24. Sun CL, Yuan JM, Koh WP, Yu MC. Green tea, black tea and breast cancer risk: a meta-analysis of epidemiological studies. *Carcinogenesis* 2006;27:1310–5.
25. Messina M, McCaskill-Stevens W, Lampe JW. Addressing the soy and breast cancer relationship: review, commentary, and workshop proceedings. *J Natl Cancer Inst* 2006;98:1275–84.
26. Seely D, Mills EJ, Wu P, Verma S, Guyatt GH. The effects of green tea consumption on incidence of breast cancer and recurrence of breast cancer: a systematic review and meta-analysis. *Integr Cancer Ther* 2005;4:144–55.
27. Nakachi K, Suemasu K, Suga K, Takeo T, Imai K, Higashi Y. Influence of drinking green tea on breast cancer malignancy among Japanese patients. *Jpn J Cancer Res* 1998;89:254–61.
28. Roy AM, Baliga MS, Katiyar SK. Epigallocatechin-3-gallate induces apoptosis in estrogen receptor-negative human breast carcinoma cells via modulation in protein expression of p53 and Bax and caspase-3 activation. *Mol Cancer Ther* 2005;4:81–90.
29. Bigelow RL, Cardelli JA. The green tea catechins, (−)-epigallocatechin-3-gallate (EGCG) and (−)-epicatechin-3-gallate (ECG), inhibit HGF/Met signaling in immortalized and tumorigenic breast epithelial cells. *Oncogene* 2006;25:1922–30.
30. Kim J, Zhang X, Rieger-Christ KM, et al. Suppression of Wnt signaling by the green tea compound (−)-epigallocatechin-3-gallate (EGCG) in invasive breast cancer cells. Requirement of the transcriptional repressor HBP1. *J Biol Chem* 2006;281:10865–75.

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Case Report

Brain Metastases after Achieving Local Pathological Complete Responses with Neoadjuvant Chemotherapy

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Background: We encountered two patients with inflammatory breast carcinoma who developed symptomatic brain metastases after achieving local pathological complete responses (pCR) with neoadjuvant chemotherapy (NAC).

Case presentations: The first patient is a 39-year-old woman (Case 1), who underwent NAC with AC (doxorubicin + cyclophosphamide) followed by weekly paclitaxel. After achieving a clinical CR (cCR), we conducted a modified radical mastectomy. Pathological evaluation confirmed no residual malignant cells within the breast tissue or lymph nodes. However, she developed neurological symptoms from brain metastases one month postoperatively. The second patient is a 44-year-old woman (Case 2). Again, no residual malignant cells were detected within the breast tissue or lymph nodes following NAC, but the patient developed symptomatic brain metastases eight months postoperatively. When primary breast tumors are locally advanced, it may be worthwhile to rule out brain metastases even if pCR is obtained after NAC.

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Key words: Brain metastasis, Pathological complete response, Breast cancer

Introduction

Neoadjuvant chemotherapy (NAC) is a standard treatment option for patients with locally advanced and/or inflammatory breast cancers. The outcomes of patients achieving pCR of their primary tumors are significantly better than those with residual disease[1-3]. Here, we introduce two patients who developed symptomatic brain metastases shortly after documented pCRs following NAC and surgery.

Case Report

Case 1

A 39-year-old premenopausal woman sought medical attention for erythematous induration of her left breast. With a working diagnosis of inflammatory breast cancer, fine needle aspiration cytology revealed adenocarcinoma. The patient was referred to the National Cancer Center Hospital for further treatment in February 2005. Physical examination revealed an indistinct 12 cm mass in the upper area of the left breast, and the surface of this lesion exhibited a peau d'orange appearance. Axillary and supraclavicular lymph nodes were palpable and measured 4 and 2 cm in diameter, respectively. The axillary lymph node was fixed to the surrounding tissue. Ultrasonography (US) revealed a 7 cm breast mass with dermal thickening, edematous subcutaneous tissue, and enlarged lymph nodes (Fig 1a). These findings were also observed on computed tomography (CT) and magnetic resonance imaging (MRI).

Core needle biopsy led to a pathological diagnosis of invasive ductal carcinoma (grade 3, nuclear grade 3, and HER-2 negative) (Fig 2a). The tumor was negative for both estrogen and progesterone receptors. Chest X-ray, bone scintigraphy, abdominal US, and chest and abdominal CT revealed no distant metastases. Due to the presumed low incidence of brain metastases at this clinical stage, brain imaging was not done at

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Abbreviations:
pCR, Pathological complete response; NAC, neoadjuvant chemotherapy; US, ultrasonography; CT, Computed tomography; MRI, Magnetic resonance imaging

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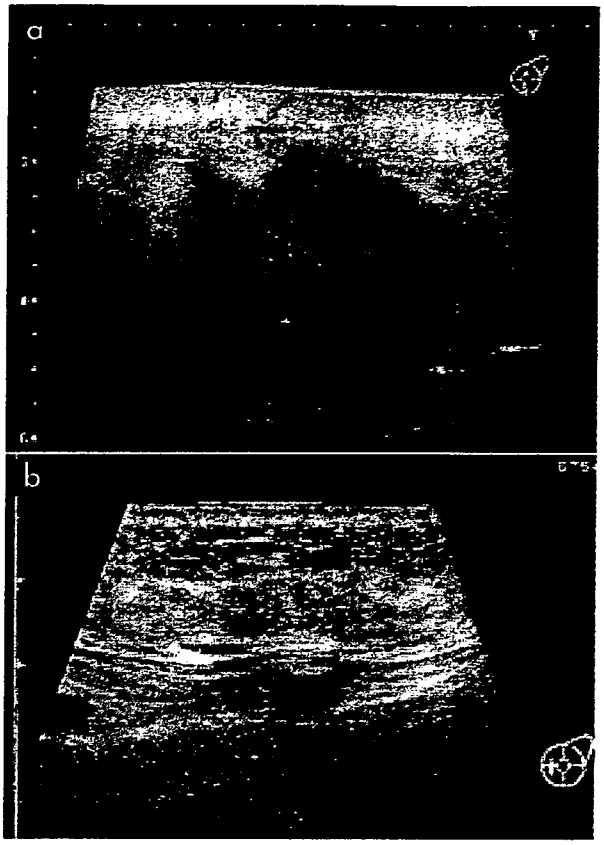

Fig 1. (a) US reveals a 7 cm breast mass with overlying skin thickening, edematous subcutaneous tissue. (b) US reveals no residual tumor following neoadjuvant chemotherapy.

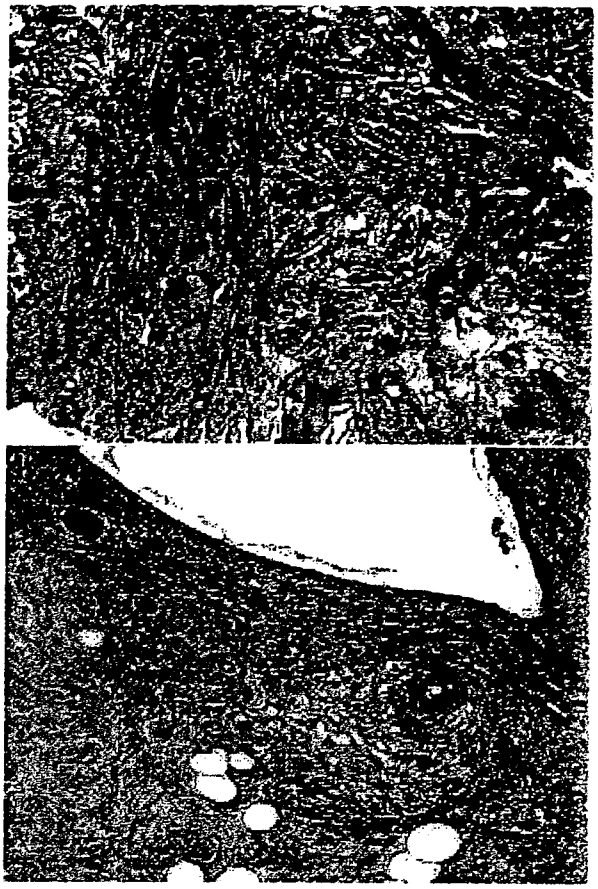

Fig 2. (a) Core needle biopsy reveals invasive ductal carcinoma, grade 3, nuclear grade 3. (b) No residual tumor is detected. The presence of inflammatory cells surrounding a duct with an increased number of enlarged capillary vessels, typical after tumor disappearance, is observed. (hematoxylin-eosin staining, ×100).

this point. Inflammatory breast cancer of the left breast was initially diagnosed, T4dN3M0, Stage IIIC, according to the general rules for clinical and pathological grading of breast cancers[4]. She received NAC from February to July consisting of doxorubicin and cyclophosphamide (60/600 mg/m^2) 4 times every 3 weeks, followed by paclitaxel (80 mg/m^2) weekly for 12 weeks. Following NAC, only induration of her left breast was apparent upon physical examination, and no breast masses or axillary lymph nodes were detected by US (Fig 1b) and CT. Additionally, serum levels of tumor markers (CEA, CA 15-3, ST 439) remained within normal limits before and after chemotherapy. We subsequently conducted a modified radical mastectomy in August, and no malignant cells were detected in the resected breast tissue and dissected axillary lymph nodes (Fig 2b). However, the patient presented with vertigo and severe headache prior to the initiation of radiotherapy to the left chest wall in September. Brain MRI revealed multiple metastatic lesions in her right frontal lobe, temporal lobe, and bilateral cerebellum (Fig 3). To control her symptoms, whole-brain radiotherapy with a total dose of 30 Gy/10 fractions was incorporated in October. However, her condition deteriorated, and she expired in December.

Case 2

A 44-year-old premenopausal woman was seen at a nearby hospital with a chief complaint of an erythematous enlarged right breast. Inflammatory breast cancer was suspected, so she was referred to our institution in December 2004.

