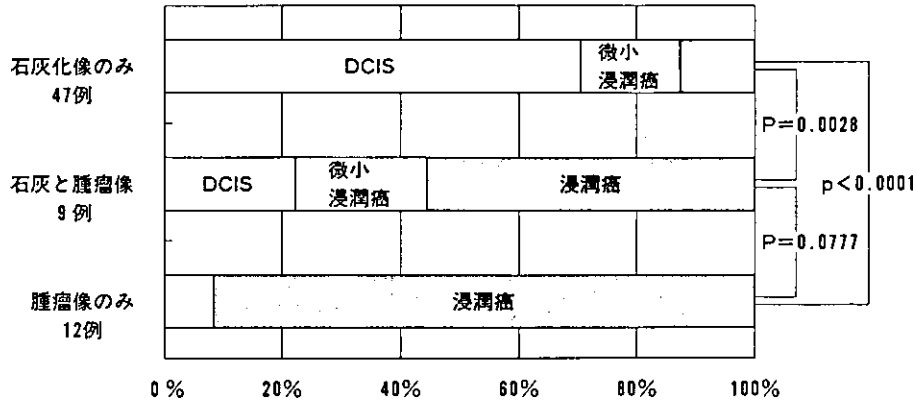

図1　マンモグラフィ所見と組織所見との比較

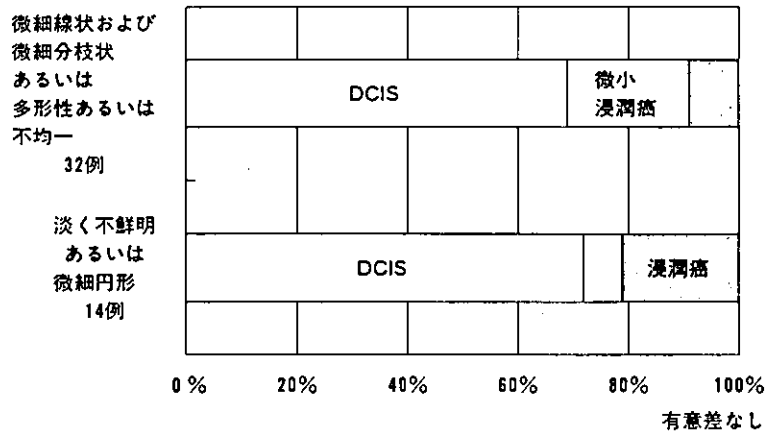

図2　石灰化像のみの症例での石灰の形態と組織像の比較

石灰と腫瘤の症例と腫瘤像のみの症例との間には有意差は認められないものの，腫瘤のみの症例に浸潤癌であることが多い傾向を示した（p＝0.0777）（図1）．

さらに，石灰化像のみの症例で，浸潤癌である可能性が高いことを示す所見の有無の検討を行った．石灰の形を分類すると石灰化像のみの47例中10例が微細線状および微細分枝状，22例が多形性あるいは不均一，3例が淡く不明瞭，11例が微細円形，1例がその他であった．その他の1例を除くそれぞれの石灰の形態別での組織分類は，微細線状および微細分枝状でDCIS7例，微小浸潤癌2例，浸潤癌1例，多形性あるいは不均一ではDCIS 15例，微小浸潤癌5例，浸潤癌2例，淡く不鮮明でDCIS 1例，微小浸潤癌1例，浸潤癌1例，微細円形でDCIS 9例，微小浸潤癌0，浸潤癌2例であった．これら各群間での組織像の有意差は認められなかった．さらに，微小浸潤癌と浸潤癌を1つの組織型としてまとめて検討しても，微細線状および微細分枝状と多形性あるいは不均一を1つのグループとし，また淡く不鮮明と微細円形とを1つのグループとして比較しても有意差を認めなかった（図2）．

石灰化像のみを示す症例で石灰化の範囲と浸潤の有無で検討してみた．石灰化の範囲が1cm以下と1.1cm以上，2cm以下と2.1cm以上，3cm以下と3.1cm以上で検討したが，いずれにおいても組織型での有意差は得られなかった（図3）．

