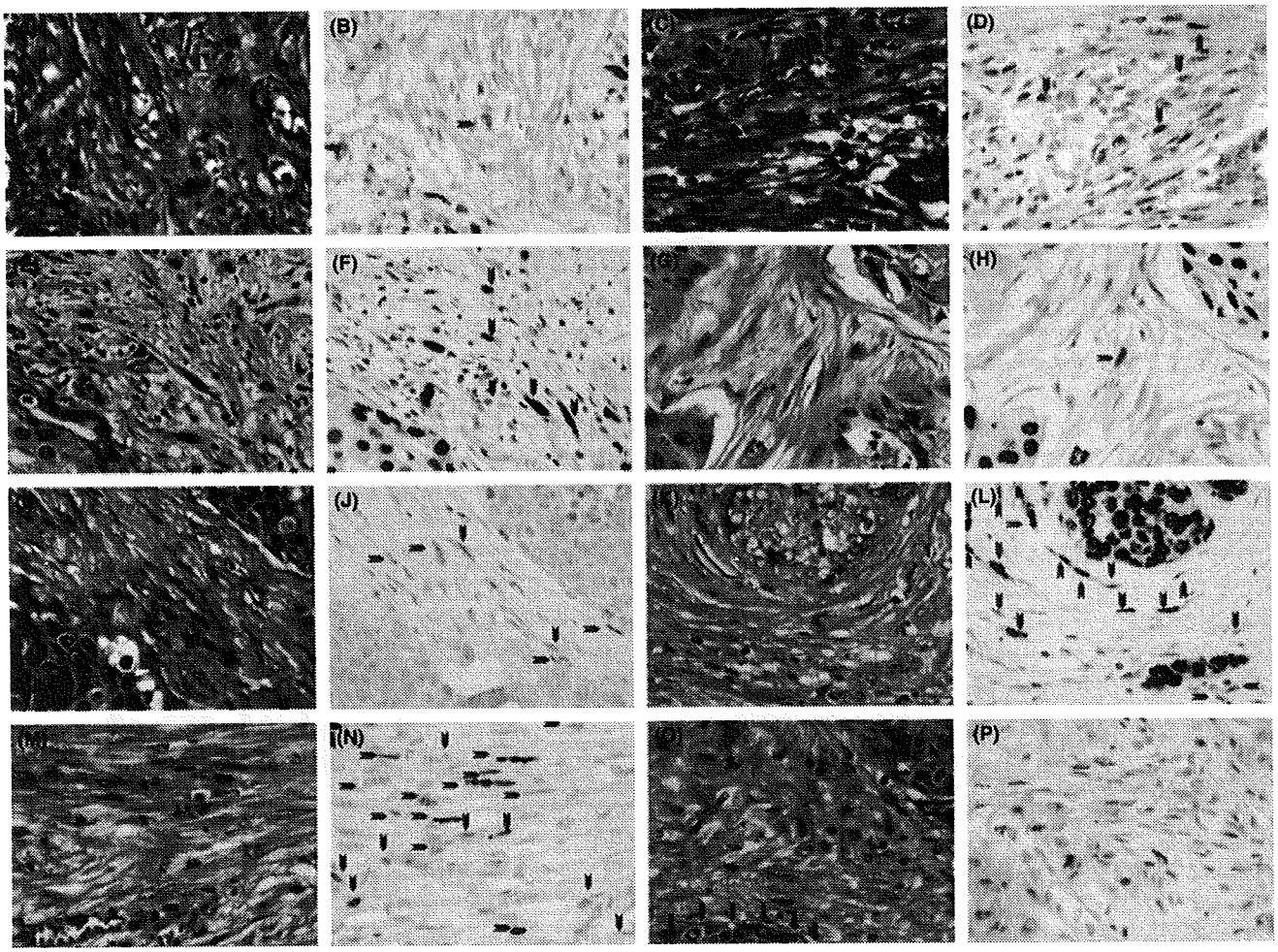


Fig. 2. (A,C,E,G,I,K,M,O) Histological features of tumor stromal fibroblasts, (B,D,F) intensity scores (IS), and (H,J,L,N,P) proportion scores (PS) for p53 expression in tumor stromal fibroblasts of invasive ductal carcinomas (IDC) in high-power fields (×40, hot spots). In general, tumor stromal fibroblasts had spindled acidophilic cytoplasm and oval nuclei, and were mixed with collagen fibers. Nucleoli of tumor stromal fibroblasts were inconspicuous. However, some tumor stromal fibroblasts exhibited epithelioid features, and had enlarged round to oval nuclei containing small nucleoli. Thus, the pathologist should confirm that cells showing p53 expression are tumor stromal fibroblasts or tumor cells not only by immunostaining, but also by hematoxylin–eosin staining. The tumor stroma contained tumor stromal fibroblasts with (A,B) an IS of 1 and (C,D) an IS of 2 for p53 expression (arrowheads). No tumor cells exhibited p53 expression (lower-right corner). (E,F) Tumor stromal fibroblasts with an IS of 3 for p53 expression were observed in the tumor stroma (arrowheads). Tumor cells with an IS of 3 or 2 for p53 expression are also observed (lower-left corner). (G,H) An Allred score (AS) of 3 for p53 expression in tumor stromal fibroblasts. One tumor stromal fibroblast in the high-power field had an IS of 2 for p53 expression (×40, hot spot, arrowhead). Tumor cells with an AS of 8 for p53 were also observed (lower-left corner and upper-right corner). (I,J) Tumor stromal fibroblasts with an IS of 1 or 2 for p53 expression were visible in the tumor stroma (arrowheads), and the PS of the tumor fibroblasts in this case was 2. Thus, the AS of the tumor stromal fibroblasts in the case was 4. Tumor cells were negative for p53 nuclear staining (upper-right corner and lower-left corner). (K,L) Tumor stromal fibroblasts with an IS of 3 or 2 for p53 expression were observed in the tumor stroma (arrowheads). The PS of the tumor stromal fibroblasts for p53 in this case was 3, and the AS of the tumor stromal fibroblasts for p53 expression in this case was 6. Tumor cells with an IS of 3 for p53 expression were also observed (upper-center and lower-right corner). (M,N) Tumor stromal fibroblasts had an IS of 3 or 2 for p53 expression (arrowheads), and the PS of the tumor stromal fibroblasts for p53 was 4. The AS of tumor stromal fibroblasts for p53 expression of this case is 7. No tumor cells are visible. (O and P) Many tumor stromal fibroblasts with an IS of 2 or 1 for p53 expression were observed in the tumor stroma between tumor cell nests (arrows), and their PS for p53 was 5. The AS of the tumor stromal fibroblasts for p53 expression in this case was 7.

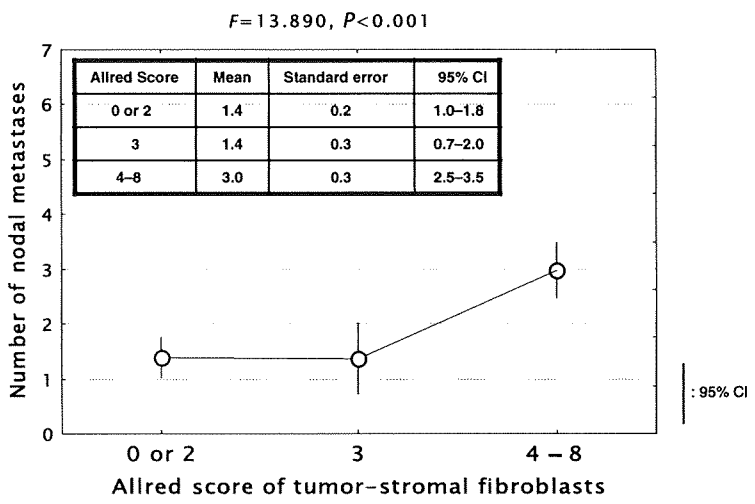
expression PS (0–5) was then to be evaluated in one high-power field (hot spot, ×40 objective and ×10 ocular) (Figs 1C,D,2G–P). The PS and IS of the tumor stromal fibroblasts were then added to obtain a total score, with possible total score of 0 and ranging from 2 to 8 (Figs 1D,2G–P). When examining tumor stromal fibroblasts for p53 staining, we always confirmed by HE stained specimen whether the cells that show positive staining for p53 is tumor-stromal fibroblasts or not. The HER2 status of the tumor cells was semiquantitatively scored on a 0–3 scale according to the level of HER2 protein expression.[31] Immunohistochemistry was used to score 1025 of the 1042 IDC for ER, PR, or HER2 expression and to score 1026 of them for p53 expression.

One author (TH) assessed all of the immunohistochemical parameters, and one of three other authors (HT, TS, or YS) identified the immunohistochemical parameters to confirm the IDC immunohistochemical characteristics recorded by TH. Discordant results were reevaluated jointly to reach a consensus. The histological and immunohistochemical examinations were carried out without knowledge of the patients' outcomes.

