the patients randomized to the high-dose treatment arm not completing high-dose therapy because of toxicity or early death. Another study has conducted a matched pair analysis including 456 patients in which first-line HD-CT was compared with standard-dose chemotherapy.[21] An 11% improvement in the 2-year overall survival rate was demonstrated in the HD-CT group and a multivariate analysis revealed the use of first-line HD-CT to be an independent positive predictive factor for improved survival. One recent phase III randomized controlled trial failed to show improvement of three cycles of standard-dose VIP chemotherapy followed by one cycle of HD-CT (carboplatin, etoposide and cyclophosphamide) compared with four cycles of VIP standard-dose chemotherapy for advanced GCT.[22] These findings suggest that first-line HD-CT might be more effective against poor prognosis testicular GCT than standard-dose chemotherapy. However, these data including the present study are limited, and large randomized clinical trials are necessary. There are two ongoing randomized clinical studies comparing multicycles of HD-CT with standard-dose chemotherapy (four cycles of BEP) for patients with poor prognostic GCT. HD-CT arms are two cycles of BEP followed by HD-CT (carboplatin, etoposide and cyclophosphamide), and one cycle of VIP followed by three cycles of HD-CT (VIP), respectively. These studies will clarify the role of HD-CT for GCT.

Overall toxicity was acceptable and the feasibility of this HD-CT regimen was demonstrated. As expected, all patients except one developed grade 4 neutropenia, but all of them recovered fully due to the stem cell support and G-CSF administration. Other hematological toxicity was also universal, but was quite manageable. Although platelet transfusions were required in all patients, there was no evidence of cumulative thrombocytopenia. No patient was removed from this study because of hematological adverse effects. Apart from hematological toxicity, side-effects consisted mainly of gastrointestinal events. Gastrointestinal side-effects were mostly manageable by supportive treatments such as anti-emetic therapy. Rhabdomyolysis was fatal only in one patient (4%). No septic death occurred during this study. Symptomatic acute severe ototoxicity, nephrotoxicity or peripheral neuropathy, which are common cisplatin-related toxicities, were rare.

Considering the high cure rate of GCT patients after first-line HD-CT, late toxicity is of particular interest. The previous report showed that 10% of patients suffered from late effects, mainly compensated renal failure and peripheral neuropathy.[23] In this study, no specific investigations regarding persistent late complications have yet been performed and therefore the incidence of late complications is unclear. However, no patient developed a therapy-related leukemia, which is an already-described serious late complication following high cumulative etoposide doses.

The results observed for the 24 poor prognosis GCT patients with a median follow up of nearly 4 years, demonstrate a 5-year disease-specific survival rate of 63%. Following standard-dose therapy, it has been known that relapses occurring more than 2 years after therapy are rare. This appears to be similar for patients receiving first-line HD-CT with only 12.5% of relapses occurring beyond 2 years.

The major goal of investigation for patients with poor-risk testicular GCT is identification of more effective chemotherapy. The results conducted at multiple centers in this study suggest that first-line HD-CT plus stem cell support for poor-risk testicular GCT might have a modest improved treatment outcome. In addition, this dose-intense chemotherapy is associated with relatively high but acceptable toxicity. Furthermore, there is only a minimal risk for severe late toxicity or secondary chemotherapy-induced cancer. However, it is necessary to define the optimal regimen for further studies. Moreover, the identification of prognostic factors for first-line HD-CT is needed and may be applied to select patients for a favorable treatment outcome, although HD-CT is effective for relapsed testicular GCT.[24]

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References

1 Einhorn LH. Treatment or testicular cancer: a new and improved model. *J. Clin. Oncol.* 1990; 8: 1777–81.
2 Bosl GJ, Motzer RJ. Medical progress: testicular germ-cell cancer. *N. Engl. J. Med.* 1997; 337: 242–53.
3 Birch R, Williams S, Cone A *et al.* Prognostic factors for favorable outcome in disseminated germ cell tumors. *J. Clin. Oncol.* 1986; 4: 400–7.
4 International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. *J. Clin. Oncol.* 1997; 15: 594–603.
5 Sonneveld DJ, Hoekstra HJ, van der Graaf WT *et al.* Improved long term survival of patients with metastatic nonseminomatous testicular germ cell carcinoma in relation to prognostic classification system during the cisplatin era. *Cancer* 2001; 91: 1304–15.
6 Kaye SB, Mead GM, Fossa S *et al.* Intensive induction-sequential chemotherapy with BOP/VIP-B compared with treatment with BEP/EP for poor prognosis metastatic nonseminomatous germ cell tumor: a randomized Medical Research Council/European Organization for Research and Treatment of Cancer study. *J. Clin. Oncol.* 1998; 16: 692–701.
7 Bower M, Newlands ES, Holden L, Rustin GJS, Begent RHJ. Treatment of men with metastatic non-seminomatous germ cell tumors with cyclical POMB/ACE chemotherapy. *Ann. Oncol.* 1997; 8: 477–83.
8 Germa-Lluch JR, Garcia-del-Muro X, Tabernero JM *et al.* BOMP/EPI intensive alternating chemotherapy for IGCCC poor-prognosis germ-cell tumors: the Spanish Germ-Cell Cancer Group experience (GG). *Ann. Oncol.* 1999; 10: 289–93.
9 Motzer RJ, Mazumdar M, Gulati SC *et al.* Phase II trial of high-dose carboplatin and etoposide with autologous bone marrow transplantation in first-line therapy for patients with poor-risk germ cell tumors. *J. Natl. Cancer Inst.* 1993; 85: 1828–35.
10 Motzer RJ, Mazumdar M, Bajorin DF, Bosl GJ, Lyn P, Vlamis V. High-dose carboplatin, etoposide, and cyclophosphamide with autologous bone marrow transplantation in first-line therapy for patients with poor-risk germ cell tumors. *J. Clin. Oncol.* 1997; 15: 2546–52.
11 Decartis MP, Wilkinson PM, Welch RS, Metzner M, Morgenstern GR, Dougall M. High-dose chemotherapy and autologous haematopoietic support in poor risk non-seminomatous germ-cell tumors: an effective first-line therapy with minimal toxicity. *Ann. Oncol.* 2000; 11: 427–34.
12 Elias AD, Eder JP, Shea T, Begg CB, Frei E, Antman KH. High-dose ifosfamide with mesna uroprotection: a phase I study. *J. Clin. Oncol.* 1990; 8: 170–8.

