[21] R. Attanoos, K. Nahar, A. Bigrigg, S. Roberts, R.G. Newcombe, S.M. Ismail, Primary adenocarcinoma of the cervix: a clinicopathologic study of the prognostic variables in 55 cases, Int. J. Gynecol. Cancer 5 (1995) 179–186.
[22] M.A. Quinn, Adenocarcinoma of the cervix: are there arguments for a different treatment policy?, Curr Opin. Obstet. Gynecol. 9 (1997) 21–24.
[23] D. Grisaru, A. Covens, B. Chapman, et al., Does histology influence prognosis in patients with early-stage cervical adenocarcinoma? Cancer 92 (2001) 2999–3004.
[24] Y.B. Kim, G.E. Kim, H.R. Pyo, et al., Differential cyclooxygenase-2 expression in squamous cell carcinoma and adenocarcinoma of the uterine cervix, Int. J. Radiat. Oncol. Biol. Phys. 60 (2004) 822–829.
[25] K. Matsukuma, N. Tsukamoto, T. Kaku, et al., Early adenocarcinoma of the uterine cervix: its histologic and immunohistologic study, Gynecol. Oncol. 35 (1989) 38–43.
[26] M.W. Jones, S. Kounelis, H. Papadaki, et al., Well-differentiated villoglandular adenocarcinoma of the uterine cervix: oncogene/tumor suppressor gene alterations and human papillomavirus, Int. J. Gynecol. Pathol. 19 (2000) 110–117.
[27] J. Folkman, Angiogenesis in cancer vascular rheumatoid and other disease, Nat. Med. 1 (1995) 27–31.
[28] P. Carmeliet, Angiogenesis in health and disease, Nat. Med. 9 (2003) 653–660.
[29] R. Kerbel, J. Folkman, Clinical translation of angiogenesis inhibitors, Nat. Rev. Cancer 2 (2002) 727–739.
[30] C.M. West, R.A. Cooper, J.A. Loncaster, D.P. Wilks, M. Bromley, Tumor vascularity: a histological measure of angiogenesis and hypoxia, Cancer Res. 61 (2001) 2907–2910.
[31] R.A. Cooper, D.P. Wilks, J.P. Logue, et al., High tumor angiogenesis is associated with poorer survival in carcinoma of the cervix treated with radiotherapy, Clin. Cancer Res. 4 (1998) 2795–2800.
[32] T. Kaku, T. Hirakawa, T. Kamura, et al., Angiogenesis in adenocarcinoma of the uterine cervix, Cancer 83 (1998) 1384–1390.
[33] S. Bandyopadhyay, S.K. Pai, S.C. Gross, S. Hirota, S. Hosobe, K. Miura, The Drg-1 gene suppresses tumor metastasis in prostate cancer, Cancer Res. 63 (2003) 1731–1736.
[34] W. Ulrix, J.V. Swinnen, W. Heyns, G. Verhoeven, The differentiation-related gene 1, Drg1, is markedly upregulated by androgens in LNCaP prostatic adenocarcinoma cells, FEBS Lett. 455 (1999) 23–26.
[35] R.P. Caruso, B. Levinson, J. Melamed, et al., Altered N-myc downstream-regulated gene 1 protein expression in African–American compared with caucasian prostate cancer patients, Clin. Cancer Res. 10 (2004) 222–227.
[36] K.F. Chin, J. Greenman, E. Gardiner, H. Kumar, K. Topping, J. Monson, Pre-operative serum vascular endothelial growth factor can select patients for adjuvant treatment after curative resection in colorectal cancer, Br. J. Cancer 83 (2000) 1425–1431.
[37] B.A. Fine, P.T. Valente, G.I. Feinstein, T. Dey, VEGF, fit-1, and KDR/fik-1 as prognostic indicators in endometrial carcinoma, Gynecol. Oncol. 76 (2000) 33–39.
[38] Y. Seo, H. Baba, T. Fukuda, M. Takashima, K. Sugimachi, High expression of vascular endothelial growth factor is associated with liver metastasis and a poor prognosis for patients with duatal pancreatic adenocarcinoma, Cancer 88 (2000) 2239–2245.
[39] M. Takahama, M. Tsutsumi, T. Tsujiuchi, et al., Enhanced expression of Tie2, its ligand angiopoietin-1, vascular endothelial growth factor, and CD31 in human non-small cell lung carcinoma, Clin. Cancer Res. 5 (1999) 2506–2510.
[40] K. Hirata, K. Masuda, W. Morikawa, et al., N-myc downstream-regulated gene 1 expression in injured sciatic nerves, Glia 47 (2004) 325–334.
[41] T. Sugiki, M. Murakami, Y. Taketomi, R. Kikuchi-Yanoshita, I. Kudo, N-myc downregulated gene 1 is a phosphorylated protein in mast cells, Biol. Pharm. Bull. 27 (2004) 624–627.
[42] S. Kose, M. Furuta, M. Koike, Y. Yoneda, N. Imamoto, The 70-kDa heat shock cognate protein (hsc70) facilitates the nuclear export of the import receptors, J. Cell Biol. 171 (2005) 19–25.

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ORIGINAL ARTICLE

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Evaluation of axillary status in patients with breast cancer using thin-section CT

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Abstract

Background. In recent years, the surgical management of patients with breast cancer has shifted to a locoregional approach, and evaluating the patient's axillary lymph node status is of the greatest importance in determining the appropriate treatment strategy. We evaluated on the efficacy of preoperative axillary staging using contrast-enhanced computed tomography (CE-CT).

Methods. Between 2000 and 2003, 235 patients with operable breast cancer who underwent CE-CT before surgery and 137 patients who received neoadjuvant chemotherapy (NAC) and underwent CE-CT before NAC and surgery were enrolled in this study. The axillary status was evaluated based on three criteria (short-axis diameter, shape, and enhancement type), and the diagnosis was correlated with the histopathological results.

Results. In patients who did not receive NAC, the size criterion of a short-axis diameter of more than 5 mm provided a sensitivity of 78%, a specificity of 75%, and an accuracy of 76% in predicting node-positive status. According to the size criterion of a short-axis diameter of more than 5 mm and the shape criterion of the absence of intranodal fat density, the specificity and accuracy were 90% and 81%, respectively, and according to the enhancement type criterion of early enhancement, the corresponding values were 89% and 78%. Evaluation was more difficult in patients who received NAC and the sensitivity of the size-based criterion in the patients who received NAC was lower than in those who did not.

Conclusion. These findings suggest that CE-CT based on size criteria is useful for evaluating the preoperative axillary status of breast cancer patients, but that evaluation is more difficult and the sensitivity is reduced in patients who have received NAC.

Key words Breast · CT · Axillary status · Neoadjuvant · Chemotherapy

Introduction

There have been remarkable advances in the treatment of breast cancer in recent years. Diagnostic techniques and methods are improving and more and more new devices are being introduced. However, their usefulness has not been established, and it is necessary to develop more detailed and accurate diagnostic methods.

In the surgical management of patients with breast cancer, conservative treatment and sentinel lymph node biopsy (SLNB) are now widely employed. For these procedures, accurate preoperative evaluation of the lesion is required. In such preoperative evaluation, the extent of the main lesion should be assessed in order to determine the range of tumor excision; also, axillary lymph node metastases should be evaluated in order to perform an SLNB procedure safely. There have been many reports on the evaluation of tumor extent, and we have published several articles on the usefulness of mammary gland computed tomography (CT) in this regard.[1–3] For the evaluation of axillary lymph node metastases, various approaches and examination techniques have been proposed to improve the diagnostic accuracy of ultrasound (US), CT, positron emission tomography (PET), and other diagnostic modalities.[4–15] However, no definitive criteria have yet been established. Mammary gland CT can be performed with the patient in nearly the same position as that during surgery, and it is

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beginning to attract attention as a modality that permits the extent of the primary lesion and axillary lymph node metastases to be evaluated simultaneously.

In chemotherapy, molecular-targeted therapeutic agents, including anthracyclines, taxanes, and trastuzumab (Herceptin; Roche, Nutley, NJ, USA) are now employed, and the antitumor effect of chemotherapy is increasing remarkably. Given this background, neoadjuvant chemotherapy (NAC) is now widely employed not only for locally advanced breast cancers but also for primary breast cancers, and excellent results have been reported.[16–18] However, new problems have begun to emerge as NAC has become more common. Because NAC is highly effective, it is difficult to visualize the residual lesions after chemotherapy. Even more accurate evaluation is therefore needed to determine the excision range. We have previously reported the usefulness of CT in the visualization of residual lesions after NAC.[1,3] In addition, several reports have suggested that the number of residual lymph node metastases after NAC is a strong prognostic factor.[16–18] The evaluation of axillary lymph node metastases after NAC is therefore of great importance. Furthermore, identifying the presence or absence of axillary lymph node metastases before and after NAC may be very important in determining whether or not SLNB is indicated after NAC.

In this study, we evaluated the usefulness of multislice CT in the evaluation of axillary lymph node metastases in order to establish suitable criteria for evaluating axillary lymph node metastases using this modality. We also examined the effectiveness of NAC for axillary lymph node metastases, using multislice CT.

Patients and methods

Patients

This study group included 235 women with operable breast cancers measuring less than or more than 30 mm in diameter who refused NAC and 137 women who received NAC. NAC was indicated in patients with clinical stage II breast cancer with a tumor larger than 3 cm, or in patients with stage III breast cancer. All patients were treated at the National Cancer Center Hospital (NCCH), Tokyo, between January 2000 and December 2003. The patients were evaluated by contrast-enhanced (CE)-CT before surgery and before NAC.

The surgical method was mastectomy or breast-conserving surgery with axillary lymph node dissection. The NAC protocol consisted of four cycles of doxorubicin (50 mg/m^2)/docetaxel (60 mg/m^2) with a 21-day cycle length (AT protocol), or four cycles of doxorubicin (60 mg/m^2)/cyclophosphamide (600 mg/m^2) plus 12 weekly cycles of paclitaxel (80 mg/m^2) (ACT protocol) followed by surgery. The initial pathologic confirmation of breast cancer was based on the findings of needle biopsy. All patients gave their informed consent to participate in the study, which was approved by the institutional review board of the NCCH.

