radiation therapy is feasible. Gynecologic oncologists should not miss the only chance for life in these patients.

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REVIEW ARTICLES

Radical hysterectomy for stage IIB cervical cancer: a review

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Abstract. Suprasert P, Srisomboon J, Kasamatsu T. Radical hysterectomy for stage IIB cervical cancer: a review. *Int J Gynecol Cancer* 2005; 15:995–1001.

Patients with stage IIB cervical cancer in some countries in Europe and Asia especially in Japan are usually treated with radical hysterectomy and pelvic lymphadenectomy. Extrauterine diseases, ie, nodal metastases, parametrial invasion, and intraperitoneal spread, can be readily identified. We present the literature review of radical hysterectomy in stage IIB cervical cancer by searching data since 1980 from Medline, and we found that the parametrial involvement of patients in this stage was only 21–55%, the incidence of pelvic node metastases was about 35–45%, and 5-year survival rate was between 55% and 77%. Lymph node metastases and the number of positive nodes were significant prognostic factors of patients in this stage.

KEYWORDS: cervical cancer, radical hysterectomy, stage IIB.

According to the National Comprehensive Cancer Network guideline version 1, 2004, the treatment of choice for stage IIB cervical cancer is concurrent cisplatin-based chemoradiation therapy. However, in some countries in Europe and Asia especially in Japan, these patients are generally treated with radical hysterectomy and pelvic lymphadenectomy using the Okabayashi or Tokyo technique. In 1983, the Japan Society of Obstetrics and Gynecology reported that 62.7% of stage IIB cervical cancer patients were treated with radical hysterectomy[1]. The advantages of this approach are avoiding the long-term complications of radiation therapy and the morbidity of concurrent chemoradiation in patients who did not have high-risk pathologic factors, ie, positive nodes, parametrial invasion, and involved surgical margins. In young patients, ovarian function and vaginal pliability can also be preserved. On the other hand, in case of lymph node metastases, the ovaries may be transposed outside the radiation field. Occult extrauterine diseases such as nodal involvement, parametrial invasion, or intraperitoneal spread can be identified, and removal of bulky positive nodes may improve survival after adjuvant radiation. Additionally, removal of the primary tumor may preclude some radioresistant cervical cancers. The disadvantage of primary surgery for stage IIB cervical cancer is the risk of morbidity associated with receiving combined treatment of chemoradiation following the radical operation.

This article presents the review of primary surgical treatment for stage IIB cervical cancer. We conducted a literature search on Medline using PubMed, from January 1980 to April 2004, using search terms "cervical cancer," "stage IIB," "surgical treatment," and "hysterectomy." Only English articles were included. All

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The pelvic node metastases

There were ten articles reporting the incidence of pelvic node metastases in stage IIB cervical cancer patients undergoing radical hysterectomy as shown in Table 1. The incidence of pelvic node metastases was approximately 35–45.8%[3–12]. Para-aortic node metastases were found in 4.5–7.2% of patients in this stage[11,12]. The most common sites of pelvic node metastases were the hypogastric[9] and the obturator[12]. The incidence of node metastases increased with the size of cervical tumor[5].

In 1984, Inoue and Okumura[3] from the Aichi Cancer Center in Nagoya, Japan, noted that most of the stage IIB cervical cancer patients had only one positive node (38%), while two, three, and more than four positive nodes were detected in 22%, 8%, and 20%, respectively. Of note is that 12% had unresectable positive nodes. Six years later, these authors reported their experience with extension of the study period from 1965–1977 to 1965–1986, with the number of patients increased from 223 to 295[4]. In this later report, they revealed that the incidence of positive pelvic nodes increased from 38% to 43%.

There were two couples of studies from the same institutes, one from the University of Graz, Austria, reported 41–44% incidence of pelvic node metastases in stage IIB cervical cancer[5,6]. The other one from the Hokkaido University of Medicine, Japan, showed such incidence of 37–39%[11,12].

In 2002, Winter *et al.*[13] from the University of Graz, Austria, evaluated the parametrial spread in patients who had negative pelvic nodes. They performed radical hysterectomy in 556 patients with stage IB, IIA, and IIB cervical cancer. Among 351 patients with negative nodes, 35 were in stage IIB. Of these 35 patients, parametrial involvement was identified only in 17%.

Benedetti-Panici *et al.*[14] evaluated the relation between parametrial and pelvic node involvement in patients with stage IB–IIA cervical cancer undergoing radical hysterectomy. The hysterectomy specimens were processed with the giant section technique to obtain a thorough three-dimensional pathologic assessment of the parametrium. Clinically, undetected parametrial involvement was found by pathologic examination in 31%, 63%, and 58% of stage IB1, IB2, and IIA patients, respectively. Metastases to the pelvic nodes were always associated with parametrial invasion.

In conclusion, the incidence of pelvic node metastases in stage IIB cervical cancer is approximately 35–45%. Pelvic node metastases are always associated with parametrial involvement.