13 Wolff SN, Johnson DH, Hainsworth JD, Greco FA. High-dose VP-16–213 monotherapy for refractory germinal malignancies: a phase II study. *J. Clin. Oncol.* 1984; 2: 271–4.
14 Nichols CR, Tricot G, Williams SD *et al.* Dose-intensive chemotherapy in refractory germ cell cancer – a phase I/II trial of high-dose carboplatin and etoposide with autologous bone marrow transplantation. *J. Clin. Oncol.* 1989; 7: 932–9.
15 Siegert W, Beyer J, Strohscheer I *et al.* High-dose treatment with carboplatin, etoposide, and ifosfamide followed by autologous stem-cell transplantation in relapsed or refractory germ cell cancer. A Phase I/II Study. *J. Clin. Oncol.* 1994; 12: 1223–31.
16 Williams SD, Birch R, Einhorn LH, Irwin L, Greco FA, Loehrer PJ. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. *N. Engl. J. Med.* 1987; 316: 1435–40.
17 Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; 47: 207–14.
18 Husband DJ, Green JA. POMB/ACE chemotherapy in non-seminomatous germ cell tumours: outcome and importance of dose intensity. *Eur. J. Cancer* 1992; 28: 86–91.
19 Fizazi K, Zelek L. Is 'one cycle every three or four weeks' obsolete? A critical review of dose-dense chemotherapy in solid neoplasms. *Ann. Oncol.* 2000; 11: 133–49.
20 Chevreau C, Droz JP, Pico JL *et al.* Early intensified chemotherapy with autologous bone marrow transplantation in first line treatment of poor risk non-seminomatous germ cell tumours. Preliminary results of a French randomized trial. *Eur. Urol.* 1993; 23: 213–17.
21 Bokemeyer C, Kollmannsberger C, Meisner C *et al.* First-line high-dose chemotherapy compared to standard-dose PEB/VIP chemotherapy in patients with advanced germ cell tumors: a multivariate and matched pair analysis. *J. Clin. Oncol.* 1999; 17: 3450–6.
22 Pico JL, Rosti G, Kramar A *et al.* A randomized trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours. *Ann. Oncol.* 2005; 16: 1152–9.
23 Schmoll HJ, Kollmannsberger C, Metzner B *et al.* Long-term results of first-line sequential high-dose etoposide, ifosfamide, and cisplatin chemotherapy plus autologous stem cell support for patients with advanced metastatic germ cell cancer: an extended phase I/II study of the German Testicular Cancer Study Group. *J. Clin. Oncol.* 2003; 21: 4083–91.
24 Bhatia S, Abonour R, Porcu P *et al.* High-dose chemotherapy as initial salvage chemotherapy in patients with relapsed testicular cancer. *J. Clin. Oncol.* 2000; 18: 3346–51.

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Clinical efficacy of alternative antiandrogen therapy in Japanese men with relapsed prostate cancer after first-line hormonal therapy

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Background: To confirm the effectiveness of alternative antiandrogen therapy (AAT) in Japanese patients with prostate cancer relapse after first-line hormonal therapy.

Methods: A total of 80 patients who had successive serum prostate-specific antigen (PSA) progression after first-line hormonal therapy (luteinizing hormone-releasing hormone agonist alone: 21 cases; combined antiandrogen blockade therapy: 59 cases) were enrolled. We evaluated the positive ratio of antiandrogen withdrawal syndrome (AWS), the PSA responses with second- and third-line AAT, and cause-specific survival in terms of the effectiveness of AAT.

Results: The overall positive AWS ratio after first-line therapy was 33%, while that after second-line therapy was 7%. There was no correlation between the first-line PSA response and the positive AWS. Of the 10 positive and the 20 negative AWS cases, secondary antiandrogen administration was effective in 50% and 60% of cases, respectively. The positive PSA responders at second- and third-line therapy were 51% and 13%, respectively. For second-line therapy, the effective rates from steroidal to non-steroidal, from non-steroidal to non-steroidal antiandrogen, and from non-steroidal to steroidal were 83%, 43%, and 14%, respectively. The cause-specific survival of the second-line responders was significantly better than that of the non-responders.

Conclusion: There was a substantial number of patients who found second-line AAT to be modestly effective. Flutamide was effective as an alternative antiandrogen for the patients' relapse treatment with bicalutamide in Japanese men.

Key words: alternative antiandrogen, antiandrogen withdrawal syndrome, prostate cancer, relapse.

Introduction

The incidence, as well as the mortality of prostate cancer in Japan, is still lower than those in Western countries.[1] However, prostate cancer is becoming a major public health concern in Japan because the age-adjusted incidence of this malignancy rapidly increased 6.5-fold between 1975 and 1998.[2] The age-adjusted mortality rate also increased 4.3-fold between 1980 and 2000. In addition to the increasing incidence and mortality rate, 40% of all registered Japanese prostate cancer cases ($n = 4529$) in 2000[3] were diagnosed at >75-years-old and ≈ 20% of the men were newly diagnosed with metastatic disease. Considering the high incidence and mortality specifically in elderly Japanese men and the substantial number with metastatic disease, antiandrogen therapy still plays a major role in treating prostate cancer. However, most patients with locally advanced or metastatic disease relapse after initial treatment with castration or combined androgen blockade (CAB) therapy. In 1997, Scher *et al.* reported that 38.5% of patients with progressive disease who relapsed after treatment with flutamide responded to alternative antiandrogen therapy (AAT).[4] Thereafter, Kojima *et al.* reported the clinical efficacy of AAT in 70 Japanese patients with prostate cancer.[5]

The aim of this study is to confirm the efficacy of AAT and to compare effectiveness in terms of steroidal and non-steroidal antiandrogen administration.

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Materials and methods

A total of 80 Japanese patients with histologically proven prostate cancer were enrolled from January 1999 to December 2004. The patients' age ranged from 52–86 years (mean ± SD: 71.7 ± 8.4 years). The median prostate-specific antigen (PSA) ranged from 7.7–8710 ng/mL (mean ± SD: 868 ± 1741 ng/mL). The follow-up time was 21–150 months (median: 42 months). All the patients were treated with hormonal therapy and had disease progression after first-line hormonal therapy (luteinizing hormone-releasing hormone [LH-RH] agonist alone: 21 cases, CAB therapy: 59 cases). Of the 59 cases with CAB, 53 cases received non-steroidal antiandrogen (flutamide [FLT], 375 mg daily: 22 cases; bicalutamide [BCL], 80 mg daily: 31 cases). The remaining six cases received steroidal antiandrogen (chlormadinone acetate [CMA], 100 mg daily).

We obtained institutional review board approval with the aim of retrospectively reviewing the patients' medical records. No patient had received prior therapy, including irradiation and cytotoxic therapies. The relevant patient characteristics are listed in Table 1. To analyse the responses to AAT in comparison with an equivalent group of Japanese men, we applied similar evaluative criteria to those in the report by Kojima *et al.*[5]

Definition of serum prostate-specific antigen responses at 3 months after first-line androgen deprivation therapy

1 A complete response (CR): normalization of PSA level (<4.0 ng/mL).
2 A partial response (PR): >50% decrease in the PSA level compared to the initial PSA level but >4.0 ng/mL.

Table 1 Clinical characteristics of the enrolled patients

Characteristic	N (%)
Gleason score:	
5–7	45 (56)
8–10	35 (44)
T category:	
T2	6 (8)
T3	54 (67)
T4	20 (25)
N category:	
N0	49 (61)
N1	31 (39)
M category:	
M0	30 (38)
M1	50 (62)
Clinical stage:	
C	26 (32)
D1	8 (10)
D2	46 (58)

3 Progression of disease (PD): >25% increase in the PSA level compared with the initial level.
4 No change: defined as between PR and PD.