Patient outcome and statistical analysis. Survival was evaluated by follow up for a median period of 52 months (range, 18–102 months) until June 2008. Of the 1042 IDC patients, 924 patients were alive and well, 118 had developed tumor recurrence, and 29 had died of their disease, and an initial distant organ metastasis was observed in 85 of the 118 IDC patients with tumor recurrence. The measurements of tumor recurrence-free survival, initial distant organ metastasis-free survival, and overall survival started on the day of surgery. Tumor relapse was considered to have occurred whenever there was evidence of metastasis.

The Allred scores for ER, PR, and p53 expression in tumor cells and tumor stromal fibroblasts were classified into three categories according to the univariate analyses by the Cox proportional hazard regression model most significantly associated with tumor recurrence: (1) the Allred scores for ER in tumor cells were classified into the three categories 0 or 2, 3–6, and 7 or 8; (2) the Allred scores for PR in tumor cells were classified into the categories 0 or 2, 3–6, and 7 or 8; (3) the Allred scores for p53 in tumor cells were classified into the three categories 0 or 2 or 3, 4–6, and 7 or 8; and (4) the Allred scores for p53 in tumor stromal fibroblasts were classified into the three categories 0 or 2, 3, and 4–8. HER2 expression in tumor cells was classified into the three categories: 0 or 1, 2, and 3.

(A)



(B) Multiple regression analyses for the increase of number of nodal metastasis in invasive ductal carcinoma patients (n = 1021)

ß	Standard error	P-value
Invasive tumor size (<=20, >20 to <=50, and >50 mm)		
0.108	0.031	<0.001
Lymph vessel invasion		
0.199	0.003	<0.001
Skin invasion (absent and present)		
0.167	0.030	<0.001
p53 Allred scores in tumor-stromal fibroblasts (0 or 2, 3, and 4 to 8)		
0.091	0.030	0.002
Blood vessel invasion (absent and present)		
0.077	0.029	0.009
Histologic grade (1, 2, and 3)		
0.076	0.032	0.018
Progesterone receptor Allred scores in tumor cells (0 or 2, 3–6, and 7 or 8)		
–0.070	0.031	0.024

Fig. 3. Associations between (A) the number of nodal metastases and Allred scores for p53 in tumor stromal fibroblasts and (B) factors that were significantly associated with the number of nodal metastases in the multivariate analyses. (A) In invasive ductal carcinoma (IDC) patients, the increase in number of nodal metastases was significantly associated with the Allred scores for p53 in tumor stromal fibroblasts. (B) Multiple regression analysis revealed the factors that were significantly associated with the increase in number of nodal metastases in IDC patients. CI, confidence interval.

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The 10 histological factors, and the Allred scores for ER, PR, and p53 in tumor cells, Allred scores for p53 in tumor stromal fibroblasts, categories of HER2 expression in tumor cells, and age (≤39 years and >39 years) were analyzed in association with nodal metastases and the outcome of the IDC patients. Univariate analysis associations with the number of nodal metastasess were carried out by ANOVA, and the factors significantly associated with the number of nodal metastases in the univariate analysis were then entered in a multiple regression analysis for multivariate analyses. Univariate analysis associations between the above factors and UICC pathological nodal status (N factor: N0, no nodal metastasis; N1, 1–3 nodal metastases; N2, 4–9 nodal metastases; and N3, 10 or more nodal metastasis) and the outcomes of the IDC patients were carried out using the Cox proportional hazard regression model. The factors significantly associated with outcome in the univariate analyses were then entered together into the multivariate analyses using the Cox proportional hazard regression model. The multivariate analyses were carried out separately in patients with and without adjuvant therapy according to UICC pTNM stage[22] and triple-negative IDC status. The case-wise and step-down method was applied until all of the remaining factors were significant at a *P*-value below 0.05. As there were fewer than 10 tumor deaths in the group of patients who did not receive adjuvant therapy, the group with UICC pTNM stage I disease, the group with UICC pTNM stage II disease, and the triple-negative-IDC group of patients, it was impossible to carry out multivariate analyses for tumor death in these groups. Survival curves were drawn by the Kaplan–Meier method.[32] All analyses were done with Statistica/Windows software (StatSoft, Tulsa, OK, USA).

Results

Analyses for the number of nodal metastases. Allred score for p53 in tumor stromal fibroblasts (Fig. 3A), Allred scores for ER, PR, and p53 in tumor cells, invasive tumor size, skin invasion, adipose tissue invasion, histological grade, fibrotic focus, lymph vessel invasion, and blood vessel invasion were significantly associated with the number of nodal metastases in the univariate analyses (data not shown). Invasive tumor size, lymph vessel invasion, skin invasion, p53 Allred score in tumor stromal fibroblasts, blood vessel invasion, histological grade, and Allred score for PR in tumor cells were significantly associated with the number of nodal metastases in the multivariate analyses (Fig. 3B).

Factors significantly associated with distant organ metastasis and tumor death. HER2 expression in tumor cells, Allred scores for p53 in tumor cells and in tumor stromal fibroblasts (Fig. 4A), Allred scores for ER in tumor cells, Allred scores for PR in tumor cells, invasive tumor size, histological grade, FF diameter, lymph vessel invasion, blood vessel invasion, UICC pN categories, and UICC pTNM stages were significantly associated with distant organ metastasis and tumor death in the univariate analyses (data not shown). Age was significantly associated with tumor recurrence in the univariate analyses, and skin invasion was significantly associated with tumor death in the univariate analyses (data not shown). Adjuvant therapy, muscle invasion, adipose tissue invasion, and tumor necrosis showed no significant association with tumor recurrence or tumor death in the univariate analyses (data not shown).

Among the patients who did not receive adjuvant therapy, only histological grade 3 significantly increased the hazard rate (HR) for distant organ metastasis in the multivariate analyses (data not shown).

In the UICC pTNM stage I patients who received adjuvant therapy, Allred scores of 4–8 for p53 in tumor stromal fibroblasts, histological grade 3, and FF diameter > 8 mm significantly increased the HR for distant organ metastasis in the multivariate analyses (Table 1).

In the UICC pTNM stage II patients who received adjuvant therapy, Allred scores of 4–8 for p53 tumor stromal fibroblasts, age ≤39 years, and FF diameter > 8 mm significantly increased the HR for distant organ metastasis in the multivariate analyses (Table 2).

Among the UICC pTNM stage III patients who received adjuvant therapy, p53 Allred scores of 4–8 in tumor stromal fibroblasts significantly increased the HR for distant organ metastasis and tumor death in the multivariate analyses (Table 3). FF diameter > 8 mm, the presence of blood vessel invasion, and category 3 HER2 expression in tumor cells significantly increased the HR for distant organ metastasis, and histological grade 3 significantly increased the HR for tumor death in the multivariate analyses (Table 3).

Among the triple-negative IDC patients, Allred scores of 4–8 for p53 in tumor stromal fibroblasts (Fig. 4B), UICC pN2 and pN3, and age ≤ 39 years significantly increased the HR for tumor recurrence in the multivariate analysis (Table 4).

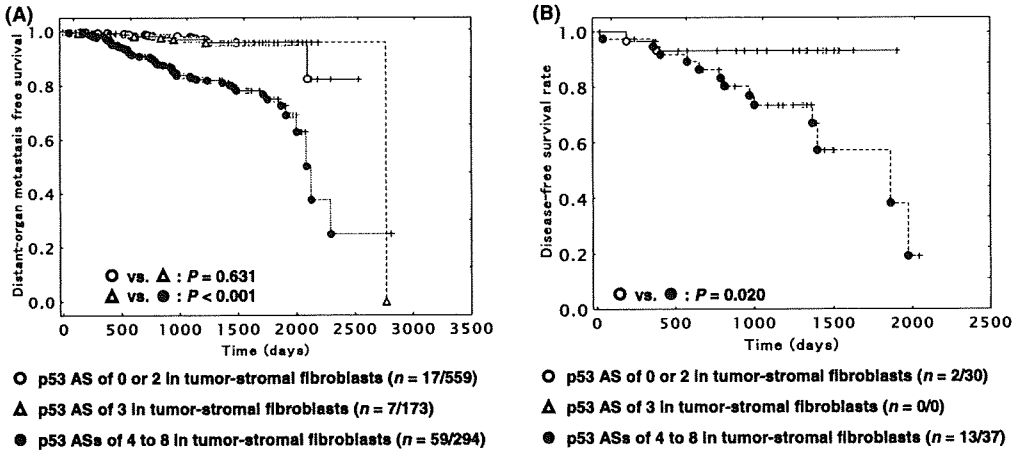

Fig. 4. (A) Distant organ metastasis-free survival curves of invasive ductal carcinoma (IDC) patients according to the Allred scores for p53 in their tumor stromal fibroblasts and (B) the disease-free survival curves of the triple-negative IDC patients. (A) Distant organ metastasis-free survival of IDC patients with Allred scores of 4–8 for p53 in tumor stromal fibroblasts is significantly shorter than that of IDC patients with other Allred scores for p53 in tumor stromal fibroblasts. (B) IDC patients with Allred scores of 4–8 for p53 in tumor stromal fibroblasts had a significantly shorter disease-free survival than IDC patients with Allred scores of 0 or 2 for p53.