The relationship between parametrial involvement and pelvic node metastases

Seven studies reported the relationship between the parametrial involvement and the positive pelvic nodes in stage IB–IIIB cervical cancer patients treated with radical surgery[2–7,9] as shown in Table 2. Of these, only one study from Kyushu University, Japan, demonstrated the relationship of parametrial status and the incidence of positive pelvic nodes in patients with stage IIB cervical cancer. Pelvic node metastases increased three times from 13.3% to 37.8% when the parametrium was involved with the tumor[7]. Invasion of the tumor to the parametrium significantly correlated with the spreading of tumor to the pelvic nodes. Such incidence increased two to six times in patients with positive parametrium.

Table 2. The relationship between parametrial status and pelvic node metastases

Authors	Year	Stage	Parametrium	Pelvic node metastases (%)
Noguchi *et al.*[9]	1987	IB–IIIB	Positive	54.8
			Negative	8.5
Burghardt *et al.*[5]	1987	IB–IIIB	Positive	75.3
			Negative	23.4
Inoue and Okumura[3]	1984	IB, IIA, IIB	Positive	57.9
			Negative	28.6
Inoue and Morita[4]	1990	IB, IIA, IIB	Positive	29.2
			Negative	14.2
Matsuyama *et al.*[2]	1984	IB, IIA, IIB	Positive	42
Giardi *et al.*[6]	1989	IB–IIB	Positive	81
			Negative	26
Kamura *et al.*[7]	1993	IIB	Positive	37.8
			Negative	13.3

Matsuyama *et al.*[2] reported the 42% incidence of pelvic node metastases when the parametrium was involved in patients with stage IB–IIIB cervical cancer who were treated with radical hysterectomy. However, such incidence in cases of negative parametrium was not mentioned. Interestingly, two series, one from Austria, another from Japan, reported the use of surgical treatment for stage IIIB cervical cancer[5,9]. From these studies, it can be concluded that parametrial involvement is strongly associated with pelvic node metastases.

Adjuvant treatment after surgery

After radical operation for stage IIB cervical cancer patients, adjuvant radiations are usually administered if any high-risk pathologic factors, ie, positive pelvic nodes, parametrial invasion, and involved surgical margins, are identified[2–5]. Some authors also gave adjuvant radiation to patients who had deep cervical stromal invasion[2,7,10] or prominent lymphovascular space invasion (LVSI)[2,12]. With various criteria for postoperative radiation therapy, the percentage of stage IIB cervical cancer patients who received adjuvant treatment in one study was surprisingly high at 72%[7]. Recently, the Japanese Patterns of Care Study Working Group[15] has conducted an extramural survey of 73 institutions in Japan on the postoperative radiation between September 1998 and March 2001. The study revealed that only 33% of stage IIB cervical cancer patients received adjuvant radiation. The summary of the indications for adjuvant radiation after surgery for stage IIB cervical cancer is shown in Table 3.

Currently, concurrent cisplatin-based chemoradiation is recommended in patients who need adjuvant radiation after radical surgery for early-stage cervical cancer[16,17]. However, Kawagoe *et al.*[8] gave chemotherapy alone to patients who had positive surgical margins or lymph node involvement.

Various types of adjuvant treatment have been used for cervical cancer patients who have high-risk pathologic factors after the operation. The Austrian Gynecologic Oncology Group has conducted a prospective, randomized, multicenter study to compare the values of adjuvant radiation, adjuvant chemotherapy, and expectant treatment in IB, IIA, and IIB cervical cancer patients who had high-risk factors identified after radical hysterectomy. Adjuvant chemotherapy or radiation did not improve the survival or reduce the recurrence after the operation when compared with observation alone[18].

In conclusion, most authors advised radiation in patients who had high-risk pathologic factors after the operation. The benefit of adjuvant treatment in these patients is inconclusive and needs further study in a prospective randomized fashion.

Table 3. Indications for adjuvant radiotherapy

Authors	PMI	Positive LN	Positive margins	Others
Okada *et al.*[10]	+	+	+	DSI
Kawagoe *et al.*[8]a	−	+	+	—
Takeda *et al.*[12]	+	+	−	LVSI, ovarian metastasis
Inoue and Morita[4]	+	+	−	—
Matsuyama *et al.*[2]	+	+	+	LVSI, DSI
Kamura *et al.*[7]	+	+	−	DSI
Trattner *et al.*[19]	+	+	+	LVSI

PMI, parametrial involvement; LN, lymph node; DSI, deep stromal invasion; LVSI, lymph vascular space invasion; +, adjuvant radiation; −, no adjuvant radiation.
[a]Adjuvant chemotherapy.

The prognostic factors

There were nine studies using multivariate analysis to determine the significance of various prognostic factors after radical hysterectomy for cervical cancer as shown in Table 4. Kamura et al[7] studied only stage IIB cervical cancer, while other authors also included stage IB, IIA, or even IIIB. Lymph node metastases and the number of positive nodes were significant prognostic factors in all studies[2,4,5,7,8,10–12,19], while parametrial involvement affected the patient survival in only four studies[2,4,10,12]. The clinical stage of cervical cancer influenced treatment outcomes in two studies[8,19]. Kawagoe *et al.*[8] noted that the tumor size was also an important prognostic factor, while LVSI and deep stromal invasion were found to affect patient survival in the series of Sakuragi *et al.*[11].