On initial examination, the right breast was firm, erythematous, and edematous with a thickened dermis. Axillary and supraclavicular lymph nodes were palpable and measured 5 cm and 1 cm

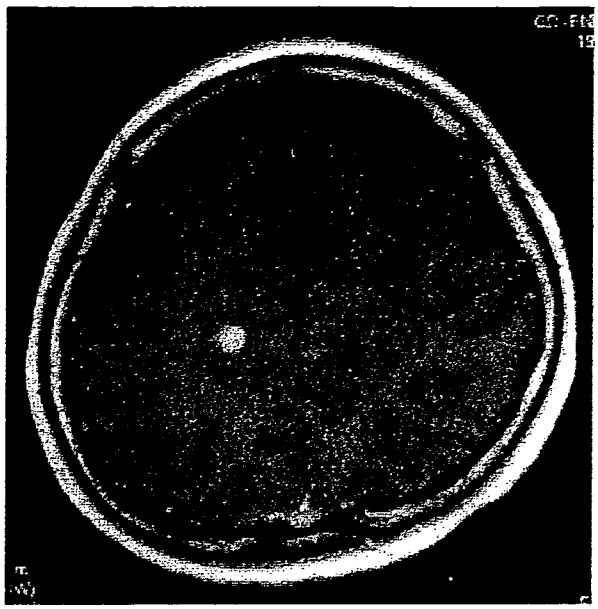

Fig 3. The metastatic lesions exhibited high signal intensity in the right temporal lobe by T1 weighted MRI.

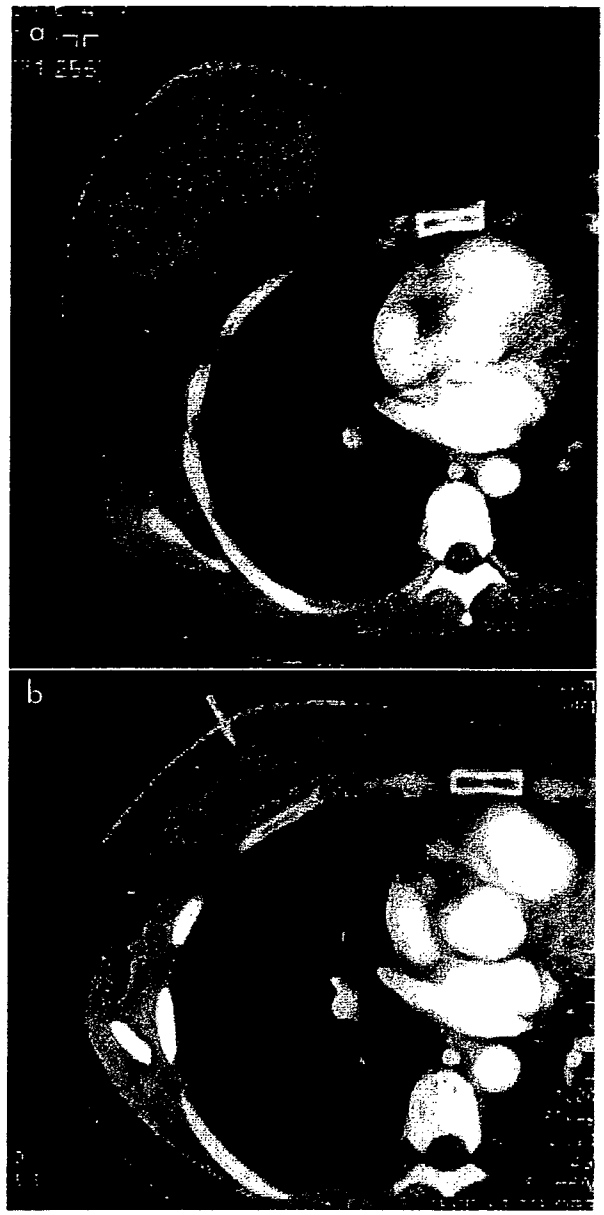

Fig 4. (a) CT shows a large right breast mass with overlying edematous subcutaneous tissue and thickened skin. This is not the early phase but late phase scan of breast CT, because only chest CT without an early phase scan was performed to detect distant metastasis instead of breast CT. (b) CT scan reveals a mass-like lesion measuring 3 cm, without enhancement, in the right breast.

in diameter, respectively. CT showed a large right breast mass with an edematous dermis and subcutaneous tissue.Additionally, the axillary and supraclavicular lymph nodes were enlarged (Fig 4a). The specimen obtained by the core needle biopsy was consistent with an invasive ductal carcinoma (solid tubular type, grade 3, nuclear grade 3, HER-2 negative, estrogen and progesterone receptor negative) (Fig 5a). No metastatic lesions were detected by bone scintigraphy, chest X-ray, chest CT, or abdominal US, though diagnostic brain imaging was not performed at that time. Serum tumor markers were elevated, with a CEA of 52.4 ng/ml, CA 15-3 of 279 U/ml, and NCC-ST 439 of 910 U/ml. Inflammatory breast cancer, T4dN3M0, Stage IIIC[4] was diagnosed. She underwent NAC from December to May 2005, using the same treatment regimen as Patient 1. Following NAC, physical examination revealed only induration of the right breast with slight thickening of the overlying skin. CT revealed a slightly enhanced, 3-cm lesion in the breast (Fig 4b) without enlarged lymph nodes. All tumor markers were within normal limits after chemotherapy. We performed a modified radical mastectomy in July, and no tumor cells were pathologically detected in the breast tissue and axillary lymph nodes (Fig 5b). Following surgery, we performed local radiotherapy with a total dose of 60 Gy/30 fractions from August through October. However, the patient developed headache and ambulatory disturbance in early December. Brain CT and MRI scans performed in March 2006 detected a tumor measuring 5 cm in diameter in her right temporal lobe with surrounding edema (Fig 6). A right frontotemporal craniotomy followed by whole-brain radiotherapy of 37.5 Gy/15 fractions was carried out from

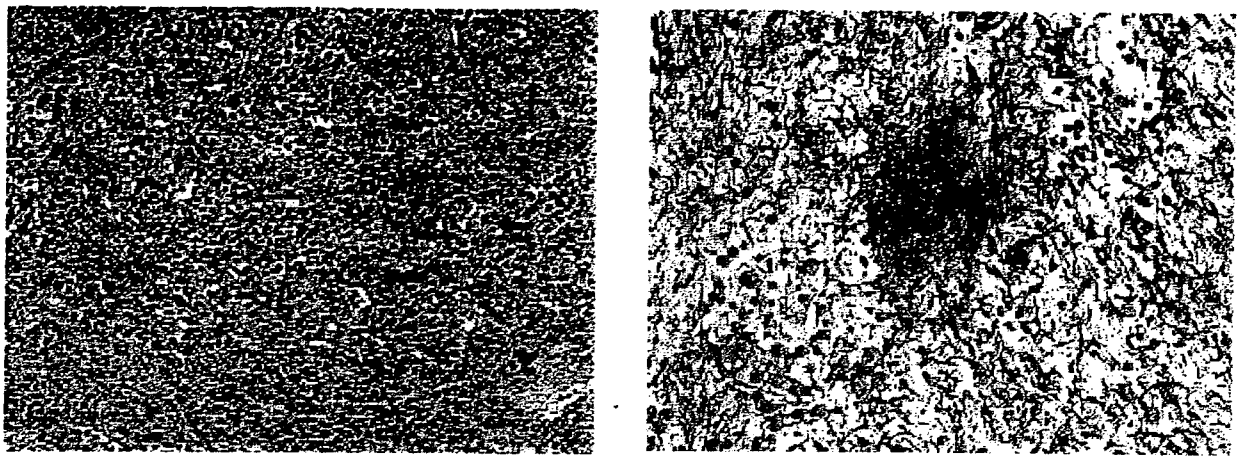

Fig 5. (a) Core needle biopsy reveals invasive ductal carcinoma, grade 3, nuclear grade 3. (b) No residual tumor is detected. Many foamy cells and a disturbance of the fiber rows after the disappearance of the tumor are observed (hematoxylin and eosin staining, ×100).

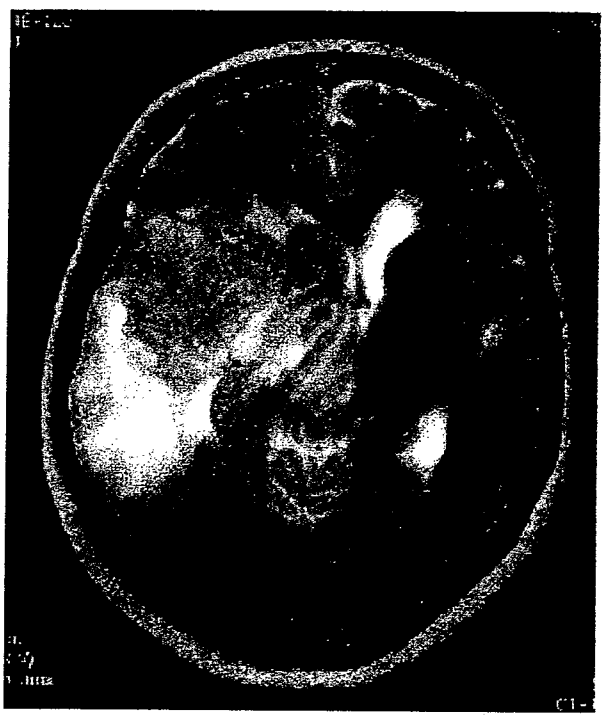

Fig 6. MRI demonstrates a tumor measuring 5 cm in diameter, with surrounding edema, in the right temporal lobe.

March through April. Intracranial recurrence is now controlled three months after radiotherapy.

Discussion

Several studies have indicated that breast cancer patients with pCR following NAC have better overall survival and disease-free survival rates[1-3]. Moreover, pCR of axillary lymph nodes is an excellent prognostic factor for locally advanced breast cancers[5-8]. The two cases presented were first diagnosed with inflammatory breast cancer with axillary and supraclavicular lymph node metastases. The patients achieved pCR for both the main tumors and the axillary lymph nodes following NAC, and favorable prognoses were expected from the published literature. However, both patients developed symptomatic brain metastases soon after mastectomy. The interval between surgery and the occurrence of neurological signs was only one month for Patient 1 and five months for Patient 2. This led us to the theory that the blood brain barrier restricted access of the chemotherapeutic agents to the central nervous system. Therefore despite locally effective NAC, occult brain metastases may continue to progress into clinical significance. This theory may help us understand the progression of brain metastases in these patients[9]. There have been no reports examining the rates of brain metastasis following NAC. Yet there are reports of patients receiving adjuvant chemotherapy having an increased incidence of brain metastases as the site of first recurrence compared to control[10,11]. In the present cases, we suspect that subclinical metastases were present in the brain before initiating NAC. It is likely that, because of inadequate delivery of cytotoxic agents to the brain, these metastases continued to grow despite effective tumor control elsewhere the body.

