

Clinicopathological Characteristics of Primary Breast Cancer in Older Geriatric Women: A Study of 39 Japanese Patients over 80 Years Old

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The number of primary breast cancers occurring in elderly women is increasing in Japan. Optimization of treatment regimens in this age group requires precise evaluation of the biological aggressiveness of these tumors as well as the performance status and extent of tumor spread. In 39 breast cancer patients who were at least 80 years old, we examined several parameters; the form of surgical therapy, the lymph node status, presence or absence of distant metastases, the histological type and grade of atypia, and overexpression of the c-erbB-2 oncoprotein in the cancer cells. They were correlated with the clinical outcome of the patient. Of the 33 patients who underwent a mastectomy and axillary lymph node dissection, five died from cancer recurrence. Only one out of 22 patients without lymph node metastases died from cancer, while four out of the eight patients with metastases to three or more lymph nodes died from cancer recurrence within 2.7 years of surgery. The overall survival curves also differed between patients with low-risk histological tumors or grade 1 or 2 invasive ductal carcinoma and those with grade 3 invasive ductal/lobular carcinoma. Overexpression of c-erbB-2 also affected survival. Regional recurrence occurred in three out of the six patients for whom only lumpectomy or simple mastectomy was performed. These results indicate that, although primary breast cancer occurring in patients over 80 years old was largely of low-grade malignancy, patients with three or more lymph node metastases, invasive ductal/lobular carcinomas of grade 3, or c-erbB-2 overexpression frequently exhibited an aggressive clinical course.

Key words: Breast cancer — Elderly women — Lymph node metastasis — Histological grade — c-erbB-2

Breast cancer is one of the commonest malignancies in women, especially in Western countries.¹⁾ The incidence of breast cancer in Japanese women has been rising; this has been attributed to an increase in the number of elderly patients.²⁾ As the life span of the population gradually elongates, primary breast cancers are beginning to be detected in patients of 80 years of age or older, posing the difficult question of how radical treatment should be. It is, however, difficult to determine the optimal therapeutic approach in the elderly patients, because of the frequent coexistence of other medical conditions, and the age-related decline in physiological function. Apart from the evaluation of the performance status of these patients, treatment choice should also be dictated by the clinicopathological features of individual breast cancers occurring in the elderly. Clinical aggressiveness of primary breast cancer is revealed not only by the number of regional lymph node metastases, but also by the histological grade of atypia and the overexpression of the c-erbB-2 oncoprotein; the latter is especially important in patients with lymph node metastases.³⁻⁸⁾

In recent years, several reports dealing with the characteristics of breast cancer in elderly women have been published.⁹⁻¹¹⁾ These reports have largely concentrated on describing the clinical aspects, especially in European and American women, with only a few studies evaluating the histological features.

In the present study, we describe the clinicopathological features of breast cancer in 39 Japanese women who were at least 80 years old. We focus on lymph node status, histological grade, and c-erbB-2 overexpression in the primary tumors and discuss the clinical and therapeutic implications of our findings in this elderly patient group.

MATERIALS AND METHODS

Patients Between 1962 and 1993, 5,628 women received surgical treatment (lumpectomy or mastectomy) for breast cancer at the National Cancer Center Hospital (Tokyo). Thirty-nine (0.7%) of these patients were 80 years or over at the time of surgery. From the pathology reports, we obtained data relating to tumor size and the number of regional lymph node metastases. The histological type⁴⁾ and grade of atypia were examined microscopically.

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ically by two pathologists (YM and HT). Histological grading was performed in terms of the sum of scores for the degree of structural and nuclear atypia, and the number of mitotic figures in primary cancer tissue, according to a system⁷⁾ based on a modification of the WHO classification.³⁾ The score was 1 in cases of low-grade atypia or 0–4 mitoses per high power field ($\times 400$), 2 in cases of moderate atypia or 5–10 mitoses, and 3 in cases of high-grade atypia or more than 10 mitotic figures. When the total score was 3 or 4, the case was classified as grade 1; a score of 5, 6, or 7 was classified as grade 2, and a score of 8 or 9 was classified as grade 3.