Takeda *et al.*[12] had pathologically stratified the cervical cancer patients after treatment with radical operation into three groups, ie, low-risk group, intermediate-risk group, and high-risk group. The low-risk group consisted of patients with tumor confined to the uterus and without LVSI. The intermediate-risk group included patients with tumor confined to the uterus with associated parametrial invasion or pelvic node metastasis. The high-risk group comprised patients with pure adenocarcinoma with associated parametrial involvement or pelvic node metastases and patients with common iliac or para-aortic node metastases. The estimated 5-year survival rates of these three groups were 100%, 85.5%, and 25%, respectively.

Aoki *et al.*[20] studied the prognostic factors in 59 cervical cancer patients with positive nodes after

Table 4. The significant prognostic factors

Authors	Year	Stage	Total number of patients	Number of stage IIB patients	The prognostic factor
Okada *et al.*[10]	1998	IB–IIB	104	30	+ PM, + LN
Burghardt *et al.*[5]	1987	IB–IIIB	800	195	Number of positive nodes
Inoue and Morita[4]	1990	IB, IIA, IIB	875	295	Number of positive nodes, + PM
Kawagoe *et al.*[8]	1999	IB, IIA, IIB	128	24	Stage, tumor size, + LN
Matsuyama *et al.*[2]	1984	IB, IIA, IIB	255	99	Number of positive nodes, + PM
Takeda *et al.*[12]	2002	IB, IIA, IIB	187	88	+ LN, + PM, LVSI, adenocarcinoma
Kamura *et al.*[7]	1993	IIB	107	107	Number of positive nodes
Trattner *et al.*[19]	2001	IB, IIA, IIB	115	35	Stage, + LN
Sakuragi *et al.*[11]	1999	IB, IIA, IIB	208	97	LVSI, DSI, + LN (para-aortic nodes, bilateral pelvic nodes, common iliac nodes)

PM, parametrium; LN, lymph node; LVSI, lymph vascular space invasion; DSI, deep stromal invasion; +, positive.

radical hysterectomy followed by adjuvant pelvic radiation. Of these patients, 37 were in stage IIB cervical cancer. The authors noted that both the number of positive nodes (≥2) and the parametrial involvement were significantly associated with decreased disease-specific survival. The 5-year recurrence rate in patients with both prognostic factors was as high as 70%, while no recurrence was found in patients who had one positive node and no parametrial invasion.

Among the patients with stage IIB cervical cancer who had negative nodes, tumor size and LVSI were the significant prognostic factors by multivariate analysis in the study of Comerci *et al.*[21]. Winter *et al.*[13] showed that parametrial involvement was of no prognostic significance in 149 stage IIB cervical cancer patients who had negative nodes.

It can be concluded that the number of positive nodes is a strongly significant prognostic factor, while the influence of parametrial invasion on patient survival is still controversial in patients with stage IIB cervical cancer.

The outcomes

There were four studies that reported the overall survival of stage IIB cervical cancer patients treated with radical hysterectomy as shown in Table 5. Matsuyama *et al.*[2] found that among 99 patients with stage IIB cervical cancer, 29 died or had disease recurrence. Three patients died of radiation complications, and one died of intercurrent disease. The overall 5-year survival rate was approximately 71%. Burghardt *et al.*[5] reported a 5-year survival rate of 77% in 191 patients with stage IIB cervical cancer treated with radical surgery, higher than that of 63% in the series of Trattner *et al.*[19]. The outcome of stage IIB patients was worse in the study of Aoki *et al.*[20], which revealed a 5-year survival rate of 55% in 37 stage IIB cervical patients who had positive nodes.

Table 5. The 5-year survival rate

Authors	Year	5-year survival rate (%)
Aoki *et al.*[20]	2000	55.2
Trattner *et al.*[19]	2001	62.9
Matsuyama *et al.*[2]	1984	70.7
Burghardt *et al.*[5]	1987	76.9

The nodal status and the number of positive nodes play an important role on the survival outcome of patients with cervical cancer. In the series of Noguchi *et al.*[9], the survival of patients decreased with the increasing number of positive nodes. The 5-year survival rates of patients who had negative nodes was 83%, while those of the patients who had 1, 2–3, and ≥4 positive nodes were 64.4%, 43.1%, and 30%, respectively. Girardi *et al.*[6] studied 219 patients with stage IIB cervical cancer treated with radical hysterectomy. The 5-year survival rate in cases of negative parametrial nodes was high at 81% and dropped to 54% when the parametrial nodes were positive. In the report of Inoue and Morita[4], which included 223 patients with stage IIB cervical cancer, the 5-year survival rate of patients with positive nodes (57%) was significantly lower than that of patients with negative nodes (91%). The 5-year survival rate decreased to 38.5% when the number of positive nodes was ≥4. In the study of Okada *et al.*[10], the outcome of patients with parametrial extension was not different from those with positive nodes. The 5-year survival rates of both groups were 76.6% and 76.3%, respectively, while that of patients with only deep stromal invasion was still high at 89.3%.