Several studies have identified risk factors for brain metastases in patients with breast cancer. Young age[12,13], unresponsiveness to the hormonal

therapies, and HER-2 over expression are reported risk factors[14-17]. Intracranial metastases are also related to the use of trastuzumab[18]. In the two patients presented here, relatively young age and the absences of both estrogen and progesterone receptor were concordant risk factors for developing brain metastases.

The combination of NAC and surgery can lead to favorable outcomes in many cases of breast cancer, but effective control over the primary lesions and the extracranial micrometastases by the cytotoxic agents may not predict future intracranial event. The blood brain barrier would likely prevent chemotherapeutic agents from reaching the central nervous system. As a consequence, brain metastases may continue to grow and become symptomatic despite pCR of primary sites and lymph node metastases. This can be a concerning factor, especially in patients at risk for developing brain metastases. Further investigations are warranted to identify the mechanisms leading to intracranial metastases, as well as pretherapeutic risk factors.

References

1) Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher R, Wickerham L, Begovic M, DeCillis A, Robidoux A, Margolese G, Cruz B, Hoehn L, Lees W, Dimitrov V, Bear D: Effect of preoperative chemotherapy on the outcome of woman with operable breast cancer. *J Clin Oncol* 16: 2672-2685, 1998.
2) Norman W, Jiping W, Eleftherios M, John B, Bernard F: Preoperative chemotherapy in patients with operable breast cancer: nine-year results from national surgical adjuvant breast and bowel project B-18. *J Natl Cancer Inst Monogr* 30: 96-102, 2001.
3) Sataloff D, Mason B, Prestipino A, Seinige U, Lieber C, Baloch Z: Pathologic response to induction chemotherapy in locally advanced carcinoma of the breast: A determinant of outcome. *J Am Coll Surg* 180: 297-306, 1995.
4) Sakamoto G, Inaji H, Akiyama F, Haga S, Hiraoka M, Inai K, Iwase T, Kobayashi S, Sakamoto G, Sano M, Sato T, Sonoo H, Tsuchiya S, Watanabe T; The Japanese Breast Cancer Society: General rules for clinical and pathological recording of breast cancer 2005. *Breast cancer* 12 (Suppl): S1-27, 2005.
5) Hennessy T, Hortobagyi N, Rouzier R, Kuerer H, Sneige N, Buzdar U, Kau W, Fornage B, Sahin A, Broglio K, Singletary E, Valero V: Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metasteses following primary chemotherapy. *J Clin Oncol* 23: 9304-9311, 2005.
6) Rouzier R, Extra M, Klijanienko J, Falcou C, Asselain B, Salomon V, Vielh P, Bourstyn E: Incidence and prognostic significance of complete axillary downstaging after primary chemotherapy in breast cancer patients with T1 to T3 tumors and cytologically proven axillary metastic lymph nodes. *J Clin Oncol* 20: 1304-1310, 2002.
7) Hennessy T, Gonzalez-Angulo M, Hortobagyi N, Cristofanilli M, Kau W, Broglio K, Fornage B, Singletary E, Sahin A, Buzdar A, Valero V: Disease-free and overall survival after pathologic complete disease remission of cytologically proven inflammatory breast carcinoma axillary lymph node metastases after primary systemic chemotherapy. *Cancer* 106: 1000-1006, 2006.
8) Kuerer M, Newman A, Smith L, Ames C, Hunt K, Dhingra K, Theriault L, Singh G, Binkley M, Sneige N, Buchholz A, Ross I, McNeese D, Buzdar U, Hortobagyi N, Singletary E: Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol* 17: 460-469, 1999.
9) Freilich J, Seidman D, DeAngelis M: Central nervous system progression of metastatic breast cancer in patients treated with paclitaxel. *Cancer* 76: 232-236, 1995.
10) Paterson G, Agarwal M, Lees A, Hanson J, Szafran O: Brain metastases in breast cancer patients receiving adjuvant chemotherapy. *Cancer* 49: 651-654, 1982.
11) Crivellari D, Pagani O, Veronesi A, Lombardi D, Nole F, Thurlimann B, Hess D, Borner M, Bauer J, Martinelli G, Graffeo R, Sessa C, Goldhirsch A: High incidence of central nervous system involvement in patients with metastatic or locally advanced breast cancer treated with epirubicin and docetaxel. *Ann Oncol* 12: 353-356, 2001.
12) DiStefano A, Yap Y, Hortobagyi N, Blumenschein R: The natural history of breast cancer patients with brain metastases. *Cancer* 44: 1913-1918, 1979.
13) Tsukada Y, Fouad A, Pickren W, Lane W: Central nervous system metastasis from breast carcinoma: autopsy study. *Cancer* 52: 2349-2354, 1983.
14) Slimane K, Andre F, Delaloge S, Dunant A, Perez A, Grenier J, Massard C, Spielmann M: Risk factors for brain relapse in patients with metastatic breast cancer. *Ann Oncol* 15: 1640-1644, 2004.
15) Clark M, Sledge W, Osborne K, McGuire L. Survival from first recurrence: relative importance of prognostic factors in 1,015 breast cancer patients. *J Clin Oncol* 5: 55-61, 1987.
16) Miller D, Weathers T, Haney G, Timmerman R, Dickler M, Shen J, Sledge W: Occult central nervous system involvement in patients with metastatic breast cancer: prevalence, predictive factors and impact on overall survival. *Ann Oncol* 14: 1072-1077, 2003.
17) Bendell C, Domchek M, Burstein J, Harris L, Younger J, Kuter I, Bunnell C, Rue M, Gelman R, Winer E: Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer* 97: 2972-2977, 2003.
18) Matsumoto K, Shimizu C, Fujiwara Y: The next step to approaching central nervous system metastasis in HER-2-positive metastatic breast cancer patients. *Asia-Pac J Clin Oncol* 2: 6-8, 2006.

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Review Article

Sentinel Lymph Node Biopsy is Feasible for Breast Cancer Patients after Neoadjuvant Chemotherapy

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Background: Despite the increasing use of both sentinel lymph node (SLN) biopsy and neoadjuvant chemotherapy (NAC) in patients with operable breast cancer, information on the feasibility and accuracy of sentinel node biopsy following neoadjuvant chemotherapy is still quite limited. Therefore, we investigated the feasibility and accuracy of sentinel lymph node biopsy for breast cancer patients after NAC.

Methods: A total of 104 patients with Stage II and III breast cancers, previously treated by NAC, were enrolled in the study. All patients were clinically node-negative after NAC. The patients underwent SLN biopsy, which involved a combination of an intradermal injection of radiocolloid and a subareolar injection of blue dye over the tumor. This was followed by completion axillary lymph node dissection (ALND).

Results: SLN could be identified in 97 of 104 patients (identification rate, 93.3%). In 93 of the 97 patients (95.9%), the SLN accurately predicted the axillary status. Four patients' SLN biopsies were false negative, resulting in a false-negative rate of 10.0%. The SLN identification rate tended to be lower among patients with T4 primary tumors prior to NAC (62.5%).

Conclusion: The SLN identification and false-negative rates were similar to rates in non-neoadjuvant studies. The SLN accurately predicted metastatic disease in the axilla of patients with tumor response following NAC.

Breast Cancer 14:10-15, 2007.

Key words: Sentinel node biopsy, Neoadjuvant chemotherapy, Breast cancer, Intradermal injection

Introduction

Currently, the status of the axillary lymph nodes is the most important prognostic indicator for breast cancer and helps guide the physician in adjuvant therapy. More than 40 peer-reviewed pilot studies, published between 1993 and 1999, have established the validity of the SLN biopsy technique for clinically node-negative breast cancer[1] and SLN biopsy has become the standard of care for axillary staging in such patients.

Recent studies report identification rates greater than 90% and false-negative rates ranging from 2 to 10%[2,3]. To ensure a high SLN identification rate and a low false-negative rate, some relative contraindications for SLN biopsy have been established, including T3 or T4 tumors, multicentric or multifocal lesions, a large biopsy cavity, previous axillary surgery, previous chest-wall irradiation, and NAC[4,5].

The application of SLN biopsy in NAC patients may identify, as in non-neoadjuvant chemotherapy groups, patients who do not necessarily require an ALND. Several studies have evaluated the use of SLN biopsy in patients with breast cancer after NAC, but the results have been varied and inconclusive[6-14].

Recently, the American Society of Clinical Oncology panel concluded that there are insufficient data to recommend SLN biopsy for patients receiving preoperative therapy, although SLN biopsy after preoperative systemic chemotherapy is technically feasible[15]. It is possible that the tumor response to chemotherapy may alter or

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Abbreviations:
SLN, Sentinel lymph node; NAC, Neoadjuvant chemotherapy; ALND, Axillary lymph node dissection.

interrupt the lymphatic drainage, thus causing lower SLN identification rates and higher false-negative rates than in non-neoadjuvant studies. We hypothesize that the lymphatic flow within the skin lesion overlying the tumor is less damaged by chemotherapy than that in the parenchyma surrounding the tumor, except in T4 tumors. Thus, the usefulness of SLN biopsy with intradermal radiocolloid injection for patients with NAC-treated breast cancer has yet to be established.

The objective of this study was to determine the feasibility and accuracy of SLN biopsy using intradermal radiocolloid injection over the tumor in clinically node-negative, NAC-treated breast cancer patients.

Patients and Methods

Between May 2003 and October 2005, 104 patients with T2-4N0-2 breast cancer underwent NAC with SLN biopsy plus ALND performed by a single surgeon. The pathologic diagnosis was established by core needle biopsy in all patients prior to NAC.

Patients under 65 of age received four cycles of 5FU (500mg/m^2) / epirubicin (100mg/m^2) / cyclophosphamide (500mg/m^2) (FEC), plus twelve weekly cycles of paclitaxel (80mg/m^2). Patients over 65 years of age received twelve weekly cycles of paclitaxel (80mg/m^2) alone. After NAC, we enrolled the 104 clinically node-negative patients into this study.