Table 1. Multivariate analyses for distant organ metastasis in UICC pTNM stage I invasive ductal carcinoma patients who received adjuvant therapy (*n* = 247)

	Cases	DOMR (%)	HR	95% CI	*P*-value
Allred scores for p53 in tumor stromal fibroblasts					
0 or 2	148	2 (1)	Referent		
3	38	0	Referent		
4 to 8	61	9 (15)	32.2	3.4–306.1	0.003
Histological grade					
1	66	0	Referent		
2	123	2 (2)	Referent		
3	62	9 (15)	7.5	1.6–35.1	0.011
Fibrotic focus, diameter					
Absent	186	6 (3)	Referent		
≤8 mm	45	3 (7)	1.7	0.4–7.6	0.457
>8 mm	20	2 (10)	9.1	1.5–56.4	0.018

CI, confidence interval; DOMR, distant organ metastasis rate; HR, hazard rate.

Table 2. Multivariate analyses for distant organ metastasis in UICC pTNM stage II invasive ductal carcinoma patients who received adjuvant therapy (*n* = 435)

	Cases	DOMR (%)	HR	95% CI	*P*-value
Allred scores for p53 in tumor stromal fibroblasts					
0 or 2	226	8 (4)	Referent		
3	87	3 (4)	1.8	0.6–4.8	0.263
4 to 8	122	18 (15)	3.8	1.8–8.1	<0.001
Age (years)					
≤39	41	7 (17)	Referent		
>39	402	24 (6)	0.3	0.1–0.7	0.006
Fibrotic focus, diameter					
Absent	265	14 (5)	Referent		
≤8 mm	101	5 (5)	1.5	0.4–6.4	0.578
>8 mm	77	12 (16)	2.8	1.3–6.0	0.006

CI, confidence interval; DOMR, distant organ metastasis rate; HR, hazard rate.

Table 3. Multivariate analyses for distant organ metastasis, and tumor death in UICC pTNM stage III invasive ductal carcinoma patients who received adjuvant therapy (*n* = 185)

	Cases	DOMR (%)	HR	95% CI	*P*-value
Distant organ metastasis					
Allred scores for p53 in tumor stromal fibroblasts					
0 or 2	88	6 (7)	Referent		
3	22	2 (9)	0.64	0.1–4.1	0.639
4 to 8	74	25 (34)	6.2	2.7–13.8	<0.001
Fibrotic focus, diameter					
Absent	97	13 (13)	Referent		
≤8 mm	46	5 (11)	0.4	0.1–1.2	0.099
>8 mm	42	15 (36)	3.4	1.6–7.0	<0.001
Blood vessel invasion					
Absent	145	19 (13)	Referent		
Present	38	14 (37)	2.7	1.3–5.7	0.006
HER2 expression					
0 or 1	119	19 (16)	Referent		
2	38	4 (11)	0.7	0.2–2.3	0.588
3	27	10 (37)	2.4	1.1–5.3	0.023
Tumor death					
Allred scores for p53 in tumor-stromal fibroblasts					
0 or 2	88	1 (1)	Referent		
3	22	0	Referent		
4 to 8	74	16 (22)	18.1	2.4–139.5	0.005
Histological grade					
1	30	0	Referent		
2	76	3	Referent		
3	79	14 (18)	3.8	1.1–12.9	0.038

CI, confidence interval; DOMR, distant organ metastasis rate; HR, hazard rate; TDR, tumor death rate; –/–, not significant.

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Table 4. Clinicopathological factors significantly associated with tumor recurrence in triple-negative invasive ductal carcinoma patients in multivariate analyses (*n* = 74)

	Cases	TRR (%)	HR	95% CI	*P*-value
Allred scores for p53 in tumor-stromal fibroblasts					
0 or 2	30	2 (7)	Referent		
3	7	0	Referent		
4 to 8	37	13 (35)	12.0	2.3–62.0	0.003
UICC pN category					
pN0	41	3 (7)	Referent		
pN1	17	4 (24)	1.4	0.3–6.9	0.701
pN2	9	4 (44)	7.8	2.0–30.6	0.004
pN3	7	4 (57)	26.8	6.0–122.6	<0.001
Age (years)					
≤39	6	3 (50)	Referent		
>39	68	12 (18)	0.2	0.04–0.8	0.022

CI, confidence interval; HR, hazard rate; TRR, tumor recurrence rate; UICC pN0, no nodal metastasis; UICC pN1, one to three nodal metastases; UICC pN2, four to nine nodal metastases; UICC pN3, 10 or more nodal metastases. Triple-negative residual invasive ductal carcinoma means: (1) Allred scores for estrogen receptor of 0 or 2; (2) Allred score for progesterone receptor of 0 or 2; and (3) HER2 expression category of 0 or 1.

Discussion

Patocs *et al.*[21] showed a significant association between p53 mutations in tumor stroma and nodal metastasis in patients with sporadic breast cancer, and the results of the multivariate analyses in the present study clearly confirmed that p53 expression in tumor stromal fibroblasts, but not in tumor cells, is an important independent factor associated with the number of nodal metastases by IDC.

The present study also clearly demonstrated that Allred scores of 4–8 for p53 expression in tumor stromal fibroblasts significantly increased the HR for distant organ metastasis and tumor death in the IDC groups independent of UICC pTNM stage or triple negativity. Thus, Allred scores of 4–8 for p53 in tumor stromal fibroblasts can be concluded to be a very important factor for accurately predicting the outcome of IDC patients independent of UICC pTNM stage or triple negativity, and it can be concluded that the modified method that we used to assign Allred scores to p53 expression in tumor stromal fibroblasts should be used to accurately evaluate the malignant potential of IDC from the standpoint of the tumor stroma.

In the present study we did not test Allred scores for p53 expression for associations with the presence of *p53* gene abnormalities in the tumor stromal fibroblasts. Although *p53* mutations in tumor stromal fibroblasts are relatively common in primary breast cancer and other cancers and have a positive effect on cancer growth,[18–21,33] some studies show no *p53* mutations observed in the tumor stroma of breast cancer,[34,35] and the possibility of technical problems (e.g. PCR artifacts for *p53* gene abnormalities) is raised by Campbell *et al.*[36] Thus, although the mechanism responsible for increasing the malignant potential of IDC related to the expression of p53 in tumor stromal fibroblasts should be investigated from the standpoint of *p53* gene abnormalities, p53 immunoreactivity in tumor stromal fibroblasts may in fact reflect specific reactive changes within the stroma that are related to the outcome of patients with IDC.

The results of the present study clearly showed that FF diameter, age, blood vessel invasion, and UICC pN2 were good prognostic factors. In previous studies we found that FF diameter was a significant prognostic factor for IDC patients,[7–10,13,37] and the significant prognostic power of FF diameter in the IDC group was confirmed in the present study. Thus, one can conclude that FF diameter is an important histological outcome predictor for IDC patients, and biological characteristics of tumor stroma, e.g. tumor stromal fibroblasts expressing p53, FF, play a very important role in tumor progression of IDC of the breast.

In conclusion, this is the first study to clearly demonstrate that p53 expression by tumor stromal fibroblasts is strongly associated with the number of nodal metastases and the outcome of IDC patients. The modified Allred scoring system is very suitable for accurately assessing p53-expressing tumor stromal fibroblasts in IDC independent of adjuvant therapy, UICC pTNM stage, or the HR or HER2 status of the IDC. The p53 expression in tumor stromal fibroblasts will probably be a very important target for tumor gene therapy of IDC, although it will be necessary to confirm that the p53 Allred score also provides significant prognostic power for IDC patients in a prospective study.

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Primary tumor resection improves the survival of younger patients with metastatic breast cancer

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Abstract. Current treatments for metastatic breast cancer (MBC) include palliation with chemotherapy and/or hormone therapy, neither of which has the effect of adequately improving survival. Local surgery to remove the primary breast tumor is performed to improve local control and prevent uncontrolled chest wall disease (UCD). From June 1962 to February 2007, 344 patients with MBC were treated at National Cancer Center Hospital. In our review of these cases, we evaluated the prognostic impact of local surgery and other clinicopathological features. One hundred and sixty patients (47%) underwent resection of primary breast tumor, while 184 (53%) patients were treated without surgery. Overall survival (OS) was prolonged in patients treated with surgery (p=0.049), younger patients (age <50, p=0.023), and patients with bone or soft tissue metastases (p=0.013). While surgery significantly improved OS in young patients (p=0.021), it did not increase OS in older patients (age >51, p=0.665) or patients with visceral metastasis (p=0.797). This study demonstrated that local surgery improved OS of patients with MBC; local surgery should therefore be considered, especially in young patients. Prospective studies are required to validate these findings and evaluate the impact of surgical intervention.