Imaging examinations

All CT examinations were performed with the patient in the prone position; from January to June 2000, a helical CT scanner (X-Vigor; Toshiba, Tokyo, Japan) was used, and from July 2000 onwards a multislice (four-row) CT scanner (Aquilion; Toshiba) was used. The first noncontrast-enhanced CT scan served as the baseline, with images acquired from the cranial end of the sternum to the inframammary fold. Subsequently, an enhanced zoomed scan was performed to visualize the entire breast. A 100-ml bolus of nonionic contrast material (300 mg I/ml of iohexol [Omnipaque Daiichisankyo Pharmaceutical, Tokyo, Japan]) was injected intravenously at a rate of 3 ml/s, using an automated injector, via an antecubital vein on the side opposite the affected breast. Image acquisition was started at 40 s after the start of bolus injection of the contrast material. The reconstruction interval was 5 mm. Metastatic lymph nodes were evaluated based on the short-axis diameter, internal fat density indicating absence of a center image, and early strong enhancement, compared with the late phase of the axillary lymph node on CT images. Benign lymph node enlargement such as hyperplasia has internal fat at the normal hilum of the lymph node and does not show early strong enhancement. We evaluated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy compared with presurgical lymph node status diagnosed by CT imaging, according to several criteria of pathological lymph node status after operation. Two authors (T. S. and K. M.) retrospectively interpreted the CT images together, and reached their conclusions by consensus.

Histopathological examinations

All nodes obtained by axillary dissection were cut into single sections and stained with hematoxylin-eosin (H&E) for analysis by breast pathologists. The pathological response of the primary tumors to NAC was classified according to the *General rules for clinical and pathological recording of breast cancer* of the Japanese Breast Cancer Society (JBCS).[19] In grade 0 tumors, no response was observed; in grade 1a tumors, degenerative changes or severe degenerative changes were observed in fewer than one-third of the cancerous cells; in grade 1b tumors, severe degenerative changes were observed in one-third to two-thirds of the cancerous cells; in grade 2 tumors, degeneration was observed in more than two-thirds of the cancerous cells; and in grade 3 tumors, a complete response was observed, with no cancerous cells remaining.

Results

Patient characteristics

Table 1 shows the clinicopathological features of the 235 patients who did not receive NAC (without NAC) and the

Table 1. Clinicopathologic features

Variable	Without NAC (n = 235) Data	NAC (n = 137) Data
Age, years, median (range)	51 (22–83)	51 (26–68)
Primary tumor size, mm, median (range)	21 (2–110)	40 (15–80)
T1a	3 (1%)	
T1b	8 (3%)	
T1c	88 (37%)	3 (2%)
T2	105 (45%)	89 (65%)
T3 and T4	31 (13%)	45 (33%)
Histology		
Invasive ductal carcinoma	218 (93%)	128 (93%)
Invasive lobular carcinoma	14 (6%)	6 (4%)
Mucinous carcinoma	1 (0.4%)	3 (2%)
Undifferentiated adenocarcinoma	2 (1%)	
Pathological lymph node status		
Negative	142 (60%)	55 (40%)
Positive	93 (40%)	82 (60%)
Pathological response to NAC		
Grade 0		1 (0.7%)
Grade 1a		66 (48%)
Grade 1b		27 (20%)
Grade 2		32 (23%)
Grade 3		9 (7%)

Table 2. Results for CT imaging of axillary lymph nodes in patients without NAC, obtained using each diagnostic criterion

Parameter	Short-axis diameter of LN		Short-axis diameter >5 mm and	
	>5 mm	>7 mm	Early enhancement	Without absence of center image
Sensitivity	78%	35%	62%	67%
Specificity	75%	94%	89%	90%
PPV	67%	80%	78%	81%
NPV	84%	69%	78%	82%
Accuracy	76%	71%	78%	81%

LN, lymph node; PPV, positive predictive value; NPV, negative predictive value

137 patients who received NAC (NAC). The size of the primary tumor was measured on the pretreatment CT images. In the patients without NAC, the median age was 51 years (range, 22–83 years). The median tumor size was 21 mm (range, 2–110 mm). In the 2 patients with undifferentiated adenocarcinomas, 1 had a matrix-producing carcinoma and 1 had stromal sarcoma. Ninety-three patients (40%) had node-positive pathology.

In the NAC patients, the median age was 51 years (range, 26–68 years). The median tumor size was 40 mm (range, 15–80 mm). Of these patients, 128 were histologically diagnosed as having invasive ductal carcinoma. Invasive lobular carcinomas and mucinous carcinomas were found in 6 and 3 patients, respectively. Eighty-two patients were node-positive after operations (60%) and there was a pathological response of the primary tumor according to the JBCS classification (Table 1).

Evaluation of axillary status in patients who did not receive NAC

Pathologically, 93 patients (40%) were diagnosed as node-positive and 142 (60%) as node-negative, based on the criterion that an axillary lymph node greater than 5 mm in short-axis diameter on the CT images was node-positive; the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 78%, 75%, 67%, and 84%, respectively (Table 2). Based on the criterion that a node greater than 7 mm in short-axis diameter was node-positive, the specificity and PPV increased while the sensitivity and accuracy decreased. When the other CT criteria were used in addition, the diagnostic accuracy was higher than that obtained using the size criteria alone. When the lymph nodes greater than 5 mm in short-axis diameter with early enhancement and those without the absence of a center image (absence of a center image means that the lymph node contains fatty tissue) were diagnosed as node-positive, the accuracy rates were 78% and 81% and false negative rates were 22% and 18%. In patients with false-negative results using the 5-mm criterion, the number of metastases was one to three nodes (78%) and in those with false-negative results using the 7-mm criterion, the number of metastases was more than four nodes (22%).

Evaluation of axillary status in patients who received NAC

Of the 137 patients who received NAC before surgery, lymph node metastases were confirmed by postoperative pathological examination in 82 (60%). The clinical stage of the patients with NAC was relatively advanced. Therefore, the pathological lymph node status was worse than that in patients without NAC. Based on the criterion that a lymph node greater than 5 mm in short-axis diameter on preoperative CT images was node-positive, the sensitivity, specificity, NPV, PPV, and accuracy were 60%, 95%, 61%, 94%, and 74%, respectively. Based on the criterion that a lymph node greater than 7 mm in short-axis diameter was node-positive, the specificity and PPV were both 100%, while the sensitivity, NPV, and accuracy were 20%, 55%, and 52%, respectively–values that were significantly lower than the values obtained using the 5-mm criterion (Table 3).

On CT imaging before NAC, a lymph node enlarged to greater than 5 mm in short-axis diameter and diagnosed as node-positive was observed in 120 patients (88%), but on comparison with preoperative CT imaging, it was found that the lymph node had become smaller after NAC in 113 (94%) of these 120 patients (Table 4). On the postoperative pathological examination, lymph node metastasis was confirmed in 82 patients. If it is assumed that the diagnosis in all 120 patients who were determined to be node-positive before NAC was correct, the pathological complete response (pCR) rate for NAC in axillary lymph node metastases can be considered to be 32%.

Table 3. Results for CT imaging of axillary LN in patients with NAC

Parameter	Short-axis diameter of LN	
	>5 mm	>7 mm
Sensitivity	60%	20%
Specificity	95%	100%
PPV	94%	100%
NPV	61%	55%
Accuracy	74%	52%

LN, lymph node; PPV, positive predictive value; NPV, negative predictive value

Discussion

In a number of studies, authors have described the usefulness of preoperative diagnostic imaging of the axillary lymph nodes in patients with breast cancer and have discussed the diagnostic criteria,[4–15] but none of these studies can be considered to be definitive. We conducted a study of the diagnosis of axillary lymph node metastases, using mammary gland CT to evaluate the extent of primary breast cancer. Unlike other modalities, mammary gland CT can be performed with the patient in almost the same position as that during surgery, and it is therefore possible to perform lymph node evaluation under the same imaging conditions as those used to evaluate the extent of the primary lesion. In most of the previous reports, the lymph nodes were evaluated in terms of their size and shape.[7–11] However, the assessment of node shape is prone to error, and this method is too complicated for routine use. In the present study, we selected size, which is relatively easy to assess, and we also added evaluation of the contrast enhancement effect to investigate the accuracy of the evaluation of metastases. When a lymph node greater than 5 mm in short-axis diameter was considered to be node-positive, the sensitivity, specificity, and accuracy were 78%, 75%, and 76%, respectively. These values are slightly lower than those in previous reports. This is mainly because, in our study, the subjects were limited to patients in whom no lymph nodes were found by palpation and in whom the size of the primary breast cancer was determined to be 3 cm or less by palpation. The clinical stage of the patients without NAC was a relatively early stage. The patients with advanced breast cancer received NAC. If palpably enlarged lymph nodes were to be included in the evaluation, the sensitivity would theoretically increase and the diagnostic accuracy would undoubtedly be improved. With regard to the lymph node size cutoff value, many recent reports have used a lymph node short-axis diameter of 5 mm as the criterion for determining it to be node-positive.[4–11] However, the number of patients in these reports was small, and detailed studies of lymph node size were not performed. In many reports on the diagnosis of mediastinal lymph node metastases, a short-axis diameter of 1 cm was used as the criterion for determining a lymph node to be node-positive, and the accuracy was reported to be 78% to 85%.[20–22] In the present study, in the patients without NAC, when it was assumed

Table 4. Efficacy of NAC for axillary LN metastases (n = 137)

Variable	Data
No. of patients with axillary lymph node metastases before NAC[a]	120 (88%)
No. of patients with residual axillary lymph node metastases after NAC[b]	82 (60%)
Size change of axillary lymph nodes after NAC in the patients with lymph node metastases before NAC (n = 120)	
Smaller	113 (94%)
Same	5 (4%)
Larger	2 (2%)

[a]Short-axis diameter >5 mm on CT images before NAC
[b]Pathologically proven metastases after axillary lymph node dissection

that a lymph node greater than 7 mm in short-axis diameter was node-positive, the sensitivity, specificity, and accuracy were 35%, 94%, and 71%, respectively. The specificity was increased to nearly 100%, but the sensitivity and accuracy were decreased compared with values for the 5-mm criterion. This result indicates that a short-axis diameter of 7 mm is not a suitable cutoff value for preoperative examination. If a short-axis diameter of greater than 3 mm is used as the criterion, visual measurement is quite difficult and the measurement may have a large degree of error. Considering the fact that a slice width of 5 mm is generally employed in CT examinations, the use of 3 mm as the criterion is not practical. Based on these results, we decided that lymph nodes with a short-axis diameter of greater than 5 mm should be considered to be node-positive.

In order to improve accuracy, we included early enhancement and the absence of fat within the lymph node, which are characteristics of lymph node metastases, in the evaluation criteria. Most previous reports also included the characteristics of the lymph node and the contrast-enhancement effect in their diagnostic criteria, in addition to node size, in order to improve diagnostic accuracy. In the present study, when a lymph node with a short-axis diameter of greater than 5 mm and with the absence of internal fat was considered to be node-positive, the diagnostic accuracy was 81%. When a lymph node with a short-axis diameter of greater than 5 mm and with early enhancement was considered to be node-positive, the accuracy was 78%. The results were improved slightly by the addition of extra criteria.