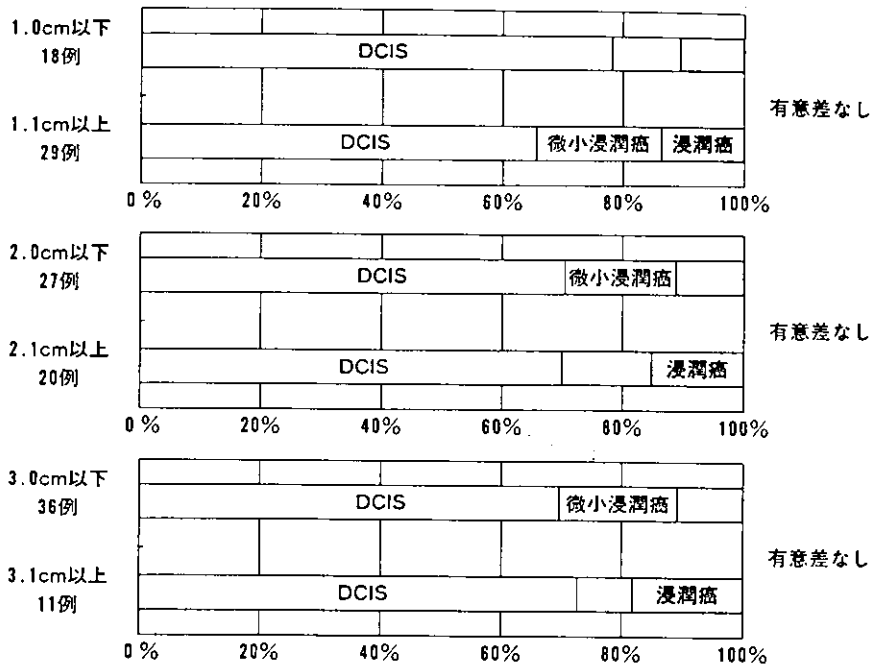

図3　石灰化像のみの症例での石灰の範囲と組織像との比較

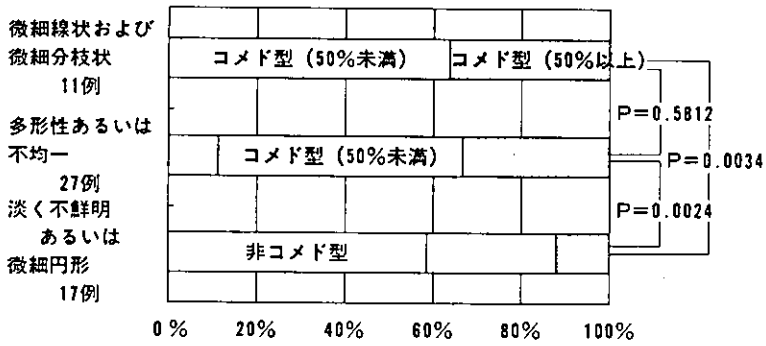

図4　石灰の形態と乳管内癌の亜分類との比較

次に石灰の形態別での乳管内癌の組織像を検討した．ここでは石灰像のみの症例と石灰と腫瘤像の両方を示す症例を含めたが，形態でその他とした1例は除外した．微細線状および微細分枝状では非コメド型0，コメド型（50%未満）7例，コメド型（50%以上）4例，多形性あるいは不均一では非コメド型3例，コメド型（50%未満）15例，コメド型（50%以上）9例，淡く不鮮明では非コメド型2例，コメド型（50%未満）2例，コメド型（50%以上）0，微細円形で非コメド型8例，コメド型（50%未満）3例，コメド型（50%以上）2例であった．ここでは淡く不鮮明の症例が少なかったため微細円形の症例と一緒に扱い有意差検定を行った．その結果，微細円形ならびに淡く不鮮明の症例と微細線状および微細分枝状の症例（$p=0.0034$）および多形性あるいは不均一の症例（$p=0.0024$）の間に統計学的有意差を認めた．一方，微細線状および微細分枝状の症例と多形性あるいは不均一の症例の間には差を認めなかった（$p=0.5812$）（図4）．

石灰化像を示した症例（石灰と腫瘤像の症例も含む）でのマンモグラフィ上の石灰の範囲と非浸

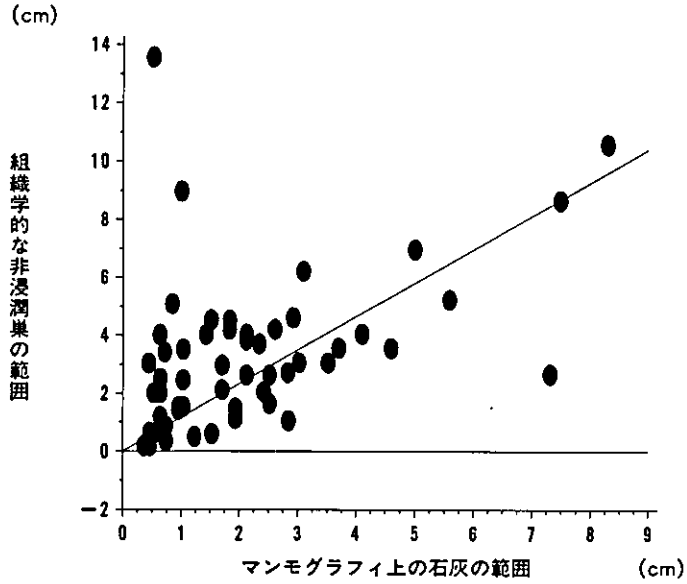

図5　マンモグラフィの石灰と組織学的非浸潤巣の範囲の比較

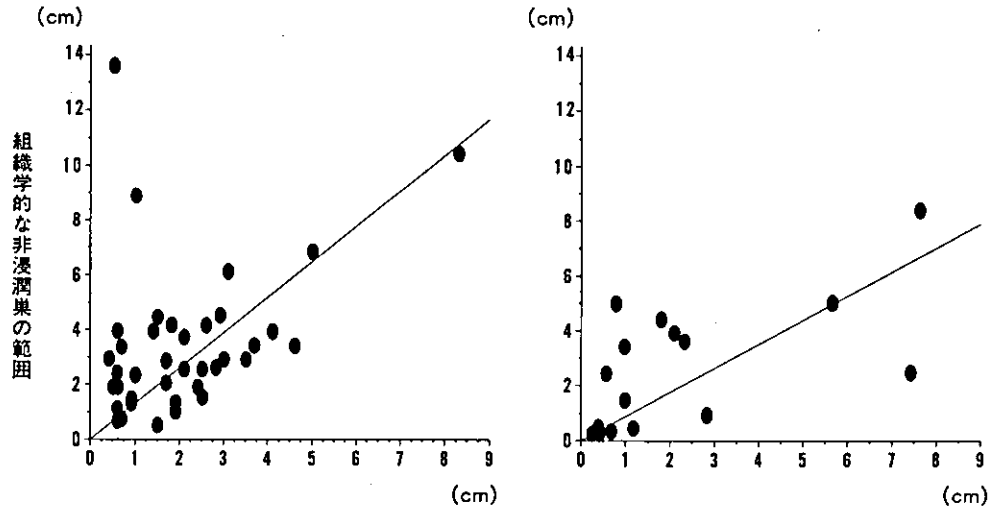

図6　マンモグラフィの石灰と組織学的非浸潤巣の範囲の比較

潤巣の範囲との相関を検討した．両者の関連が原点を通る直線で示される場合，相関係数0.768と相関は比較的良く，その傾き（回帰係数）は1.145とマンモグラフィ上の石灰の範囲よりも実際は非浸潤巣の範囲の方がやや広いことが多いことが示された（図5）．

この関係を石灰の形態別に微細線状および微細分枝状ならびに多形性あるいは不均一の症例と淡く不鮮明ならびに微細円形の症例の2群に分けて，それぞれに上記と同様の解析をすると前者で相関係数0.766，回帰係数1.298，後者で相関係数0.820，回帰係数0.912と前者の方でマンモグラフィでの石灰の範囲よりも非浸潤巣の範囲がより広い傾向が示された（図6）．

考　察

欧米でのマンモグラフィを用いた乳癌検診のトライアルのデータに基づき，日本でも乳癌検診にマンモグラフィを用いる自治体が増加している．

その結果として，触知不能なマンモグラフィ上の異常が多数見つかってきている．触知不能病変から診断された乳癌は初期である可能性がきわめて高いため，患者としては乳房温存療法を希望する場合が多くなることが予測される．さらに，マンモグラフィ発見の非触知乳癌の多くが，非浸潤性乳管癌であるため，腋窩に対する処置をどうするかも問題となる．