In conclusion, the 5-year survival rate of stage IIB cervical cancer patients treated with radical

hysterectomy ranged between 55% and 77%. The most important prognostic factor is the number of positive nodes.

The complications

There were few studies reporting the complications of surgical treatment in patients with stage IIB cervical cancer. The complications increased when the patients received adjuvant radiation after radical hysterectomy compared with surgery alone[2,22]. The complications also increased with radiation dosage. Bowel obstruction, fistula, and rectal hemorrhage occurred in 8.5% and 13.6% of patients receiving radiation of 5000 cGy and 6000 cGy, respectively[2].

Conclusion

Patients with stage IIB cervical cancer may be treated with radical hysterectomy and pelvic lymphadenectomy. Approximately 50–80% of patients are overstaged due to difficulty in differentiation between the parametrial involvement and the inflammatory change of the paracervical tissue. Parametrial invasion significantly correlated with pelvic node metastases. Adjuvant radiation is recommended in patients who have high-risk pathologic factors, ie, positive nodes, parametrial involvement, and involved surgical margins. The strongest prognostic factor is the number of positive nodes. The complications appear to be higher in patients who receive both surgery and adjuvant radiation.

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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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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.

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D. センチネルリンパ節生検法

Halsted 法に始まる近代的な乳癌の外科手術は，胸筋切除から胸筋温存へ，乳房全切除から乳房温存へと変遷してきた．しかし，腋窩リンパ節郭清は現在も標準的外科治療として行われている[1]．1990 年代前半から，乳癌におけるセンチネルリンパ節生検は欧米を中心にその同定法と診断法について検証が進められてきた．センチネルリンパ節は腫瘍からのリンパ流を直接受けるリンパ節と定義される（図 4-30）．センチネルリンパ節に組織学的に転移を認めなければ，腋窩リンパ節郭清を行わずにセンチネルリンパ節生検のみの腋窩リンパ節非郭清が可能となるかもしれない．今日でも腋窩リンパ節郭清は乳癌の標準的な外科治療に位置

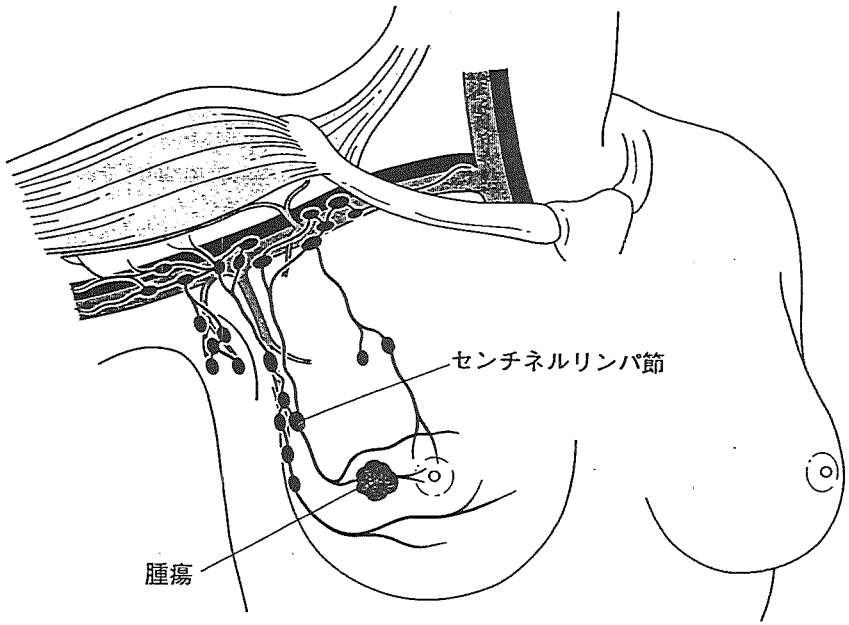

図 4-30　腫瘍からのリンパ流を受けるセンチネルリンパ節

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

乳癌におけるセンチネルリンパ節生検は，1993 年に Krag が放射性薬剤を用いて[2]，1994 年に Giuliano が色素法を用いて報告して以来[3]，この仮説の正当性・信頼性を検証する臨床研究が進められてきた．センチネルリンパ節生検における feasibility study の代表的な結果を示す（表 4-6）[4-10]．90%以上の同定率と 95%以上の正診率，さらに腋窩リンパ節転移陽性症例の約半数がセンチネルリンパ節転移のみであるという事実から，この仮説は実証されたものと考えられ，本邦においても急速に普及してきた．現在，臨床的リンパ節転移陰性乳癌を対象として腋窩リンパ節郭清とセンチネルリンパ節生検とを比較する第Ⅲ相臨床比較試験（ACOSOG-Z0010, -Z0011, NSABP-B32, EORTC10981）が実施されておりその結果が待たれる．