Many studies are currently under way on the preoperative evaluation of lymph node metastases in patients who have received NAC. It is much more difficult to evaluate the axillary lymph nodes in patients who have received NAC than in those who have not.[2,3] In our examinations for the preoperative evaluation of lymph node metastases in patients who had received NAC, the sensitivity, specificity, and accuracy were 60%, 95%, and 74%, respectively, when a node greater than 5 mm in short-axis diameter was considered to be node-positive. When a node greater than 7 mm in short-axis diameter was considered to be node-positive, the corresponding values were 20%, 100%, and 52%, respectively. In the patients who had received NAC, the size of the metastatic lymph nodes was reduced due to the administration of anticancer agents. However, even when a lymph node becomes smaller, it may still contain malignant cells. We decided that this was the reason that the sensitivity was reduced in the patients with NAC compared with that in the patients without NAC. On the other hand, the number of reactively enlarged lymph nodes after NAC was smaller than that before NAC, and this is the reason that the specificity was higher when lymph nodes were evaluated by size alone. In the present study, based on the criterion of a short-axis diameter greater than 7 mm, the specificity was 100%; however, when the criterion of a short-axis diameter greater than 5 mm was used, the accuracy was higher than that for the 7-mm criterion.

SLNB is starting to be widely employed. Candidates for an SLNB procedure are said to be patients in whom no metastatic axillary lymph nodes are found on preoperative examination. It is therefore necessary, during the preoperative examination of patients who may be candidates for SLNB, to correctly identify patients with nodal metastases and exclude them as SLNB candidates. When SLNB is being considered, methods that can provide high specificity and PPV, rather than high accuracy or sensitivity, are more useful for the preoperative diagnosis of axillary lymph node metastases. CT studies can be very useful in this regard. As for SLNB after NAC, however, it is difficult to apply the primary theory of SLNB even if the specificity and PPV are 100% in a CT study, because pathological diagnosis is difficult and the effects of NAC appear to be relatively nonuniform. In our study, in the patients who did not receive NAC and who showed false-negative findings, the number of pathological lymph node metastases was low, and we need to diagnose these metastases in patients who are to have SLNB. Although the lymph node size had become small in the patients with NAC, malignant tumor cells existed sparsely in these lymph nodes. These findings indicate that SLNB after NAC is very difficult. Further investigations are required.[23–26]

We conducted this study to determine suitable criteria for the diagnosis of axillary lymph node metastases, in terms of node size, using mammary CT, the objective being to have criteria that are easy to understand and can be employed at any institution. Our results suggest that the most suitable criterion is to consider an axillary lymph node to be node-positive if it is greater than 5 mm in short-axis diameter, and the accuracy of this criterion was found to be favorable. More accurate diagnosis was possible by adding evaluation of the absence or presence of internal fat and the contrast enhancement effect in each patient. It was also found that the evaluation of axillary lymph node metastases was more difficult after NAC, and further advances in imaging and diagnostic methods will be necessary for evaluation in these patients. At the present time, it is recommended that comprehensive evaluation be performed using a combination of mammary CT and another modality. The results of this study have shown that mammary CT, as employed to diagnose the extent of the primary lesion, is also useful for the preoperative evaluation of axillary lymph node metastases.

References

1. Akashi-Tanaka S, Fukutomi T, Sato N, et al. (2004) The use of contrast-enhanced computed tomography before neoadjuvant chemotherapy to identify patients likely to be treated safely with breast-conserving surgery. Ann Surg 239:238–243
2. Akashi-Tanaka S, Fukutomi T, Miyakawa K, et al. (1998) Diagnostic value of contrast-enhanced computed tomography for diagnosing the intraductal component of breast cancer. Breast Cancer Res Treat 49:79–86
3. Akashi-Tanaka S, Fukutomi T, Watanabe T, et al. (2001) Accuracy of contrast-enhanced computed tomography in the prediction of residual breast cancer after neoadjuvant chemotherapy. Int J Cancer 96:66–73
4. Okuyama N, Murakuni H, Ogata H (2004) The use of Doppler ultrasound in evaluation of breast cancer metastasis to axillary lymph nodes. Oncol Rep 11:389–393

5. Loehberg CR, Lux MP, Ackermann S, et al. (2005) Neoadjuvant chemotherapy in breast cancer: which diagnostic procedures can be used? Anticancer Res 25:2519–2526
6. Khan A, Sabel MS, Nees A, et al. (2005) Comprehensive axillary evaluation in neoadjuvant chemotherapy patients with ultrasonography and sentinel lymph node biopsy. Ann Surg Oncol 12:697–704
7. Ogawa Y, Nishioka A, Nishihgawa T, et al. (2003) Thin-section CT evaluation and pathologic correlation of therapeutic nodes of clinically node-positive breast cancer patients. Oncol Rep 10:985–989
8. Hata Y, Ogawa Y, Nishioka A, et al. (1998) Thin section computed tomography in the prone position for detection of axillary lymph node metastasis in breast cancer. Oncol Rep 5:1403–1406
9. Yuen S, Sawai K, Ushijima Y, et al. (2002) Evaluation of axillary status in breast cancer. CT-based determination of sentinel lymph node size. Acta Radiol 43:579–586
10. Yuen S, Yamada K, Goto M, et al. (2004) CT-based evaluation of axillary sentinel lymph node status in breast cancer: value of added contrast-enhanced study. Acta Radiol 45:730–737
11. Miyauchi M, Yamamoto N, Imanaka N, et al. (1999) Computed tomography for preoperative evaluation of axillary nodal status in breast cancer. Breast Cancer 6:243–248
12. Kvistad KA, Rydland J, Smethrust HB, et al. (2000) Axillary lymph node metastases in breast cancer: preoperative detection with dynamic contrast-enhanced MRI. Eur Radiol 10:1464–1471
13. Lernevall A (2000) Imaging of axillary lymph nodes. Acta Oncol 39:276–281
14. Michel SCA, Keller TM, Frohlich JM, et al. (2002) Preoperative breast cancer staging: MR imaging of the axilla with ultrasmall superparamagnetic iron oxide enhancement. Radiology 225:527–536
15. Sapino A, Cassoni P, Zanon E, et al. (2003) Ultrasonographically guided fine-needle aspiration of axillary lymph nodes: role in breast cancer management. Br J Cancer 88:702–706
16. Bonadonna G, Valagussa P, Brambilla C, et al. (1998) Primary chemotherapy in operable breast cancer: 8-year experience at the Milan Cancer Institute. J Clin Oncol 16:93–100
17. Cameron DA, Anderson EDC, Levack P, et al. (1997) Primary systemic therapy for operable breast cancer: 10-year survival data after chemotherapy and hormone therapy. Br J Cancer 76: 1099–1105
18. Pierga JY, Mouret E, Dieras V, et al. (2000) Prognostic value of persistent node involvement after neoadjuvant chemotherapy in patients with operable breast cancer. Br J Cancer 83:1480–1487
19. The Japanese Breast Cancer Society (2004) General rules for clinical and pathological recording of breast cancer, 15th edn. Kanehara, Tokyo
20. Kamiyoshihara M, Kawashima O, Ishikawa S, et al. (2001) Mediastinal lymph node evaluation by computed tomographic scan in lung cancer. Int J Cancer 42:119–124
21. Georgian D, Rice TW, Mehta AC, et al. (1990) Intracystic lymph node evaluation by CT and MRI with histopathologic correlation in non-small cell bronchogenic carcinoma. Clin Imaging 14:35–40
22. Daly BD Jr, Faling LJ, Bite G, et al. (1987) Mediastinal lymph node evaluation by computed tomography in lung cancer. An analysis of 345 patients grouped by TMN staging, tumor size, and tumor location. J Thorac Cardiovasc Surg 94:664–672
23. Brady EW (2002) Sentinel lymph node mapping following neoadjuvant chemotherapy for breast cancer. Breast J 8:97–100
24. Piato JRM, Barros ACSD, Pincerato KM, et al. (2002) Sentinel lymph node biopsy in breast cancer after neoadjuvant chemotherapy. A pilot study. Eur J Surg Oncol 29:118–120
25. Kinoshita T, Takasugi M, Iwamoto E, et al. (2006) Sentinel lymph node biopsy examination for breast cancer patients with clinically negative axillary lymph nodes after neoadjuvant chemotherapy. Am J Surg 191:225–229
26. Cody HS 3rd (2001) Clinical aspects of sentinel node biopsy. Breast Cancer Res 3:104–108

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Clinical Efficacy of S-1 in Pretreated Metastatic Breast Cancer Patients

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Background: S-1, an oral fluoropyrimidine carbamate, is an active and well-tolerated agent against solid cancer. However, the clinical efficacy of S-1 in patients with metastatic breast cancer has not been determined.
Methods: We retrospectively evaluated the efficacy of S-1 and identified its adverse effects in patients with metastatic breast cancer who had failed to respond to prior chemotherapy regimens. All the patients were treated at the National Cancer Center Hospital and received S-1 twice daily at a dose of 80 mg/m^2 for 4 weeks, followed by a 2-week rest interval.
Results: Between 2003 and 2007, 37 women with metastatic breast cancer received S-1 as a third line or greater chemotherapy regimen. All the patients had been previously treated with both anthracyclines and taxanes prior to S-1 chemotherapy. The median order of S-1 administration was as a fifth-line treatment, and 23 patients (62%) received S-1 as their final anticancer drug. One (3%) partial response and two (5%) stable diseases were observed. The median time to progression (TTP) was 84 days. Grade 2 adverse events, such as diarrhea, stomatitis and neutropenia occurred in 5 (16%), 1 (3%) and 1 (3%) patients, respectively.
Conclusions: S-1 was safety administered to heavily treated metastatic breast cancer patients with limited efficacy. Further evaluation of S-1 is necessary to elucidate its clinical role in breast cancer treatment.

Key words: S-1 – metastatic breast – cancer – chemotherapy

INTRODUCTION

Treatment of patients with metastatic breast cancer (MBC) aims to prolong survival while relieving symptoms and maintaining a good quality of life (QOL).

Capecitabine is an orally administered fluoropyrimidine that has been reported to be effective in both monotherapy and combination therapy regimens. Capecitabine as a single agent produced an overall response rate (RR) of 29% and a median time to disease progression of 4.6 months in large phase II trials in taxane-pretreated MBC patients (1–3). Since capecitabine can sustain the QOL of MBC patients, it has been widely used as a third-line or subsequent chemotherapy regimen for heavily treated patients.

On the other hand, S-1 is another orally administered fluorinated pyrimidine that has been reported to be a well-tolerated and active agent against solid cancers. In a phase II study of S-1, the RR was 41.7% and the median survival time was 872 days among taxane-pretreated patients with MBC; S-1 has been approved in Japan as a salvage chemotherapy for patients who have received anthracycline and taxane (4,5). In addition, S-1 has been used mainly for the treatment of cancers of the digestive tract (6–8), and its efficacy is well known. However, the clinical usefulness of S-1 in patients with MBC is uncertain. Here, we describe the efficacy and tolerability of S-1 in a clinical setting.