Immunohistochemistry Overexpression of the c-erbB-2 oncoprotein was examined immunohistochemically by using polyclonal rabbit antibody against the synthetic carboxy-terminal peptide of c-erbB-2 protein (Nichirei Inc., Tokyo). The formalin-fixed, paraffin-embedded tissue blocks were cut into 5 μ m sections and immunostained with the polyclonal antibody by the avidin-biotin complex immunoperoxidase method.⁸⁾ The intensity of the staining was categorized into three groups; negative (–), weakly positive (+), or strongly positive (++) , according to the criteria described previously.⁸⁾ When the sur-

face of cell membrane was distinctly stained for c-erbB-2, the intensity of staining was judged as strongly positive. The weakly positive group showed faint staining in which the difference between membrane and cytoplasm was often unclear. Although the duration of formalin fixation varied from one day to seven days, the judgment of distinct membrane staining was possible without difficulties. As a control of strongly positive immunoreaction, we used tissue sections of a breast cancer which had been shown to have amplification of the c-erbB-2 gene.⁸⁾

Statistical analysis Overall survival curves were calculated using the Kaplan-Meier method.¹²⁾ Differences between the survival curves were compared using the log-rank test.¹³⁾ The patients who died of disease other than breast cancer or of unknown causes were regarded as censored.

RESULTS

Clinicopathological features The number of operations for breast cancer in elderly patients showed an increase over the years: there were three operations between 1962 and 1969, 11 in the 1970s, 11 in the 1980s, and 14 be-

Table I. Breast Cancer Patients Aged 80 Years or More without Axillary Lymph Node Metastasis (n=22)

Case no./ Age/ Side	Tumor size (cm)	Histological type	Histo- logical grade	c-erbB-2 ^{a)}	Opera- tion	Adjuvant therapy	Disease-free survival (years)	Overall survival (years)
1/82/R	unknown	IDC	1	–	radical	none	4.7 + ^{b)}	4.7 ^{c)} (unknown)
2/81/R	2.0	IDC	2	–	radical	none	5.7+	5.7 (heart failure)
3/81/R	2.5	IDC	3	–	radical	none	8.7+	8.7 (unknown)
4/81/L	4.0	IDC	1	–	simple	none	7.3+	7.3 (unknown)
5/81/L	2.5	medullary	3	–	radical	none	20.0+	20.0+
6/83/R	2.5	IDC	2	+	radical	5-fluorouracil	4.6 ^{d)} (lung)	4.8
7/84/L	1.2	IDC	1	–	simple	radiation (30 Gy)	4.1+	4.1+
8/81/L	1.3	IDC	2	unknown	simple	none	4.5+	5.6 (unknown)
9/81/R	4.8	predominantly DCIS	2	++	radical	none	6.2+	6.2 (gastric cancer)
10/83/R	1.0	IDC	2	unknown	radical	none	2.1+	2.1 (heart failure)
11/88/R	1.1	IDC	1	–	radical	none	8.8+	8.8+
12/80/L	1.5	DCIS	1	–	radical	none	6.8+	6.8+
13/80/R	1.0	IDC	1	–	radical	none	8.9+	8.9+
14/91/L	3.5	DCIS	1	–	radical	none	4.3+	4.3 (renal failure)
15/82/L	1.5	mucinous	2	+	radical	none	6.1+	6.1+
16/82/R	1.2	IDC	2	+	radical	none	2.8+	2.8+
17/83/R	1.1	IDC	2	+	radical	none	3.7+	3.7+
18/81/R	2.5	IDC	2	–	radical	none	1.6+	1.6+
19/85/R	1.3	IDC	1	–	radical	none	1.8+	1.8+
20/80/L	unknown	IDC	2	+	radical	none	6.9+	6.9 (unknown)
21/81/R	2.2	IDC	2	+	radical	tamoxifen	2.3+	2.3+
22/86/L	1.3	IDC	2	++	radical	none	0.6+	0.6+