Definition of prostate-specific antigen progression and antiandrogen withdrawal syndrome

Prostate-specific antigen progression was defined as three successive PSA level increases. After PSA progression, primary antiandrogen administration was discontinued in all the 59 cases with CAB (>4 weeks for FLT and CMA, >8 weeks for BCL), while the LH-RH analog agonist continued. The positive antiandrogen withdrawal syndrome (AWS) was defined as >50% decrease of the PSA level compared with that at the time of discontinuing the primary antiandrogen.

Prostate-specific antigen evaluation after alternative antiandrogen therapy

The PSA responders at second- and third-line therapy were classified as those who had a 50% decrease of the PSA level at the end of first- and second-line antiandrogen therapy, respectively.

Definition of response duration

Response duration was defined as the time from the start of hormonal therapy until progression.

Statistical analyses

For the statistical analysis of data, the Student's *t*-test, χ^2 test or Fisher's exact test were applied using StatView software (SAS Institute, Cary, NC, USA). The statistical significance was defined as $P < 0.05$. To compare the cause-specific survival rates, Kaplan-Meier curves were constructed.

Results

Of the enrolled 80 patients, 35 cases (43.7%) had CR of the PSA level at 3 months after first-line therapy (47.6%, 10/21) with the LH-RH agonist alone, compared with 42.3% (25/59) with CAB therapy ($P = 0.79$). Of the 21 cases with the LH-RH agonist alone and the 59 cases with CAB therapy, 95.2% (20/21) and 94.9% (56/59) reached CR or PR, respectively. Of the 76 patients with CR or PR of the PSA level, there was no significant difference in the duration of response for first-line hormonal therapy between the LH-RH agonist-alone group (22.3 ± 23.0 months) and the CAB therapy group (10.7 ± 11.9 months). In addition, there was no significant difference in the duration of the response based on steroidal or non-steroidal antiandrogen administration (CAB using BCL: 7.6 ± 7.8 months, CAB using FLT: 13.9 ± 14.7 months, CAB using CMA: 17.0 ± 17.5 months).

Relationship between first-line prostate-specific antigen response and positive antiandrogen withdrawal syndrome rate after primary antiandrogen and second alternative therapy

A total of 30 cases (51%, 30/59) could be evaluated for the AWS rate after primary antiandrogen therapy. The remaining 29 cases were excluded because of the shortage of observation for the AWS. Secondary antiandrogen (FLT or CMA) was started <8 weeks after the discontinuing of BCL in 27 (93%) of the 29 cases.

We compared the positive AWS rate after primary antiandrogen and the second alternative therapy in terms of the PSA response. Of the 30 cases that were evaluated for the AWS rate, the PSA decreased to PR or CR (>50%) in 10 cases (33%, response of duration mean ± SD: 6.7 ± 4.0 months). Of the 15 patients, one patient (7%) responded to the second-line antiandrogen withdrawal and the positive AWS was not observed in any of the three cases after the third-line hormonal therapy was discontinued. Comparing the CR cases with the PR cases, there were no significant differences in the positive AWS rate (CR: 32%, 6/19; PR: 36%, 4/11) or in the duration of the antiandrogen withdrawal response (CR: 6.6 ± 4.7 months; PR: 8.5 ± 4.4 months). The positive AWS rates in men treated with CMA, FLT, and BCL were 40% (2/5), 33% (2/6), and 32% (6/19), respectively. There were no significant differences between the AWS responses and the antiandrogens.

Of the 10 positive and the 20 negative AWS cases, secondary antiandrogen was effective in five (50%) and 12 (60%) cases, respectively. There was no significant difference between the AWS response and the effect of subsequent hormonal therapy. In our series, the AWS response could not predict the effect of subsequent hormonal therapy.

Efficacy of second-line and third-line antiandrogen therapy

To compare our series with the previous report by Kojima *et al.*[5] simultaneously, we set the two figures (Fig. 1a,b) based on the efficacy of AAT against relapsed prostate cancer. The effective rate in men who were given additional steroidal or non-steroidal antiandrogen after androgen suppression monotherapy was 71% in our series. In our series, the effective rates from CMA to non-steroidal antiandrogen (FLT or BCL) and from non-steroidal antiandrogen to CMA were 83% (5/6) and 14% (1/7), respectively. The rates from FLT to BCL and from BCL to FLT were 53% (9/17) and 38% (11/29), respectively. The change in antiandrogen from second-line to third-line is shown in Figure 1b. Of the 15 cases, the effective rate was 13% in our series,

a)

First-line		Second-Line	Effectiveness (%)	Duration of response* (mos.)
AS	→	MAB with CMA	6/10 (60%)	15.8±5.6
	→	MAB with FLT	4/5 (80%)	10.7±6.0
	→	MAB with BCL	5/6 (83%)	29.2±6.4
MAB with CMA	→	MAB with FLT	3/3 (100%)	12.0±7.1
	→	MAB with BCL	2/3 (67%)	4.3±2.1
MAB with FLT	→	MAB with CMA	1/5 (20%)	4.5
	→	MAB with BCL	9/17 (53%)	5.5±4.9
MAB with BCL	→	MAB with FLT	11/29 (38%)	5.1±5.2
		MAB with CMA	0/2 (0%)	
			41/80 (51%)	8.6±4.6

b)

Second-Line		Third-Line	Effectiveness (%)	Duration of response** (mos.)
MAB with CMA	→	MAB with FLT	0/1 (0%)	
	→	MAB with BCL	1/3 (33%)	5.2
MAB with FLT	→	MAB with BCL	1/3 (33%)	4.8
	→	MAB with CMA	0/6 (0%)	
MAB with BCL	→	MAB with CMA	0/1 (0%)	
	→	MAB with FLT	0/1 (0%)	
		Total	2/15 (13%)	5.0

Fig. 1 Efficacy of alternative antiandrogen therapy in the enrolled patients. (a) Change of antiandrogen between first- and second-line therapy. *, duration of the response to second-line therapy (months). (b) Change of antiandrogen between second- and third-line therapy. **, duration of response to third-line therapy (months).

while that in Kojima *et al.* was 29.4% (5/17).[5] In our series, no responder was treated with CMA as third-line therapy (0/7).

Cause-specific survival in terms of the response to second-line therapy

Similar to the results in the previous report,[5] the survival of second-line responders in all cases (stages C, D1, and D2) was significantly better than that of the non-responders (5-year survival rates = 91.7% and 62.2%, respectively; $P = 0.002$) (Fig. 2a). In the cases with stages D1 and D2 alone, there was also a significant difference between the responders and non-responders (5-year survival rates = 80.0% and 53.0%, respectively; $P = 0.012$) (Fig. 2b). Comparing the PSA response during first-line therapy between the responders and non-responders, the proportion of responders in second-line therapy who had achieved PSA CR (PSA response at 3 months starting after first-line therapy; 18/26) was statistically higher than those without CR (12/40, $P = 0.004$).