Introduction

Recently, breast cancer became the most common cancer in Japanese women; and its incidence continues to increase. The incidence of metastatic breast cancer (MBC), defined as a primary breast tumor with distant metastasis, is increasing, comprising ~3% of newly diagnosed breast cancers in Japan, which is similar to the 6% seen in the United States according to the Surveillance, Epidemiology, and End Results (SEER) data. Treatment for breast cancer has also been progressing rapidly. Surgical interventions have become significantly less invasive with the introduction of breast-conserving therapy and sentinel lymph node biopsy; systemic chemotherapeutic agents have become increasingly safe and effective. Although such treatments have made better control of MBC possible, the therapeutic guidelines for MBC have not changed. Palliative treatment remains standard care, utilizing systemic therapy with chemotherapeutic, hormonal, and biologic agents (1,2). Resection of the primary tumor was not considered curative treatment; it has been used solely as local therapy to prevent uncontrolled wall disease. Therefore, local surgery was performed relatively late in treatment and only if the primary tumor and metastases could not be reduced and controlled with systemic therapy.

The possibility that surgical procedures improve the survival of those patients has been reported retrospectively (3-6); this issue is still hotly debated at major breast conferences. The details of these studies, such as tumor sensitivity to systemic therapy and timing of surgery with respect to systemic treatment, were unclear. Improvements in primary systemic therapies have increased the numbers of MBC patients with resectable small primary tumors and controllable metastatic lesions after treatment. With all of these new developments, we need definitive guidelines for the treatment of these patients. In this study, we evaluate the efficacy of primary tumor resection at prolonging the overall survival of MBC patients and analyzed the relationship between response to surgery and clinicopathological features.

Patients and methods

Patients and treatments. Records of all patients with metastatic breast cancer (MBC) treated between June 1962 and February 2007 at the National Cancer Center Hospital (NCCH) was extracted from the database for inclusion in this retrospective study. Baseline information collected included patient demographics, tumor characteristics (size, node status, histological characteristics, estrogen and progesterone receptor status, and Her2/neu status), tumor site, number of metastases, type and timing of operative intervention, and use of hormonal therapy and chemotherapy. We classified patients into two categories based on the age when primary treatment began;

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younger patient was defined as <50 years old, while older included patients >51 years old. Sites of metastases were categorized as bone and/or soft tissue (bone, lymph nodes) or visceral (lungs, pleura, mediastinum, peritoneum, liver, and brain) metastases. All patients were treated with some form of systemic therapy, including chemotherapy and/or hormonal therapy.

In later years of the study (only after 2002), trastuzumab was administered to patients with tumors exhibiting HER2 overexpression. In the group who underwent surgery, surgical procedures included Halstead operation, modified radical mastectomy and breast conserving surgery with axillary dissection and simple mastectomy without axillary dissection. All primary breast tumors were removed completely. Time to surgery was calculated from the date in which primary treatment begun.

Metastatic involvement was determined by physical examination, biochemical analysis, and initial routine imaging procedures before or within one month of beginning primary treatment. Bone scans alone were not considered diagnostic of bone involvement. Abnormalities seen on bone scan were confirmed by radiography. Liver involvement was determined by computed tomography or ultrasound findings consistent with metastases. Pleural or peritoneal involvement was determined by positive cytology of effusion fluid and appropriate imaging studies. Cervical or contralateral lymph node involvement was classified as distant soft tissue metastases. Chest wall recurrence was excluded from soft tissue metastases.

Evaluation of pathological factors. Surgical specimens were sectioned at 7-10 mm for evaluation of the pathological response by pathologists. Expression levels of ER (1D5, Dako Cytomation), PgR (1A6, Novocastra), and HER2 (HercepTest®, Dako Cytomation) were examined by immunohistological staining. ER and PgR were classed as positive when >10% of cancer cell nuclei exhibited positive staining, regardless of intensity. HER2 was scored as follows: (0), negative for cells; (1+), slightly positive in >10% of cancer cells; (2+), moderately positive in >10% of cancer cells; and (3+), markedly positive in >10% of cancer cells. Immunohistochemistry (IHC) with scores of (2+) or (3+) were defined as HER2-positive.

Statistical analysis. Overall survival (OS) was calculated from the date upon which treatment was initiated to the date of death or last visit. Kaplan-Meier plots and log-rank test were used to assess differences in survival. All comparisons were two-tailed. Cox-proportional hazards models were fit for OS. $P<0.05$ were considered statistically significant.

Results

The medical records of 344 MBC patients treated at NCCH were reviewed in this study. Table I lists patient characteristics. The median age at initiation of primary treatment was 54 years (28-82). We evaluated 141 (41%) young patients <50 years of age and 203 (59%) older patients >51 years of age. Sixty-six (19%) patients were diagnosed between 1962-1980, 62 (18%) between 1981-1990, 96 (28%) between 1991-2000, and 120 (35%) between 2001-2007. Clinical tumor size at diagnosis was assessed as T1 in 21 (6%), T2 in 60 (17%), T3 in 53 (15%), and T4 in 208 (60%) patients. ER, PgR, and HER2 positivity was detected in 106 (31%), 87 (25%), and 84 (24%) patients, respectively. The ER/PgR and HER2 status of 137 (40%) and 149 (43%) patients, respectively,

Table I. Patient characteristics and Cox proportional hazard model for overall survival.

Parameters	No. of patients (%)	Hazard ratio (95% CI)
Age, median (range)	54 (28-82)	
≥51	203 (59)	1.00
≤50	141 (41)	0.87 (0.77-0.98)
Period of diagnosis		
1962-1980	66 (19)	1.00
1981-1990	62 (18)	0.87 (0.69-1.07)
1991-2000	96 (28)	0.95 (0.78-1.15)
2001-2007	120 (35)	0.85 (0.69-1.03)
Clinical T stage		
T1	23 (6)	1.00
T2	60 (17)	0.92 (0.65-1.41)
T3	53 (15)	1.01 (0.70-1.54)
T4	208 (60)	1.11 (0.82-1.63)
Estrogen receptor		
Positive	106 (31)	1.00
Negative	100 (29)	1.12 (0.93-1.33)
Unknown	138 (40)	1.25 (1.07-1.46)
Progesterone receptor		
Positive	87 (25)	1.00
Negative	120 (35)	1.10 (0.92-1.30)
Unknown	137 (40)	1.28 (1.10-1.50)
HER2		
Positive	84 (24)	1.00
Negative	111 (32)	0.96 (0.80-1.14)
Unknown	149 (43)	1.13 (0.96-1.31)
Site of metastases		
Bone/soft tissue	169 (49)	1.00
Visceral	175 (51)	1.16 (1.03-1.29)
Chemotherapy		
Yes	315 (88)	1.00
No	29 (12)	1.21 (0.96-1.48)
Hormone therapy		
Yes	172 (50)	1.00
No	146 (42)	0.90 (0.75-1.09)
Unknown	26 (8)	1.64 (1.22-2.13)
Local surgery		
No	184 (53)	1.00
Yes	160 (47)	0.89 (0.79-1.00)

were unknown. Bone and/or soft tissue and visceral metastases were present in 169 (49%) and 174 (51%) patients, respectively.

Three hundred and fifteen (88%) patients received chemotherapy, while 172 (50%) patients received hormonal therapy. Local surgery was performed for 160 (47%) patients. Surgical procedures included Halstead operation (n=101, 63%), modified radical mastectomy (n=34, 21%) and breast conserving surgery (n=4, 3%) with axillary dissection, and 21 patients (13%) underwent simple mastectomy without axillary dissection. All primary breast tumors were removed completely. One hundred and fifty (94%) of which underwent local surgery as primary therapy. The other patients underwent local surgery to avoid uncontrolled chest disease at late period of treatment when the primary tumors were regrowing. Local radiation after surgery was not used. There were patients without local surgery who underwent local radiation therapy.

Median follow-up time was 33 months (95% confidence interval, 29.2-38.0 months). We plotted overall survival on Kaplan-Meier curves of the patient cohort according to each parameter (Fig. 1). OS was significantly prolonged in patients receiving surgery [surgery vs. no surgery, median survival time (MST): 27 vs. 22 months, p=0.049], younger patients (younger vs. older, MST: 28 vs. 22 months, p=0.023), and patients with bone/soft tissue metastasis (bone/soft tissue vs. visceral, MST: 29 vs. 21 months, p=0.013). Hormonal therapy was also associated with improved OS (Fig. 1). Patients receiving hormonal therapy had a better prognosis than those who did not receive hormonal therapy. Chemotherapy was not associated with an improved OS. ER, PgR, and HER2 status, clinical tumor size, and period of diagnosis had no significant effects on OS (Table I).