R, right; L, left; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma *in situ*.

a) Status of c-erbB-2 immunohistochemistry: –, negative; +, weakly positive; ++, strongly positive.

b) +, Alive at the last follow-up examination.

c) Cases in parentheses died of the indicated diseases other than spread of breast cancer. unknown, died of unknown cause.

d) Case in parenthesis showed metastasis to the indicated organ.

Table II. Breast Cancer Patients Aged 80 Years or More with Axillary Lymph Node Metastases ($n=11$)

Case no./ Age/Side	Tumor size (cm)	Histo- logical type	Histo- logical grade	c- erbB- 2 ^{a)}	Axillary LN status ^{b)}	Operation	Adjuvant therapy	Disease-free survival (years)	Overall survival (years)
1/82/R ^{c)}	7.5	IDC	2	—	11/14	simple	none	—	0.3
2/80/R	2.2	IDC	3	++	16/20	radical	none	1.3 ^{d)} (local LN)	2.7
3/80/R	unknown	IDC	1	—	2/14	radical	mitomycin C	1.1+ ^{e)}	1.1 ^{f)} (unknown)
4/84/L	2.4	IDC	3	—	2/6	radical	carbarylquinone	13.3+	13.3 (cerebral infarction)
5/84/R	2.0	IDC	3	++	18/18	radical	tamoxifen	0.7 (local LN)	1.4
6/83/L	1.8	IDC	3	—	1/6	radical	none	8.2+	8.2+
7/80/R	2.0	IDC	3	+	3/11	radical	tamoxifen	1.3 (pleura)	2.2
8/82/R	2.2	IDC	2	+	3/12	radical	tamoxifen	2.2+	2.2 (heart failure)
9/81/R	2.2	IDC	2	—	5/30	radical	none	2.3+	2.3+
10/86/L	4.8	IDC	2	—	14/15	radical	tamoxifen	1.8+	1.8+
11/84/R ^{g)}	2.2	IDC	2	—	4/11	lumpectomy	tamoxifen	—	1.8+

R, right; L, left; IDC, invasive ductal carcinoma; LN, lymph node.

a) c-erbB-2 immunohistochemistry status: —, negative; +, weakly positive; ++, strongly positive.

b) Axillary lymph node status, number of metastatic lymph nodes/number of lymph nodes examined.

c) Stage IV case, having metastasis to the lung at surgery.

d) Cases in parentheses showed metastasis to the indicated organs.

e) +, Alive at the last follow-up examination.

f) Cases in parentheses died of the indicated diseases other than spread of breast cancer. unknown, died of unknown cause.

g) Stage IV case, having metastasis to the bone at surgery.

tween 1990 and 1993. Thirty-seven of the patients were in their 80s, while two were over 90 years old. Three out of the 39 patients had experienced contralateral breast cancer, and five had other primary tumors before or after operation for the breast cancer (stomach cancer in two, and urinary bladder, colon, and endometrium in one each). Thus, eight (21%) of the patients were categorized as having multiple tumors. Two other patients had a history of (intraductal) papilloma in the contralateral breast.

The primary tumors were detected in the right breast of 25 patients, and in the left of 14 patients. The size of the primary tumor was always 5.0 cm or smaller, except for one patient with a tumor which was 7.5 cm in size; the size was not recorded in three of the patients.

Histologically, invasive ductal carcinoma (IDC; 32 of 39, 82%) was the commonest type, and comprised seven tumors of grade 1, 18 of grade 2, and seven of grade 3. Other histological types included ductal carcinoma *in situ* (DCIS; $n=2$), IDC with a predominant DCIS ($n=1$), mucinous carcinoma ($n=2$), invasive lobular carcinoma (ILC; $n=1$), and medullary carcinoma ($n=1$). At operation, two of the patients were already stage IV, with distant metastases to bone and lung.