1 実施基準

センチネルリンパ節生検では，放射性製剤や色素を用いてセンチネルリンパ節を同定する．センチネルリンパ節生検で用いられる色素によるアレルギー反応は数%発生することが報告されている[11]．従って色素の投与は充分に注意して行うべきである．放射性製剤による患者の被曝線量は，現行の核医学検査をはるかに下回る線量であるため，これの投与

表 4-6　センチネルリンパ節生検の feasibility study

報告者	年	方法	症例数	同定率	正診率	敏感度	センチネルのみリンパ節転移
Giuliano[4]	1997	IB	107	93%	100%	100%	67%　(28/42)
Galimberti[5]	1998	CA	241	99%	98%	95%	36%　(39/109)
Borgstein[6]	1998	CA	130	94%	99%	98%	59%　(26/44)
Cox[7]	1998	S+IB	466	94%	100%	99%	—
Krag[8]	1998	S	443	93%	97%	89%	53%　(60/114)
Veronesi[9]	1999	CA	376	99%	96%	93%	44%　(73/168)
Hill[10]	1999	S+IB	492	93%	95%	89%	61%　(69/114)
Imoto	1999	RI+IC	56	96%	98%	96%	48%　(13/27)

CA: technetium-99m (^{99m}Tc)-colloidal albumin
S: ^{99m}Tc-sulfur colloid
RI: ^{99m}Tc-human serum albumin and ^{99m}Tc-tin colloid
IB: isosulfan blue
IC: indigocarmine

に伴う有害事象は極めて稀であると考える．まずセンチネルリンパ節生検＋腋窩リンパ節生検すなわち feasibility study を施行することは，標準治療の範囲内であり患者の不利益にはならない．推奨される feasibility study の成績は，少なくとも 30〜50 例程度の症例に実施し，同定率 95% 以上，偽陰性率 5% 以下を目標に腋窩郭清を省略する observation study に進むのが妥当とされている．

センチネルリンパ節生検を行う場合には，この方法について特別なインフォームドコンセントが必要である．内容としては，①試験的な段階にあるリンパ節転移診断法であること，②実施方法，③発生しうる有害事象とその頻度，④患者の利益と不利益，⑤実施に関する費用は研究者負担となること，⑥observation study ならば施設あるいは個人での成績，など説明して被験者の同意を得る必要がある．現時点では，ベネフィットばかり強調して標準治療のごとく説明して同意を得ることは望ましくないと考える．

2 適応基準

①臨床的リンパ節転移陰性乳癌である．
②インフォームドコンセントが得られている．
③色素にアレルギー反応の既往がない．
④腫瘍径に関しての基準はないが，早期乳癌（腫瘍径 2cm 以下）から開始して適応を拡げていくのが安全であると考える．
⑤放射線照射に既往のある乳房やステージⅢB 乳癌，炎症性乳癌は適応にすべきではない．

3 方法

1）準備

センチネルリンパ節生検を始めるにあたって，各診療部門の充分な理解と連携が求められる．センチネルリンパ節生検は，施設内倫理審査委員会あるいはこれに準ずる委員会で承認を経てから実施されるべきである．現時点ではセンチネルリンパ節生検は健康保険の適応ではないので，実施に関する費用は研究者負担であり診療請求することはできない．

2）試薬（色素）

①indigocarmine
②indocyanine green
③sulfan blue（patent blue violet）
④isosulfan blue

3）試薬（放射性製剤）

①technetium-99m tin colloid
②technetium-99m colloidal rhenium sulphide
③technetium-99m human serum albumin

④technetium-99m phytate

4）投与部位

①peritumoral injection

②subdermal injection

③intradermal injection

④subareolar injection

投与部位は推奨されるものはないので，症例によって適宜選択するのが望ましい．

5）リンフォシンチグラフィ

センチネルリンパ節を術前に視覚的に捉える方法として，リンフォシンチグラフィは有用である．著者の手技は，手術前日に核医学検査室内にて technetium-99m phytate を腫瘍直上の皮内と乳輪下に 50〜80 MBq を 1，2 カ所に分けて投与する．皮内注は組織圧が高まるため，また乳輪下はリンパ流が豊富なためマッサージは不要である．投与後 30 分間の dynamic early image ならびに 6 時間後の static delayed image を撮影する．著者は斜位像のみ撮影しているが，通常，投与部位からリンパ管流を受けた 1 個から数個のセンチネルリンパ節が腋窩に観察される（図 4-31）．10%弱の症例に穿通枝を介する胸骨傍にもセンチネルリンパ節が観察されることもある（図 4-32）．著者はこのような症例に関しては，現在の胸骨傍リンパ節転移の位置付けから判断して積極的には胸骨傍リンパ節生検は実施していない．図 4-31，32 に紹介した症例は，局所進行例であったため同日のリンフォシンチグラフィの施行前に骨シンチを実施しているためセンチネルリンパ節の解剖学的局在を把握するのが容易である．通常の症例（骨シンチを施行していない）では，テクネシウムをわずかに吸った注射器を用い被験者のボディラインをなぞる．注射器から発するγ線の軌跡をシンチカメラがとらえてセンチネル