The demographics and tumor characteristics of MBC patients treated with or without surgery are compared in Table II. Patients who underwent surgery tended to be younger (p=0.02) and were diagnosed earlier in the study period (p<0.0001) than patients who did not undergo surgery. Clinical tumor size did not differ between the two groups (p=0.39). Patients with bone/soft metastasis (p<0.0001) or those who received hormonal therapy (p=0.05) were more likely to undergo surgery. There was no significant factor to predict survival in multivariate analysis (data not shown).

Fig. 2 displays Kaplan-Meier curves describing the OS of patient cohorts who received local surgery or no surgery as classified according to age and site of metastases. Surgery was associated with a better prognosis in younger patients (surgery vs. no surgery, MST: 35 vs. 24 months, p=0.021). However, local surgery did not improve OS in older patients (p=0.665) and those with visceral metastases (p=0.797) and bone/soft tissue metastasis (p=0.095).

Discussion

The treatment of MBC has traditionally been palliative care with chemotherapy, hormonal therapy, and radiation therapy. According to the Hortobagyi algorithm (7), hormonal therapy is chosen as the first therapy for hormone receptor-positive MBC without visceral metastases. If MBC is hormone receptor-negative or resistant to hormone therapy, chemotherapy is used, but has the possibility of severely

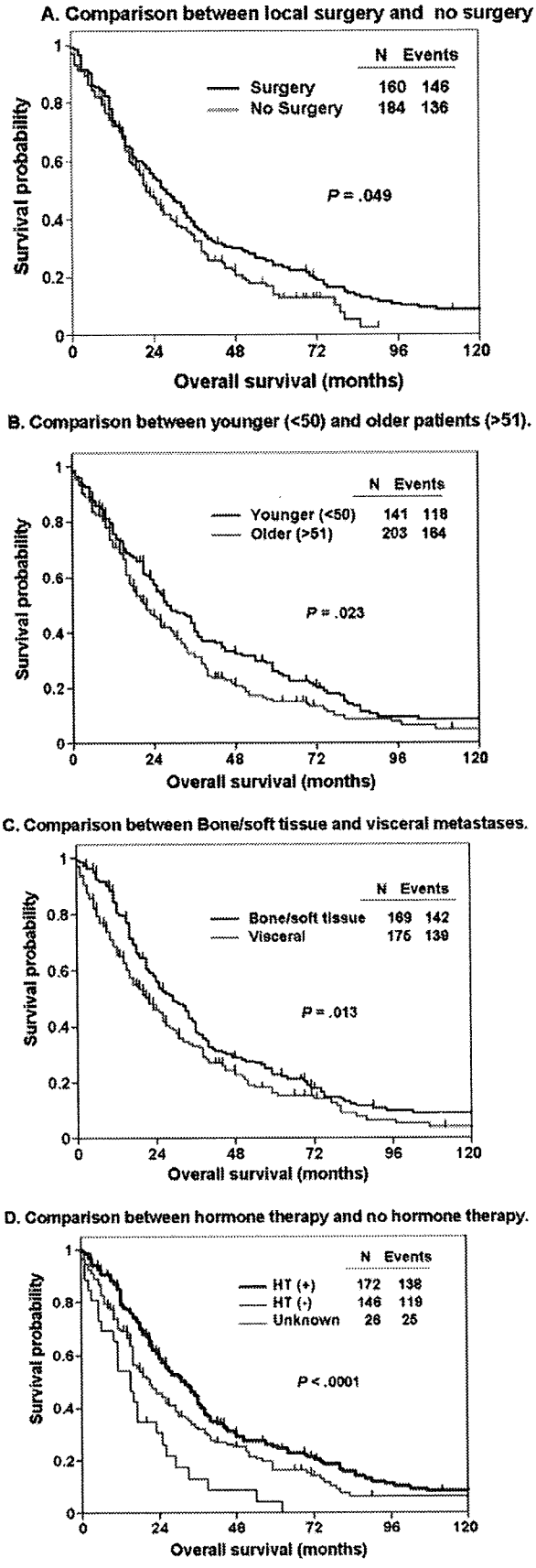

Figure 1. Kaplan-Meier curves of overall survival for MBC patients: (A) comparison of local surgery and no surgery; (B) comparison of younger (≤50) and older patients (≥51); (C) comparison of bone/soft tissue and visceral metastases; (D) comparison of hormone therapy and no hormone therapy.

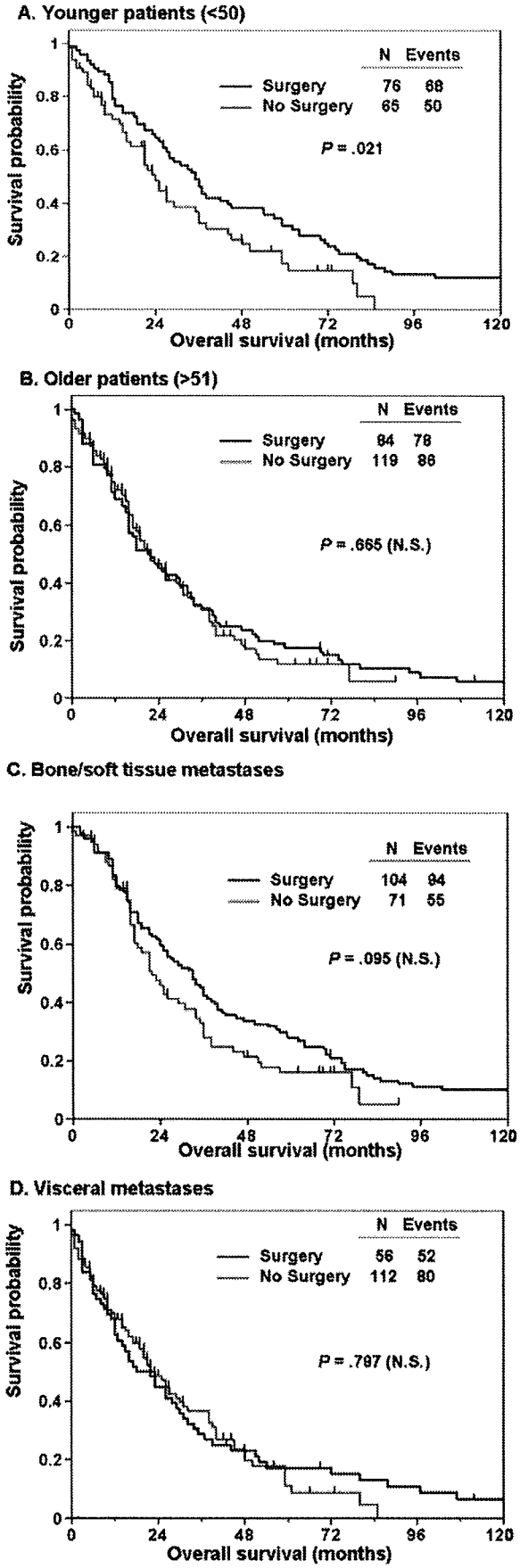

Figure 2. Kaplan-Meier curves of overall survival in the local surgery and no surgery groups: (A) younger patients (≤50); (B) older patients (≥51); (C) bone/soft tissue metastases; (D) visceral metastases.

Table II. Patient characteristics by surgery group.

Parameters	No. of pts (%) no surgery	Surgery	P-value
Age, median (range)			
<50	119 (59)	84 (41)	
>51	65 (46)	76 (54)	0.02
Period of diagnosis			
1962-1980	8 (12)	58 (88)	
1981-1990	8 (13)	54 (87)	
1991-2000	53 (55)	53 (45)	
2001-2007	115 (96)	5 (4)	<0.0001
Clinical T stage			
T1	12 (57)	9 (43)	
T2	29 (48)	31 (52)	
T3	23 (43)	30 (57)	
T4	119 (57)	89 (93)	0.39
Site of metastases			
Bone/soft tissue	67 (40)	102 (60)	
Visceral	116 (67)	58 (33)	<0.0001
Hormonal therapy			
Yes	84 (49)	88 (51)	
No	89 (61)	57 (39)	
Unknown	11 (42)	15 (58)	0.05

impacting quality of life. Current anti-tumor drugs, such as the anthracyclines and taxanes, are quite effective, as are molecularly targeted drugs such as trastuzumab. Using these drugs, the response rate of patients with locally advanced breast cancer was 80-90%; many primary breast cancers were reduced and resected in breast-conserving surgery (8,9). Other effective agent with fewer side effects, such as aromatase inhibitors and oral 5-fluorouracil, can prevent further disease progression, keeping patients stable and maintaining their quality of life for extended periods. Therefore, the control and/or reduction of both primary and metastatic lesions using systemic therapies has improved the living conditions of patients with MBC.