まず，腋窩リンパ節転移について，文献的にはDCISの場合，腋窩リンパ節転移を認める率は0～2％とされている[3~5]．最近のDCIS症例のセンチネルリンパ節の連続切片の検索や免疫染色の結果でDCISでも転移を6～12％に認めるとの報告はあるが[6,7]，現時点での微小転移の臨床的意義は確立されていないので，とりあえずDCIS症例にはリンパ節郭清ならびにセンチネルリンパ節生検は不要と思われる．微小浸潤癌のリンパ節転移率はそれぞれの文献で微小浸潤癌の定義が微妙に異なるため判断が難しいが，0～10％とされている[8,9]．今回の微小浸潤癌症例10例中郭清を受けていた6例で，組織学的にリンパ節転移を認めたものはなかった．もし，微小浸潤癌であることが術前にわかれば，リンパ節郭清ならびにセンチネルリンパ節生検の重要性は低いといえる．一方，今回2mm以上の浸潤を認めた22例中14例が郭清を受けていたが，このうち2例（14.3％）にリンパ節転移を認めている．その転移リンパ節個数はいずれの症例でも1個ずつで，その原発巣の浸潤部の大きさはそれぞれ0.8cm，0.7cmと小さなものであった．浸潤癌に対しては，それが触知できない症例であっても，リンパ節郭清あるいはセンチネルリンパ節生検の意義は大きいと思われる．

術前に病変を外科的生検する場合，組織所見が判明しているので，上記のことを参考に腋窩の処置を考慮すればよいが，細胞診で診断する場合は癌であることが判明しても全体の組織像はわからない．組織が採れてくる針生検の診断の場合も手術材料での最終診断と異なる場合もまれでなく起こる[10]．さらに，採取組織量の多いマンモトーム生検での生検診断も必ずしも最終病理診断と一致するとは限らない[11]．そこで，病変が癌であった場合，マンモグラフィの所見から組織所見の予測がどこまで可能かを調べる目的で今回の検討を行った．

腫瘤像のみの場合，そのほとんどは浸潤癌であり，石灰化に腫瘤像を伴う場合も浸潤癌であることが多い．したがって，これらの所見，特に腫瘤像のみを示す場合はそれに対して，リンパ節郭清あるいはセンチネルリンパ節生検を行う方がよいであろうと思われる．マンモグラフィ所見で石灰化像のみを示す場合は，非浸潤性乳管癌であることが特に多いことはよく知られている[12~14]．今回，石灰化像のみの47病変中33病変（70.2％）に生検材料ならびに切除材料いずれにも浸潤巣を認めなかった．さらに浸潤のあった14病変中8病変が微小浸潤癌であった．微小浸潤癌の場合，組織学的リンパ節転移の頻度が低いことを考えると，石灰化像のみの病変が癌であった場合に，腋窩郭清やセンチネルリンパ節生検を要する可能性は低いといえるかも知れない．

マンモグラフィで石灰化像のみを示す場合，浸潤癌である可能性を絞り込めないかどうかをさらに検討した．石灰の形態ならびに石灰の範囲とで検討したが，いずれの所見においても浸潤の有無の予測には有用ではない，という結果になった．石灰の形態は乳管内癌の組織亜型と相関しており，特に微細線状および微細分枝状のものはコメド型と微細円形は非コメド型とほぼ対応している，とされている[15~17]．コメド型の乳管内癌では浸潤を伴うことが多いとされているため[18]，形態別に検討したが今回の結果は予測とは異なった．念のため石灰の形態とDCISの組織亜分類との関連を確認したが，確かに今回の結果は上記のことを支持するものであるが，コメド壊死の石灰がまだ十分に成熟していない場合でも微細円形の形をとりうることも示唆された．Stomperらはlinearの石灰の場合の方がgranularの石灰より，浸潤を認めることが有意に多いと報告しているが，その率はそれぞれ44％，29％とその差はあまり大きくなく[19]，

今回石灰の形態と浸潤を認める率に有意差が認められなかったのは症例数が少なかったためかも知れない．

石灰の存在する範囲での今回の検討結果でも，浸潤巣の存在と有意な相関は見られなかった．Wahednaらも石灰の範囲と浸潤との間に有意な相関を認めていない[20]．ただ，上記のStomperらはこれらの間に有意な相関を示している[19]．彼らは304例を検討しており，石灰の範囲が11mm以上のときで浸潤を40%に認め，10mm以下のときで26%と，ここでも大きな差を認めてはいないが症例数が多いため有意となっている．さらに彼らは11mm以上では石灰の範囲が広くなっても浸潤を認める率に変化を認めておらず，この点は我々の検討結果でも同様の傾向が認められている．

乳房温存療法を行う場合，切除材料の組織学的断端を陰性にすることは乳房内再発を少なくする上で重要であるが，石灰化病変での石灰の範囲が切除範囲決定に役立つかどうかも検討した．その結果，石灰の範囲を越えて非浸潤巣があることが多く，個々の症例である程度のばらつきがあることが示された．石灰の形態別に見ると，微細線状および微細分枝状および多形性あるいは不均一の方が，淡く不鮮明あるいは微細円形のときよりも非浸潤巣の範囲が広い傾向にあることも示唆された．このことも予想外であった．それは，Hollandらがコメド型のDCISよりも非コメド型のDCISの方が，石灰の範囲よりも広くDCISが拡がることが多いと報告しているからである[15]．上記のように石灰の形とDCISの組織亜型とに強い相関があったが，完全には一致していないため，非浸潤巣の組織亜型別に石灰の範囲と非浸潤巣の範囲での検討も行った．本論文ではデータを示さないが，やはり，コメド型の方で，非コメド型に比して非浸潤巣の範囲が石灰の範囲よりも広い傾向にあった．この違いの原因として，Hollandらは乳房切除症例のみを検討の対象としたこと，組織学的検索方法が異なること，組織亜型の定義が異なることなどが考えられた．

非触知乳癌のマンモグラフィ所見はある程度，その組織所見を反映しているが，特に石灰化像のみの症例での浸潤のある症例の同定，ならびに非浸潤巣の範囲の決定はかなり困難で，MRI，CT，エコーなど他の画像診断との組み合わせで診断精度の向上を目指すべきであると思われる．

おわりに

今回の検討で示されたマンモグラフィ発見の非触知乳癌でマンモグラフィ所見から得られる手術に役立つ情報としては，腫瘤像を認めるとき，特に腫瘤像のみの場合はほとんどが浸潤癌であるが，石灰化像のみの場合は逆に大半が非浸潤癌であることである．さらに，非浸潤巣の範囲は石灰化像の範囲よりもやや広めである可能性が高いことも乳房温存術の際，重要な所見と思われた．

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Panel Discussion I

Sentinel Lymph Node Biopsy without Axillary Dissection after an Intraoperative Negative Histological Investigation in 358 Invasive Breast Cancer Cases

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Background: Sentinel lymph node biopsy (SLNB) is an important treatment option for breast cancer patients, as it can accurately predict axillary status. Our previous study using dye with or without radioisotope showed the accuracy and sensitivity of SLNB to be 97% and 94%, respectively. Based on these results, axillary lymph node dissection (ALND) was eliminated starting in January, 1999 in patients with intraoperatively negative SLNB at our institution. The present study shows the results and outcomes of SLNB as a sole procedure for patients with invasive breast cancer.