Lymphatic mapping was performed using a 3 ml combination of blue dye (Patent blue V®, TOC Ltd., Tokyo, Japan) and 30-80 megabecquerels of technetium-99m-labeled Phytate (Daiichi RI Laboratory, Tokyo, Japan). One day prior to surgery, the radiotracer was intradermally injected into the area overlying the tumor, while blue dye was intraoperatively injected into the subareolar site. For nonpalpable lesions, injections were performed using mammographic or ultrasonic needle localization. Sentinel lymph nodes were identified as blue stained, radioactive, or both. SLN biopsy was then followed by a standard level I/II ALND. For 32 patients, lymphscintigraphy was also performed prior to NAC, and was compared to lymphatic mapping after NAC.

All sentinel nodes were histologically evaluated by creating 3-5 mm serial sections and staining with hematoxylin and eosin (H&E). Lymph nodes submitted as part of the axillary dissection were submitted in their entirety and evaluated using standard H&E staining.

Table 1. Patient demographics

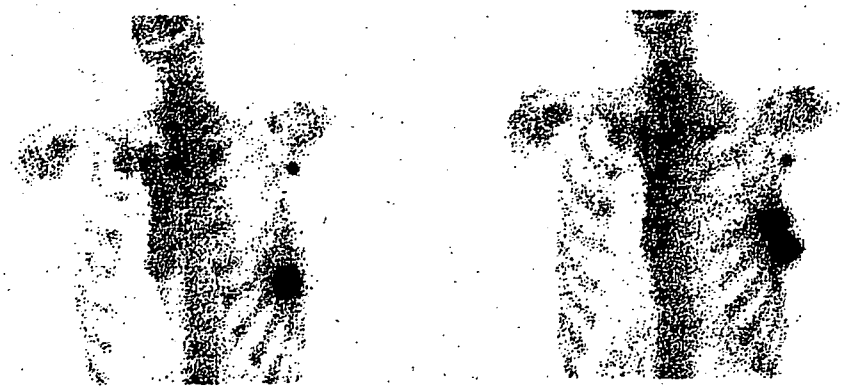
	Number of patients
Age (years)	
Mean	50.2
Range	27-77
Clinical tumor size (cm)*	
Mean	4.89
Range	2.5-12
Tumor classification*	
T2	61 (58.7%)
T3	35 (33.6%)
T4	8 (7.7%)
Lymph node status*	
N0	54 (52.0%)
N1	40 (38.5%)
N2	10 (9.5%)
Tumor type	
Invasive ductal	102 (98.1%)
Invasive lobular	2 (1.9%)
Type of NAC	
FEC plus paclitaxel	100 (96.2%)
paclitaxel alone	4 (3.8%)
Clinical response of the tumor	
CR	55 (52.9%)
PR	41 (39.4%)
SD	8 (7.7%)
Pathological response of the tumor	
pCR	23 (22.1%)
pINV	81 (77.9%)
Pathological nodal status	
Negative	60 (57.7%)
Positive	44 (42.3%)

*Before NAC.
pCR = pathological complete response; pINV = pathological invasive.
CR = Complete response; PR = Partial response; SD= Stable disease

Results

The patient characteristics, type of chemotherapy, clinical response of the tumor, and pathological findings are summarized in Table 1. All patients underwent breast-conserving therapy or mastectomy and were clinically node-negative at the time of operation.

Based on lymphscintigraphy studies before and after NAC, the results of lymphatic mapping were quite similar in 30/32 patients, as shown in Fig 1. SLN were not detected in two cases with a



1a 1b

Fig 1. Lymphscintigraphy before and after NAC (1a and 1b, respectively) revealed one sentinel node at the axilla. The bone scintigram was performed simultaneously to detect bone metastasis.

Table 2. Results of sentinel node biopsy

	Number of patients
Total no. of patients	104
SLN identified	97 (93.4%)
SLN positive	36 (34.6%)
SLN was only positive lymph node	16 (44.4%)
SLN identification method	
Radiocolloid and blue dye	91 (87.5%)
Blue dye only	13 (12.5%)

Table 3. Comparison of lymph node status of SLNs and non-SLNs (n=97)

	Non-SLN status	
SLN status	Positive	Negative
Positive	20	16
Negative	4	57

False-negative rate, 10%; overall accuracy, 96%; negative predictive value, 93%; positive predictive value, 100%

T4d primary tumor.

As seen in Table 2, the overall SLN identification rate was 93.4% (97 of 104). Of the 97 patients in whom an SLN could be identified, 36 (34.6%) had positive SLNs. In 16 of these patients (44.4%), the SLN was the only positive node. SLNs were identified by both radiocolloid and blue dye in 91 patients (87.5%) and by blue dye alone in 13 patients (12.5%).

The pathological status of the SLNs and non-SLNs is outlined in Table 3.

The SLNs accurately predicted axillary status in 93/97 patients (95.9%). Four patients had false-negative SLN biopsies, a false-negative rate of 10.0% (4/40). Fifty-seven patients had pathologically negative SLN or non-SLN.

Table 4. Comparison of lymph node status of SLNs and non- SLNs among tumor classifications before NAC

	T2 (n=59)		T3/T4 (n=38)	
	Non- SLN status			
SLN status	Positive	Negative	Positive	Negative
Positive	7	7	13	9
Negative	2	43	2	14
	SLN identified, 59/61 (97%) False-negative rate, 13%		SLN identified, 38/43 (88%) False-negative rate, 8%	

The pathological status of the SLNs and non-SLNs was analyzed according to tumor classifications before NAC, clinical lymph node status before NAC, and the response of the tumor after NAC.

In T2 tumors before NAC, the SLN identification rate was 97% (59 of 61), and 2 patients had false-negative SLN biopsies, or a false-negative rate of 13%. In T3 and T4 tumors, the results were 88.4% (38 of 43) and 8%, respectively (Table 4). The SLN identification rate tended to be higher in patients with a T2 primary tumor before NAC than in those with T3/T4 primary tumor before NAC, but the difference was not statistically significant.

In the SLN biopsy results, there was no significant difference between nodal status prior to NAC.

Table 5. Comparison of lymph node status of SLNs and non- SLNs among nodal status before NAC

	N0 (n=52)		N1/N2 (n=45)	
	Non- SLN status			
SLN status	Positive	Negative	Positive	Negative
Positive	4	8	16	8
Negative	2	38	2	19
	SLN identified, 52/54 (96%) False-negative rate, 14%		SLN identified, 45/50 (90%) False-negative rate, 7%	

Table 6. Comparison of lymph node status of SLNs and non- SLNs among clinical response after NAC

	CR (n=50)		PR/SD (n=47)	
	Non- SLN status			
SLN status	Positive	Negative	Positive	Negative
Positive	6	5	14	11
Negative	2	37	2	20
	SLN identified, 50/55 (91%) False-negative rate, 15%		SLN identified, 47/49 (96%) False-negative rate, 7%	

Table 7. Success rate of sentinel node identification according to tumor characteristics

	No. of Attempted	Success Rate (%)	P
Tumor classification			
T2	61	97 %	*N.S.*
T3	35	94 %	
T4	8	63 %	
Clinical nodal status			
Negative	54	96 %	*N.S.*
Positive	50	90 %	
Clinical tumor response			
CR	55	91 %	*N.S.*
PR/SD	49	96 %	
Pathological tumor response			
pCR	23	91%	*N.S.*
pINV	81	94 %	

In the patients with clinically negative lymph nodes (N0) before NAC, the SLN identification rate was 96.3% (52 of 54), and two patients had a false-negative SLN biopsy, a false-negative rate of 14%. In the patients with clinically positive lymph nodes (N1/N2), the results were 90% (45 of 50) and 7%, respectively (Table 5). In the SLN biopsy results, there was no significant difference between nodal status prior to NAC.

For patients with complete tumor response (CR) after NAC, the SLN identification rate was 91.0% (50/55) and two patients had false-negative SLN biopsies, resulting in a false-negative rate of 15%. For patients with partial tumor response (PR) and stable disease (SD), the results were 96.0% (47/49) and 7%, respectively (Table 6). The SLN identification rate tended to be lower, although the difference was not statistically significant, after NAC in patients with CR after NAC as compared to those with PR and SD.

There was no significant difference in the false-negative rate according to the tumor classification before NAC, the clinical lymph node status before NAC, or the tumor responses after NAC.

There was also no significant difference in the success rate of SLN identification according to tumor classifications before NAC, the clinical lymph node status before NAC, the clinical response of the tumor after NAC, or the pathological response of the tumor after NAC, although the success rate tended to be lower in patients with a T4 primary tumor (Table 7).

Discussion

Although the use of SLN biopsy has dramatically increased over the past several years, and some experienced surgeons are performing this procedure without completing axillary dissection, it is unlikely that SLN biopsy will become the generally accepted standard of care in axillary staging until results from ongoing randomized trials

Table 8. Studies of SLN biopsy after NAC

	No. of patients	Stage	Tumor size (cm)	No (%) of successful SLN biopsies	False negative (%)
Breslin et al.2000 [6]	51	II or III	5.0	43 (84.3)	3 (12)
Miller et al., 2002 [7]	35	T1-3N0	3.5	30 (86.0)	0 (0)
Stearns et al.2000 [8]	34	T3-4, any N	5.0	29 (85.0)	3 (14)
Haid et al.2001 [9]	33	T1-3, any N	3.3	29 (88.0)	0 (0)
Julian et al.2002 [10]	31	I or II	NS	29 (93.5)	0 (0)
Tafra et al.2001 [12]	29	Any T, N0	NS	27 (93.0)	0 (0)
Nason et al.2000 [13]	15	T2-4, N0	NS	13 (87.0)	3 (33)
Shimazu et al.2004 [14]	47	II or III	4.5	44 (93.6)	4 (12)
Current study	104	T2-4, any N	4.9	97 (93.0)	4 (10)

demonstrate the equivalence of this procedure with axillary dissection in terms of axillary recurrence and overall survival. At the same time, it is unlikely that the value of sentinel node biopsy following NAC will be established[11]. The main reason for this is that only a small proportion of operable breast cancer patients currently receive NAC, making a randomized trial quite difficult. Another reason is that when the results from the ongoing randomized trials are disclosed, if they are favorable towards the SLN biopsy procedure, the majority of surgeons will extrapolate the applicability of these results to patients who have received NAC. Thus, it is quite possible that demonstrating the feasibility and efficacy of SLN biopsy after NAC will depend on the retrospective data of single-institution experiences.