Surgery for breast cancer has also become safer and less invasive with the advent of improved surgical techniques and diagnosis, such as breast-conserving surgery and sentinel lymph node biopsy (10-12). These surgeries have few complications. However, several intensive chemotherapies have destructive high-grade and long-term side effects. Moreover, chemotherapy needs to be continued. According to the Hortobagyi algorithm, minimal surgery performed early in the treatment of MBC does not negatively impact quality of life. We need to evaluate prospectively the difference between local surgery and intensive chemotherapy. As studies have also demonstrated that local surgery for MBC avoids uncontrolled chest disease (13), local surgery for MBC should be discussed with patients as early as possible.

We evaluated the efficacy of local surgery in MBC patients treated at NCCH through a comprehensive chart review. The medical oncologists currently follow the principles of MBC treatment outlined by the current National Cancer Institute (NCI) guidelines (1). Only rarely do MBC patients undergo local surgery; the aims of such surgeries were to avoid uncontrolled chest disease late in treatment. From 1960 to 1990, however, early primary tumor resection was significantly more common because there were far fewer effective drugs. In addition, there were patients who were discovered to have MBC immediately after surgery for the primary lesion, because in those days we could not examine and get the results of tests for metastases immediately. Therefore, it was more common for MBC patients diagnosed in previous decades to undergo local surgery. While this retrospective cohort study has several selection biases, the results demonstrate an efficacy of local surgery in MBC similar to previous studies.

Moreover, in our data many patients with local surgery treated in the early period of the study when we could not use effective chemotherapy (taxane and/or anthracycline), these active local surgery prolonged survival. However, in previous studies the time of surgeries were unclear. The time of local surgery is important to decide and consider the strategy of treatment for MBC patients. We think that the active local surgeries which prolong survival and prevent uncontrolled chest disease should be performed relatively early because treatment after a series of chemotherapy and radiation therapy, primary lesion becomes large and a more invasive surgical procedure is needed. The less invasive surgery can be performed in the time when the effective chemotherapy makes the primary lesion smaller. We also examined the efficacy of early local surgery, however, analysis of patients receiving early surgery did not reach statistically significant levels.

Of other clinicopathological features, age at diagnosis and site of metastasis were significantly predictive of improved OS for MBC patients. As expected the overall survival of young patients or patients with bone metastases was longer than old patients or with visceral metastases. In additional analysis, there was a clear benefit of local surgery especially for younger patients <50 years old. In older patients, there was no survival benefit of local surgery. These results demonstrate the possibility to change the strategy of treatment for stage IV breast cancer by age. The difference reported in previous studies (3-6) was not significant for patients with bone and soft tissue metastasis compared with those with visceral metastases. Almost all long-term survivors who underwent local surgery were younger patients with bone and/or soft tissue metastases who went into complete remission following systemic therapy.

We previously reported that MBC patients who had complete remissions at metastatic sites following systemic therapy had a better prognosis in comparison to other patients (14). The number of controllable patients with a good prognosis will hopefully increase with the effective new anti-tumor drugs such as trastuzumab (8). In this study, it was difficult to establish a relationship between overall survival and hormonal therapy or hormone receptor expression because the data from patients treated at the beginning of the study period lacked sufficient information.

Herein we report that local surgery improved overall survival in MBC patients. This effect was especially notable in patients <50 years. In addition, patients with bone and/or soft tissue metastases had a better prognosis. In other metastatic cancer types, several studies have reported the efficacy of primary tumor debulking surgery (15-18). Almost all of these reports were retrospective studies; only one prospective report indicated a benefit of surgery in renal cancer patients (17). In addition, there is a report that self-seeding from primary cancer decides the incidence and growth of metastatic disease (19). However, the biological mechanisms underlying such a response remain unclear.

The aim of local surgery was to avoid uncontrolled chest disease late in treatment. However, in late period of treatment local surgery becomes relatively invasive for complete resection because the primary tumor is regrowing. We think the primary tumor can be removed less invasively in early period of treatment when the primary tumor is reduced by effective systemic therapy. Additional cases and prospective studies are required to investigate the biological underpinnings of treatment to better understand the appropriate treatment for metastatic cancer.

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トピックス：最近のがん治療

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プライマリ・ケアにおけるポイント

乳癌は世界的に見ても女性が罹患するがんのトップであり，がんで亡くなる女性のうち最も多いのも乳癌である．一方，欧米諸国のなかには罹患率の増加にストップがかかり，死亡率の減少が見られる国もあるが，日本はいまだに罹患率，死亡率ともに増加している．この対策として，マンモグラフィ検診の普及・啓発による早期乳がんの発見機会の増加が期待されている．日本人の場合，84歳までに4.5%（22人に1人）の女性が乳癌になり，そのうち1.1%が亡くなると推計されている．また，罹患年齢のピークが40～50歳にあるのも特徴である．乳癌は，罹患率と死亡率の格差が大きいことから，比較的予後がよいこと，また，固形がんとしては薬物療法・放射線治療の効果が期待でき，これらを組み合わせることによる外科手術の低侵襲化か急速に進んでいる．

手術療法のポイントとしては，乳房温存療法とセンチネルリンパ節生検法の組み合わせによる低侵襲治療の標準化が可能となり，さらに臨床試験としてnon-surgical ablationなどの非切除治療も試みられ始めている．

薬物療法の特徴としては，ホルモン療法や分子標的療法による治療の個別化が実現しつつあるが，治療が長期化するため副作用の管理などが重要なポイントとなる．乳癌診療はオンコロジーの手本であり，幅広い領域の知識と治療手段が要求されることを知っておいていただきたい．

I 手術療法

乳癌の手術は，乳房切除と腋窩リンパ節切除の組み合わせが基本である．ただし，術前に切除生検などにて非浸潤がんと確定した場合は，腋窩リンパ節切除の省略が可能である．

1 乳房切除

乳房の手術に関しては乳房全切除と部分切除がある．部分切除の場合は切除後，乳房照射を組み合わせた乳房温存療法が原則である．乳房温存療法のガイドラインを表1に示す[1]．放射線治療との組み合わせで，乳房内再発は10年間で5～10%程度となる．切除断端陽性が乳房内再発のリスクファクターの一つである．高齢者でホルモン感受性のある低悪性度の症例以外は，放射線治療を省略すべきではない．わが国でも乳房温存率は60%程度にまで上昇しているが，欧米では乳房温存療法後の乳房内再発が予後に影響を与えることが明らかになってきており，慎重な乳房温存療法の適応決定が望まれる．

乳房温存療法が難しい，あるいは悩む症例には，乳房全切除を選択し，乳房再建（二期的あるいは同時）を併用することも治療のオプションとして提示する必要がある．乳房再建の方法・時期に関してはそれぞれメリット・デメリットがあるため，十分な検討が必要である．

2 腋窩リンパ節の手術

1990年代前半から，乳癌におけるセンチネルリンパ節生検は，欧米を中心にその同定法と診断法について検証が進められてきた．センチネルリン

表1　乳房温存療法の適応

腫瘍の大きさ	腫瘍径3cm以下（良好な整容性が保たれる場合は4cm程度まで許容）
年　齢	若年者とくに35歳以下では乳房内再発率が高いことを念頭に適応を決める
リンパ節転移の程度	炎症性乳癌型乳房内再発のリスクファクターになるが，適応決定因子にはならない
乳頭腫瘤間距離	整容性が保たれれば，乳頭近傍の腫瘍でも適応となり得る
多発病巣	2個の病巣が近傍に存在し，整容性と安全性が保たれれば可
乳管内進展巣の画像評価	マンモグラフィ上，広範囲の石灰化を有する症例は適応外 MRI，超音波検査などで広範囲の乳管内進展巣を有さない症例
放射線照射	原則として併用できる症例

（文献1）より改変）

表2　センチネルリンパ節生検の適応

臨床状況	適応の可否	エビデンスレベル
T1もしくはT2腫瘍	可	高い
T3もしくはT4腫瘍	推奨されない	不十分
多中心性腫瘍	可	限定的
炎症性乳癌	推奨されない	不十分
乳房切除術を伴う非浸潤性乳管癌	可	限定的
乳房切除術を伴わない非浸潤性乳管癌	推奨されない（拡がり5cmより大きい針生検で診断された非浸潤性乳管癌もしくは微小浸潤癌あるいは疑い）	不十分
腋窩リンパ節転移の疑い	推奨されない	高い
高　齢	可	限定的
肥　満	可	限定的
男性乳癌	可	限定的
妊　娠	推奨されない	不十分
内胸リンパ節の評価	可	限定的
乳房生検後	可	限定的
腋窩手術の既応	推奨されない	限定的
乳房手術の既応（乳房形成・再建など）	推奨されない	不十分
術前薬物療法後の後	推奨されない	不十分
術前薬物療法前の前	可	限定的