Patients and Methods: Three-hundred-fifty-four patients and 358 cases of invasive breast cancer (4 bilateral breast carcinoma) treated with SLNB alone after an intraoperative negative SLNB were studied prospectively from January 1999 to December 2001.

Results: The number of the identified SLNs per case ranged from 1 to 8 (mean, 2.5). Of a total of 358 cases, 297 (83%) were treated with hormone therapy and/or chemotherapy, and 281 (78%) were treated with radiotherapy to the conserved breast (50 Gy ± 10 Gy boost), the axilla (50 Gy), or the both sites. After a median follow-up of 21 (range 6-42) months, no patient developed an axillary relapse. Four cases initially recurred in distant organs and one case in the conserved breast.

Conclusions: Our results indicate that an intraoperative negative SLNB without further ALND may be a safe procedure when strict SLNB is performed. To better assess the safety, however, may require longer follow-up.

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Key words: Sentinel lymph node biopsy, Axillary lymph node dissection, Breast cancer

Surgery for breast cancer has dramatically changed during the past century. En bloc removal of the draining lymphatics was considered to be important for surgical cure of breast cancer by Halstead's radical mastectomy[1]. Extended radical mastectomy, which includes dissection of internal mammary lymph nodes, however, did not improve the prognosis of breast cancer patients[2]. Axillary lymph node dissection (ALND) was considered to be a procedure which could predict the prognosis. Recently, the increasing incidence of early-stage breast cancer, survival improvement with adjuvant chemoendocrine therapy, and surgical morbidity of ALND have forced surgeons to reassess the significance of ALND. Sentinel lymph node biopsy (SLNB) can avoid the morbidity of unnecessary ALND for breast cancer patients.

The SLN is the lymph node that receives direct drainage from the primary tumor and is therefore the node most likely to contain metastatic tumor cells[3]. This concept was developed in the 1980's by Morton and his colleagues, based on mapping the drainage patterns of cutaneous melanoma[4]. SLNB for breast cancer was reported in 1993 and

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Abbreviations:
SLNB, Sentinel lymph node biopsy; ALND, Axillary lymph node dissection; UFT, Tegafur and uracil; NSABP, National Surgical Adjuvant Breast and Bowel Project; ACOSOG, American College of Surgeons Oncology Group

1994 by Krag *et al.*[5] and Giuliano *et al.*[6], respectively, then followed by several SLNB teams worldwide. Reportedly, SLNB accurately predicted the nodal status with an accuracy of about 98%[7].

In our feasibility study of SLNB followed by completion ALND for breast cancer patients, the accuracy and sensitivity were 97% and 94%, respectively[8]. These results were comparable with those reported from other institutes in Japan[9]. Although SLNB without ALND is a matter of debate, from 1999 SLNB alone has been performed in patients whose SLN is tumor-free by intraoperative frozen section analysis. The present study provides the data of 354 patients with 358 invasive breast cancers treated with SLNB alone.

Patients and Methods

From January 1999 to December 2001, 354 consecutive patients with 358 invasive breast cancers (four bilateral breast carcinomas) who underwent only SLNB after confirming the SLNs to be tumor-free by intraoperative histological investigation were studied prospectively. Written informed consent was obtained from all study patients.

Our dye- and gamma probe-guided method to identify the SLN is briefly described here. A dose of 0.5 mCi of ^{99m}Tc-labeled human serum albumin (Dai-ichi Radioisotope Laboratory Co., Tokyo, Japan) in a volume of 1 ml was injected subdermally above the tumor 1 to 6 hours prior to the operation. From November 2001, ^{99m}Tc-labeled human serum albumin was replaced by ^{99m}Tc-labeled stannous phytate (Dai-ichi Radioisotope Laboratory Co.) with the identical dose and volume. A 1% solution of patent blue dye (CI42045; Wako Pure Chemical Industry, Osaka, Japan) was injected in a volume of 2.5 ml after the induction of anesthesia before preparing the patient for the surgical procedure. The breast was compressed and massaged for 5 minutes.

A blue-stained lymphatic channel draining into the SLN was visualized with good exposure and a bloodless field using electrocautery for dissection. All of the blue-stained SLNs were harvested. Small non-stained lymph nodes happened to be also harvested in this procedure. Individual radioactivity of all the harvested lymph nodes was counted by a gamma detection probe (Auto Suture, Tokyo, Japan). In addition, enlarged lymph nodes if suspicious for metastasis, were also removed and counted. Finally, the absence of other SLNs was confirmed by the gamma detection probe. Harvested lymph nodes were bisected; one half of each node was intraoperatively examined by HE staining of frozen sections, the other half was fixed with formalin and postoperatively examined by HE staining of paraffin-embedded sections. The former half node was then placed in formalin for postoperative paraffin section histology.

Patients were followed by physical examination and blood tests at 3 to 6 month intervals after operation. Locoregional ultrasound was performed every 6 months for patients who underwent breast conserving surgery. Abdominal ultrasound, chest X-ray and bone scintiscan were performed every 12 months.

Results

The patient and tumor characteristics are shown in Table 1. Patients' ages ranged from 25 to 82 years (mean, 54.7 years). One-hundred-eleven cases had stage I disease, and 240 and 7 cases had stage II and III disease, respectively. Breast conserving surgery was performed in 330 cases and mastectomy in 28 cases. Invasive ductal carci-

Table 1. Characteristics of 358 Invasive Breast Cancers Treated with Sentinel Lymph Node Biopsy Alone

Age (years)	55 (25-82)
Menopausal status	
Premenopausal	162
Postmenopausal	196
Stage	
I	111
IIA	168
IIB	72
IIIA	5
IIIB	2
Type of surgery	
Breast conserving surgery	330
Mastectomy	24
Subcutaneous mastectomy	4
Histological type	
Invasive ductal	320
Mucinous	23
Other	15
Receptor Status	
ER + PR +	176
ER + PR −	44
ER − PR +	32
ER − PR −	80
Unknown	26

ER, Estrogen receptor; PR, Progesterone receptor

noma was found in 320 cases, mucinous carcinoma in 23 and other types of carcinoma in 15. Two-hundred-fifty-two cases were hormone-responsive tumors.