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PATIENTS AND METHODS

Patients

A retrospective analysis was performed on patients with MBC who received S-1 monotherapy between January 2003 and December 2006 at the National Cancer Center Hospital (NCCH). The patient population was identified from a

database at the NCCH. All the patients had received chemotherapy previously. They were followed up until death or, if they were still alive, to their last visit prior to March 2007.

The best response for each patient was assessed according to the WHO criteria (8). A complete response (CR) was defined as the disappearance of all clinical and radiographic evidence during two observations performed at least 4 weeks apart. A partial response (PR) was defined as a decrease of 30% or more in the sum of the products of the biperpendicular diameters of measurable lesions. Stable disease (SD) was defined as a <30% decrease and a <25% increase in the sum of the products of the biperpendicular diameters of measurable lesions and no appearance of new lesions; these conditions had to be maintained for at least 12 weeks. Progressive disease was defined as a greater than 25% increase in the sum of the products of the biperpendicular diameters of measurable lesions or the appearance of new lesions. The clinical benefit rate was defined as the proportion of patients who achieved either a CR, PR or SD. The National Cancer Institute common toxicity criteria (9) were adopted to determine toxicity.

Treatment

S-1 was administered orally twice daily (80 mg/m^2) for 28 days followed by 14 days of rest. Treatment was continued until disease progression, unacceptable adverse effects or withdrawal of the patient's consent. In the case of Grade 2 or worse toxicity, S-1 administration was interrupted and not resumed until the toxicity had resolved or improved to Grade 1.

The time to progression (TTP) was calculated from the day of commencement of S-1 administration until the day of documented progression. Overall survival (OS) was calculated from the start date of S-1 to the date of death from any cause. TTP and OS were analysed according to the Kaplan–Meier estimates.

RESULTS

Thirty-seven patients received S-1 as a greater than second-line chemotherapy for MBC between January 2003 and December 2006 at NCCH. Table 1 shows the patient's characteristics. The median age was 49 (28–70) years. The Eastern Cooperative Oncology Group (ECOG) performance statuses of the patients were all <2. The sites of metastatic disease were the bone and/or soft tissue in only six patients (16%) and involved visceral sites in 31 patients (84%). Table 2 shows the chemotherapy regimens that were administered prior to S-1. The median number of chemotherapy regimens used before the administration of S-1 including adjuvant and neoadjuvant treatments, was 4, and 23 patients (62%) received S-1 as their final chemotherapy regimen. All the patients had previously received both anthracyclines and taxanes, 13 patients (35%) had received vinorelbine and 11 patients (30%) had received oral 5FU-derivatives prior to the administration of S-1. All the patients who had responded to treatment had exhibited adequate progression-free intervals from the prior taxane administration until the subsequent taxane administration. Three patients received the same taxane regimen twice, once as adjuvant chemotherapy and the second time in combination with Trastuzumab after recurrence. Prior oral 5FU-derivatives included in other regimens were CMF (five patients), UFT (five patients), 5'DFUR (five patients) and CPT-11 (one patient). Sixteen patients (43%) with ER-positive diseases had received hormone therapy, and 13 patients (35%) with HER2-positive diseases had received Trastuzumab as a monotherapy or in combination with taxane or vinorelbine.

Table 1. Patient characteristics

	No. of patients (n = 37)	% of patients
Median age (years; range)	49 (28–70)	
Metastatic sites involved		
Bone/Soft tissue	6	16
Visceral	31	84
Oestrogen receptor		
Positive	16	43
Negative	21	57
Progesteron receptor		
Positive	17	46
Negative	20	54
HER2/neu status		
Positive	13	35
Negative	24	65

Table 2. Prior chemotherapy

Prior chemotherapy	No. of patients (n = 37)	% of patients
No. of regimens used		
2/3/4/5/6/7/8	4/10/10/4/2/0/3	
Median (range)	4 (2–8)	
Neoadjuvant chemotherapy	6	16
Adjuvant chemotherapy	17	46
S-1 was the last regimen	23	62
Prior chemotherapy		
Anthracycline	37	100
Taxane	37	100
Vinorelbine	13	35
Capecitabine	1	3

The median number of administration days was 70 (6–415 days). The RR was 3%, with no cCR and 3% (1/37) PR. The overall clinical benefit rate (CR, PR and SD for more than 6 months) was 8% (3/37). The median TTP was 84 days (range, 6–415) (Fig. 1; note that a colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org). The median OS from the start of S-1 treatment was 284 days (range, 14–1511), and six patients (16%) were still alive at the last follow-up. Nine patients (24%) received S-1 for more than 100 days. Six out of these nine patients had visceral involvement. Two out of seven patients had oestrogen receptor-positive diseases and four of them were HER2-positive.

Overall, S-1 was well tolerated. Table 3 shows the adverse events in response to S-1 chemotherapy. Toxicities of Grade 3 or more were not reported. The most common toxicities arising from S-1 administration were diarrhea (33%) and nausea (30%). Most of the adverse events were Grade 1, and none of the S-1-related adverse events were fatal. The most frequent reasons for treatment discontinuation were disease progression (30 patients, 81%) and adverse event (seven patients, 19%). The adverse events that were encountered were Grade 2 diarrhea (five cases), Grade 2 stomatitis (one case) and Grade 2 neutropenic fever (one case).

Table 3. Treatment-related adverse event of TS-1

	Gradre 1 (%)	Grade 2 (%)
Diarrhea	7 (19)	5 (14)
Stomatitis	5 (14)	1 (3)
Nausea/vomitting	11 (30)	0 (0)
Neutropenia	1 (3)	1 (3)
Disorder of liver function	2 (6)	0 (0)

DISCUSSION

The number of patients with MBC who have been pretreated with anthracyclines and/or taxanes are increasing. However, the optimal chemotherapy for patients with MBC who have been pretreated with both anthracyclines and taxanes has not been determined. These patients require palliative therapy that offers a chance of prolonging life with minimal toxicity according to the antitumor response and the alleviation of tumor-related symptoms.

In this study, S-1 chemotherapy produced a 3% RR and an 8% rate of clinical benefit in previously treated patients with MBC who were refractory to both anthracyclines and taxanes. The median TTP was 84 days, and 24% of the patients received S-1 for more than 100 days. These results were worse than those reported in clinical trials. This discrepancy is probably because 11 patients had received other 5FU-derivatives prior to S1, the median order of S-1 administration was fifth line (most of the patients received S-1 chemotherapy as their final treatment), and most of the patients had multiple metastatic sites (84% had visceral metastases). The toxicity of S-1, however, was mild in these heavily treated patients, and S-1 is considered to be a feasible palliative chemotherapy in heavily treated MBC patients.

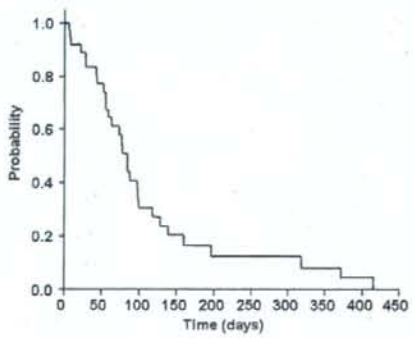

Figure 1. Kaplan–Meier curve for time to progression (TTP). Median TTP was 84 (range 6–415) days.

Several oral 5FU-derivatives have been used to treat MBC, but only S-1 and capecitabine have been tested in taxane-refractory MBC patients (10). The treatments were administered based upon physicians' decisions, but the reason why S-1, and not capecitabine, was selected in this study population is unclear. S-1 is a fluoropyrimidine that consists of 1-(2-tetrahydrofuryl)-5-fluorouracil (FTO), a pro-drug of 5-FU, and two other compounds, 5-chloro-2, 4-dihydroxypyrimidine (CDHP; gimestat) and potassium oxonate (OXO; otastat), in molar proportions of 1:0.4:1. CDHP is an inhibitor of dihydropirimidine dehydrogenase (DPD), which degenerates 80% of 5-FU in the liver and maintains the 5-FU level above a minimal effective concentration level. On the other hand, capecitabine is converted to 5'-DFUR either by human carboxyesterase (CE) or cytidine deaminase (CD), which is mainly localized in the human liver. 5'-DFUR is converted to the active form of 5-FU by thymidine phosphorylase (dThdPase) in human tumors. Low CE and CD activity levels are thought to protect the digestive wall and bone marrow from capecitabine toxicity.

Clinically, the reported RRs of capecitabine and S-1 in taxane-pretreated MBC patients are similar, but the toxicity profile seems to be different. Relatively severe diarrhea (14%, Grade 3) and hand-foot syndrome (10%, Grade 3) were observed in a phase II study for capecitabine (2,3), whereas the incidence of Grade 3 or severe diarrhea was relatively low (0.9%) and no hand-foot syndrome was observed in a phase II study of S-1 for MBC (4). A direct comparison of capecitabine and S-1 monotherapy is surely necessary, and since the antitumor activity of capecitabine might be relatively low in tumor cells with high DPD levels, an evaluation of the efficacy of S-1 after progression with

capecitabine or in tumors with high DPD expression levels is warranted.

Moreover, while the efficacy of capecitabine in combination therapy with other cytotoxics (11–16) or as first-line chemotherapy (17) has already been reported, few evidence of the efficacy of S-1 in combination therapy or first-line chemotherapy is available (18,19). The efficacy and safety of S-1 in combination with molecular-targeted drugs, such as antibodies and small molecule tyrosine kinase inhibitors, are also unknown. Further studies are thus required to elucidate the clinical role of S-1 in the management of breast cancer patients.

Conflict of interest statement

None declared.