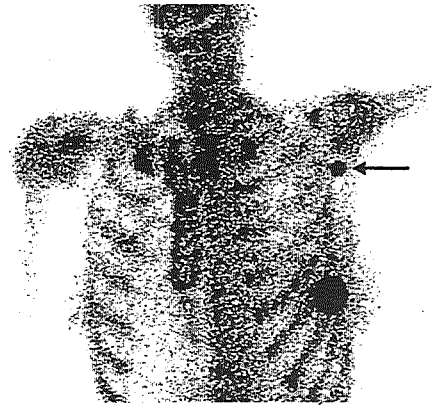

図 4-31　リンフォシンチグラフィ（1）
同日に骨シンチを施行．腋窩にセンチネルリンパ節（矢印）が観察される．

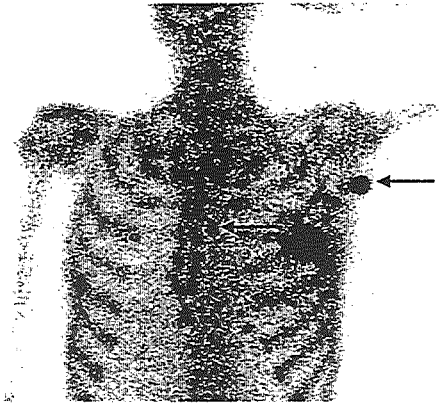

図 4-32　リンフォシンチグラフィ（2）
同日に骨シンチを施行．腋窩と胸骨傍領域にセンチネルリンパ節が観察される．

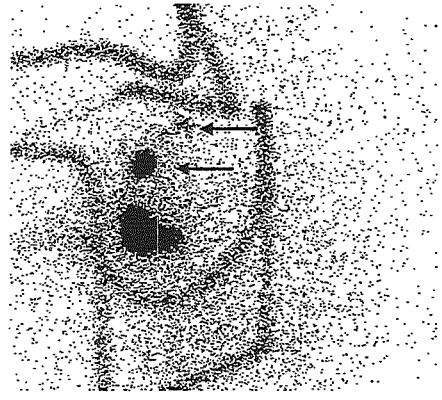

図 4-33　リンフォシンチグラフィ（3）
体輪郭のイメージを重ね合わせて再現している．腋窩にセンチネルリンパ節（矢印）が観察される．

リンパ節と重ね合わされることにより，センチネルリンパ節の解剖学的局在を容易にイメージできる（図 4-33）．

また，この用意した注射器をシンチカメラのモニター画面下で hot spot であるセンチネルリンパ節に重ね合わせて，皮膚にその局在を示す

マーキングを実施することも可能である．このようにリンフォシンチグラフィを施行することによりセンチネルリンパ節の解剖学的位置が推定できる．

6）色素法

全身麻酔の導入後，青い色素であるパテントブルー 2～5ml を乳輪下あるいは腫瘍周囲に注射して同部位を数十秒間よくマッサージする（図 4-34，35）．15～20 分後腋窩のやや尾側に小切開を加える（図 4-36）．小血管からの出血は視野を不良にして，センチネルリンパ節の同定を困難にするので，充分に止血操作をしながら剥離をすすめていく．青く染まったリンパ管を発見し（図 4-37），これを追って流入する青く染まったリンパ節すなわちセンチネルリンパ節に到達し摘出する（図 4-38，39）．色素法は，30～50 例の手技の経験と学習効果を必要とするが，最終的に 90%近い同定率での実施が可能となる．不成功の理由としては，肥満，腋窩の脂肪組織が厚くリンパ管やリンパ節がみつけにくい場合や剥離の際にリンパ管をすでに切断してしまった場合などが考えられる．

7）ガンマプローブ法

ガンマプローブ法は，放射性製剤が移行したセンチネルリンパ節からのγ線を高感度γ線検出装置（図 4-40）を用いて同定する方法である．ガンマプローブの先端部を用いて，最もγ線が検出される部位を同定してマーキングを施行する（図 4-41）．同部位を目指して皮膚を切開し，radioactivity を確認しながら腋窩脂肪組織の剥離を進め，目的とするセンチネルリンパ節を同定し摘出する（図 4-42）．radioactivity の高いリンパ節であれば，色素法よりも容易で初心者でも容易にセンチネルリンパ節を検出できる．また，胸骨傍リンパ節やレベルⅠ以外のリンパ節がセンチネルリンパ節である場合は，色素法よりガンマプローブ法が同定しやすい．同定されたリンパ節の radioactivity を *in vivo* と *ex vivo* で測定する．測