SLNB was performed using patent blue dye in 32 cases, isotope in one case, and a combination technique in 325 cases. The mean number of identified SLNs per case was 2.5 (range, 1 to 8). The mean number of removed lymph nodes per case including non-SLNs was 3.3 (range, 1 to 11). All the harvested nodes were intraoperatively diagnosed as tumor-free using frozen section histology. Thirty-four cases (9.5%), however, were postoperatively diagnosed as tumor-positive on examination of the formalin-fixed paraffin embedded sections. Of these 34 cases, 1 (3%) had metastasis only on the intraoperative frozen section reexamined postoperatively, 20 (59%) in the half of the SLN fixed with formalin, 9 (26%) in the other half of the SLN, saved for frozen section analysis and then fixed with formalin, and 4 (12%) in both halves of the SLNs; 31 (91%) had only one SLN involved, and 3 (9%) had two SLNs involved. Eighteen (53%) had micrometastasis (≦2 mm), and 6 (18%) had tumor cells found only in the lymphatics in the lymph node capsule. As mentioned above, these intraoperative false-negative cases were treated without further ALND.

Adjuvant systemic treatment and postoperative radiotherapy are shown in Table 2. Of a total of 358 cases, 297 (83%) were treated with hormone therapy and/or chemotherapy, and 281 (78%) were treated with radiotherapy to the conserved breast (50 Gy ± 10 Gy boost), the axilla (50 Gy), or the both sites. Only 31 cases (9%) were observed without any further treatment. Of 34 intraoperative false-negative cases, 26 (76%) underwent radiotherapy to the axilla, the conserved breast or both sites. Only one case, who was 70 years old, was observed without any treatment.

After a median follow-up of 21 (range 6-42) months, no patient developed an axillary relapse. Four patients initially recurred in distant organs and one patient in the conserved breast. Recurrent cases are summarized in Table 3. All four patients who recurred in distant organs were premenopausal, all of their tumors were either ER-negative or PR-negative, and three of them were grade Ⅲ invasive ductal carcinomas, larger than 2.1 cm in largest dimension.

Table 2. Postoperative Systemic Therapy and Radiotherapy in 358 Invasive Breast Cancers Treated with Sentinel Lymph Node Biopsy Alone

Systemic therapy	
None	61
Hormone therapy	197
Chemotherapy + hormone therapy	39
Chemotherapy	61
Radiation therapy	
None	74
Breast and axilla	130
Breast	150
Axilla	1
Nipple	3

Discussion

ALND has three potential benefits: to provide prognostic information, to maintain local control in the axilla, and potential therapeutic benefit[10]. If ALND proves to be no more than a staging procedure without survival advantage, accurate staging

Table 3. Characteristics of 5 Recurrent Cases Out of 358 Invasive Breast Cancers Treated with Sentinel Lymph Node Biopsy Alone

Pt	Age	Stage	Surgery	SLN Involvement	Histological Type	ER/PR	Breast/Axilla Radiotherapy	Adjuvant Therapy	Recurrent Site	RFS#	OS#
1	36	ⅡA	BCS	No	IDC NG3	P/N	Yes/Yes	Tamoxifen + UFT	Bone	11	31 (Died of BC)
2	32	ⅡA	BCS	No	IDC NG3	N/N	Yes/Yes	None	Ovary	18	19 (Died of BC)
3	52	Ⅰ	BCS	Yes*	IDC NG1	N/P	Yes/No	Tamoxifen	Lung	24	29 (Survive)
4	67	ⅡA	BCS	No	ILC	P/P	No/No	Toremifene	Breast	24	26 (Survive)
5	38	ⅡB	BCS	No	IDC NG3	N/N	Yes/Yes	UFT	Lung	11	27 (Survive)

SLN, Sentinel lymph node; ER, Estrogen receptor; PR, Progesterone receptor; RFS, Relapse-free survival; OS, Overall survival; BCS, Breast conserving surgery; IDC, Invasive ductal carcinoma; NG, Nuclear grade; P, Positive; N, Negative; UFT, Tegafur and uracil; BC, Breast cancer; ILC, Invasive lobular carcinoma

#, Months after operation; *Micrometastasis was postoperatively found on permanent section analysis.

with SLNB would eliminate the need for further axillary surgery. However, it has not been validated that SLNB as a sole procedure can provide the same benefit as ALND for curing breast cancer patients. To verify the therapeutic significance of SLNB alone, the NSABP B-32 trial[11] is ongoing to compare the survival and regional control between patients with histologically negative SLN treated with SLNB alone and those treated with completion ALND. Furthermore, the ACOSOG trials (Z0010 and Z0011)[11] are also ongoing to validate the curative benefit of completion ALND for patients with histologically positive SLN in comparison with SLNB alone.

In the present study, thirty-four (9.5%) of a total of 358 cases were postoperatively proved to have tumor-positive SLN. The reliability of intraoperative examination of SLN using frozen sections improves with an increase in the number of sections[12]. An international consensus conference convened in Philadelphia, 2001, stated the SLNs should be cut longitudinally into frozen sections of 1.5-2.0 mm thickness, each of which should be cut at three levels[13]. Veronesi *et al.*[14] intraoperatively analyzed SLNs with serial sectioning at 50 to 100 μm intervals for HE staining, plus immunohistochemical staining if the results of the HE staining were doubtful. Compared with these techniques, our handling of the SLN specimen is simple and practical for detecting tumor-positive SLNs. Although the refined techniques more easily identify micro-metastasis in SLNs, the prognostic significance of micrometastasis is not fully elucidated. The ongoing ACOSOG trials can resolve this question in the future. Also, long-term follow-up results from observational studies will help to define the clinical significance of micrometastasis.