NAC can reduce tumor size and significantly increase the ability to perform breast-conserving therapy[16-18]. After NAC, axillary downstaging is similarly affected. NAC with anthracycline/cyclophosphamide-containing regimens has been shown to neutralize the involved axillary nodes in about 30% of patients[16]. The addition of taxanes to anthracycline/cyclophosphamide-containing regimens has increased the conversion rate to around 40%[19, 20]. With the number of patients receiving NAC increasing, the question arises as to whether SLN biopsy is an option for these patients. We summarize the studies regarding SLN biopsy after NAC in Table 8, but they are inconclusive[6-14]. Breslin *et al.*[6] reported a study of 51 patients who underwent SLN biopsy after NAC and concluded that SLN biopsy following NAC is accurate. They had an identification rate of 84.3% and a false-negative rate of 12.0%. Nason *et al.*[13] reported a smaller number of patients who hard received NAC, and their identification and false-negative rates were 87.0% and 33.3%, respectively. They concluded that SLN biopsy resulted in an unacceptably high false-positive rate. However, in these small series, even 1 or 2 patients with false-negative SLNs can greatly affect the conclusions in a different direction. We report here a study of 104 patients who received NAC and had an identification rate of 93.4% and false-negative rate of 10.0%. We conclude in our study that SLN biopsy after NAC is accurate and feasible even for large tumors and patients with positive axillary nodal status before NAC without inflammatory breast cancer.

It has been speculated that among patients who have had their axillary lymph node status downstaged by NAC, tumors also typically respond to NAC and shrink so that damage to and alteration of the lymphatic flow from tumor tissues to the axillary basin are more likely to occur. This might then cause an increased false-negative rate for SLN biopsy and a decreased identification rate of SLN biopsy. However the hypothesis of the present study is that the lymphatic flow around skin lesions is rich and less influenced by the effects of chemotherapy and tumor size than that in the parenchyma surrounding the tumor. The lymphscintigraphy in this study results before and after NAC demonstrated that the effect of NAC did not at all change the lymphatic flow of the breast.

The results of our study suggest that SLN biopsy after NAC using intradermal injection of radiocolloid is feasible and can accurately predict axillary lymph node status for patients with clinically negative lymph node status following NAC. This procedure could help patients who have had their

axillary lymph node status downstaged from positive to negative and patients with large tumors qualify as appropriate candidates for SLN biopsy.

Further, multicenter studies, involving a larger number of patients from a variety of clinical locations, will be required to fully establish the feasibility and accuracy of SLN biopsy for patients with breast cancer who have been treated with NAC.

References

1) Cody HS 3rd: Clinical aspects of sentinel node biopsy. *Breast Cancer Res* 3:104-1088. 1B, 2001.
2) Cody HS, Borgen PI: State-of-the-art approaches to sentinel node biopsy for breast cancer: study design, patient selection, technique and quality control at Memorial Sloan-Kettering Cancer Center. *Surg Oncol* 8:85-91, 1999.
3) Krag D, WeaverD, Ashikaga T, Moffat F, Klimberg VS, Shriver C, Feldman S, Kusminsky R, Gadd M, Kuhn J, Harlow S, Beitsch P: The sentinel node in breast cancer-a multicenter validation study. *N Engl J Med* 339:941-946, 1998.
4) Anderson BO: Sentinel lymphadenectomy in breast cancer: an update on NCCN Clinical Practice Guidelines. *J Natl Compr Cancer Network* 1 Suppl 1:S64-70, 2003.
5) Reintgen D, Giuliano R, Cox C: Lymphatic mapping and sentinel lymph node biopsy for breast cancer. *Cancer J* 8 Suppl 1:S15-21, 2002.
6) Breslin TM, Cohen L, Sahin A, Fleming JB, Kuerer HM, Newman LA, Delpassand ES, House T, Ames FC, Feig BW, Ross MI, Singgletary SE, Buzdar AU, Hortobagyi GN, Hunt KK: Sentinel lymph node biopsy in accurate after neoadjuvant chemotherapy for breast cancer. *J Clin Oncol* 18:3480-3486, 2000.
7) Miller AR, Thompson VE, Yeh IT, Alrakwan A, Sharkey FE, Stauffer J, Otto PM, Mckay C, Kahlenberg MS, Phillips WT, Cruz AB Jr: Analysis of sentinel lymph node mapping with immediate pathologic review in patients receiving preoperative chemotherapy for breast carcinoma. *Ann Surg Oncol* 9:243-247, 2002.
8) Stearns V, Ewing CA, Slake R,Panannen MF, Hayes DF, Tsangaris TN: Sentinel lymphadenectomy after neoadjuvant chemotherapy for breast cancer may reliably represent the axilla except for inflammatory breast cancer. *Ann Surg Oncol* 9: 235-242, 2000.
9) Haid A, Tausch C, Lang A, Lutz J, Fritzsche H, Prschina W, Breitfellner G, Sege W, Aufschnaiter M, Sturn H, Zimmermann G: Is sentinel lymph node biopsy reliable and indicated after preoperative chemotherapy in patients with breast carcinoma? *Cancer* 92:1080-1084, 2001.
10) Julian TB, Patel N, Dusi D, Olson P, Nathan G, Jasnosz K, Isaacs G, Wolmark N: Sentinel node biopsy after neoadjuvant chemotherapy for breast cancer. *Am J Surg* 182:407-410, 2001.
11) Julian TB, Dusi D, Wolmark N: Sentinel node biopsy after neoadjuvant chemotherapy for breast cancer. *Am J Surg* 184:315-317, 2002.
12) Tafra L, Verbanac KM, Lannin DR: Preoperative chemotherapy and sentinel lymphadenectomy for breast cancer. *Am J Surg* 182:312-315, 2001.
13) Nason KS, Anderson BO, Byrd DR, Dunnwald LK, Eary JF, Mankoff DA, Livingston R, Schimidt RA, Jewell KD, Yeung RS, Moe RE: Increased false negative sentinel node biopsy rates after preoperative chemotherapy for invasive breast carcinoma. *Cancer* 89:2187-2194, 2000.
14) Shimazu K, Tamaki Y, Taguchi T, Akazawa K, Inoue T, Noguchi S: Sentinel lymph node biopsy using periareolar injection of radiocolloid for patients with neoadjuvant chemotherapy-treated breast carcinoma. *Cancer* 100:2555-2561, 2004.
15) Lyman GH, Giuliano AE, Somerfield MR, Bensen AB, Bodurka DC, Burstein HJ, Cochran AJ, Cody III HS, Edge SB, Galper S, Hayman JA, Kim TY, Perkins CL, Podoloff DA, Sivausbramaniam VH, Turner RR, Wakl R, Weaver RW, Wolff CA, Winer EP: American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *JCO* 23:2540-2545, 2005.
16) Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, Cruz AB Jr, Fisher ER, Wicferham DL, Wolmark N, DeCillis A, Hoehn JL, Lees AW Dimitrov NV: Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from the National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 15:2483-2493, 1997.
17) Hutcheon AW, Heys SD, Miller ID: Improvements in survival in patients receiving primary chemotherapy with docetaxel for breast cancer: a randomized control trial. Presented at the 24th Annual San Antonio Breast Cancer Symposium. San Antonio, Texas, December 2001.
18) O'Hea BJ, Hill AD, El-Shirbiny AM, Yeh SD, Rosen PP, Coit DG, Borgen PI, Cody HS 3rd: Sentinel lymph node biopsy in breast cancer: Initial experience at Memorial Sloan-Kettering Cancer Center. *J Am Coll Surg* 186:423-427, 1998.
19) Mamounaus E, Brown A, Smith R: Accuracy of sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: update results from NSABP B-27. *Proc Am Soc Clin Oncol* 21:36a, 2002.
20) Gianni L, Baselga H, Eiermann W: First report of European Cooperative Trial in operable breast cancer (ECTO): effect of primary systemic therapy (PST) on local-regional disease. *Proc Am Soc Clin Oncol* 21:34a, 2002.

Radical Cystectomy for Invasive Bladder Cancer: Results of Multi-institutional Pooled Analysis

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Background: We report the outcome of radical cystectomy for patients with invasive bladder cancer, who did not have regional lymph node or distant metastases, at 21 hospitals.
Methods: Retrospective, non-randomized, multi-institutional pooled data were analyzed to evaluate outcomes of patients who received radical cystectomy. Between 1991 and 1995, 518 patients with invasive bladder cancer were treated with radical cystectomy at 21 hospitals. Of these, 250 patients (48.3%) received some type of neoadjuvant and/or adjuvant therapy depending on the treatment policy of each hospital.
Results: The median follow-up period was 4.4 years, ranging from 0.1 to 11.4 years. The 5-year overall survival rate was 58% for all 518 patients. The 5-year overall survival rates for patients with clinical T2N0M0, T3N0M0 and T4N0M0 were 67%, 52% and 38%, respectively. The patients with pT1 or lower stage, pT2, pT3 and pT4 disease without lymph node metastasis had 5-year overall survivals of 81%, 74%, 47% and 38%, respectively. The patients who were node positive had the worst prognosis, with a 30% overall survival rate at 5 years. Neoadjuvant or adjuvant chemotherapy did not provide a significant survival advantage, although adjuvant chemotherapy improved the 5-year overall survival in patients with pathologically proven lymph node metastasis.
Conclusions: The current retrospective study showed that radical cystectomy provided an overall survival equivalent to studies reported previously, but surgery alone had no more potential to prolong survival of patients with invasive cancer. Therefore, a large-scale randomized study on adjuvant treatment as well as development of new strategies will be needed to improve the outcome for patients with invasive bladder cancer.