Discussion

In the previous studies, a substantial amount of AWS responses has been reported in men with advanced prostate cancer prior to the starting of AAT.[5,6] However, the positive response rates were widely ranged based on the dosage of the primary or secondary antiandrogen administration. Kojima *et al.* speculated that a low daily dose of FLT in Japan induced a lower positive AWS response.[5] As described, all the subjects in this study were Japanese and daily doses for FLT, BCL, and CMA were very similar to those in the previous study.[5] Furthermore, in terms of the characteristics of the enrolled patients, there were no significant

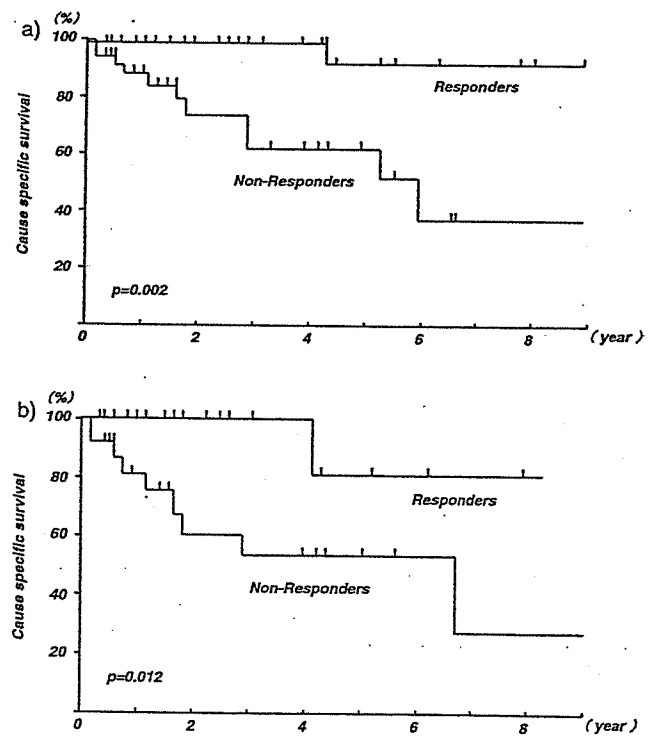

Fig. 2 Cause-specific survival in terms of the response to second-line therapy. (a) All patients whose stages were C, D1, and D2. The survival was evaluated from the time of progression of the first-line therapy. (b) Patients with stage D1 and D2 alone. The survival was evaluated from the time of progression of the first-line therapy.

differences in the distribution of age, initial PSA range, biopsy Gleason score, TNM categories,[7] and clinical stage between the two studies.[5] We speculate the homogeneity of patient background in the two retrospective studies explains the similarity of results for the PSA response at 3 months after the initiation of hormonal therapy (overall CR or PR rates in our study and the previous study were 95.0% and 95.7%, respectively), as well as the duration of response (months) based on antiandrogen administration (BCL: 7.6 ± 7.8 months [our study] versus 9.3 ± 6.0 months [Kojima *et al.*[5]]; FLT: 13.9 ± 14.7 months [our study] versus 14.6 ± 10.3 months [Kojima *et al.*[5]]; CMA: 17.0 ± 17.5 months [our study] versus 29.4 ± 38.3 months [Kojima *et al.*[5]]).

The similarity of patients' backgrounds also resulted in a similar positive AWS rate after CAB as the first-line hormonal therapy (33.3% [10/30] in this study compared to 35.8% [19/53] in Kojima *et al.*[5]). Interestingly, the positive AWS rates after second-line therapy also were similar (7% [1/15] in this study versus 8.0% [2/25] in Kojima *et al.*[5]). Similarly, the results of first-line hormonal therapy (CR and PR) did not significantly affect the AWS response rate (31.5% versus 36.3% in this study, 30.0% versus 42.9% in Kojima *et al.*[5]). Our results enhanced the evidence that the primary PSA response could not predict the AWS response.

In the results regarding the change of antiandrogens between first- and second-line therapy, the overall effective rate in our study was ≈ 12% higher than that in the previous study (51% versus 39.6%, $P = 0.52$). The reason for the higher rate in our study might originate from the difference in the effective rate concerning cases in which antiandrogen administration was added in second-line therapy (71% in our study versus 46% in Kojima *et al.*[5]). In our series, the effective rates from CMA to non-steroidal antiandrogen (FLT or BCL) and from non-steroidal antiandrogen to CMA were 83% (5/6) and 14% (1/7), respectively, while those in Kojima *et al.* were 36% (8/22) and 0% (0/4), respectively (Fig. 1).[5] Interestingly, the effectiveness in the change from CMA (steroidal) to non-steroidal antiandrogen (BCL or FLT) revealed a higher rate (46%, 13/28, when combining the two studies[5]) compared with the rate from non-steroidal to CMA (9%, 1/11, when combining the two studies[5]). Furthermore, no case where the patient went from the non-steroidal antiandrogen to CMA was effective in the change of antiandrogen from second- to third-line therapy (0%, 0/7) in our study or Kojima *et al.*[5] Combining the two sets of results, we speculate that the change to CMA might be less effective compared with the change from CMA to a non-steroidal antiandrogen. However, in the change in first- and second-line therapy, the effective rates between our study and Kojima *et al.*'s study revealed similar results in the change from non-steroidal to other non-steroidal antiandrogens (43% [20/46] in our study and 50% [7/14] in the Kojima *et al.*[5]). The PSA response rates in the change from FLT to BCL were previously reported as being from 38.5–42.9%.[4,8] Considering other results, second-line AAT, from non-steroidal to non-steroidal, was effective in a substantial number of men with advanced prostate cancer, regardless of differences in their race. In 2006, Lam *et al.* demonstrated that there was no report of responses of FLT following BCL therapy.[9] However, Kojima *et al.* already have reported that FLT was effective as an alternative antiandrogen for relapse treatment with BCL in Japanese men.[5] Combining this report's results with the results from our study, we also found that FLT was effective after relapse with BCL.

As is well-known, androgen receptor (AR) mutation might play a key role in AWS.[10,11] Suzuki reported that AR hyper-activated mutation might cause so-called anti-AWS.[12] In addition to the occurrence of AWS, AR mutation, such as the codons 877 and 741, might influence the effectiveness of AAT.[11,13] Primary non-steroidal antiandrogen administration in time might select for mutant AR, which can be stimulated by this agent but inhibited by the alternative non-steroidal antiandrogen.[8] The results of this study revealed that previous antiandrogen treatment altered the response to subsequent hormonal therapy.