References

1. Yap YS, Kendall A, Banerji U, Johnston SRD, Smith IE, O'Brien M. Clinical efficacy of capecitabine as first-line chemotherapy in metastatic breast cancer – How low can you go? *Breast* 2007;1:1–5.
2. Blum JL, Dees EC, Chacko A, Doane L, Ethirajan S, Hopkins J, et al. Phase II trial of capecitabine and weekly paclitaxel as first-line therapy for metastatic breast cancer. *Cancer* 2001;24(27):4384–90.
3. Fumoleau P, Largillier R, Clippe C, et al. Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. *Eur J Cancer* 2004;40: 536–42.
4. Saeki T, Takashima S, Sano M, Horikoshi N, Miura S, Shimizu S, et al. A phase II study of S-1 in patients with metastatic breast cancer – a Japanese trial by the S-1 Cooperative Study Group, Breast Cancer Working Group. *Breast Cancer* 2004;11:194–202.
5. Taira N, Aogi K, Ohsumi S, Takashima S, Nishimura R, Doihara H, et al. S-1 (TS-1) maintained complete response for approximately 10 years in a case of metastatic breast cancer. *Breast Cancer* 2006;13:220–4.
6. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur–0.4 M gimestat–1 M otastat potassium) in advanced gastric cancer patients. *Eur J Cancer* 1998;34:1715–20.
7. Kinoshita T, Nashimoto A, Yamamura Y, Okamura T, Sasako M, Sakamoto J, et al. Feasibility study of adjuvant chemotherapy with S-1 (TS-1; tegafur, ginmeracil, oteracil potassium) for gastric cancer. *Gastric Cancer* 2004;7:104–9.
8. Koizumi W, Kurihara M, Nakano S, Hasegawa K. Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. For the S-1 Cooperative Gastric Cancer Study Group. *Oncology* 2000;58:191–7.
9. World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment. WHO Offset Publication No. 48. Geneva: World Health Organization 1979.
10. Fujiwara Y. Current status of oral anticancer drugs in Japan. *J Clin Oncol* 1999;17(10):3362–5.
11. Blum JL, Dieras V, Lo Russo PM, Horton J, Rutman O, Buzdar A, et al. Multicenter, Phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. *J Clin Oncol* 2006;92(7):1759–68.
12. Lee SS, Lee JL, Ryu MH, Chang HM, Kim TW, Kang HJ, et al. Combination chemotherapy with capecitabine (x) and cisplatin (p) as first line treatment in advanced gastric cancer: experience of 223 patients with prognostic factor analysis. *Jpn J Clin Oncol* 2007;37(1):30–7.
13. Mackey JR, Tonkin KS, Koski SL, Scarfe AG, Smylie MG, Joy AA, et al. Final results of a phase II clinical trial of weekly docetaxel in combination with capecitabine in anthracycline-pretreated metastatic breast cancer. *Clin Breast Cancer* 2004;5(4):287–92.
14. Kellokumpu-Lehtinen PL, Sunela K, Lehtinen I, Joensuu H, Sjostrom-Mattson J. Finnish Breast Cancer Group. A phase I study of an all-oral combination of vinorelbine/capecitabine in patients with metastatic breast cancer previously treated with anthracyclines and/or taxanes. *Clin Breast Cancer* 2006;7(5):401–5.
15. Welt A, Minckwitz GV, Oberhoff C, Borquez D, Schleucher R, Loibl S, et al. Phase I/II study of capecitabine and vinorelbine in pretreated patients with metastatic breast cancer. *Ann Oncol* 2005;16:64–9.
16. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002;20:2812–23.
17. Oshaughnessy JA, Blum J, Moiseyenko V, Jones SE, Miles D, Bell D, et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/ metastatic breast cancer. *Ann Oncol* 2001;12(9):1247–54.
18. Suto A, Kubota T, Fukushima M, Ikeda T, Takeshita T, Ohmiya H, et al. Antitumor effect of combination of S-1 and docetaxel on the human breast cancer xenograft transplanted into SCID mice. *Oncol Rep* 2006;15(6):1517–22.
19. Nukatsuka M, Fujioka A, Nakagawa F, Oshimo H, Kitazato K, Uchida J, et al. Antimetastatic and anticancer activity of S-1, a new oral dihydropyrimidine-dehydrogenase-inhibiting fluoropyrimidine, alone and in combination with paclitaxel in an orthotopically implanted human breast cancer model. *Int J Oncol* 2004;25(6):1531–6.

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ORIGINAL ARTICLE

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Long-term prognostic study of carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA 15-3) in breast cancer

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Abstract

Background. Tumor markers are frequently used for screening and monitoring in oncology. We investigated the use of preoperative tumor marker (carcinoembryonic antigen [CEA] and carbohydrate antigen [CA] 15-3) levels in estimating the prognosis of breast cancer patients.

Methods. We conducted a retrospective study in patients who underwent breast cancer surgery at National Cancer Center Hospital between 1975 and 1994 and whose serum CEA ($n = 1663$) and CA 15-3 ($n = 1500$) levels were measured prior to operation. When we excluded patients with stage IV disease from the study, the CEA level was within the normal range in 1470 patients, while 150 patients had an elevated CEA level. For CA 15-3, 1395 patients were within the normal range, while 70 patients exhibited an elevated level.

Results. The 5-year and 10-year survival rates for patients with normal CEA levels were 87% and 76%, respectively. However, the 5-year and 10-year survival rates for patients with elevated CEA levels were 76% and 65%, respectively. At both time points, patients with normal CEA levels had higher survival rates ($P < 0.05$). The 5-year and 10-year survival rates for the patients with normal CA 15-3 levels were 86% and 76%, respectively, while only 71% and 52% patients with elevated CA 15-3 levels survived at 5 and 10 years, respectively. These differences were also significant ($P < 0.05$). However, there were no significant differences in disease-free survival (DFS) according to CEA or CA 15-3 levels.

Conclusion. There was a positive correlation between CEA levels and CA 15-3 levels and patient prognosis. Thus, the levels of these tumor markers may help to determine prognosis in breast cancer patients.

Key words Breast cancer · Long-term survival · CEA · CA 15-3 · Retrospective study

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Introduction

Tumor markers, which are proteins or enzymes produced by tumor cells or generated by host cells in response to tumorigenesis, are frequently used for screening and monitoring in oncology. The expression of tumor-specific antigens varies, however, and, in general, tumor cells express several different unique antigens. Therefore, the most effective cancer screening protocols would combine multiple markers for increased specificity.

A number of tumor markers (e.g., carcinoembryonic antigen [CEA] and carbohydrate antigen 15-3 [CA 15-3]) are used clinically in the treatment of breast cancer, but the sensitivity of these markers is low, so that they are not useful as screening tools.[1] However, abnormally elevated levels of tumor markers prior to surgery in a patient with primary breast cancer suggest the presence of undetectable metastatic foci, and this is a negative prognostic factor. In addition, tumor marker levels tend to increase as tumor progression occurs; therefore, tumor markers, while of limited diagnostic use, are important for determining the prognosis of breast cancer.[1] In this study, we investigated the use of preoperative tumor marker (CEA and CA 15-3) levels in estimating the prognosis of breast cancer patients.

Patients and methods

We conducted a retrospective study in patients who underwent breast cancer surgery at National Cancer Center Hos-

Table 1. Characteristics of the patients

Stage	No. of patients							
	0	I	IIA	IIB	IIIA	IIIB	IV	Not known
CEA normal ($n = 1495$)	19	431	774	2	90	57	25	97
CEA high ($n = 168$)	1	29	69	1	24	22	18	4
CA15-3 normal ($n = 1418$)	18	413	744	3	80	49	23	88
CA15-3 high ($n = 82$)	0	4	32	0	13	20	12	1

pital between 1975 and 1994 and whose serum CEA and CA 15-3 levels were measured prior to operation. For serum CEA measurement, an enzyme immunoassay (EIA) was used until 1989 ($n = 462$), while a latex photometric immunoassay (LPIA) was used between 1990 and 1992 ($n = 706$). Until 1993, serum CA 15-3 was measured with a quantitative sandwich radioimmunoassay (RIA) utilizing two monoclonal antibodies (115D8, DF3; $n = 1017$). However, since 1993, a chemiluminescent enzyme immunoassay (CLEIA) has been used to measure both CEA and CA 15-3 (CEA, $n = 495$; CA 15-3, $n = 483$).

We set the criteria as follows. Normal values (thresholds) for CEA and CA 15-3 were set at less than 5.0 ng/ml and less than 28 U/ml, respectively. In this study, the CEA level was within the normal range in 1495 patients, while 168 patients had an elevated CEA level. As for CA 15-3, 1418 patients were within the normal range, while 82 patients exhibited an elevated level. When we excluded stage IV patients from the study, CEA level was within the normal range in 1470 patients, while 150 patients had an elevated CEA level. As for CA 15-3, 1395 patients were within the normal range, while 70 patients exhibited an elevated level. The clinical stages of the patients in each group are listed in Table 1. We used the Japanese Breast Cancer Society classification of breast cancer[2] for the stage classification.

Statistical analyses

The Kaplan-Meier method was used to calculate the cumulative survival rates for the different groups: CEA (normal and elevated levels), and CA 15-3 (normal and elevated levels). Statistical significance was tested using the log-rank test. P values of less than 0.05 were considered as significant.

Results

We found that the 5-year and 10-year survival rates for patients with normal CEA levels ($n = 1470$) were 87% and 76%, respectively. However, the 5-year and 10-year survival rates for patients with elevated CEA levels ($n = 150$) were 76% and 65%, respectively. At both time points, patients with normal CEA levels had higher survival rates ($P < 0.05$; Fig. 1). The 5-year and 10-year survival rates for the patients with normal CA 15-3 levels ($n = 1395$) were 86% and 76%, respectively, and only 71% and 52% patients with elevated CA 15-3 levels ($n = 70$) survived at 5 and 10 years, respectively. These differences were also significant ($P < 0.05$; Fig. 2). However, there were no significant differences in disease-free survival (DFS) according to either CEA or CA15- levels. The 5-year DFS rate in patients with normal CEA levels was 82%, and the rate in patients with elevated CEA levels was 73% (Fig. 3). The 5-year DFS rate in patients with normal CA 15-3 levels was 83%, and the rate in those with elevated CA 15-3 levels was 67% (Fig. 4).