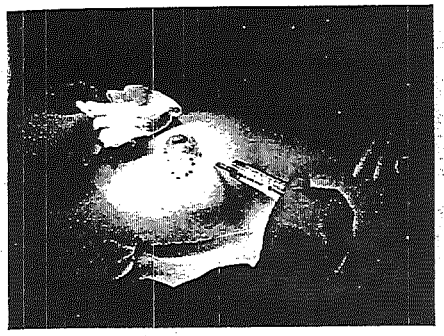

図 4-34　色素法（1）
加刀前に乳輪下に色素 3ml を注射する．

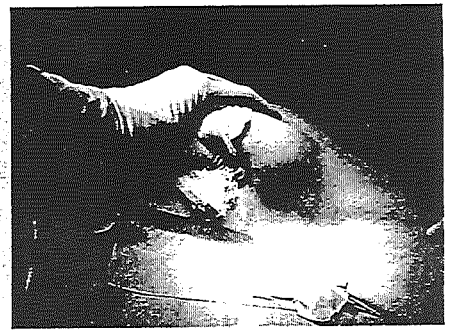

図 4-35　色素法（2）
腋窩方向に向かってよくマッサージする．

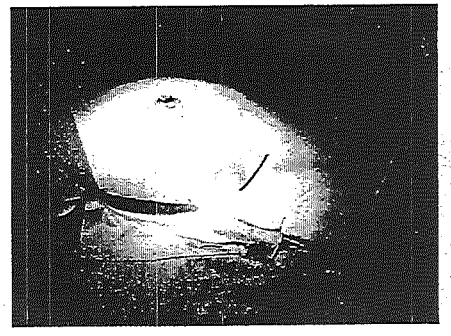

図 4-36　色素法（3）
腋窩のやや尾側に皮切を加える．

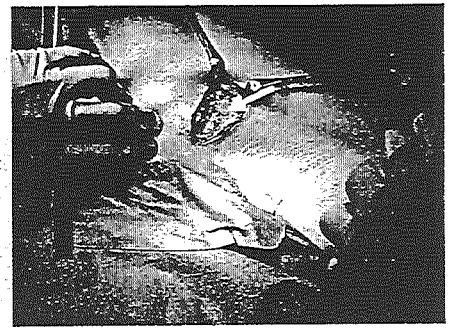

図 4-37　色素法（4）
青く染まったリンパ管をみつけ出す．

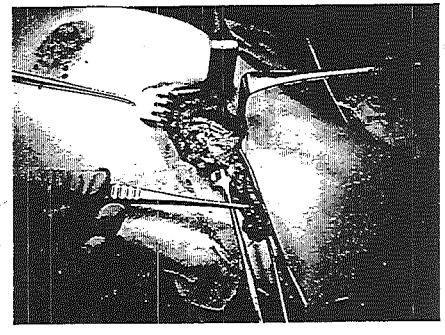

図 4-38　色素法（5）
青く染まったリンパ管を追いかけて青く染まったセンチネルリンパ節を同定し摘出する．

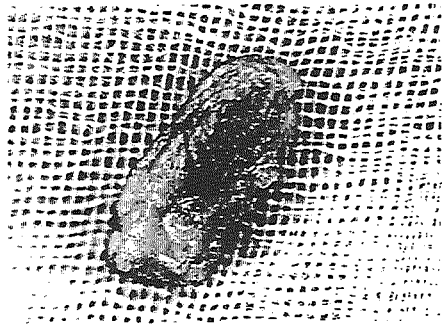

図 4-39　センチネルリンパ節
青く染まったリンパ節．センチネルリンパ節として迅速病理診断にて検査する．

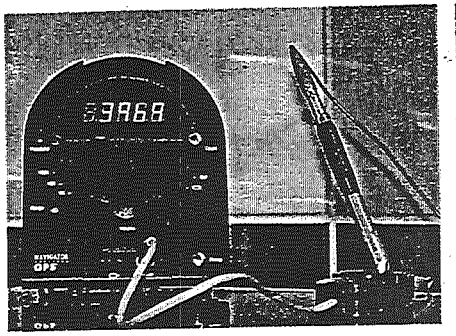

図 4-40　ガンマプローブ法（1）
当院にて使用している高感度γ線検出装置.

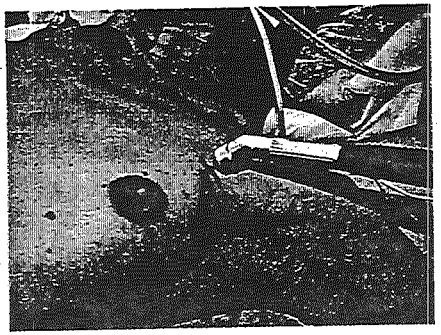

図 4-41　ガンマプローブ法（2）
ガンマプローブを用いて加刀前にマーキングしておく.

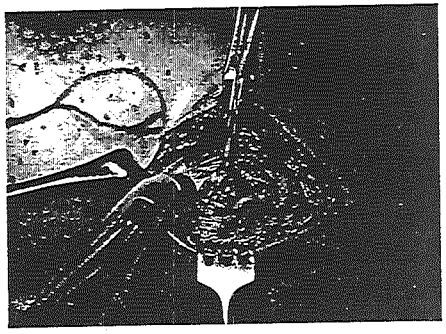

図 4-42　併用法
ガンマプローブと色素を用いて，目的とするセンチネルリンパ節を検出する.