Radical mastectomies, standard or modified, or simple mastectomies with axillary lymph node dissection were performed in 33 patients, who had no coexistent critical medical condition at surgery. Lymph node metastases were detected in 11 patients. Lumpectomies or simple

mastectomies without lymph node dissection were performed in six patients. At operation, one of these six patients was recovering from cerebral infarction, and another was recovering after total cystectomy for urinary bladder cancer. The other four patients had no coexistent critical medical condition.

Patients without lymph node metastases Thirty-three patients had axillary lymph node dissection; 22 of these were negative for metastases (Table I). Three of these 22 cases were DCIS or predominantly DCIS of histological grade 1 or 2, one was a mucinous carcinoma, and one was a medullary carcinoma. Adjuvant therapy was given to only three of the 22 patients. Among the 17 patients with IDC, six were grade 1, and 10 were grade 2. There was only one grade 3 IDC. Only one patient died of cancer recurrence 4.8 years after the initial radical mastectomy. Overexpression of c-erbB-2 oncoprotein was detected in two cases without tumor recurrence.

Patients with lymph node metastases Eleven patients had lymph node metastases (Table II). All of the 11 tumors were IDC, and were either grade 1 ($n=1$), grade 2 ($n=5$), or grade 3 ($n=5$). Adjuvant chemotherapy or endocrine therapy with a single agent was given to seven of the 11 patients (tamoxifen to five patients, carbarylquinone to one, and mitomycin C to one). Four patients including one patient with stage IV disease (case 1) died from the spread of breast cancer within 2.7 years of surgery; three were grade 3 and one was grade 2 and stage IV at operation. Three patients with one or two

Table III. Breast Cancer Patients Aged 80 Years or More on Whom No Axillary Lymph Node Dissection Was Performed (*n* = 6)

Case no./ Age/Side	Tumor size (cm)	Histo- logical type	Histo- logical grade	c-erbB-2 ^{a)}	Operation	Adjuvant therapy	Disease-free survival (years)	Overall survival (years)
1/90/R	3.5	IDC	2	+	simple	none	0.4 ^{b)} (local LN)	2.4 ^{c)} (unknown)
2/80/R	1.8	mucinous	1	--	lumpectomy	tamoxifen	2.3+ ^{d)}	2.3+
3/81/R	2.5	IDC	3	++	lumpectomy	tamoxifen	1.3 (local LN)	1.5
4/81/R	2.5	ILC	3	-	lumpectomy	tamoxifen	1.1 (local LN)	2.4+
5/87/L	1.7	IDC	2	+	lumpectomy	tamoxifen	2.9+	2.9+
6/86/L	4.4	IDC	2	-	lumpectomy	tamoxifen	2.1+	2.1+

R, right; L, left; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LN, lymph node.

a) c-erbB-2 immunohistochemistry status: -, negative; +, weakly positive; ++, strongly positive.

b) Cases in parentheses showed metastasis to the indicated organ.

c) Case in parenthesis died of unknown cause.

d) +, Alive at the last follow-up examination.