We also performed a prognostic analysis of the levels of these tumor markers in relation to disease stage. In patients with stage II disease, those with normal CA 15-3 levels had

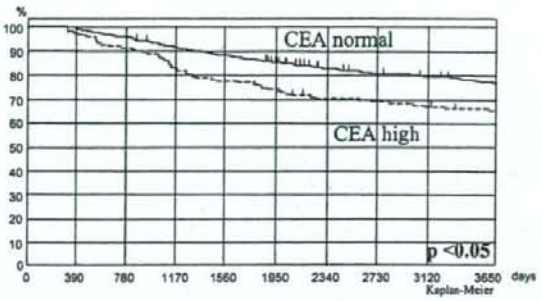

Fig. 1. The 5-year and 10-year survival rates for patients in relation to carcinoembryonic antigen (*CEA*) levels. *CEA normal* denotes normal CEA levels, and *CEA high* denotes elevated CEA levels

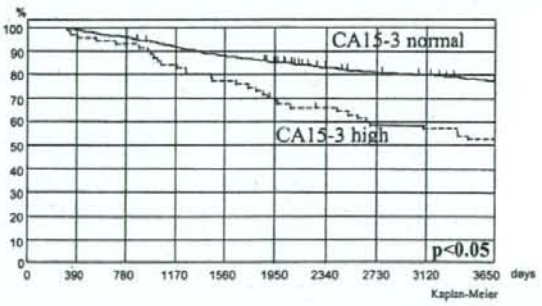

Fig. 2. The 5-year and 10-year survival rates for patients in relation to carbohydrate antigen 15-3 (*CA 15-3*) levels. *CA 15-3 normal* denotes normal CA 15-3 levels, and *CA 15-3 high* denotes elevated CA 15-3 levels

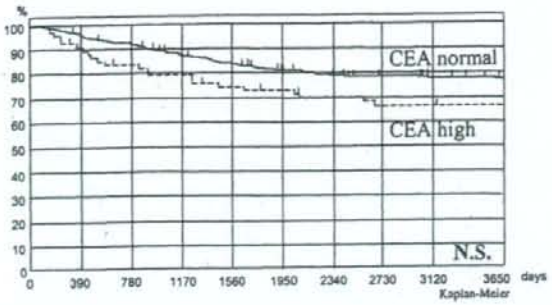

Fig. 3. Disease-free survival rates for patients in relation to CEA levels. *N.S.*, Not significant

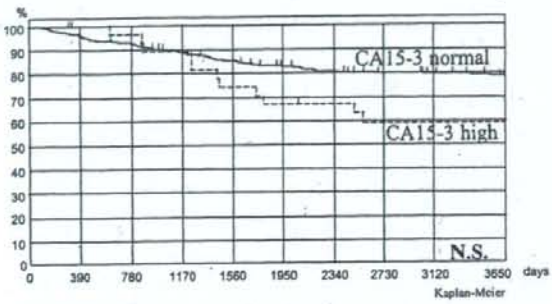

Fig. 4. Disease-free survival rates for patients in relation to CA 15-3 levels

a significantly better prognosis than those with elevated CA 15-3 levels. However, in patients with other disease stages, there was no significant difference in prognosis between those with normal levels and those with elevated levels of either tumor marker.

Discussion

During cellular transformation and progression to cancer, cancer cells release unique enzymes or proteins. Additionally, host cells can produce proteins in response to cancer. Such proteins are termed tumor markers and can be used to screen and monitor disease progression in oncology. Different tumor cells typically produce several unique tumor makers, and, while the specificity of any one marker may be low, the combination of several appropriate tumor markers is a powerful clinical tool.

Carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA 15-3) are tumor markers commonly used in the screening for breast cancers. CEA is a glycoprotein that is overexpressed in various adenocarcinomas, while CA 15-3 is a mucin-like glycoprotein that is produced in stem cells in response to tumorigenesis.[1]

We conducted a retrospective study in breast cancer patients (excluding stage IV patients) treated at our hospital between 1975 and 1994, and investigated the relationship between CEA and CA 15-3 levels (measured at the time of first medical examination) and patient survival. Interestingly, the 5-year and 10-year survival rates of patients with normal CEA levels were 87% and 76%, while those of patients with elevated CEA levels were 76% and 65%, respectively. Thus, the prognosis of patients whose CEA level was within the normal range at the time of diagnosis was significantly better than the prognosis of those with elevated CEA levels (log-rank; $P < 0.05$). In addition, the 5-year and 10-year survival rates of patients with normal CA 15-3 levels were 86% and 76%, while these rates in the patients with elevated CA 15-3 levels were 71% and 52%, respectively. As with the CEA levels, the long-term survival of breast cancer patients with CA 15-3 levels within the normal range at the time of diagnosis was significantly better than the survival of patients with elevated CA 15-3 levels (log-rank; $P < 0.05$). Previous studies have identified an inverse relationship between tumor marker levels and prognosis when comparing patients with tumors of the same clinical stage.[3] Our results further demonstrate a relationship between preoperative tumor marker levels and long-term survival. Further work is needed to clarify which marker is superior for predicting prognosis, but both may be suitable. However, CA 15-3 may be more sensitive than CEA. The American Society of Clinical Oncology (ASCO) has reported that CA27-29, a MUC-1 marker, is better at tracking tumor recurrence than CA 15-3 (also a MUC-1 marker). Regardless of which marker is better, measuring the levels of MUC-1 markers is likely to be highly effective for monitoring tumor progression or recurrence.[1] Some studies have reported that tumor markers are effective for the early screening of recurrence,[4–7] but the sensitivity varies in these reports. Similar variation was observed when tumor markers were used in the diagnosis of primary breast cancer.[3,8,9] Of note, ASCO has reported that: (i) CEA is not recommended for screening, diagnosis, staging, or routine surveillance of breast cancer patients after primary therapy (1997, 2000, 2007 recommendation); (ii) routine use of CEA for monitoring the response of metastatic disease to treatment is not recommended; and (iii) in the absence of readily measureable disease, elevated levels of MUC-1 markers (CA 15-3 and/or CA27-29) or a rising CEA level may suggest treatment failure.[1]

Significant differences in CA 15-3 expression levels between those in benign tumors and those in stage III and IV disease have been reported.[10] However, Gion et al.[11] reported that no differences were seen in CA 15-3 expression between benign tumors and stage I and II disease. Tumor marker levels tend to rise as disease progresses; therefore, tumor markers may be important prognostic factors.[1] Detecting elevated levels of preoperative tumor markers in patients with primary breast cancer may suggest the presence of undetectable metastatic foci; therefore, increased tumor marker levels are one factor that may predict a poor prognosis. Molina et al.[3,8] conducted a study of locoregional breast cancer and reported that the preoperative sensitivities of CEA and CA 15-3 were 11.7%–13% and 12.7%–18.8%, respectively. In addition, the sensitivities of CEA and CA 15-3 after recurrence were 30%–70%

Table 2. Past reports

Author	Year	No. of patients	Tumor marker	Sensitivity (%)	Patients state
Present study	2007	1620/1465	CEA, CA 15-3	CEA=9.11; CA 15-3=5.36	Preoperative
Soletormos[15]	2004	406	CEA, CA 15-3, TPA	CEA=or CA 15-3 or TPA=44–69	Recurrence
Molina[8]	2003	503	CEA, CA 15-3	CEA=11.7; CA 15-3=12.7	Locoregional breast cancer
Molina[3]	2003	1057	CEA, CA 15-3	CEA=13; CA 15-3=18.8	Locoregional breast cancer
Guadagni[9]	2001	2191	CEA, CA 15-3	CEA=16.7, CA 15-3=33.0, CEA+CA 15-3=39	Stage I–IV or metastatic disease
				CEA=38.5, CA 15-3=60, CA 15-3 and/or CEA=60	Recurrence
Lumachi[16]	2000	62	CEA, CA 15-3	CEA=40.3, CA 15-3=41.9, CEA+CA 15-3=59.7	Recurrence
Lumachi[17]	1999	103	CEA, CA 15-3	CEA=38.1, CA 15-3=61.1	Recurrence
Sutterlin[10]	1999	664	CEA, CA 15-3	CEA=30.3, CA 15-3=48.7	Recurrence
Molina[18]	1999	250	CEA, CA 15-3	CEA=31.6,CA 15-3=46.3, CEA+CA 15-3=59	Recurrence
Sutterlin[19]	1999	76	CEA, CA 15-3	CEA=30, CA 15-3=49,	Recurrence
Lauro[20]	1999	70	CEA, CA 15-3	CEA=35, CA 15-3=79, CEA+CA 15-3=79	Recurrence
Pectasides[21]	1996	68	CEA, CA 15-3	CEA=34, CA 15-3=68, CEA+CA 15-3=68	Recurrence
Jezersek[22]	1996	56	CEA, CA 15-3	CEA=70, CA 15-3=75	Recurrence

and 41.9%–79%, respectively (Table 2). In addition to well-known prognostic factors such as T-factor, N-factor, and hormone receptors, several references have acknowledged the relevance of tumor markers and prognosis.

In the present study, there were no significant differences in DFS according to preoperative levels of the tumor markers CEA and CA 15-3. Many studies have examined the relationship between recurrence and rising tumor marker expression levels. However, there is a delay between increases in marker levels and the confirmation of clinical recurrence, and this time period differs for each patient. In current practice, although a rise in marker expression may be detected, a patient will not be treated unless clinical recurrence is confirmed. A recent study compared the 7-year survival rates of patients undergoing surveillance treatment upon the detection of a rise in marker expression (n = 36) and those who were treated after the recurrence was confirmed by imaging (n = 32). Interestingly, tumor marker-guided salvage treatment prolonged the survival of the breast cancer patients.[12] However, a large-scale study conducted in 1320 postoperative breast cancer patients by the GIVIO investigators[13] found no significant differences in time to detection of recurrence between an intensive surveillance group and a control group. Furthermore, another study of postoperative breast cancer patients (n = 1243) found no difference in 5-year overall mortality between an intensive surveillance group and a control group.[14] Despite differences in the accuracy of current test methods, most studies have not found any differences in survival between groups undergoing intensive surveillance treatment for recurrence at an early stage and control groups; therefore, we believe that tumor marker-guided salvage treatment may not improve patient prognosis.

While tumor marker monitoring may not be useful for the detection of disease recurrence, our data support a role for CEA and CA 15-3 levels at least in helping to determine preoperative prognosis. We found that patients with elevated preoperative tumor marker levels had a significantly worse long-term prognosis than those patients with levels in the normal range. In relation to disease stage, stage II patients with normal CA 15-3 levels had a significantly better prognosis than those with elevated CA 15-3 levels. However, there were no significant differences in prognoses according to either CEA or CA 15-3 levels in patients with any other disease stage. This result suggested that the tumor marker level at the time of diagnosis was an independent prognostic factor. The early detection of recurrent foci may be accomplished using highly sensitive tumor markers, together with modern imaging technologies. Although the results of randomized controlled trials have demonstrated that the timing to initiate treatment for recurrence does not affect the overall survival rate, advances in imaging technology and improved treatment regimens may allow the early detection of recurrent foci and lead to improved patient survival. As diagnostic and treatment techniques improve, tumor markers will likely become more important in cancer therapy.