（文献2）より改変）

パ節は腫瘍からのリンパ流を直接受けるリンパ節と定義される．センチネルリンパ節に組織学的に転移を認めなければ，腋窩リンパ節郭清を行わずにセンチネルリンパ節生検のみの腋窩リンパ節非郭清が可能となった．今日では，センチネルリンパ節生検と腋窩リンパ節郭清は乳癌の標準的な腋窩外科治療に位置づけられる．

腋窩リンパ節郭清による利点は，①癌の局所コントロールが可能になること，②リンパ節転移は最も重要な予後因子であり，正確な病期診断ができること，③リンパ節転移の有無によって術後の補助化学内分泌療法が選択されることなどがあげられる．反面，最近では組織学的リンパ節転移陰性であっても腫瘍本体の悪性度などによって補助化学内分泌療法が選択されることや，早期乳癌症例では4人中3人に実際に腋窩リンパ節転移がないという事実も明らかである．また，腋窩リンパ節郭清に伴う術後の患側上肢の後遺症（浮腫・疼痛・挙上障害・知覚障害・だるさなど）は，今日でも対症療法しかなく患者のQOLを著しく低下

させている．センチネルリンパ節生検は標準治療としての地位を確立しているが，表2の適応を満たす乳癌に対してのみ，現状では実施されるべきである[2]．

3 Non-surgical ablation

早期乳癌における手術に替わる局所治療として，cryo abalation（凍結療法），radiofrequency abalation（RFA：ラジオ波焼灼療法），MR guided focused ultrasound surgery（MRgFUS：MRガイド下集束超音波療法）などが行われている．いずれも保険未承認あるいは適応外となるため，臨床試験や高度医療下の評価が行われているはずである．適応や成績，整容性におけるメリットに関して，引き続き十分な検討・研究が必要である．

Ⅱ 薬物療法

1 術後薬物療法の実際

術後薬物療法の適応は，腫瘍および宿主側の要因として，予後および薬物療法の効果・リスクを評価し，患者との協議のうえ決定する．薬物療法の具体的な適応やレジメンについては，最新の日本乳癌学会のガイドライン，アメリカnational comprehensive cancer networkのガイドラインや，ザンクトガレン国際早期乳がん治療会議の推奨を参考にして診療が行われているので参照されたい．

これらのうち，とくに影響力のある2007年のザンクトガレン国際早期乳癌治療会議における乳癌患者のリスクカテゴリーと治療選択を表3，4に示した[3,4]．今回，2009年度に改訂されたものの概略を表5，6に示した．改訂版に対応した乳癌に実施臨床は今後明らかになってくるものと考えるが，今回の改訂では，ハイリスク患者を選別し術後薬物療法を施行するばかりでなく，ホルモン感受性やHER2の発現状況など，腫瘍の生物学的特性から効果が期待できる患者を抽出し治療を集中するという方針に変更されている点が注目される．

a. ホルモン療法

ホルモン療法は乳癌患者の60～70%を占めるホルモン受容体陽性患者への投与が推奨される．現在，主力である閉経後乳癌患者へのアロマターゼ阻害薬の投与方法を表7に示し，主な副作用を表8に示した．自覚する副作用は化学療法と比較して軽度であるが，治療が長期にわたるため，長期的副作用に対するサポートが今後問題となる．閉経前女性に対してはタモキシフェン5年間内服を標準とし，黄体ホルモン放出ホルモンアナログ

表3 St. Gallen乳癌術後患者のリスクカテゴリー（2007年版）

低リスク	腋窩リンパ節転移陰性で以下のすべてに該当する症例 病理学的腫瘍径2cm以下 Grade 1 腫瘍周囲の広域な脈管浸潤がない HER2タンパク過剰発現/遺伝子増幅がない ERand/orPgR発現あり 年齢35歳以上
中間リスク	腋窩リンパ節転移陰性で以下のいずれかに該当する症例 病理学的腫瘍径2cmを超える Grade 2，3 腫瘍周囲の広域な脈管浸潤がある HER2タンパク過剰発現/遺伝子増幅がある ER，PgRともに発現なし 年齢35歳未満 腋窩リンパ節転移1～3個陽性で以下のすべてに該当する症例 HER2タンパク過剰発現/遺伝子増幅がない ERand/orPgR発現あり
高リスク	腋窩リンパ節転移1～3個陽性で以下のいずれかに該当する症例 HER2タンパク過剰発現/遺伝子増幅がある または，ER，PgRともに発現なし 腋窩リンパ節転移4個以上陽性

ER陰性，PgR陰性，HER2陰性のいわゆる「triple negative」症例は，2005年版では中間リスクに分類されたが，2007年版では高リスクに分類された．（文献3）より改変）

表4　治療標的およびリスクカテゴリーに基づく治療選択

リスクカテゴリー	HER2/neu遺伝子の過剰発現およびまたは増幅	HER2陰性			HER2陽性		
	内分泌反応性	高度反応性	不完全反応性	非反応性	高度反応性	不完全反応性	非反応性
	閉経時期	前　後	前　後	前&後	前　後	前　後	前&後
低リスク	腋窩リンパ節転移陰性で以下のすべてに該当する症例 pT≦2cm，Grade 1，脈管浸潤がない．HER2（−）， ERor/andPgR発現あり，年齢≧35歳	E　E	E　E				
中間リスク	腋窩リンパ節転移陰性で以下のいずれかに該当する症例 pT＞2cm，Grade 2〜3，脈管浸潤がある．　HER2（＋） ERおよびPgRがともに発現なし， 年齢＜35歳	E　E C→E C→E	C→E C→E E　E	C	C→E C→E +Tr　+Tr	C→E C→E +Tr　+Tr	C +Tr
	腋窩リンパ節転移1〜3個陽性でかつ以下のすべてに該当する症例 HER2（−），ERor/andPgR発現あり	E　E C→E C→E	C→E C→E E　E				
高リスク	腋窩リンパ節転移1〜3個陽性でかつ以下のいずれかに該当する症例 HER2（＋）， ERおよびPgRがともに発現なし			C	C→E C→E +Tr　+Tr	C→E C→E +Tr　+Tr	C +Tr
	腋窩リンパ節転移4個以上陽性	C→E C→E	C→E C→E	C	C→E C→E +Tr　+Tr	C→E C→E +Tr　+Tr	C +Tr

推奨される順序で記載している（E：内分泌治療，C：化学療法，Tr：トラスツズマブ）
2007年St. Gallenで分類されたリスクカテゴリーとこれにHER2状況，ホルモン反応性によって推奨される治療法を示す．低リスク以外ではいずれも化学療法が推奨されている．またHER2陽性症例にはすべてトラスツズマブ併用が推奨されている．

（文献3）より改変）

表5　乳がん薬物療法のthresholds

薬物療法の種類		適　応	コメント
	ホルモン療法	ほとんどのER陽性症例に（＋）	リスク，患者背景に応じて
	anti-HER2療法	HER2陽性症例に（＋）	浸潤径1cm未満でn0は適応外
化学療法	HER2（＋）例	anti-HER2療法に化学療法が併用されることが多い	
化学療法	HER2陰性，ホルモンレセプター陰性（トリプルネガティブ）	ほぼ化学療法の適応あり	リンパ節転移陰性で低リスクあるいは特殊型乳癌の一部は除外

（文献4）より改変）

表6　ER陽性，HER2陰性乳癌の治療

臨床病理組織学的因子	化学療法追加の適応あり	中　間	ホルモン療法のみ
ER and PgR	低発現レベル		高発現レベル
histological grade	Grade3	Grade2	Grade1
proliferation Ki67-labelling index	high	intermediate	low
リンパ節転移	4個以上	1〜3個	0個
PVI（peritumoral vasucular invasion）	＋		−
病理学的浸潤径（pT size）	＞5cm	2.1〜5cm	≦2cm
患者の嗜好	できることはやりたい		化学療法の副作用は絶対避けたい
multigene assays gene signature	high score	intermediate score	low score

（文献4）より改変）

表7　閉経後乳癌患者/術後ホルモン療法におけるアロマターゼ阻害薬の投与方法

up-front法	アロマターゼ阻害薬5年間
switching法	タモキシフェン2～3年間内服後，アロマターゼ阻害薬2～3年間（計5年間）
extension法	タモキシフェン5年間内服後，アロマターゼ阻害薬3～5年間