There have been four papers published overseas in which follow-up results of patients who were treated with SLNB as a sole procedure after a negative histological investigation of SLNB were reported[14-17]. The number of reported cases ranged from 67 to 285 (a total of 535 cases). The median follow-up period ranged from less than 24 to 39 months. In these cases, only one woman, aged 46 years, developed an axillary relapse[16]. She presented with residual axillary disease 14 months after the initial sentinel node procedure, and within 2 months she developed pulmonary and bone metastases and died from brain metastasis 12 months after axillary relapse. The short interval between initial SLNB and recurrence in the axilla and distant organs means her disease was systemic at the initial operation. In Japan, Noguchi reviewed observational studies on the elimination of ALND based on the results of SLNB[9]. Although the follow-up periods were short and the numbers of patients observed were small, no axillary recurrence was reported.

Based on the 94% sensitivity of SLNB from our previous feasibility study, if the incidence of true-positive nodes is 40%, the expected number of patients with residual nodal involvement after a negative SLNB without further ALND is 4%. Accordingly, if 40% was the true node-positive incidence in our patients undergoing SLNB during the same period, 13 cases (4%) out of 324 cases with negative SLNB should be node-positive. In addition, our unpublished data showed additional nodal metastasis was found in 36% of T1-3, N0 patients with intraoperatively positive SLNB who underwent completion ALND. Therefore, out of 34 cases with positive SLNB in this study, 12 (36%) were estimated to have residual nodal metastasis. Thus, 25 (13 plus 12) (7%) of a total of 358 cases were expected to have metastasis in the residual axillary nodes. The present study shows that, after a median follow-up of 21 months, no patient had axillary nodal recurrence. The present data seem to be better than expected, which may be due to two reasons. One is the short follow-up period of this study. In the NSABP B-04 study, however, half of patients with breast cancer treated with mastectomy and observation of the axillary nodes reportedly developed their axillary recurrence within 2 years[18]. The other is the effect of the adjuvant systemic treatments and/or radiotherapy, which were given to most (91%) of the patients.

Axillary radiotherapy is performed without major side effects[19]. A randomized clinical trial has shown equivalent regional control obtained by axillary radiation therapy compared with axillary dissection[20]. Therefore, in a case with intraoperatively false-negative SLNB, the substitution of radiation may be more favorable than further surgery. It is unclear whether axillary irradiation as a separate field is required instead of ALND. Radiotherapy to the conserved breast with the use of opposing tangential-field radiation may destroy any metastases in the lower axillary lymph nodes[13]. The results of the present study suggest that axillary radiotherapy and/or adjuvant systemic treatments may be important for the control of axillary relapse. A current European clinical trial is exam-

ining the role of axillary radiotherapy compared to axillary dissection in sentinel node positive patients[13].

In conclusion, our results indicate that although most patients were treated with adjuvant systemic therapy and/or radiotherapy, an intraoperatively negative SLNB without further ALND may be a safe procedure when strict SLNB is performed. To assess safety, however, may require longer follow-up.

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Review Article

The Role of Neoadjuvant Chemotherapy for Breast Cancer Treatment

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Neoadjuvant chemotherapy has become popular, especially for patients with advanced breast cancer. The pros and cons of neoadjuvant chemotherapy for treating breast cancer patients are reviewed. The advantages of neoadjuvant chemotherapy are 1) overall survival and recurrence-free survival rate are the same as post-operative chemotherapy, 2) serves as an *in vivo* sensitivity test, 3) increases the rate of breast conserving therapy, 4) facilitates the study of cancer biology. On the other hand, the disadvantages of neoadjuvant chemotherapy are 1) it modifies the stage, 2) treatment delay of PD cases, 3) residual intraductal component may be left behind after breast conserving surgery, 4) there are some cases of over-treatment. Combination chemotherapy is one possible way to increase the pathological CR rate, although the optimal order and cycles have not been determined. To avoid residual cancer cells after breast conserving surgery, the shrinkage pattern should be evaluated by MRI. Core needle biopsy should be performed before neoadjuvant chemotherapy to avoid over-treatment. It is essential to develop more effective regimens and stratify patients based on predictive factors.

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Key words: Breast cancer, Neoadjuvant chemotherapy, Preoperative chemotherapy

Neoadjuvant chemotherapy has become popular, especially for patients with advanced breast cancer. It is mandatory to understand the present status of neoadjuvant chemotherapy and also the pros and cons of neoadjuvant chemotherapy for breast cancer patients. A summary of the pros and cons of neoadjuvant chemotherapy is listed in Table 1.

Survival, pCR

Theoretically, prolongation of overall survival or relapse-free survival is expected from neoadjuvant chemotherapy[1,2], but the NSABP-B18 trial demonstrated no advantage of neoadjuvant chemotherapy in terms of overall survival or recurrence-free survival[3]. Other prospective randomized trials also failed to demonstrate a survival advantage[4-7] although the sample size of each trial was too small to obtain a definitive conclusion (Table 2). Subgroup analyses demonstrated the patients with pathological CR (pCR) had a good prognosis in the NSABP trial. The frequency of pCR ranges from 3 to 24% (Table 3)[8-20] although the definition of pCR differed somewhat among the trials. There are two possible ways to achieve a higher pCR rate. One is to increase the chemotherapeutic dose intensity and the other is to combine drugs. Dose escalation has been demonstrated not to contribute to survival in advanced or metastatic disease, or in adjuvant settings[21]. Also, there is a ceiling effect that occurs with the dose escalation[21]. This scenario may also be true in the neoadjuvant setting because the pCR rate is not correlated with chemotherapeutic dosage intensity[14]. However, Green *et al.* recently reported a high pCR rate after weekly paclitaxel followed by FAC (5-FU, adriamycin, cyclophosphamide) therapy compared to triweekly paclitaxel followed by FAC[25]. The response rate correlates with the cycles performed, although the optimal number has not been determined. The longer the cycle performed, the higher the pCR rate[26]. This has resulted in speculation that patients who respond to neoadjuvant chemotherapy may receive another

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Abbreviations:
PD, Progressive disease; CR, Complete response; MRI, Magnetic resonance image; pCR, Pathological complete response; NSABP, National Surgical Adjuvant Breast and Bowel Project; BCT, Breast conserving treatment; ER, Estrogen receptor; MDR, Multiple drug resistance; RFS, Recurrence-free survival; OS, Over-all survival

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Table 1. Pros and Cons of Neoadjuvant Chemotherapy

Pros	Cons
1) Improves RFS, OS ?	1) Modifies the stage
2) Serves as a sensitivity test	2) Possibility of PD cases
3) Increases breast conserving rate	3) Over-treatment cases
4) Facilitate studies of the biology of cancer	4) Residual intraductal component may be left behind at breast
	5) Increases false negative rate of sentinel node biopsy ?