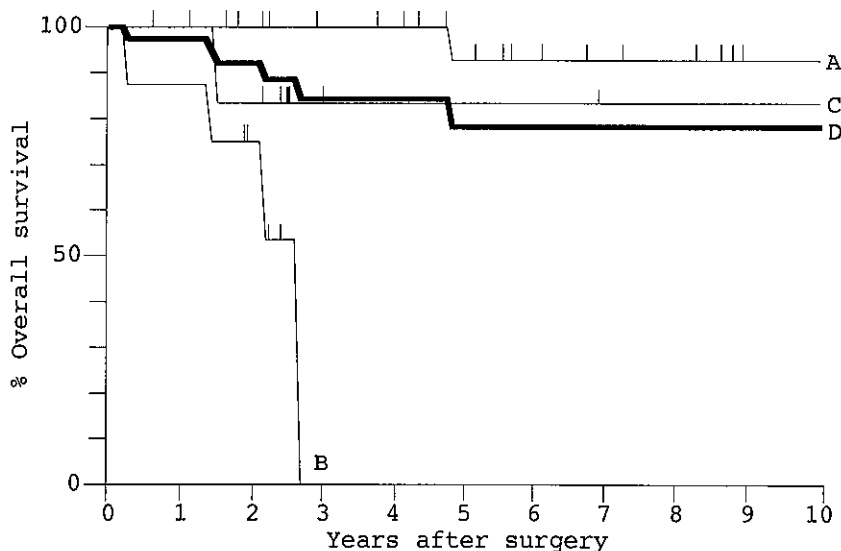


Fig. 1. The overall survival curves for A, patients with zero, one, or two lymph node metastases (*n* = 25); B, patients with three or more lymph node metastases (*n* = 8); C, patients who were treated with either lumpectomy alone or simple mastectomy without lymph node dissection (*n* = 6); and D, all patients aged 80 years or older (*n* = 39). The vertical bars represent the end point of follow-up or death from causes other than recurrent breast cancer.

lymph node metastases at operation did not die of cancer. In the other eight patients with involvement of three or more lymph nodes, cancer death occurred in four. The other stage IV patient (case 11) is alive 1.8 years after surgery. Two patients who were strongly positive for c-erbB-2 died of the cancer.

Breast cancer patients who received lumpectomy or simple mastectomy without axillary lymph node dissection Six patients with invasive carcinoma received only lumpectomy or simple mastectomy without axillary lymph node dissection (Table III). One patient who had

a simple mastectomy (case 1) experienced a recurrence of the tumor in the ipsilateral axillary lymph nodes five months after surgery. The other five patients had lumpectomy and adjuvant tamoxifen administration. Two patients (cases 3 and 4) with invasive carcinoma of grade 3 developed local cancer recurrence within 1.3 years of surgery. One patient (case 3) showed overexpression of the c-erbB-2 oncoprotein and died of recurrent cancer.

Survival curves The overall survival curve for all 39 patients after surgery is shown in Fig. 1. After death from other diseases or unknown causes were excluded,

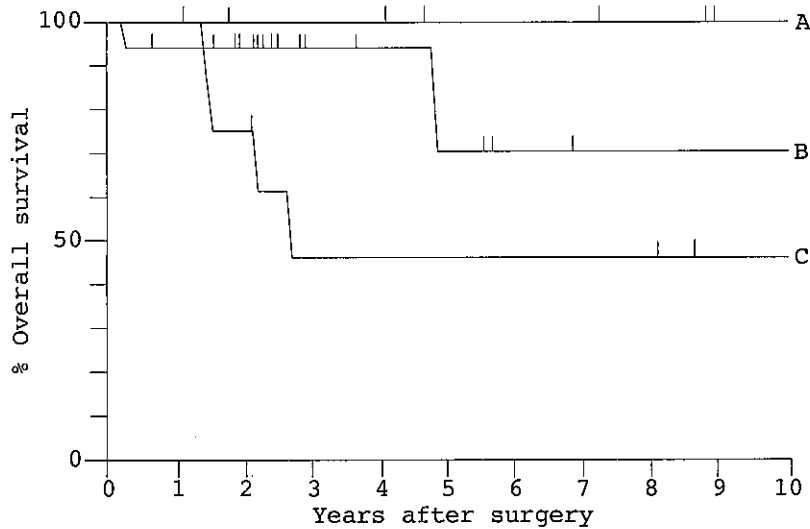


Fig. 2. The overall survival curves for three groups with breast cancer of different histological types and grades. A, Patients with grade 1 invasive ductal carcinoma, or with low-risk histological types ($n=13$); B, patients with grade 2 invasive ductal carcinoma ($n=18$); and C, patients with grade 3 invasive ductal/lobular carcinoma ($n=8$). The vertical bars represent the end point of follow-up or death from causes other than recurrent breast cancer.