表8　おもなホルモン剤と毒性

薬　剤	対　象	急性毒性	慢性毒性	抗腫瘍効果以外の有益な作用
LH-RHアゴニスト	閉経前	●局所硬結 ●アナフィラキシー ●低エストロゲン症状	●骨塩量減少 ●低エストロゲン症状	
タモキシフェン	閉経前 閉経後	●低エストロゲン症状	●低エストロゲン症状 ●子宮内膜増殖症，癌 ●血栓症 ●白内障	●LDL低下 ●心疾患減少 ●骨塩量増加（閉経後）
アロマターゼ阻害薬	閉経後	●低エストロゲン症状 ●関節痛	●低エストロゲン症状 ●関節痛 ●骨塩量減少 ●病的骨折	●タモキシフェンと比較して低エストロゲン症状，子宮内膜癌，血栓症の発症頻度が低い

低エストロゲン症状：ほてり，熱感，のぼせ，肩こり，頭痛，不眠，めまい，発汗，うつ症状など．

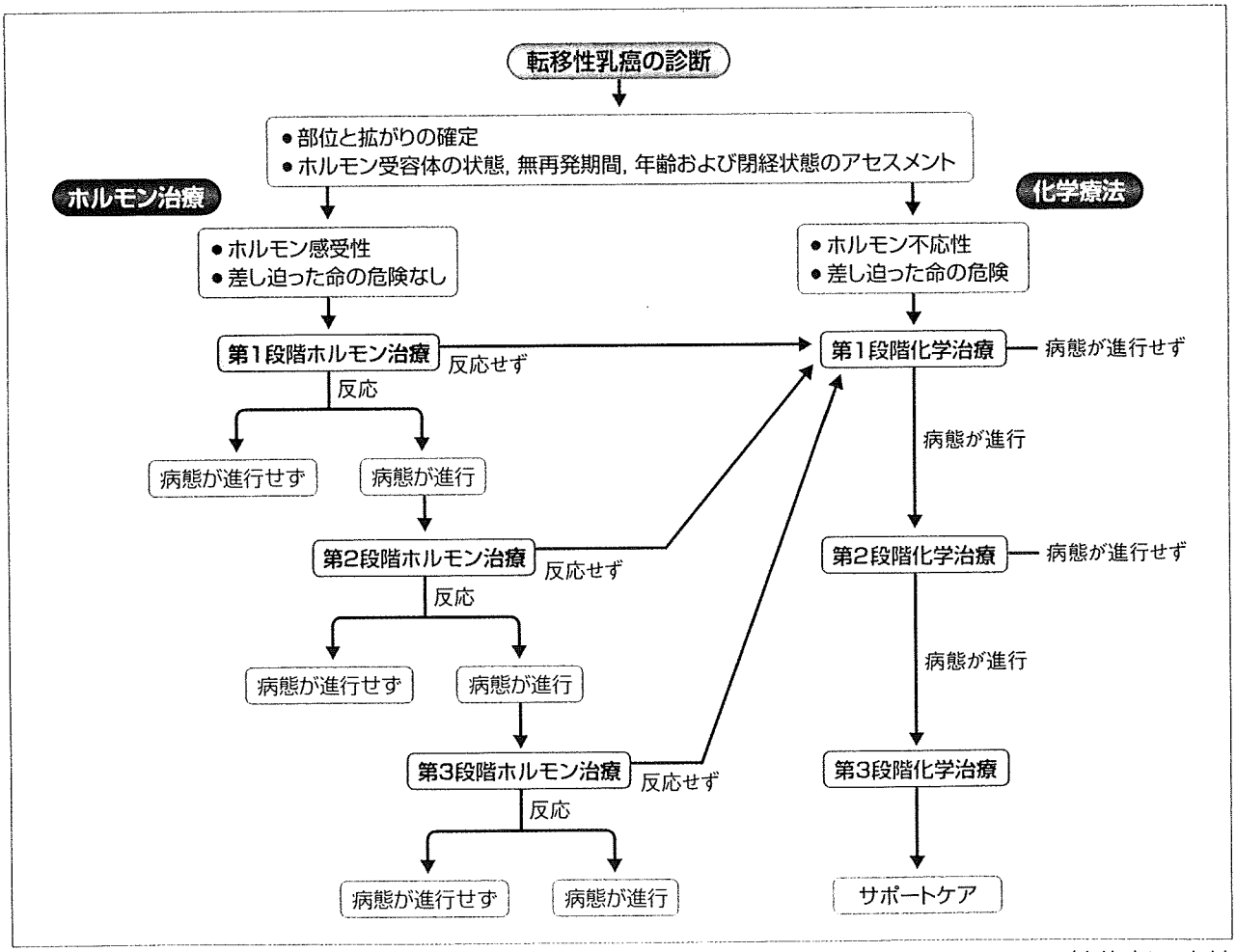

図1　転移性乳癌治療薬のアルゴリズム　（文献5）より改変）

(LH-RHa)2～5年間皮下注射をリスクに応じて追加する.

b, 化学療法

適応に関しては, 表3～6, 図1を参考にしていただきたい.

c. 分子標的療法(トラスツマブ, ラパチニブ)

乳癌の約20～30%にHER2タンパクの過剰発現を認める. HER2過剰発現を認める乳癌は予後不良であることがわかっている. 複数に試験においてトラスツマブ(anti HER2療法)による術後薬物療法のHER2過剰発現例に対する有用性が示された. 投与時に留意すべき点は, 初回投与時のインフュージョン反応(発熱・悪寒)と心不全である. 放射線治療や化学療法併用時に心不全の発症リスクが高い. 同じanti HER2療法薬であるラパチニブは経口薬であるが, 副作用として下痢や発疹が特徴的である.

2 転移性乳癌における薬物療法の役割

転移性乳癌は全身性疾患であり, 現時点では治癒不可能な疾患である. 治療の主体は薬剤による全身的治療であり, 治療の目的は腫瘍縮小により症状を緩和したり, 症状の発現を遅らせること, および延命である. 症状の緩和が得られることによりQOLの向上を図ることが可能である. Hortobagyiによる転移性乳癌の薬物療法の選択を図1に示した[5].

Ⅲ 放射線治療

1 乳房温存療法における放射線治療の役割

部分切除後の放射線療法は乳房内再発率を低下させ, 長期生存率を上昇させる. 放射線は乳房内再発を1/3～1/4程度減らすといわれている. 放射線の早期有害事象には, 全身倦怠感, 疲労感, まれに悪心が認められる. 乳房腫脹および疼痛, 皮膚炎などが開始10日前後から認められる. 遅発性副作用としては, 放射線肺臓炎が照射後2～6ヵ月に1～2%の頻度で認められる. その他, 上腕リンパ浮腫, 腕神経叢障害, 皮膚線維化, 肋骨骨折, 2次がんなどがあげられる. 以前問題になっ

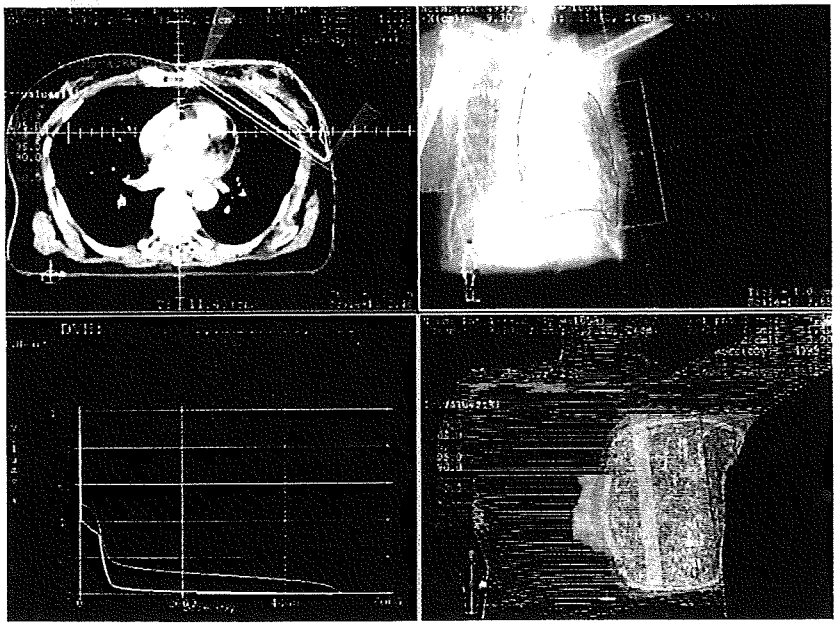

図2 乳房温存療法での放射線治療(CTを用いた3次元原体照射法)
乳房部分切除後に放射線治療を行うと乳房内再発率が低下し, 乳癌による死亡率も低下することがわかっているので, 放射線治療を行うことが標準的である乳房全体を治療し, 肺や心臓になるべく照射されないように接線照射で行う. 肺, 心臓のどのくらいの容積にどの程度の放射線線量が照射されたかが把握できる.