Table 2. Prospective Randomized Trials of Neoadjuvant Chemotherapy

Group	Author	N	Med F/U	Regimen	RFS	OS
IBBGS	Mauriac	272	124 Months	EVcM × 3→MiThV × 3→S S→EVcM × 3→MiThV × 3	NS	NS
Royal Marsden	Markis	309	48 Months	2MT × 4→S→2MT × 4 S→2MT × 8	NS	NS
NSABP	Fisher 1998	1523	6 Years (average)	AC→S S→AC	NS	NS
S6	Scholl 1994	414	54 Months	FAC × 4→R/S R/S→FAC × 4	NA > Adj $p = 0.09$	NA > Adj $p = 0.039$
ABCSG	Jakesz 2001	423	–	CMF × 3→S→CMF/CE S→CMF × 3→CMF/CE	NS	NS

EVcM: epirubicine, vincristine, methotrexate; MiThV: mitomycin C, thiotepa, vindesine; 2MT: mitozantrone, methotrexate, (± mitomycin C), tamoxifen; AC: adriamycin, cyclophosphamide; FAC: adriamycin, cyclophosphamide, 5-fluorouracil; CMF: cyclophosphamide, methotrexate, 5-fluorouracil; CE: cyclophosphamide, epirubicine

cycle of the same regimen postoperative's to achieve better survival. Combining chemotherapeutic agents is another method. A good example of combined neoadjuvant therapy is the Aberdeen trial, which treated 145 patients with CVAP as the first phase of chemotherapy. Patients who did not respond to the first phase of chemotherapy received four cycles of docetaxel. Patients who responded to the first phase of chemotherapy were randomized to receive either four cycles of docetaxel or four cycles of CVAP (cyclophosphamide, vincristine, adriamycin, prednisolone). Among the patients who responded to first phase chemotherapy, the response rate was 94% in those treated with docetaxel as a second phase agent, while the response rate was 66% in those treated with CVAP as a second phase regimen[27]. These results indicate the effectiveness of combination chemotherapy including docetaxel. Doxorubicin with docetaxel is one of the most investigated combinations. Several studies of this combination have been done, with the results indicating a relatively high response rate with a slightly increased pathological response (Table 3). Other combinations are under investigation. Herceptin combined with chemotherapy is one of the most promising regimens because chemotherapy is effective treatment of the invasive component and Herceptin may effectively treat the non-invasive component, which is usually Her2/neu positive. Burstein et al reported a response rate of 64% and a pCR rate of 20% with Herceptin combined with paclitaxel[23].

Prognostic Factors and Predictive Factors

Pathological CR is a prognostic factor. Clinical response may also predict survival[28]. If the tumor responds to neoadjuvant chemotherapy, the most important prognostic factors including nodal status, tumor size, and nuclear grade may change. However, nodal status is a powerful prognostic factor even after neoadjuvant chemotherapy[9, 10]. To achieve good response, it is mandatory to determine predictive factors. So far, no good predictive factors have been determined. Her-2/neu is reportedly a predictive factor of chemotherapy response including to anthracyclines[29]. ER negative tumors tend to respond to chemotherapy[30]. A high fraction of cycling cells is predictive of good response[31]. The wash-

Table 3. Response Rate and Breast Conserving Rate of Neoadjuvant Chemotherapy

Author	Type of Study Enrolled pts	Regimen	RR (%)	pCR (%)	BCT (%)	PD (%)
Scholl[4]	randomized 414	F500 (1, 3, 5, 8) A25 (1, 8) C500 (1, 8) × 4→R/S R/S→FAC × 4	82		82	–
Gradishar[8]	pII 33	Doc100 × 4	85	3	–	
Morrell[9]	pII 55	M30 (1) V3 (2, 15, 22) A30C70 (2) q4W × 3 – 5	89	11	–	0
Markis[5]	randomized 309	2MT × 4→S→2MT × 4 S→2MT × 8	84	6	89 77	1
Fisher[3]	randomized 1523	A60C600→S S→AC	79	13§	68 60	3
Bonadonna[10]	536	CMF, FAC or FEC × 3 – 4	76	3	85	
Cocconi[11]	randomized 57	MPEMi × 4 MPEpiE × 4 MPEpiV × 4	91	12		
Buzdar[12]	randomized 174	Paclitaxel 250 × 4 F500A50C500 × 4	80 79	6 18	46 35	1 3
Ezzat[13]	pII 72	Paclitaxel 135 Cisplatin 75 × 3 – 4	90	22§	24	–
Kuerer[14]	randomized 372	doxorubicin containing regimen × 4		16		
Mauriac[6]	randomized 272	Epi50Vc1M20 × 3→Mi10Th20V4 × 3→S S→EVcM × 3→MiThV × 3			63	
Minckwitz[15]	open pII 42	A50Doc75 × 4	93	5	59	
Miller[16]	randomized pII 40	A75 × 3→Doc100 × 3 A56Doc75 × 4	 87	13		
Luporsi[17]	randomized pII 90	FEC100 × 6 E100Doc75 × 6	72 84	24 24	69 85	
Raab[18]	randomized pII 250	A50Doc75q2W × 4 A50Doc75q2W × 4 + TAM	– –	10 9	70 69	
Tubiana-Hulin[19]	pII 39	A50Doc75	80	12		
Lara[20]	20	A50Doc75 × 4	87	20		
Limentani[21]	pII 19	A50Doc75 × 4	89	–		
Ikeda[22]	pII 29	(Doc60→A50C500) × 2	74	4	26	6
Burstein[23]	pII 40	Paclitaxel 175 × 4/Herceptin × 12	64	20		

FAC: 5-fluorouracil, adriamycin, cyclophosphamide; MVAC: methotrexate, vinblastine, doxorubicin, cisplatin; 2MT: mitozantrone, methotrexate, (mitomycin-C), tamoxifen; Doc: docetaxel; A: adriamycin; MPEMi: methotrexate, cisplatin, etoposide, mitomycin C; MPEpiE: methotrexate, cisplatin, etoposide, epirubicin; MPEpiV: methotrexate, cisplatin, epirubicin, vincristine; PC: paclitaxel, cisplatin; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; Epi: epirubicin; RR: response rate; R: radiation; S: surgery

§: including residual intraductal component

out rate of Tc-99m sestamibi on scintigraphy has been reported to correlate with MDR gene expression and also response to anthracyclines[32,33] because sestamibi serves as a P-glycoprotein substrate. Other factors are under investigation[35]. These predictive factors should be considered before starting

neoadjuvant chemotherapy to better achieve pathological response, which may lead to better survival.