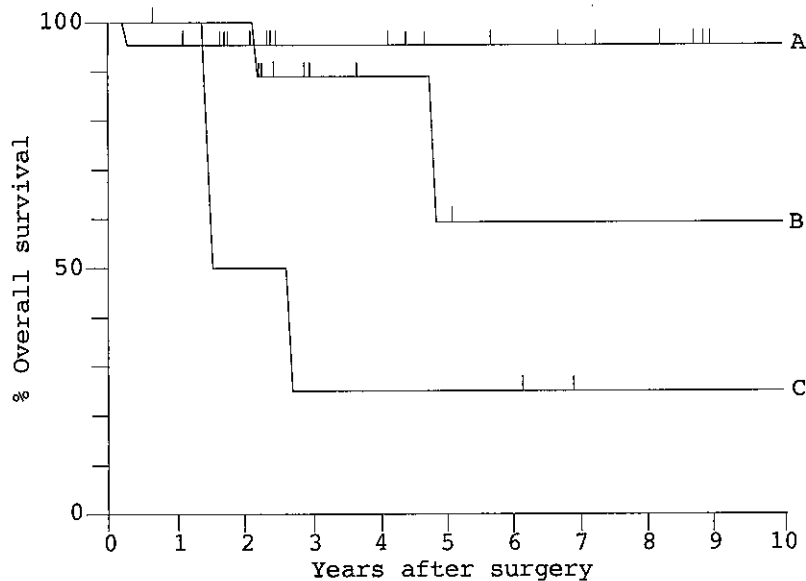


Fig. 3. The overall survival curves for three groups with differential expression of the c-erbB-2 oncoprotein as assessed by immunohistochemistry. A, Patients negative for c-erbB-2 ($n=22$); B, patients weakly positive for c-erbB-2 ($n=10$); and C, patients strongly positive for c-erbB-2 ($n=5$). The vertical bars represent the end point of follow-up or death from causes other than recurrent breast cancer.

both the 5- and 10-year survival rates after surgery were estimated to be 78%. There were no fatal post-operative complications in this series. The survival curves for pa-

tients with zero, one, or two lymph node metastases and with three or more lymph node metastases, and for the group that received only lumpectomy or simple mastec-

tomy without lymph node dissection are also shown in Fig. 1. The survival curves for the three groups with different histological grades and those for the groups with different c-erbB-2 expression levels are shown in Figs. 2 and 3, respectively. Of the eight patients with grade 3 IDC/ILC, five had a recurrence within 1.3 years, and four died within 2.7 years. In contrast, of the 18 patients in the grade 2 IDC group, one of the stage IV cases and one without lymph node metastasis died of cancer spread. Seven patients with grade 1 IDC and the other six in the low-risk histology groups, i.e., DCIS, predominantly DCIS, mucinous carcinoma, and medullary carcinoma, did not develop recurrence.

There were significant differences in the survival curves between (i) patients with zero, one, or two lymph node metastases and those with three or more lymph node metastases ($P < 0.001$), (ii) patients with grade 1 or 2 IDC or the low-risk histology groups, and the grade 3 IDC/ILC group ($P < 0.005$); and (iii) patients with c-erbB-2 overexpression and those with weak or no c-erbB-2 expression ($P < 0.001$).