In this study, the cause-specific survival rate of second-line responders in all cases, as well as the cases with stage D disease, was significantly better than that of the non-responders. Kojima *et al.*'s study also revealed significant differences between the responders and non-responders.[5] These two studies might lead to the speculation that other options, such as chemotherapy and experimental trials, need to be examined in non-responders without choosing third-line hormonal therapy. Furthermore, it is very important to predict the response of second-line therapy. Similar to Kojima *et al.*'s results,[5] pretreatment parameters, such as age, clinical stage, and pretreatment PSA value, could not predict the response of second-line therapy (data not shown). However, our result showed a certain correlation between first-line responsiveness (PSA CR) and second-line responsiveness. The PSA response after first-line therapy might be a possible parameter in predicting the response of second-line therapy, combining the data from Kojima *et al.*[5] with our results. Based on their data, the proportion of responders in second-line therapy who had achieved PSA CR (14/21) also was higher than those without CR (14/33, $P = 0.08$).

To clarify whether the PSA response can be a critical factor prior to second-line AAT, further analysis with a larger number of men will be necessary.

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References

1 Crawford ED. Epidemiology of prostate cancer. *Urology* 2003; **62** (Suppl. 6A): 3–12.
2 The Research Group for Population-based Cancer Registration in Japan. Cancer incidence and incidence rates in Japan 1999: estimates based on data from 11 population-based cancer registries. *Jpn. J. Clin. Oncol.* 2004; 34: 352–6.
3 Cancer Registration Committee of the Japanese Urological Association. Clinicopathological statistics on registered prostate cancer patients in Japan: 2000 report from the Japanese Urological Association. *Int. J. Urol.* 2005; **12**: 46–61.
4 Sher HI, Liebertz C, Kelly WK *et al.* Bicalutamide for advanced prostate cancer: the natural versus treated history of disease. *J. Clin. Oncol.* 1997; **15**: 2928–38.
5 Kojima S, Suzuki H, Akakura K, Shimbo M, Ichikawa T, Ito H. Alternative antiandrogens to treat prostate cancer relapse after initial hormone therapy. *J. Urol.* 2004; **171** (2 Pt 1): 679–83.
6 Nieh PT. Withdrawal phenomenon with the antiandrogen casodex. *J. Urol.* 1995; **153**: 1070–2.
7 Harmanker P, Hutter RVP, Sobin LH, Wager G, Witteking Ch. Prostate. In: *TNM Atlas*, 4th edn. Springer Verlag, New York, 1997; 272.
8 Joyce R, Fenton MA, Rode P *et al.* High dose bicalutamide for androgen independent prostate cancer: effect of prior hormonal therapy. *J. Urol.* 1998; **159**: 149–53.
9 Lam JS, Leppert JT, Vemulapalli SN, Shvarts O, Belldegrun AS. Secondary hormonal therapy for advanced prostate cancer. *J. Urol.* 2006; **175**: 27–34.

10 Kelly WK, Scher HI. Prostate specific antiandrogen decline after antiandrogen withdrawal: the flutamide withdrawal syndrome. *J. Urol.* 1993; 149: 607–9.
11 Suzuki H, Nihei N, Sato N, Ichikawa T, Mizokami A, Shimazaki J. Codon 877 mutation in the androgen receptor gene in advanced cancer: relation to antiandrogen withdrawal syndrome. *Prostate* 1996; 29: 153–8.
12 Suzuki H, Ueda T, Ichikawa T, Ito H. Androgen receptor involvement in the progression of prostate cancer. *Endocr. Relat. Cancer* 2003; 10: 209–16.
13 Bohl CE, Gao W, Miller DD, Bell CE, Dalton JT. Structural basis for antagonism and resistance of bicalutamide in prostate cancer. *Proc. Natl Acad. Sci. USA* 2005; 102: 6201–6.

講座

術前化学療法後のセンチネルリンパ節生検

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Sentinel Lymph Node Biopsy for Breast Cancer Patients after Neoadjuvant Chemotherapy：Kinoshita T*1, Fukutomi T*2, Seki K*3 (*1,2Surgical Oncology Division, *3Department of Pathology, National Cancer Center)

Despite the increasing use of both sentinel node biopsy and neoadjuvant chemotherapy in patients with operable breast cancer, there is still limited information on the feasibility and accuracy of sentinel node biopsy following neoadjuvant chemotherapy. So, the feasibility and accuracy of sentinel lymph node (SLN) biopsy for breast cancer patients with clinically node negative after neoadjuvant chemotherapy (NAC) has been investigated under the administration of a radiocolloid imaging agent injected intradermally over a tumor. Also, conditions which may affect SLN biopsy detection and false-negative rates with respect to clinical tumor response and clinical nodal status before NAC were also analyzed.

Our results show that SLN identification rate and false-negative rate after NAC are similar to those in nonneoadjuvant studies.

Key words：Breast cancer patients, After neoadjuvant chemotherapy, Sentinel node biopsy
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はじめに

近年，センチネルリンパ節生検による腋窩郭清の省略と術前化学療法の併用により乳癌の外科治療は急速に縮小化の方向に進んでいる．センチネルリンパ節生検は，1990年代に始まり，従来の色素法にRIを用いたガンマプローブ法を組み合わせるなどの技術的改良と外科医自身の学習効果により，その成績も90％を超える同定率と5～10％の偽陰性率の達成が可能になってきている[1]．海外における69の施設と10,000人以上の患者を対象とした早期乳癌に対するセンチネルリンパ節生検のメタアナリシスの結果は，全体の同定率が90％以上で偽陰性率も8.4％と報告されている[2]．センチネルリンパ節生検の結果，腋窩郭清の省略が可能になった患者は，腋窩郭清を施行された患者と比較して術後合併症の頻度が低く，患手のむくみ，痺れ，運動障害などが軽度でQOLもより良好であると考えられる[1]．海外におけるセンチネルリンパ節生検の比較試験の長期的な成績が待たれるが，本邦においても多くの施設が既にセンチネルリンパ節生検の安全性試験を終了し実地医療へと移行しているものと考えられる．

一方，術前化学療法の導入により多くの症例でダウンステージ効果により乳房温存療法が可能になってきた．術前化学療法は従来，病期ⅢB以上のいわゆる局所進行癌を対象に非切除例を切除可能にする目的で実施されてきたが，近年は病期ⅡAからⅢAの症例も術前化学療法の対象とし，原発巣が巣縮小した結果，多くの症例で乳房温存療法が可能となっている．これらの効果は，原発巣ばかりではなく当然，腋窩リンパ節転移巣にも確認されている．アンスラサイクリン系を含む術前化学療法では，腋窩リンパ節転移を約30％減じ[3]，さらにタキサン系を加えたレジメンでは約40％減ずると報告されている[4,5]．当院

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表4　国立がんセンターにおけるセンチネルリンパ節生検の成績

センチネルリンパ節の転移	非センチネルリンパ節の転移	
	陽性	陰性
陽性	16	14
陰性	3	48

False negative rate, 9.1%; overall accuracy, 96.3%; negative predictive value, 94.1%; positive predictive value, 100%