Key words: multi-institutional pooled analysis – radical cystectomy – invasive bladder cancer

INTRODUCTION

Radical cystectomy has been considered the standard curative treatment for invasive bladder cancer all over the world (1,2). Recent improved surgical techniques in addition to development of perioperative care and anesthesia have reduced morbidity and mortality. Furthermore, advances in orthotopic urinary tract reconstruction have improved the quality of life of

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patients undergoing radical cystectomy. However, while about half of patients are cured, the remainder still suffer from local recurrence and distant metastasis within 2–3 years. Thus, in an attempt to improve treatment outcome, many investigators have tried combinations of neoadjuvant or adjuvant chemotherapy with surgery (3–5). Unfortunately, the impact of neoadjuvant or adjuvant chemotherapy on survival remains controversial. Recently, the South Western Oncology Group (SWOG) showed an improvement in overall survival with three cycles of neoadjuvant chemotherapy consisting of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) (6). Furthermore, more recent meta-analysis demonstrated that neoadjuvant chemotherapy provided a significant survival advantage in patients with invasive bladder cancer (7).

In this study, we evaluate outcomes of patients with invasive bladder cancer who underwent radical cystectomy with/without pelvic lymph node dissection in 21 hospitals.

PATIENTS AND METHODS

This study included 518 patients with clinically invasive bladder cancer without regional lymph node or distant metastases (T2–4N0M0). All were treated with radical cystectomy with/without pelvic lymph node dissection at 21 hospitals between 1991 and 1995. Using these data, non-randomized, multi-institutional pooled data were analyzed to evaluate the treatment results of radical cystectomy. Tumors were staged according to the criteria of the 3rd edition of General Rules for Clinical and Pathological Studies on Bladder Cancer of the Japanese Urological Association and Japanese Society of Pathology (8). Urothelial carcinoma was the predominant histological type in all patients. Patients with pure squamous cell carcinoma and adenocarcinoma were excluded from this study. Because the pathology of surgical specimens was not reviewed by central pathologist(s), tumor grade was not included in this analysis.

Almost half of the patients received some type of neoadjuvant and/or adjuvant therapy. The type and dose of the additional therapy depended on each institution's preference.

The overall survival was calculated from the date of operation to death from any cause. The overall survival rate was calculated by the Kaplan–Meier method. The statistical significance of differences was determined by the log-rank test. Spearman's rank correlation test was used to analyze correlations between two factors. A P-value of <0.05 was considered statistically significant. All analyses were performed using StatView 5.0 for Macintosh (SAS Institute, NC, USA).

RESULTS

Patient Characteristics

Patient characteristics are shown in Table 1. More than two-thirds of the patients were male. The mean age at operation was 65.4 years (range, 33–87 years). Half of the patients had a clinical stage of T2N0M0. Pathological examination revealed that patients with pT2 and pT3 accounted for almost 60% of the total, followed by those with pT1 and lower stages and those with pT4. Nearly 90% of patients received lymph node dissection. Lymph node metastasis was histopathologically proven in 86 patients (16.6%), who accounted for 18.4% of those who received node dissection (Table 2). Its incidence was significantly linked with clinical stage ($P < 0.01$ by Spearman's rank correlation test). The incidence clearly increased with progression of the pathological stage from 5.9% in patients with superficial cancer to 32.5% of those with pT4 ($P < 0.01$ by Spearman's rank correlation test).

Table 1. Patient characteristics

Characteristics		No. of patients (%)
Gender	Male	400 (77.2)
	Female	118 (22.8)
Age (years)	33–87 (mean: 65.4)	
Clinical T classification	T2	271 (52.3)
	T3	178 (34.4)
	T4	69 (13.3)
Pathological T classification	≤pT1	119 (23.0)
	pT2	156 (30.2)
	pT3	152 (29.4)
	pT4	90 (17.4)
Lymph node metastasis	pNx	53 (10.2)
	pN0	379 (73.2)
	≥pN1	86 (16.6)
Additional therapy	No	268 (51.7)
	Yes	250 (48.3)
Type of additional therapy	Neoadjuvant	118 (47.2)
	Adjuvant	85 (34.0)
	Neoadjuvant and adjuvant	47 (18.8)

Neoadjuvant and/or adjuvant therapies were performed for 48.3% of 518 patients together with radical cystectomy (Table 3). Of these, 118 patients (47.2%) received some type of therapy in the neoadjuvant setting. These included systemic chemotherapy for 80 patients, intraarterial chemotherapy for 32, radiation for one and combined systemic chemotherapy and local radiation for five. Among the systemic chemotherapies, MVAC, the most popular regimen for urothelial cancer (9), was frequently used. In the adjuvant setting, systemic chemotherapy was administered most frequently. More than half of the patients received MVAC chemotherapy.

Outcome

The follow-up period ranged from 0.1 to 11.4 years with a median of 4.4 years. The 5-year overall survival rate was 58% for all 518 patients (Fig. 1), 67% for patients with clinical T2N0M0, 52% for those with T3N0M0 and 38% for those with T4N0M0 (Fig. 2). According to pathological stage, the 5-year

Table 2. Relationships among clinical stage, pathological stage and lymph node metastasis

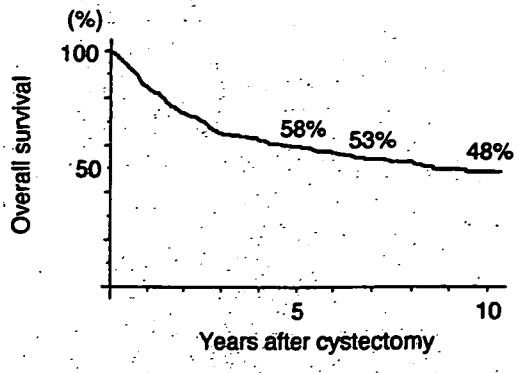
Clinical stage	Pathological stage	No. of patients with radical cystectomy	No. of pathologically node positive patients/no. of patients with node dissection (%)
T2	pT0	26	1/24 (4.1)
	≤pT1	54	4/48 (8.3)
	pT2	110	8/101 (7.9)
	pT3	57	20/53 (37.7)
	pT4	23	6/19 (31.5)
	All	270	39/245 (15.9)
T3	pT0	7	0/4 (0)
	≤pT1	23	2/18 (11.1)
	pT2	41	2/36 (5.5)
	pT3	78	15/71 (21.1)
	pT4	29	9/28 (32.1)
	All	178	28/157 (17.8)
T4	pT0	5	0/5 (0)
	≤pT1	4	0/3 (0)
	pT2	5	2/5 (40.0)
	pT3	17	5/16 (31.2)
	pT4	38	12/36 (33.3)
	All	69	19/65 (29.2)
T2–4	≤pT1	119	7/119 (5.9)
	pT2	156	12/142 (8.4)
	pT3	152	40/140 (28.5)
	pT4	90	27/83 (32.5)

$P < 0.01$ (Spearman's rank correlation test).

Table 3. Type of additional therapy

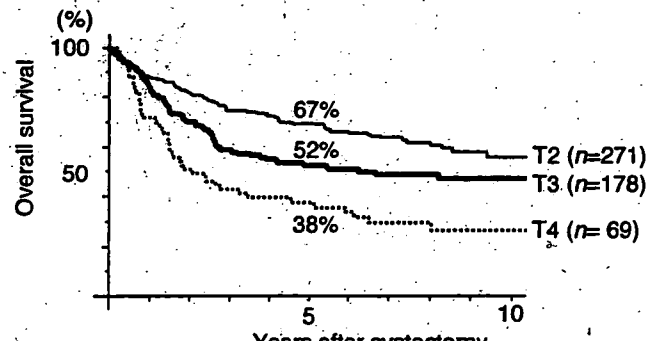
Type		No. of courses (median)	No. of patients
Neoadjuvant			118
Systemic chemotherapy	MVAC*	1–4 (2)	49
	MEC*	1–4 (2)	13
	CDDP-based chemotherapy	1–2 (2)	18
Local therapy	Intraarterial chemotherapy (CDDP-based)	1–2 (1)	32
	Radiation only		1
Systemic and local therapy	Chemotherapy and radiation		5
Adjuvant			85
Systemic chemotherapy	MVAC	1–4 (2)	48
	CISCA*	1–3 (2)	5
	MEC	1–2 (2)	4
	CDDP-based chemotherapy	1–6 (2)	24
	Others		4
Neoadjuvant and adjuvant			47
Intraarterial→systemic			13
Systemic and radiation→systemic			4
Systemic→systemic			30

*MVAC, methotrexate, vincristine, doxorubicin and cisplatin, (21); MEC, methotrexate, epirubicin and cisplatin, (22); CISCA, cisplatin, cyclophosphamide and doxorubicin.



No. at risk 518 411 348 295 272 242 207 148 99 54 29

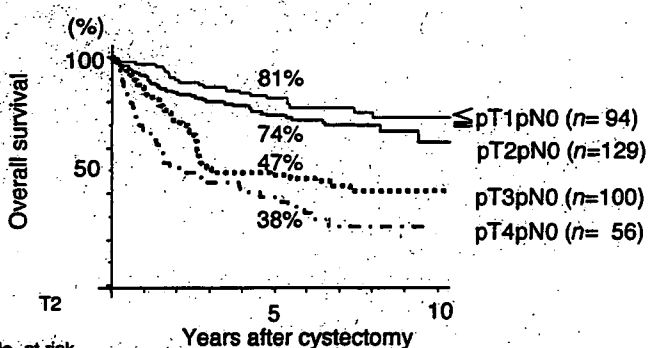
Figure 1. Overall survival rate in all 518 patients.



No. at risk

T2	271	229	207	184	172	153	132	94	60	32	20
T3	178	137	109	85	78	70	59	41	30	16	7
T4	69	45	32	26	22	19	16	12	9	5	2

Figure 2. Overall survival rate according to clinical stage. T2 versus T3, $P < 0.01$; T2 versus T4, $P < 0.001$; T3 versus T3, $P < 0.01$ (log-rank test).