DISCUSSION

As can be seen in Fig. 1, the outcome of breast cancer in patients who are 80 years of age or over, taken as a group, is not poor, with 77% having disease-free survival and 78% surviving for 10 years following surgery. In 65 patients aged 51–79 and 110 patients aged 50 or younger, who received mastectomies in the National Cancer Center Hospital between 1974 and 1976, the survival rates 10 years after surgery were 72% and 62%, respectively (unpublished data). The relatively excellent prognosis in the elderly age group is compatible with several previous reports.^{14,15} However, some of the elderly breast cancer patients in this series had highly aggressive tumors, with survival of the five patients who died of cancer being 4.8 years or shorter.

By using the number of metastatic lymph nodes as an indicator, breast cancers in such elderly patients can be classified into high- and low-risk groups for cancer recurrence and death. The former group, comprising 24% (8/33) of the patients, for whom lymph node dissection was performed, was characterized by three or more regional lymph node metastases. Of the eight cases in the high-risk group, four died of cancer with the clinical course being very rapid. In contrast, the low-risk group, which comprised two-thirds (25/33) of the cases, was characterized by either no or up to two regional lymph node metastases; cancer recurrence and death occurred in only one of the patients in this group.

Yancik *et al.*⁹ reported that the survival of elderly patients with cancer localized to the breast was not different from the survival in younger patients, but when

the breast cancer involved the adjacent tissue(s) or organs, or when there were positive regional lymph nodes, the prognosis in the elderly was significantly worse.

The incidence of patients with breast cancer of grade 3 and c-erbB-2 overexpression in the elderly group was lower than that in younger age groups. Actually, in the group aged 51–79 and the group aged 50 or younger, the percentages of patients with grade 3 carcinoma were 45% and 44%, and those with carcinoma showing c-erbB-2 overexpression were 28% and 33%, respectively (unpublished data). However, the eight patients who had grade 3 IDC/ILC tumors and the five patients who had overexpression of c-erbB-2 also had a poorer prognosis than the patients with grade 1/2 tumors and those with negative or weakly positive staining for c-erbB-2, respectively. All the patients in these groups who died had three or more lymph node metastases, or did not receive lymph node dissection. Four grade 3 or c-erbB-2-overexpressing IDC/ILC cases with zero, one, or two lymph node metastases did not suffer a recurrence. As the total number of patients studied is small, it is difficult to ascertain whether grade 3 histology and c-erbB-2 overexpression are indicators of prognosis independent of the number of lymph node metastases in women aged 80 years or over.

Local recurrence after lumpectomy or simple mastectomy without lymph node dissection occurred in three of the six patients. Swanson *et al.*¹⁰ also reported high local and regional treatment failure rates after lumpectomy only. In addition, they also reported that, in patients of 80 years of age or over, the outcome was similar between the group given primary radiation therapy and that treated by mastectomy. Veronesi *et al.*,¹⁶ in contrast, suggested that there was no need for radiotherapy in postmenopausal (55 years old or greater) patients who underwent quadrantectomy with axillary dissection.

In order to make a rational decision regarding the use of adjuvant therapy, information on lymph node status, distant metastases, and probably, histological type and grade, as well as the performance status of patients, is important. Adjuvant therapy appeared unnecessary in the low-risk group of these elderly patients with grade 1 or 2, or low-risk histology tumors, i.e., DCIS, predominantly DCIS, medullary carcinoma, and mucinous carcinoma, with either no metastases or involvement of one or two regional lymph nodes. In patients with three or more positive lymph nodes, if the primary tumor is grade 1 or 2 with positive estrogen and/or progesterone receptor status, the effect of hormone therapy has been established, regardless of the extent of metastases.¹⁷ However, the validity of adjuvant chemotherapy for the estrogen receptor-negative and/or grade 3 tumors has not been established, and it may be better to take the physical condition of the patient into account.¹⁷

From the data presented in this report, we feel that in order to obtain optimal local disease control, radical

mastectomy or lumpectomy with postoperative radiotherapy should be undertaken for healthy elderly patients without distant metastases, as is currently performed in younger patients. Adjuvant chemotherapy may be considered for high-risk, estrogen receptor-negative elderly patients with good performance status.

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