け実施した．術前化学療法後に原発巣がPR以上の効果を示し，かつ，治療後腋窩リンパ節転移が陰性であった88例をセンチネルリンパ節生検の対象とした．これらの平均腫瘍径は4.9cm（2.5cm～12.0cm）で，T4が6例，治療前に明らかにリンパ節転移を認めた42例も対象となっている（表3）．センチネルリンパ節生検は，色素－RI法を用いたものが80例で，色素法単独が8例となっている．結果として，センチネルリンパ節が同定できた症例は80例で，同定率は92%となる．これらの症例のセンチネルリンパ節とノンセンチネルリンパ節の転移の有無をまとめたものを表4に示す．センチネルリンパ節に転移を認めず，ノンセンチネルリンパ節に転移を認めたものは3例で偽陰性率は9%であり，全体として96%の症例においてセンチネルリンパ節が腋窩リンパ節全体の状況を正確に反映していることが証明された．臨床的諸因子とセンチネルリンパ節の同定率との関連を検討したが，治療前のリンパ節転移の有無，臨床的治療効果，病理組織学的治療効果は関連せず，唯一，T4d（炎症性乳癌）症例のみがセンチネルリンパ節の同定を困難にしていることが明らかとなった．一方，センチネルリンパ節が同定できた症例中，偽陰性になった症例は3例のみであったため，術前化学療法も含めてこれらに影響を与える因子は明らかではなかった．

まとめ

当院での術前化学療法後センチネルリンパ節生検の結果から，炎症性乳癌以外の術前化学療法が著効した症例において，センチネルリンパ節生検は十分に安全に実施できると結論づけられた．同定率は92%，偽陰性率は9%で，早期乳癌における成績と遜色のないものとなった．海外における最近の報告や多施設からの報告は，当院の結果を支持するものである．一方，2005年度にJournal of Clinical Oncology（JCO）に発表されたAmerican Society of Clinical Oncology（ASCO）のガイドラインでは，Preoperative systemic therapy後のセンチネルリンパ節生検に関して，①技術的には安全に実施することはできる，②Preoperative systemic therapy後のn0の意義が明らかでない，③これらの症例では，正確な腋窩リンパ節の転移状況の把握が治療方針を決める際に重要であること，④エビデンスが十分でない，ことより推奨されていない．正確な腋窩リンパ節の情報を得るという目的からするとセンチネルリンパ節生検をPreoperative systemic therapyの前に施行し，Preoperative systemic therapy後に実施する場合でもN0症例に限られるべきだと強調している[18]．

当院での成績から，強力で安定した化学療法の後，色素－RI法を用い熟練した手技のもとにセンチネルリンパ節生検は，安全に実施できることが確認された．術前化学療法が著効した乳癌症例では，腋窩リンパ節陽性率が25%程度になることから術前化学療法後にセンチネルリンパ節生検を実施することに意義があるものと考える．ただし，本対象が進行癌であるということを十分に認識し，腫瘍内科医，病理医，放射線診断医との連携のもとに，慎重に適応を決めて本手技を修練，実施することが望まれる．

文　献

1）Veronesi U, Pagenelli G, Viale G, et al：A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 349：546-553, 2003

2) Kim T, Agboola O, Lyman GH, et al : Lymphatic mapping and sentinel lymph node sampling in breast cancer : meta-analysis. *Proc Am Soc Clin Oncol* **21** : 36a, 2002
3) Fisher B, Brown A, Mamounas E, et al : Effect of preoperative chemotherapy of local-regional disease in women with operable breast cancer : findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* **15** : 2483-2493, 1997
4) Mamounaus E, Brown A, Smith R, et al : 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
5) Gianni L, Baselga H, Eiermann W, et al : First report of European Cooperative Trial in operable breast cancer (ECTO) : effect of primary systemic therapy (PST) onlocal-regional disease. *Proc Am Soc Clin Oncol* **21** : 34 a, 2002
6) Breslin TM, Cohen L, Sahin A, et al. 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, et al : 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, et al : Sentinel lymphadenectomy after neoadjuvant chemotherapy for breast cancer may reliable represent the axilla except for inflammatory breast cancer. *Ann Surg Oncol* **9** : 235-242, 2000
9) Haid A, Tausch C, Lang A, et al : Is sentinel lymph node biopsy reliable and indicated after preoperative chemotherapy in patients with breast cancer? *Cancer* **92** : 1080-1084, 2001
10) Julian TB, Dusi D, Wolmark N : Sentinel node biopsy after neoadjuvant chemotherapy for breast cancer. *Am J Surg* **184** : 315-317, 2002
11) Tafra L, Verbanac KM, Lannin DR : Preoperative chemotherapy and sentinel lymphadenectomy for breast cancer. *Am J Surg* **182** : 312-315, 2001
12) Nason KS, Anderson BO, Byrd DR, et al : Increased false negative sentinel node biopsy rates after preoperative chemotherapy for invasive breast carcinoma. *Cancer* **89** : 2187-2194, 2000
13) Shimazu K, Tamaki Y, Taguchi T, et al : Sentinel lymph node biopsy using periareolar injection of radiocolloid for patients with neoadjuvant chemotherapy-treated breast carcinoma. *Cancer* **100** : 2555-2561, 2004
14) Mamounas E, Brown A, Anderson S, et al : Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer : Results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* **23** : 2694-2702, 2005
15) Krag D, Weavre D, Ashikaga T, et al : The sentinel node in breast cancer—A multicenter validation study. *N Engl J Med* **339** : 941-946, 1998
16) Tafra L, Lannin DR, Swason MS, et al : Multicenter trial of sentinel node biopsy for breast cancer using both technetium sulfur colloidal and isosulfan blue dye. *Ann Surg* **223** : 51-59, 2001
17) McMaster KM, Tuttle TM, Carison DJ, et al : Sentinel lymph node biopsy for breast cancer : A suitable alternative to routine axillary dissection in multi-institutional practice when optimal technique in used. *J Clin Oncol* 18 : 2560-2566, 2000
18) Lyman GH, Giuliano MR, Somerfield MR, et al : American Society of Clinical Oncology guideline recommendation for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol* **23** : 7703-7720, 2005

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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.

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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%

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%	

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.

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[1]. 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.

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Sentinel lymph node biopsy examination for breast cancer patients with clinically negative axillary lymph nodes after neoadjuvant chemotherapy

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Abstract

Background: The feasibility and accuracy of sentinel lymph node (SLN) biopsy examination for breast cancer patients with clinically node-negative breast cancer after neoadjuvant chemotherapy (NAC) have been investigated under the administration of a radiocolloid imaging agent injected intradermally over a tumor. In addition, conditions that may affect SLN biopsy detection and false-negative rates with respect to clinical tumor response and clinical nodal status before NAC were analyzed.

Methods: Seventy-seven patients with stages II and III breast cancer previously treated with NAC were enrolled in the study. All patients were clinically node negative after NAC. The patients then underwent SLN biopsy examination, which involved a combination of intradermal injection over the tumor of radiocolloid and a subareolar injection of blue dye. This was followed by standard level I/II axillary lymph node dissection.