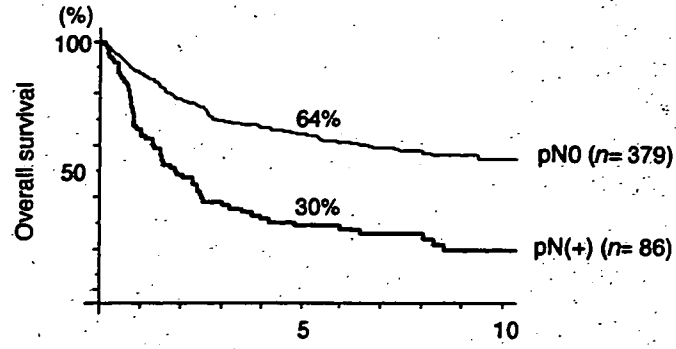


No. at risk

≦pT1pN0	94	88	79	71	69	65	56	45	30	15	9
pT2pN0	129	116	105	100	93	80	72	48	29	16	9
pT3pN0	100	82	67	47	43	39	35	22	12	6	4
pT4pN0	56	33	25	21	19	17	12	6	5	3	0

Figure 3. Overall survival rate according to pathological stage. ≦pT1pN0 versus pT3pN0, pT4pN0, $P < 0.001$; pT2pN0 versus pT3pN0, pT4pN0, $P < 0.001$; pT3pN0 versus pT4pN0, $P = 0.02$ (log-rank test).

overall survival rate was significantly higher for patients with pT1 or a lower stage, or pT2 than for those with pT3 or pT4 disease, when those who were pathologically node negative were considered (Fig. 3). Patients who were pathologically proven to be node positive clearly had a lower 5-year overall survival rate (30%) than those who were node negative (Fig. 4, $P < 0.001$ by log-rank test).



No. at risk

pN0	379	319	276	239	224	201	175	122	76	40	22
pN(+)	86	53	37	29	23	20	18	14	13	8	3

Figure 4. Overall survival rate according to lymph node metastasis. pN0 versus pN(+), $P < 0.001$ (log-rank test).

Impact of Additional Therapy

When we evaluated whether neoadjuvant chemotherapy could improve survival, there was no significant difference with regard to the 5-year overall survival between patients with and without the therapy (65% versus 56%, $P = 0.13$ by log-rank test) (Fig. 5). Furthermore, neoadjuvant chemotherapy did not influence the overall survival among all clinical stages. Similarly, adjuvant chemotherapy did not improve the prognosis because the 5-year overall survival rates for all patients with and without this therapy were 57% and 56%, respectively. When we investigated the influence of adjuvant chemotherapy on the 5-year overall survival in patients with pT2 or a lower stage without lymph node metastasis, there was no significant difference between patients with and without the therapy. No survival benefit was found for the therapy in patients with pT3 or pT4 without pathologically proven lymph node metastasis. However, the therapy improved the 5-year overall survival in patients with lymph node metastasis, with a significant difference between those with and without it ($P < 0.001$, by log-rank test) (Fig. 6).

DISCUSSION

In this study we evaluated the treatment outcomes of patients with invasive bladder cancer who underwent radical cystectomy with/without pelvic lymph node dissection in 21 hospitals from 1991 to 1995. The study enabled us to analyze the 5-year survival rates of a large volume of patients. The analysis showed that the 5-year overall survival rate for patients with T2N0M0, T3N0M0 and T4N0M0 tumors were 67%, 52% and 38%, respectively. These results are similar to/better than a previous report that the 5-year survival rates were 49% (95% CI: 39–59%) for patients with T2, 25% (95% CI: 10–50%) for those with T3 and 17% (95% CI: 5–45%) for those with T4,

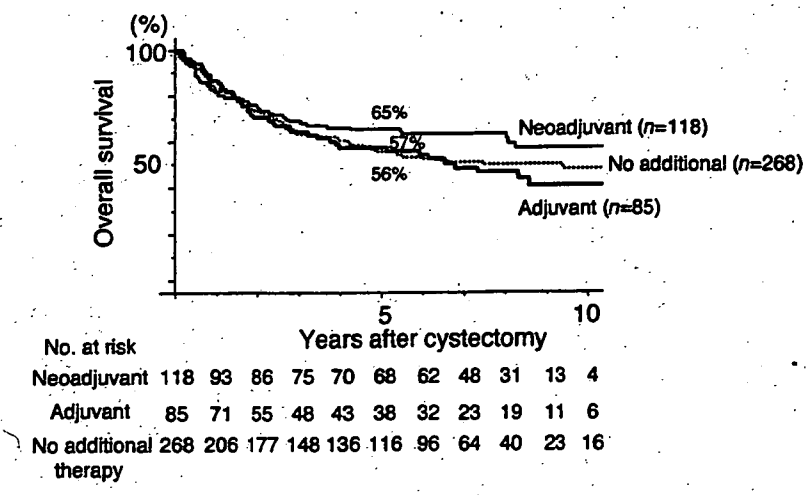


Figure 5. Overall survival rate according to additional therapy. Neoadjuvant versus no additional therapy, $P = 0.13$ (log-rank test); adjuvant versus no additional therapy, $P = 0.72$ (log-rank test).

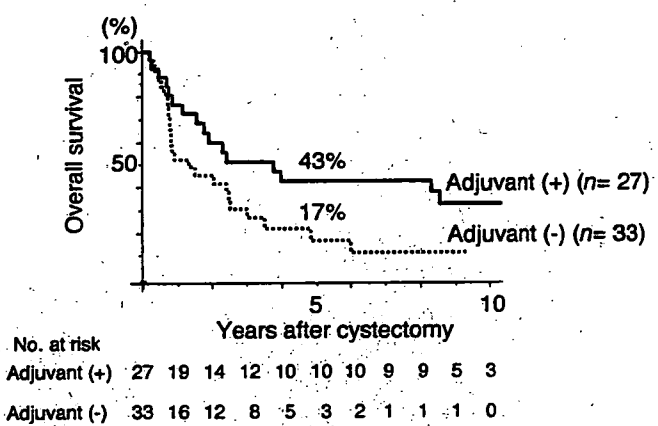


Figure 6. Overall survival rate according to adjuvant therapy in patients with lymph node metastasis. Adjuvant (+) versus adjuvant (–), $P = 0.03$ (log-rank test).

although this report was published 10 years ago (10). Similarly, the analysis according to pathological stage revealed results consistent with those in previous studies showing that the 5-year survival was 76–85% for pT1 or lower stage, 64–84% for pT2pN0, 25–56% for pT3pN0 and 19–44% for pT4pN0 (1,11,12). In Japan, the analysis of 351 patients who underwent radical cystectomy at a single institute showed a similar result (13).

In the present study pathologically proven lymph node metastasis was seen in 18% of patients with lymph node dissection. Some reports indicated that lymph node metastasis was present in 15–34% of patients who underwent radical cystectomy (10,14–16). The variation in the incidence of positive nodes may stem from the heterogeneous profiles of patients, extent of lymph dissection, and the number of lymph nodes removed. Indeed, Leissner et al. (14) reported a correlation between the number of lymph nodes removed (≥16 lymph nodes) and the percentage of patients with positive nodes, especially in locally advanced bladder cancer. Lymph node metastasis is reported to be an independent poor prognostic factor (14–16). Our study supported previous results since the present study also showed that patients with positive nodes had a worse prognosis. Recently, the number of positive lymph nodes, rather than the size, was reported to be associated with death from bladder cancer (15,16). Unfortunately we did not assess the number of lymph nodes in this study. Further study will be necessary to confirm these results. At present it remains controversial whether lymph node dissection has a therapeutic effect or is merely a staging tool. Some investigators advocate extensive bilateral lymphadenectomy as a potentially curative procedure (14,16).

Since the 5-year survival rate with radical cystectomy alone seems to reach a plateau, especially in patients with locally advanced bladder cancer, various trials of additional treatments before and/or after surgery have been carried out (3–5). Unfortunately, it remains undefined whether neoadjuvant or adjuvant chemotherapy with surgery improves the survival (17). However, in the SWOG study, patients with three cycles of neoadjuvant MVAC achieved survival benefit with the median survival of 77 months, as compared with 46 months among patients with surgery alone, although the difference was not significant when it was analyzed by a two-sided stratified log-rank test (6). Furthermore, more recent meta-analysis demonstrated that neoadjuvant cisplatin-based combination chemotherapy provided a survival advantage over a definitive local therapy (7). Our group started a prospective phase III study evaluating the survival benefit of two cycles of MVAC followed by surgery over surgery alone in patients with T2–4N0M0 bladder cancer with the support of the Japanese Clinical Oncology Group.

On the other hand, our retrospective study showed that patients with lymph node metastasis had a survival benefit from adjuvant chemotherapy, although only a small number of patients were included. Some investigators also reported the impact of adjuvant chemotherapy on survival of these patients in retrospective studies (15,16). Furthermore, prospective studies demonstrated a significant survival benefit (18–20). However, these studies were criticized due to their small

numbers of patients, early termination of trials and confusing methodology for analysis. Therefore, the role of adjuvant chemotherapy remains a matter of debate. To evaluate the impact of immediate adjuvant chemotherapy after cystectomy, the European Organization for Research and Treatment of Cancer has launched a large randomized trial that plans to enroll 1344 patients. In the near future its results will tell us whether immediate adjuvant chemotherapy is necessary in high-risk patients.

In summary, our retrospective, multi-institutional analysis showed that radical cystectomy provided an overall survival for patients with clinically invasive bladder cancer similar to that of previous reports. Thus, it is clear that surgery alone will not provide better survival than we have now. Therefore, additional therapy is mandatory to improve the treatment outcome. Further large-scale randomized studies will be needed to clarify the timing and type of additional therapy.