References

1. Harris L, Frische H, Mennel R, et al. (2007) American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. Clinical practice guidelines of American Society of Clinical Oncology. J Clin Oncol 25:5287–5312
2. Japanese Breast Cancer Society (2004) General rules for clinical and pathological recording of breast cancer, 15th edn (in Japanese). Kanehara, Tokyo
3. Molina R, Filella X, Alicarte J, et al. (2003) Prospective evaluation of CEA and CA 15-3 in patients with locoregional breast cancer. Anticancer Res 23:1035–1042
4. Hayes DF, Zurawski VR, Kufe DW (1986) Comparison of circulating CA 15-3 and carcinoembryonic antigen levels in patients with breast cancer. J Clin Oncol 4:1542–1546
5. Molina R, Filella X, Mengual P, et al. (1990) MCA in patients with breast cancer: correlation with CEA and CA 15-3. Int J Biol Markers 5:14–21
6. Molina R, Ballesta AM (1991) Evaluation of several tumor markers (MCA, CA 15-3, BCM, and CA549) in tissue and serum of patients with breast cancer. In: Ceriani RL (ed) Breast epithelial antigens. Molecular biology to clinical applications. Plenum, New York, pp 161–163
7. Dnistrian AM, Schwartz MK, Greenberg EJ, et al. (1991) Evaluation of CAM26, CAM29, CA 15-3 and CEA as circulating tumor markers in breast cancer patients. Tumor Biol 12:1282–1290

8. Molina R, Fiella X, Zanon G, et al. (2003) Prospective evaluation of tumor markers (c-erb B-2 oncoprotein, CEA, CA 15-3) in patients with locoregional breast cancer: Anticancer Res 23: 1043–1050
9. Guadagni F, Ferroni P, Carlini S, et al. (2001) A re-evaluation of carcinoembryonic antigen (CEA) as a serum marker for breast cancer: a prospective longitudinal study. Clin Cancer Res 7:2357–2362
10. Sutterlin M, Bussen S, Trott S, et al. (1999) Predictive value of CEA and CA 15-3 in the follow up of invasive breast cancer. Anticancer Res 19:2567–2570
11. Gion M, Mione R, Leon AE, et al. (2001) CA27-29: a valuable marker for breast cancer management. A confirmatory multicentric study on 603 cases. Eur J Cancer. 37:355–363
12. Nicolini A, Carpi A, Michelassi C, et al. (2003) Tumour marker guided salvage treatment prolongs survival of breast cancer patients: final report of a 7-year study. Biomed Pharmacother 57:452–459
13. The GIVIO investigators (1994) Impact of follow up testing on survival and health-related quality of life in breast cancer patients. JAMA 271:1587–1592
14. Turco M, Cariddi D, Pacini S, et al. (1994) Intensive diagnostic follow-up after treatment of primary breast cancer. JAMA 271:1593–1597
15. Soletormos G, Nielsen D, Schioler V, et al. (2004) Monitoring different stages of breast cancer using tumour markers CA 15-3, CEA and TPA. Eur J Cancer 40:481–486
16. Lumachi F, Brandes AA, Ermani M, et al. (2000) Sensitivity of serum tumor markers CEA and CA 15-3 in breast cancer recurrences and correlation with different prognostic factors. Anticancer Res 20:4751–4756
17. Lumachi F, Brandes AA, Boccagni P, et al. (1999) Long-term follow-up study in breast cancer patients using serum tumor markers CEA and CA 15-3. Anticancer Res 19:4485–4490
18. Molina R, Jo J, Filella X, et al. (1999) C-erb b-2 CEA and CA 15-3 serum levels in the early diagnosis of recurrence in breast cancer patients. Anticancer Res 19:2551–2556
19. Sutterlin M, Bussen S, Trott S, et al. (1999) Predictive value of CEA and CA 15-3 in the follow-up of invasive breast cancer. Anticancer Res 19:2526–2570
20. Lauro S, Trasatti L, Bordin F, et al. (1999) Comparison of CEA, MCA, CA 15-3 and CA27-29 in follow-up and monitoring therapeutic response in breast cancer patients. Anticancer Res 19: 3511–3516
21. Pectasides D, Pavlidis N, Gogou L, et al. (1996) Clinical value of CA 15-3, mucin-like carcinoma-associated antigen, tumor polypeptide antigen, and carcinoembryonic antigen in monitoring early breast cancer patients. Am J Clin Oncol 19:459–464
22. Jezersek B, Cervek J, Rudolf Z, et al. (1996) Clinical evaluation of potential usefulness of CEA, CA 15-3 and MCA in follow-up of breast cancer patients. Cancer Lett 110:137–144

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症　例

破骨細胞様巨細胞の出現を伴う乳癌の9例

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1999年から2007年の9年間における破骨細胞様巨細胞（OCGC）の出現を伴う乳癌（OCGC乳癌）の自験例につき臨床病理学的，免疫組織化学的特徴を検討した．OCGC乳癌は9症例であり，全乳癌における頻度は0.3%であった．臨床病期はStage Ⅰ：4例，Stage ⅡA：3例，Stage ⅡB：2例であった．最大腫瘍径は1.5cm—6.0cm（平均3.1cm），リンパ節転移を4例（44%）に認めた．腫瘍組織型は全例浸潤性乳管癌，組織学的異型度は全例grade2であった．estrogen receptorは5例（56%），progesteron receptorは6例（67%）で陽性，HER2は7例で検討し，1例（14%）で陽性であった．予後は原病死1例を認めた以外は無再発生存中（平均観察期間4年10カ月）である．OCGC乳癌は臨床病期，組織学的異型度，リンパ節転移，ホルモン受容体発現状況等から悪性度は中等度，あるいは比較的良好の可能性があることが示唆された．

索引用語：乳癌，破骨細胞様巨細胞

緒　言

破骨細胞様巨細胞（Osteoclast-like giant cell，以下OCGC）の出現をみる乳癌（以下OCGC乳癌）は0.5～1.2%と極めて稀であり，OCGC出現機序は生物学的，臨床病理学的側面からも興味深い．今回われわれは1999年から2007年の間に当院で経験したOCGC乳癌9症例についてその臨床病理学，免疫組織化学的特徴について検討したので若干の文献的考察を加えて報告する．

対象および方法

1999～2007年の9年間に当院で手術した乳癌3546症例のうち，摘出標本にてOCGC乳癌と診断された9症例（0.3%）を対象とした．OCGC乳癌は組織学的に腫瘍胞巣内あるいは腫瘍間質内にOCGCの出現を認めるもの，と定義した（図1，2）．臨床病理学的検討は「乳癌取扱い規約」[1]に準拠した．さらにestrogen receptor（以下ER），progesteron receptor（以下PgR），HER2，p53の免疫組織化学的検討を行った．これらの結果を1999年～2006年に当院で手術された全浸潤性乳管癌症例（対照群）と比較検討した．

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成　績

年齢は38～72歳（平均50歳）で女性8例，男性1例であった（表1）．発生部位は右側7例，左側2例と右側に多く，C領域が6例で最も多かった．臨床病期はStage Ⅰ：4例（44%），Stage ⅡA：3例（33%），Stage ⅡB：2例（22%）であった．対照群ではStage Ⅰ：33.4%，Stage Ⅱ：57.6%，Stage Ⅲ：8.9%で両群間に差異を認めなかった．施行術式は乳房温存部分切除術＋腋窩リンパ節郭清術：5例，両胸筋温存乳房切除術＋腋窩リンパ節郭清術：3例，乳房温存部分切除術＋センチネルリンパ節生検術：1例であった．リンパ節転移を4例（44%）に認め，1例に5個以上の転移を認めた．リンパ節転移の頻度は対照群（44%）と同等であった．手術摘出標本の肉眼所見では腫瘍割面は赤褐色調を含むものが多く，通常経験される乳腺浸潤癌の肉眼像と異なっていた．病理学的最大腫瘍径は1.5cm～6.0cm（平均3.1cm），組織学的には全例浸潤性乳管癌であり，優位な組織像は乳頭腺管癌が8例，硬癌が1例であった（表2）．腫瘍胞巣内および腫瘍間質内にOCGCを漫慢性に認めた．OCGC乳癌は組織学的に①腫瘍成分が未分化な肉腫様パターンを示し，高率に骨や軟骨化生を伴うmetaplastic carcinoma with OCGC，②比較的分化型の腺癌に伴うもので肉腫様成分や骨，軟骨化生のないcarcinoma with reactive

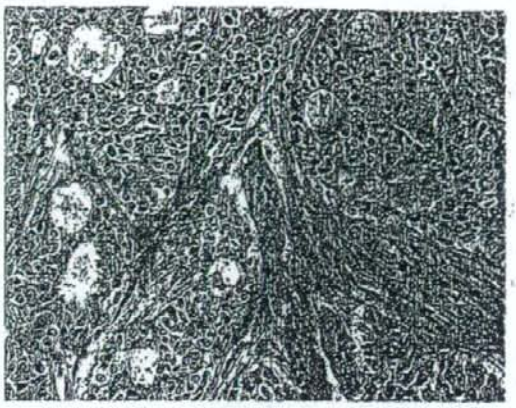

図1　病理組織所見：腫瘍は浸潤性乳管癌（乳頭腺管癌）であり，腫瘍間質にはOCGCの浸潤を散在性に認める（症例1，HE染色，対物20倍）．

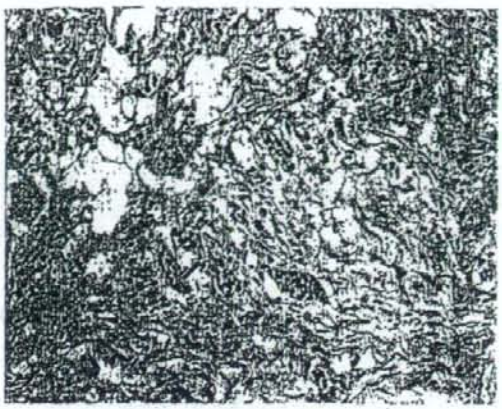

図2　病理組織所見：腫瘍周囲間質に出現した多数のOCGC（症例3，HE染色，対物20倍）．

stromal giant cells，③上皮性成分がなく，骨の巨細胞腫に類似性が求められるextraskeletal osteoclastomaに分類可能とされる[2]が，自験例は全て②に相当するものであった．OCGCの出現数には各症例間でばらつきがみられたが，その形態には違いがみられなかった．組織学的異型度（modified Bloom-Richardson分類）は全例grade2，リンパ管侵襲を3例に認めたものの，静脈侵襲は全例陰性であった．7例で脂肪浸潤を，1例で真皮への浸潤をきたしていた．高度乳管内進展を3例に認めた．いずれの症例においても扁平上皮化生や間質の骨・軟骨化生は認められなかった．対照群では組織学的異型度はgrade1：10%，grade2：48%，grade3：42%であり，対照群のほうが異型度が高い傾向にあった．免疫組織化学的検査ではERが5例（56%），PgRが6例（67%）で陽性であり，検討した7例中1例（14%）でHER2蛋白の過剰発現を認めた．またER，PgRがいずれも陽性であったのは3例（33%）であった．なおER，PgRは免疫染色で10%以上の腫瘍細胞が染まるものを陽性とした．p53は2例で陽性，5例で弱陽性であった．対照群ではERが72%，PgRが67%の症例で陽性，HER2の過剰発現を20%の症例で認めた．ER，PgRがいずれも陽性であったのは60%であった．OCGC乳癌症例では対照群と比較するとER陽性率が低い傾向にあった．術前穿刺吸引細胞診を施行された6例のうち当院で検討されたのは4例で，異型上皮細胞と多核巨細胞をともに認めたものは2例であった．予後は1例が術後5年10カ月で多発骨転移，多臓器転移にて死亡したものの，他症例は無再発生存中（平均観察期間4年10カ月）である．