Results: The SLN could be identified in 72 of 77 patients (identification rate, 93.5%). In 69 of 72 patients (95.8%) the SLN accurately predicted the axillary status. Three patients had a false-negative SLN biopsy examination result, resulting in a false-negative rate of 11.1% (3 of 27). The SLN identification rate tended to be higher, although not statistically significantly, among patients who had clinically negative axillary lymph nodes before NAC (97.6%; 41 of 42). This is in comparison with patients who had a positive axillary lymph node before NAC (88.6%; 31 of 35).

Conclusions: The SLN identification rate and false-negative rate were similar to those in nonneoadjuvant studies. The SLN biopsy examination accurately predicted metastatic disease in the axilla of patients with tumor response after NAC and clinical nodal status before NAC. This diagnostic technique, using an intradermal injection of radiocolloid, may provide treatment guidance for patients after NAC.

Keywords: Sentinel node biopsy; Neoadjuvant chemotherapy; Clinically node negative; Intradermal injection

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

Recent studies report identification rates of more than 90%, with 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 examination have been established: these include T3 or T4 tumors, multicentric or multifocal lesions, a large biopsy cavity, previous axillary surgery, previous chest-wall irradiation, and neoadjuvant chemotherapy (NAC) [4,5].

The application of SLN biopsy examination in NAC-treated patients may, as in nonneoadjuvant chemotherapy groups, identify patients who do not necessarily require an axillary lymph node dissection (ALND). Several studies

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Table 1
Patient demographics

	Number of patients
Age, y	
Mean	51.1
Range	27–75
Clinical tumor size, cm*	
Mean	4.82
Range	2.7–12
Tumor classification*	
T2	50 (65.0%)
T3	24 (31.2%)
T4	3 (3.8%)
Lymph node status*	
N0	42 (54.5%)
N1	28 (36.4%)
N2	7 (9.1%)
Tumor type	
Invasive ductal	74 (96.1%)
Invasive lobular	3 (3.9%)
Type of NAC	
FEC plus paclitaxel	73 (94.9%)
Paclitaxel alone	4 (5.1%)
Clinical response of the tumor	
CR	41 (53.2%)
PR	28 (36.4%)
SD	8 (10.4%)
Pathologic response of the tumor	
pCR	17 (22.1%)
pINV	60 (77.9%)
Pathologic nodal status	
Negative	47 (61.0%)
Positive	30 (39.0%)

CR = complete response; FEC = fluorouracil/epirubicin/cyclophosphamide; PR = partial response; SD = stable disease; pCR = pathologic complete response; pINV = pathologic invasive.
* Before NAC.

have evaluated the use of SLN biopsy examination in patients with breast cancer after NAC but results are varied and inconclusive [6–14].

Recently, several studies have shown the feasibility and accuracy of SLN biopsy examination using peritumoral injection of radiocolloid for patients with NAC-treated breast cancer. However, false-negative rates varied considerably among these studies [6–13]. It is possible that tumor response to chemotherapy may alter or interrupt the lymphatic drainage, thus causing the lower SLN identification rates and higher false-negative rates as opposed to nonneoadjuvant studies. Our hypothesis is that the lymphatic flow within the skin lesion overlying the tumor is less damaged by the chemotherapy than that in the parenchyma surrounding the tumor, except in T4 tumors. Thus, the usefulness of SLN biopsy examination with intradermal injection of radiocolloid for patients with NAC-treated breast cancer has yet to be established.

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

Methods

Between May 2003 and January 2005, 77 patients with T2-4N0-2 breast cancer underwent NAC with SLN biopsy examination plus ALND performed by a single surgeon. The pathologic diagnosis was established by core needle biopsy examination in all patients.

Patients younger than 65 years of age received 4 cycles of 5-fluorouracil (500 mg/m^2)/epirubicin (100 mg/m^2)/cyclophosphamide (500 mg/m^2) plus 12 weekly cycles of paclitaxel (80 mg/m^2), and patients older than 65 years of age received 12 weekly cycles of paclitaxel (80 mg/m^2) alone. After NAC, we enrolled the 77 clinically node-negative patients in this study.

Lymphatic mapping was performed using a 3-mL combination of blue dye (Patent blue V; TOC Ltd, Tokyo, Japan) and 30 to 80 MBq of technetium-99m–labeled Phytate (Daiichi RI Laboratory, Ltd, Tokyo, Japan). The day before surgery, the radiotracer was injected intradermally into the area overlying the tumor, and blue dye was injected into the subareolar site intraoperatively. For nonpalpable lesions, injections were performed under mammographic or ultrasonic needle localization. Sentinel lymph nodes were identified as being stained blue, radioactive, or both. The SLN biopsy procedure then was followed by a standard level I/II ALND.

All sentinel nodes were evaluated histologically by submitting each node as a 3-mm to 5-mm serial section stained with hematoxylin-eosin. Lymph nodes submitted as part of the axillary dissection were totally submitted and evaluated using standard hematoxylin-eosin staining.

Results

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

As shown in Table 2, the overall SLN identification rate was 93.5% (72 of 77). Of the 72 patients in whom an SLN could be identified, 24 (33.3%) had positive SLNs. Within

Table 2
Results of sentinel node biopsy examination

	Number of patients
Total number of patients	77
SLN identified	72 (93.5%)
SLN positive	24 (33.3%)
SLN was only positive lymph node	11 (45.8%)
SLN identification method	
Radiocolloid and blue dye	53 (73.6%)
Radiocolloid only	11 (14.3%)
Blue dye only	8 (11.1%)

Table 3
Comparison of lymph node status of SLNs and non-SLNs

SLN status	Non-SLN status	
	Positive	Negative
Positive	13	11
Negative	3	45

False-negative rate = 11.1%.

11 of these patients (45.8%), the SLN was the only positive node. SLNs were identified by both radiocolloid and blue dye in 53 patients (73.6%), by radiocolloid alone in 11 patients (14.3%), and by blue dye alone in 8 patients (11.1%).

The pathologic status of the SLNs and non SLNs is shown in Table 3.

The SLNs accurately predicted the axillary status in 69 of 72 patients (95.8%). Three patients had a false-negative SLN biopsy examination result, resulting in a false-negative rate of 11.1% (3 of 27). Forty-five patients had pathologically negative SLNs and non-SLNs.

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

In T2 tumors before NAC, the SLN identification rate was 94% (47 of 50), and 2 patients had a false-negative SLN biopsy examination result, resulting in a false-negative rate of 14.3%. In T3 and T4 tumors, results were 92.6% (25 of 27) and 7.7% (2 of 27), respectively (Table 4). For the results of SLN biopsy examination, there was no significant difference between T2 and T3/T4 tumors before NAC.