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References

1. Schoenberg M. Management of invasive and metastatic bladder cancer. In Walsh PC, et al., editors. Campbell's Urology, 8th edition. Philadelphia: Saunders, 2002;2803–17.
2. Carrion R, Seigne J. Surgical management of bladder carcinoma. *Cancer Control* 2002;9:284–92.
3. Dreicer R. Neoadjuvant chemotherapy in the management of muscle-invasive bladder cancer. *Semin Urol Oncol* 2001;19:180–85.
4. Lehmann J, Retz M, Stockle M. The role of adjuvant chemotherapy for locally advanced bladder cancer. *World J Urol* 2001;19:133–40.
5. Sternberg CN. Neo-adjuvant and adjuvant chemotherapy of bladder cancer: Is there a role? *Ann Oncol* 2002;13(Suppl 4):273–9.
6. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003;349:859–66.
7. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Lancet* 2003;361:1927.
8. Japanese Urological Association, Japanese Society of Pathology. General Rules for Clinical and Pathological Studies on Bladder Cancer, 3rd edition. Tokyo: Kanehara 2001 (in Japanese).
9. Sternberg CN, Yagoda A, Scher HI, Watson RC, Geller N, Herr HW, et al. Methotrexate, vinblastine, doxorubicin and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. *Cancer* 1989;64:2448–58.
10. Paulson DF. Critical review of radical cystectomy and indicators of prognosis. *Sem Urol* 1993;11:205–13.
11. Dalbagni G, Genega E, Hashibe M, Zhang ZF, Russo P, Herr H, et al. Cystectomy for bladder cancer: a contemporary series. *J Urol* 2001;165:1111–6.
12. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001;19:666–75.
13. Kuroda M, Meguro N, Maeda O, Saiki S, Kinouchi T, Usami M, Kotake T. Stage specific follow-up strategy after cystectomy for carcinoma of the bladder. *Int J Urol* 2002;9:129–33.
14. Leissner J, Hohenfellner R, Thuroff JW, Wolf HK. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. *BJU Int* 2000;85:817–23.
15. Stein JP, Cai J, Groshen S, Skinner DG. Risk factors for patients with pelvic lymph node metastases following radical cystectomy with en bloc pelvic lymphadenectomy: concept of lymph node density. *J Urol* 2003;170:35–41.
16. Frank I, Cheville JC, Blute ML, Lohse CM, Nehra A, Weaver AL, et al. Transitional cell carcinoma of the urinary bladder with regional lymph node involvement treated by cystectomy: clinicopathologic features associated with outcome. *Cancer* 2003;97:2425–31.
17. Juffs HG, Moore MJ, Tannock IF. The role of systemic chemotherapy in the management of muscle-invasive bladder cancer. *Lancet Oncol* 2002;3:738–47.
18. Skinner DG, Daniels JR, Russell CA, Lieskovsky G, Boyd SD, Nichols P, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. *J Urol* 1991;145:459–64.
19. Stockle M, Meyenburg W, Wellek S, Voges GE, Rossmann M, Gertenbach U, et al. Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long-term results of a controlled prospective study and further clinical experience. *J Urol* 1995;153:47–52.
20. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. *J Urol* 1996;155:495–9.
21. Kuroda M, Kotake T, Akaza H, Hinotsu S, Kakizoe T. Efficacy of dose-intensified MEC (Methotrexate, Epirubicin, Cisplatin) chemotherapy for advanced urothelial carcinoma: a prospective randomized trial comparing MEC and M-VAC (Methotrexate, Vinblastine, Doxorubicin and Cisplatin). *Jpn J Clin Oncol* 1998;28:497–501.
22. Lynch DF Jr. Preoperative and postoperative adjuvant chemotherapy using CISCA (cyclophosphamide, doxorubicin, and cisplatin) in the treatment of invasive transitional-cell carcinoma of the bladder. *Urol Clin North Am* 1991;18:543–6.

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Dynamic Computed Tomography and Color Doppler Ultrasound of Renal Parenchymal Neoplasms: Correlations with Histopathological Findings

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Background: We evaluated whether color Doppler ultrasound (US) had diagnostic accuracy equal to dynamic computed tomography (CT) and whether performing dynamic CT and Doppler US together would be more informative in preoperative diagnosis of renal solid tumors.
Methods: A total of 110 renal solid tumors smaller than 7 cm were evaluated with dynamic CT and Doppler US. We compared the enhancement and the color flow patterns with the histopathological subtypes.
Results: Eighty-seven (95.6%) of 91 clear cell carcinomas showed rich enhancement in the cortical nephrographic phase (CNP) and 82 (90.1%) of them had color flow in the Doppler US. Of the total of 110 tumors, nine (8.1%) did not show color flow in spite of rich enhancement in the CNP. Conversely, eight (7.2%) of the 110 tumors showed color flow in spite of poor enhancement, including two chromophobe cell carcinomas and two metastatic renal tumors.
Conclusions: The enhancement pattern in dynamic CT and the color flow pattern in Doppler US were different among the subtypes of RCC. Color Doppler US had diagnostic accuracy equal to dynamic CT in most patients with renal solid tumors. Although Doppler US may play a unique role in the diagnosis of some renal parenchymal solid tumors, it is sufficient to perform dynamic CT alone for diagnosis of clear cell carcinoma.

Key words: color Doppler ultrasonography – computed tomography – kidney – neoplasm – renal cell carcinoma

INTRODUCTION

In recent years, computed tomography (CT) and ultrasound (US) have dramatically improved the early detection of renal masses. Most renal cell carcinomas (RCCs) are characterized by abnormal vascular structures (1). Dynamic CT is an established method of imaging renal masses and evaluating their vascularity via pooling of contrast medium in the tumor (2). Clear cell carcinoma (conventional RCC) is described as an attenuated tumor in the arterial phase of dynamic CT (3). The enhancement pattern in dynamic CT has been reported to be different among the subtypes of renal cell carcinoma (4). To the best of our knowledge, however, there has been no report showing the patterns of color Doppler US among the subtypes of renal neoplasms. Moreover, some patients are allergic to the contrast medium used for dynamic CT and patients are also exposed to a large amount of X-rays in CT scanning. Hence there is a need for diagnosis of RCC by another method less invasive than CT. Doppler US allows for non-invasive assessment of vascular flow signals from neovascularity in tumors (5). Thus, we first hypothesized that color Doppler US may also show different patterns like dynamic CT findings. Second, we also hypothesized that we could obtain more accurate information about the histopathological subtypes of renal parenchymal neoplasms if both dynamic CT and color Doppler US were performed. In this study, we compared the histopathological distribution of the dynamic CT findings for renal solid tumors with the color Doppler US findings and evaluated whether dynamic CT is more informative in preoperative diagnosis of renal solid tumors.

PATIENTS AND METHODS

PATIENTS

Between August 1996 and May 2001, 110 patients with solid masses smaller than 7 cm in diameter and with pathological

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results confirmed by surgical removal of tumors were eligible for this study. The patients (75 men and 35 women) ranged in age from 22 to 85 years (median 62 years) and tumor size ranged from 1.0 to 7.0 cm (median 3.6 cm) in diameter. These patients were suspected to have RCC by US and/or CT at other hospitals and were introduced to us for further evaluation and treatment of those tumors. By initially performed B-mode US, angiomyolipomas (AMLs) were excluded.

Dynamic CT

Dynamic CT was performed using a Toshiba X-Vigor with 7 mm/s table feed for 7 mm slice helical scans. An unenhanced scan was carried out initially to obtain baseline attenuation values of lesions and to identify calcification. After bolus administration of 100–120 ml of contrast medium intravenously (injection rate 2.5–3.0 ml/s), two phases of renal enhancement were recognized. Initially, 30 s after the contrast medium injection, there was enhancement of the cortex, but not the medulla, so that cortical nephrographic differentiation was seen [cortical nephrographic phase (CNP)]. Five minutes after the injection, additional scanning was performed to obtain images of its excretion by the pelvic caliceal system (excretory phase). If the tumor density in the CNP was higher than that of the renal medulla, it was defined as rich enhancement. If it was lower than that of the renal medulla but higher than that in the pre-enhancement phase, it was defined as poor enhancement.

Color Doppler US

Color Doppler US examinations were performed with commercially available real-time scanners (Toshiba SSA380A) by the same senior radiologist (Y.M.). The radiologist had no information about the dynamic CT findings. Patients were examined in the supine and lateral decubitus positions, using transverse, intercostal and parasaggital scanning. The insonating frequency of the sector scanner was 4.7 mHz. The Toshiba unit incorporates a real-time scanner and range-gated pulse Doppler velocity meter. The wall filter was set as low as possible and the real-time B-mode was used to locate the tumors. The Doppler US scanning was performed under conditions of no color flow in the normal renal parenchyma. If color flow was detected in the tumor, it was defined as positive flow.

Classification

Histopathological findings were reviewed for the subtypes of neoplasms, according to the classifications of the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) (6). By the findings and estimation of detection of early enhancement patterns in dynamic CT and color flow in Doppler US, four distinct patterns could be identified: group 1, tumors with both rich enhancement and color flow; group 2, with rich enhancement and without color flow; group 3, with poor enhancement and with color flow; and group 4, with poor enhancement and without color flow.

Table 1. Histopathological findings and patterns of dynamic CT and Doppler US

	Group 1	Group 2	Group 3	Group 4	Total
Enhancement in CNP of CT	+	+	–	–	
Color flow in Doppler US	+	–	+	–	
Clear cell carcinoma	81	6	1	3	91
Papillary RCC	1		1	3	5
Granular cell carcinoma	1	2	1		4
Chromophobe cell carcinoma			2		2
Spindle cell carcinoma	1		1		2
Collecting-duct carcinoma		1			1
Metastatic renal tumor			2		2
Benign renal tumor	3				3
Total	87	9	8	6	110

CNP: cortical nephrographic phase.

RESULTS

Histopathological Distribution of All 110 Tumors

Histopathological examination revealed that, of the 110 neoplasms, 91 were clear cell carcinomas, five were papillary RCCs, four were granular cell carcinomas, three were benign renal tumors, two were chromophobe cell carcinomas, two were spindle cell carcinomas, two were metastatic renal tumors and one was a collecting-duct carcinoma.

One of the metastatic tumors was malignant melanoma. There were no other metastatic sites in the patient. The other was thyroid papillary cancer. Although the patients also had lung, retroperitoneal and mediastinal lymph node metastases, primary renal neoplasm could not be denied because only the renal tumor had grown in a short time.

The three benign tumors were composed of an oncocytoma, a leiomyoma and an AML.

Patterns of Dynamic CT and Color Doppler US (Table 1)

Group 1 (n = 87)

Eighty-one (93.1%) of the 87 tumors were clear cell carcinomas. The remainder consisted of one granular cell carcinoma, one papillary RCC, one spindle cell carcinoma and three benign tumors (an AML, an oncocytoma and a leiomyoma). All the benign tumors were diagnosed as renal cell carcinoma before the surgical treatment.

Group 2 (n = 9)

Six (66.7%) of the nine tumors were clear cell carcinomas. The others were two granular cell carcinomas and one collecting-duct carcinoma.