考　察

OCGCの出現を伴う癌の報告はさまざまな臓器でみられるが極めて稀であり，乳癌においても同様でその頻度は0.5～1.2%[3)-5)]といわれている．1931年にLeroux[6]が初めて報告して以来約100例の報告があるのみである．臨床的特徴として，通常型乳癌と比較して若年齢，閉経前の症例が多いとの報告が散見される[4)7)]が，自験例では平均50歳，閉経前が6例，自然閉経後と子宮卵巣摘出術後がそれぞれ1例ずつであり，通常型乳癌との差異を認めなかった．

男性に発症したOCGC乳癌の報告はなく，自験例が初めての症例であった．当症例は組織像においても，嚢胞内にポリープ状に発育し乳頭状～一部胞巣状に増殖した乳頭腺管癌で，本邦で従来報告されたOCGC乳癌はすべて充実性の発育を示している点からも極めて稀な症例と考えられる．本症例は術後2年で胸骨転移を，5年10カ月で上腕骨転移，多臓器転移をきたし死亡した．

腫瘍の組織型として1995年のViacavaらは多彩な組織型を報告している[8]が，とりわけ本邦においては大多数が浸潤性乳管癌である[9)-12)]．自験例でも全症例が浸潤性乳管癌であった．

免疫組織化学的検討について，OCGC乳癌がER陽性，HER2陰性の傾向があることを示した報告[10]や，それとは異なりER陰性，PgR陽性症例が多いとする報告[4)13)]もある．予後についても通常型乳癌と比較し良好とするもの[11)14)]や，差異がないとするもの[15]，一方で比較的進行した症例が多いとするもの[4]まで様々で一

表1　OCGC乳癌症例の臨床所見

症例	年齢（歳）	性別	TNM	術式	術後経過（術後観察期間）
1	41	女	T1cN0M0	Bp+SLN	no rec.（3M）
2	45	女	T2N0M0	Bt+Ax	no rec.（37M）
3	45	女	T1cN0M0	Bp+Ax	no rec.（42M）
4	57	女	T1cN0M0	Bp+Ax	no rec.（71M）
5	38	女	T2N0M0	Bp+Ax	no rec.（69M）
6	41	女	T2N0M0	Bp+Ax	no rec.（99M）
7	72	男	T2N1M0	Bt+Ax	胸骨転移（70M）
8	44	女	T1bN0M0	Bp+Ax	no rec.（51M）
9	64	女	T2N1M0	Bt+Ax	no rec.（81M）

Bp+SLN：乳房温存部分切除術＋センチネルリンパ節生検術，Bt+Ax：両胸筋温存乳房切除術＋腋窩リンパ節郭清術，Bp+Ax：乳房温存部分切除術＋腋窩リンパ節郭清術，no rec.：無再発生存中

表2　OCGC乳癌症例の病理組織所見と免疫組織化学所見

症例	腫瘍径（cm）	リンパ節転移	組織型（優位組織像）	G/NG	ly/v	ER/PgR	HER2	p53
1	5.1	n0(0/2)	IDC(pap)	2/3	(−)/(−)	(+)/(+)	(−)	…
2	3.5	n1(4/24)	IDC(pap)	2/1	(+)/(−)	(+)/(+)	(−)	(±)
3	1.5	n1(1/12)	IDC(pap)	2/2	(−)/(−)	(−)/(+)	(−)	(±)
4	2.0	n0(0/23)	IDC(pap)	2/3	(−)/(−)	(+)/(−)	(−)	(−)
5	2.1	n0(0/14)	IDC(pap)	2/2	(−)/(−)	(−)/(+)	(−)	(±)
6	2.3	n0(0/31)	IDC(pap)	2/2	(−)/(−)	(+)/(+)	…	(+)
7	5.0	n1(7/24)	IDC(pap)	2/2	(+)/(−)	(−)/(−)	…	(+)
8	0.8	n0(0/15)	IDC(sci)	2/2	(−)/(−)	(−)/(+)	(−)	(±)
9	6.0	n1(3/21)	IDC(pap)	2/2	(+)/(−)	(+)/(−)	(+)	(±)

IDC：浸潤性乳管癌，pap：乳頭腺管癌，sci：硬癌，G：組織学的異型度（modified Bloom-Richardson分類），NG：組織学的核異型度，ly：リンパ管侵襲，v：静脈侵襲，ER：estrogen receptor，PgR：progesteron receptor

定の見解が得られていない．自験例ではER陽性率が対照群より低い傾向にあった．津田[16]はリンパ節転移の程度と組織学的異型度（modified Bloom-Richardson分類）を最も重要な独立した予後因子としているが，今回の臨床病期，リンパ節転移の程度，ホルモン受容体発現状況の検討からはその悪性度は通常型乳癌とほぼ同等であるものと考えられる一方，臨床病期Stage IIBであった1例が術後5年10カ月後に原病死した以外全例無再発生存中であること，組織学的異型度がOCGC乳癌症例のほうが低い傾向にあったことは，OCGC乳癌の予後が比較的良好であることを示唆している．

術前画像診断についてOCGC乳癌は境界明瞭な腫瘤を形成する頻度が高いため，マンモグラフィにて良悪性の鑑別が困難であることが多く，そのことが予後を悪くしている可能性があるとの報告がある[4]．自験例では1症例がマンモグラフィ，超音波検査にて良悪性鑑別困難な嚢胞性腫瘤と診断され1年間経過観察となっている．他の1症例はマンモグラフィにて異常所見を認めず，超音波検査でも質的診断困難な低エコー腫瘤との診断であったが，造影MRIでの腫瘤の形状，造影パターンにて浸潤性乳管癌を疑われ，穿刺針生検にて浸潤性乳管癌と診断された．他の7症例ではマンモグラフィにて辺縁不整な，spiculaあるいは石灰化を伴う腫瘤等の所見により，乳癌あるいはその疑いと指摘された．自験例からは良悪性の鑑別が困難な傾向は認められなかった．

術前穿刺吸引細胞診についてOCGC乳癌の診断に有用であるとの報告があるが[17]，今回細胞診を検討した4例中，異型上皮細胞とOCGCをともに認め，OCGC乳癌が疑われたのは2例であった．OCGCの出現数に各症例間でばらつきがあったことがその原因と

考えられる．

OCGCの発生起源として過去の報告では間質系の組織球由来とする見解でほぼ一致している[9)~12),17)]．1症例のみの検討であるが，自験例でも免疫染色で単球・マクロファージ系にCD68が陽性となっておりその見解と矛盾しない．

OCGCの出現機序としては不明な点が多い．OCGCは腫瘍部位にのみ認められ，電子顕微鏡による検討では組織球の融合にて形成されるとの報告もみられる[11)]．またマウスを用いた実験でinterleukin-1(IL-1)が破骨細胞の多核細胞化と骨吸収活性の誘導を促したという報告があり[18)]，癌細胞と関連してサイトカインが放出されOCGCが誘導されるとも考えられる．in-vitroでOCGCがparathormoneからの刺激にて溶骨能を持つことから，骨転移との関連を指摘する報告もある[10)]．因果関係は不明であるが，自験例での死亡症例も骨転移をきたした．今後更なる研究によりその出現機序が解明されればOCGC乳癌の生物学的特性，予後等が明らかになっていくものと考えられる．

結　語

OCGCの出現を伴う乳癌は稀な特殊型である．今回の検討ではその悪性度は中等度，あるいは比較的低い可能性があることが示唆された．OCGCの出現機序はまだ不明な点が多いが，その解明は腫瘍の生物学的特性を考える上で役立つものと考えられる．

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文　献

1) 日本乳癌学会編：臨床・病理乳癌取扱い規約．第15版，金原出版，東京，2004
2) 布山繁美：破骨細胞様巨細胞が多数出現した乳癌の1例．日臨細胞会誌　30：1115—1119，1991
3) Rosen PP: Rosen's Breast Pathology. second edition, LIPPINCOTT WILLIAMS & WILKINS, Philadelphia, 2001, p517—526
4) Holland R, van Haelst UJ: Mammary carcinoma with osteoclast-like giant cells: additional observation of six cases. Cancer 53: 1963—1973, 1984
5) Ichijima K, Kobayashi Y, Ueda Y, et al: Breast cancer with reactive multinucleated giant cells: report of three cases. Acta Pathol Jpn 36: 449—457, 1986
6) Leroux R: Reaction giganto cellulaire du stroma dans un epithelioma mammaire. Bull Cancer 20: 692—697, 1931
7) Page DL, Anderson TJ: Diagnostic histopathology of the breast. Churchill Livingstone, Edinburgh, London Melbourne, New York, 1987, p290—292
8) Viacava P, Naccarato AG, Nardini V, et al: Breast carcinoma with osteoclast-like giant cells: Immunohistochemical and ultrastructual study. Tumori 81: 135—141, 1995
9) 清水　健，正和信英，三枝　圭他：破骨細胞様巨細胞の出現を伴う乳癌について．日臨細胞会誌　31：52—59，1992
10) 松井栄美，阿部　仁，津田隆洋他：破骨細胞様巨細胞を伴う乳癌6例の検討．日臨細胞会誌　42：200—205，2003
11) 大岡　出，小沢邦寿，菅野　勇他：破骨細胞様巨細胞を伴う乳癌の1例．癌の臨　44：889—894，1998
12) 石井辰明，金　仁洙，井谷史嗣他：破骨細胞様巨細胞を伴う乳癌の1例．日臨外会誌　66：587—590，2005
13) Tavassooli FA, Norris HJ: Breast carcinoma with osteoclast-like giant cells. Arch Pathol Lab Med 110: 636—639, 1986
14) Factor SM, Biempica L, Ratner I, et al: Carcinoma of the breast with multinucleated reactive stromal giant cells. Virchows Arch A 374: 1—12, 1977
15) Agnantis NT, Rosen PP: Mammary carcinoma with osteoclast-like giant cells. Am J Clin Pathol 72: 383—389, 1979
16) 津田　均：乳癌の組織像と癌遺伝子増幅との関連並びにそれらの予後因子としての重要性．乳癌の臨　6：9—17，1991
17) Cai G, Simsir A, Cangiarella J: Invasive mammary carcinoma with osteoclast-like giant cells diagnosed by fine-needle aspiration biopsy. Diagnostic Cytopathology 30: 396—400, 2004
18) Jimi E, Nakamura I, Duong L, et al: Interleukin 1 induces multinucleation and bone-resorbing activity of osteoclasts in the absence of osteoblasts/stromal cells. Experimental Cell