定値は，background（周囲組織）の数十倍～数百倍である.

著者は，術中に先に腫瘍の生検を施行する症例に対しては，色素法が困難となるためガンマプローブ法単独でセンチネルリンパ節生検を施行している.

8）併用法（図 4-42）

上記の色素法とガンマプローブ法を組み合わせて実施する方法である．著者はセンチネルリンパ節生検の精度向上のため色素とガンマプローブの併用法を通常行っている．視覚でも確認ができること，時間の

制約が比較的ないこと，radioactivity で確認しながら容易に目的とするリンパ節を同定できること，レベルⅠ以外のリンパ節にセンチネルリンパ節が存在する場合でも同定可能であることなどが併用法で実施している理由である．この方法によりセンチネルリンパ節をより確実に同定することが可能となる.

4 センチネルリンパ節の病理検査

センチネルリンパ節生検によって，摘出された 1 個から数個のセンチネルリンパ節を術中に迅速病理診断をするいくつかの試みが行われている．基本は凍結切片作成による組織診断で，多数切片の作成や抗サイトケラチン抗体などによる免疫組織染色による転移診断や捺印細胞診断などによるセンチネルリンパ節転移診断の向上に関する工夫が報告されている[12-15]．ただし，パラフィン固定後の HE（hematoxylin-eosin）染色による詳細な永久組織診断が基本であり，迅速にて転移陰性とされたセンチネルリンパ節内に転移巣が発見される場合が 10%程度ある．施設毎の病理部門においてセンチネルリンパ節に関する精度の高い検査法を確立することが重要である．また，最近注目されている微小リンパ節転移例（0.2～2mm の転移巣）の取り扱いに関しては，腋窩郭清や放射線治療を追加すべきか結論は得られていない．いずれにしても，永久組織診断で転移ありと判断された場合は，腋窩郭清を追加する方向でインフォームドコンセントをとるべきであると考える.

乳癌診療におけるセンチネルリンパ節生検は，外科手術の個別化・低侵襲化という流れの中で，確固たる地位を築きつつある．腫瘍外科医にとっては，色素法にせよ，ガンマプローブ法にせよ，併用法にせよ，手技の習得は必須である．ただし，一歩間違えるとただのいい加減な治療にもなり得る手法なので，各自が充分な経験と倫理性をもって，患者の充分な理解と同意の後に実施してほしい.

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【木下貴之】

JCLS 498-06036

5 薬物療法

A. 術前化学内分泌療法

ごく初期の段階をのぞいて，乳癌は全身病であるとの認識に基づき，局所進行癌だけでなく，より早期の乳癌に対しても術前化学（内分泌）療法が行われつつある．特に術前化学療法については多くの研究成果が報告されており，いまや術前化学療法は腫瘍径の大きな乳癌や，リンパ節転移陽性乳癌に対して標準的な治療と考えられるにいたっている．しかし，日常臨床の場において，どこまでが標準であり，何が研究なのかが混同されがちである．どのような対象に何を目的で行うかを明確にしておくことが大切である．術前内分泌療法もまた近年増加している．術前内分泌療法はまだ研究段階の治療と考えられるが，いくつかの有望な成績が示されつつある．

1 術前化学療法

局所進行乳癌（Stage ⅢB）や炎症性乳癌に対する集学的治療の一環と

JCLS 498-06036

Ipsilateral Breast Tumor Recurrence (IBTR) after Breast-Conserving Treatment for Early Breast Cancer

Risk Factors and Impact on Distant Metastases

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BACKGROUND. The clinical features of ipsilateral breast tumor recurrence (IBTR) after breast conserving therapy (BCT) for early stage breast cancer were analyzed from long-term follow-up of BCT in Japan. The purpose of this study was to clarify risk factors of IBTR and the impact of IBTR on development of distant metastases in this ethnic group.

METHODS. Patients (N = 1901)with unilateral breast cancer ≤ 3 cm in diameter who underwent BCT at 18 Japanese major breast cancer treatment institutes from 1986 to 1993 were registered in this study. Survival rates, the incidences of IBTR and distant metastases, and annual rates of IBTR and distant metastases after primary operation were calculated by the Kaplan–Meier method. A Cox proportional hazards model was used to estimate the risks of IBTR and distant metastases. A Cox model was also used to estimate the risks of distant metastases after IBTR in the group of IBTR.

RESULTS. At a median follow-up time of 107 months, the 10-year overall and disease-free survival rates were 83.9% and 77.8%, respectively. The 10-year cumulative rates of IBTR were 8.5% in the patients with postoperative irradiation and 17.2% in the patients without irradiation. The 10-year cumulative distant metastasis rate was 10.9%. On multivariate analysis, young age, positive surgical margin, and omission of radiation therapy were significant predictors of IBTR. In addition, IBTR significantly correlated with subsequent distant metastases (hazard ratio, 3.93; 95% confidence interval, 2.676–5.771; $P < 0.0001$). Among patients who

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