In the patients with clinically negative lymph nodes (N0) before NAC, the SLN identification rate was 97.6% (41 of 42), and 1 patient had a false-negative SLN biopsy examination result, resulting in a false-negative rate of 10%. In the patients with clinically positive lymph nodes (N1/N2), the results were 88.6% (31 of 35) and 11.2% (4 of 35), respectively (Table 5). The SLN identification rate tended to be higher, although not statistically significantly, among patients who had clinically negative lymph nodes before NAC compared with patients who had positive axillary lymph nodes before NAC.

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

SLN status	Non-SLN status			
	T2 (n = 50)		T3/T4 (n = 27)	
	Positive	Negative	Positive	Negative
Positive	6	6	7	5
Negative	2	33	1	12
Total number of SLNs identified	47 (94%)		25 (92.6%)	
False-negative rate	14.3%		7.7%	

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

SLN status	Non-SLN status			
	N0 (n = 42)		N1/N2 (n = 35)	
	Positive	Negative	Positive	Negative
Positive	3	6	10	5
Negative	1	31	2	14
Total number of SLNs identified	41 (97.6%)		31 (88.6%)	
False-negative rate	10%		11.2%	

For patients with complete tumor response after NAC, the SLN identification rate was 92.0% (37 of 41), with 1 patient having a false-negative SLN biopsy examination result, resulting in a false-negative rate of 12.5%. For patients with a partial tumor response and stable disease, the results were 97.2% (35 of 36) and 10.5% (1 of 36), respectively (Table 6). The SLN identification rate tended to be lower, although not statistically significantly, among patients with complete tumor response after NAC, compared with partial tumor response and patients with stable disease after NAC.

There was no significant difference in the false-negative rate according to tumor classifications before NAC, clinical lymph node status before NAC, and response of the tumor after NAC.

Comments

ALND is the surgical standard for treatment of the axilla in breast cancer patients. The rationales for ALND are exact staging and prognosis, regional control of the axilla, and the possibility of improved survival. The extent of axillary lymph node involvement is one of the most important independent prognostic factors for recurrence and survival. The SLN biopsy procedure is an accurate minimally invasive method for axillary staging in early breast cancers. In many clinics the SLN biopsy examination is replacing standard ALND because of minimal morbidity. However, with the increasing size of tumors, lymphatic mapping becomes

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

SLN status	Non-SLN status			
	CR (n = 41)		PR/SD (n = 36)	
	Positive	Negative	Positive	Negative
Positive	3	4	10	7
Negative	1	29	2	16
Total number of SLNs identified	37 (90.2%)		35 (97.2%)	
False-negative rate	12.5%		10.5%	

Table 7
Studies of SLN biopsy procedures after NAC

	Number of patients	Stage	Tumor size, cm	Number (%) of successful SLN biopsy procedures	False negative (%)
Breslin et al [6], 2000	51	II or III	5.0	43 (84.3)	3 (12)
Miller et al [7], 2002	35	T1-3N0	3.5	30 (86.0)	0 (0)
Stearns et al [8], 2000	34	T3-4, any N	5.0	29 (85.0)	3 (14)
Haid et al [9], 2001	33	T1-3, any N	3.3	29 (88.0)	0 (0)
Julian et al [11], 2002	31	I or II	NS	29 (93.5)	0 (0)
Tafra et al [12], 2001	29	Any T, N0	NS	27 (93.0)	0 (0)
Nason et al [13], 2000	15	T2-4, N0	NS	13 (87.0)	3 (33)
Shimazu et al [14], 2004	47	II or III	4.5	44 (93.6)	4 (12)
Current study	77	T2-4, any N	4.8	72 (93.5)	3 (11)

NS = not specified.

less accurate [15,16]. NAC can reduce tumor size and significantly increase the ability to perform breast-conserving therapy [17,18]. After NAC, axillary downstaging is affected similarly. NAC with anthracycline/cyclophosphamide-containing regimens has been shown to neutralize involved axillary nodes in about 30% of patients [17]. The addition of taxanes to anthracycline/cyclophosphamide-containing regimens has increased the conversion rate to around 40% [19,20]. With the increasing number of patients receiving NAC, the question arises of whether the SLN biopsy examination is an option for these patients. We summarized the studies concerning SLN biopsy examination after NAC in Table 7, but they are inconclusive [6–14]. Breslin et al [6] reported a study of 51 patients who underwent an SLN biopsy examination after NAC and concluded that an SLN biopsy examination is accurate after NAC. They had an identification rate of 84.3% and a false-negative rate of 12.0%. Nason et al [13] reported on a smaller number of patients who received NAC. Their identification rate was 87.0% and their false-negative rate was 33.3%, concluding that the SLN biopsy examination resulted in an unacceptably high false-positive rate. We have to understand that in most of these small series, even 1 or 2 patients with a false-negative SLN node can sway the conclusions in a different direction. We report a study of 77 patients who received NAC, and had an identification rate of 93.5% and a false-negative rate of 11.1%. We conclude in our study that an SLN biopsy examination after NAC is accurate even for large tumors and positive axillary nodal status before NAC without inflammatory breast cancer.

It has been speculated that among patients who have 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 may cause an increase in the false-negative rate for SLN biopsy examination and a decreasing identification rate for SLN biopsy examination. Our hypothesis is that the lymphatic flow around the skin lesion is rich and less influenced by the effect of chemotherapy and tumor size than that in the parenchyma around the tumor. Our results were not significantly influenced by tumor size, tumor response, or nodal status before NAC.

In conclusion, the results of our study suggest that an SLN biopsy procedure after NAC using intradermal injection of radiocolloid is feasible and can predict axillary lymph node status with high accuracy for patients with clinically negative lymph node status after NAC. This procedure could make patients who have had their axillary lymph node status downstaged from positive to negative and patients with large tumors appropriate candidates for an SLN biopsy examination.

Further studies involving a larger number of patients will be required to establish fully the feasibility and accuracy of the SLN biopsy procedure 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 2001;3:104–8.
[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 1999;8:85–91.
[3] Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer—a multicenter validation study. N Engl J Med 1998;339:941–6.
[4] Anderson BO. Sentinel lymphadenectomy in breast cancer: an update on NCCN Clinical Practice Guidelines. J Natl Compr Cancer Network 2003;1(Suppl 1):S64–70.
[5] Reintgen D, Giuliano R, Cox C. Lymphatic mapping and sentinel lymph node biopsy for breast cancer. Cancer J 2002;8(Suppl 1):S15–21.
[6] Breslin TM, Cohen L, Sahin A, et al. Sentinel lymph node biopsy in accurate after neoadjuvant chemotherapy for breast cancer. J Clin Oncol 2000;18:3480–6.
[7] Miller AR, Thompson VE, Yeh IT, et al. Analysis of sentinel lymph node mapping with immediate pathologic review in patients receiving preoperative chemotherapy for breast carcinoma. Ann Surg Oncol 2002;9:243–7.
[8] Stearns V, Ewing CA, Slake R, et al. Sentinel lymphadenectomy after neoadjuvant chemotherapy for breast cancer may reliable represent the axilla except for inflammatory breast cancer. Ann Surg Oncol 2000;9:235–42.