Sensitivity Test

There is neither a perfect predictive factor nor an effective sensitivity test for breast cancer. However, neoadjuvant chemotherapy serves as an *in vivo* sensitivity test. If the portion of patients with progressive disease after neoadjuvant chemotherapy is small, there is no indication for post-operative adjuvant chemotherapy with the same regimen. The response rate of neoadjuvant chemotherapy correlats with the number of courses performed. The optimal number of cycles has not been determined but most of the trials performed four cycles of chemotherapy for three months before operation. It depends upon the objectives of neoadjuvant chemotherapy. If achieving breast-conserving surgery is the goal, neoadjuvant chemotherapy should be performed until the tumor shrinkage is sufficient to meet criteria for breast-conserving surgery. If determining sensitivity to the drugs, four cycles may be enough. If the patient responds to neoadjuvant chemotherapy, she may receive the same adjuvant chemotherapy to eradicate micrometastasis. However, popular combined chemotherapy becomes in the neoadjuvant setting, how to combine chemotherapeutic drugs is an issue. Miller *et al.* concluded that a sequential treatment schedule increases toxicity but may result in more substantial lymph node clearance than combination therapy[36]. Ikeda *et al.* reported a rotating regimen with doxorubicin and doxetaxel[22]. This may be an optional way to determine drug sensitivity earlier. It has not been demonstrated that chemotherapy sensitive tumors are necessarily biologically low-grade with good prognosis.

Breast Conserving Surgery

If the overall survival is the same between adjuvant and neoadjuvant groups, the increased frequency of breast conserving surgery is obviously one of the major advantages of neoadjuvant therapy (Table 3). This end point is a very soft one however. The indications for breast-conserving surgery depend on the decision of the surgeons and also patients' preference, and not only on reduction of tumor size. The frequency of breast conserving operation increased 7.8% in the NSABP-B 18 trial and 12% in the Royal Marsden Trial. It should be used as secondary endpoint.

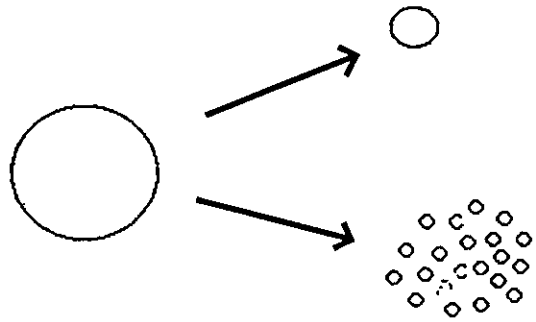

Fig 1. Shrinkage pattern after neoadjuvant chemotherapy. There are two patterns of shrinkage after neoadjuvant chemotherapy; concntric and honeycomb. It is necessary to differentiate these two patterns before breast conserving surgery.

Local Recurrence after BCT in the Case of Tumor Shrinkage

There are two types of tumor shrinkage patterns, the concentric type and the honeycomb type (Fig 1). The intraductal component is reportedly resistant to chemotherapy. Even after the disappearance of an invasive component, the non-invasive component persists. This may cause a higher local recurrence rate after breast conserving operation following neoadjuvant chemotherapy. The local recurrence rate is higher in the patients undergoing neoadjuvant chemotherapy, especially those downstaged to lumpectomy; 14.5% compared to 6.9% in the NSABP B-18 trial[3]. The breast conserving rate decreases with time after operation because of local recurrence. Scholl showed a 73% local control rate at five years after operation compared to 82% initially. Mauriac reported a 45% local control rate at median follow up of 124 months compared with an initial 63% breast conserving rate at first operation. It is important to note the shrinkage pattern before operation. Abraham *et al.* reported that MRI accurately estimated residual disease after neoadjuvant chemotherapy[37]. MRI with gadolinium enhancement is recommended to detect intraductal spread[38].

Progressive Disease

The response rate of neoadjuvant chemotherapy is reported to be around 60 to 90%. Most of the rest of the cases are stable disease. However there remains the scenario of progressive disease. The frequency of patients with progressive disease is 0-6%. The frequency of progressive disease may depend upon the protocol used. The reported rate of progressive disease and protocols are listed in table 3. Although the number is small, progressive

disease results in delay of operation and enormous psychological damage.

Over-Treatment

For the patients with non-invasive carcinoma, neoadjuvant chemotherapy is not indicated because of favorable prognosis. For the same reason, patients with mucinous cancer, tubular cancer, and invasive ductal cancer with predominant intraductal component, are usually not candidates for neoadjuvant chemotherapy. Out of 440 cases in our personal series, operated upon between 1991 and 1999, the number of non-invasive ductal carcinomas was 17 (3.9%), and that of mucinous cancers was 7 (0.7%) for tumors over 3 cm. To avoid this scenario, it is mandatory to confirm breast cancer with a core needle biopsy and not with a fine needle aspiration before starting neoadjuvant chemotherapy. If the indications for neoadjuvant chemotherapy are widened to early breast cancer, the frequency of patients with node negative, ER positive, grade 1/2 tumors less than 2 cm is estimated to be 15% from our data. These patients should be carefully selected for neoadjuvant chemotherapy, because adjuvant chemotherapy is usually not indicated in these patients.

Others

An increased false negative rate of sentinel node biopsy after neoadjuvant chemotherapy has been reported[39], although other reports show no increased false negative rate[40]. One reason for conflicting results is the different method of sentinel node biopsy. Sentinel node biopsy should be performed cautiously in the patients undergoing neoadjuvant chemotherapy until these issues are settled.

The place of neoadjuvant chemotherapy for new drug development is another important point. Adjuvant chemotherapy needs a very long time to prove drug efficacy in terms of overall survival. The response rate may serve as a surrogate endpoint for overall survival, but the patients with metastatic disease often have several confounding factors to evaluate. In contrast, the patients undergoing neoadjuvant chemotherapy have relatively homogeneous background factors, and these are almost the same as in patients undergoing adjuvant chemotherapy. Therefore, the response to neoadjuvant chemotherapy may serve as a surrogate endpoint and the specimens obtained during neoadjuvant chemotherapy may facilitate biological studies to analyze the drug mechanism. The place of neoadjuvant chemotherapy in new drug development is between metastatic disease and adjuvant chemotherapy (Fig 2).

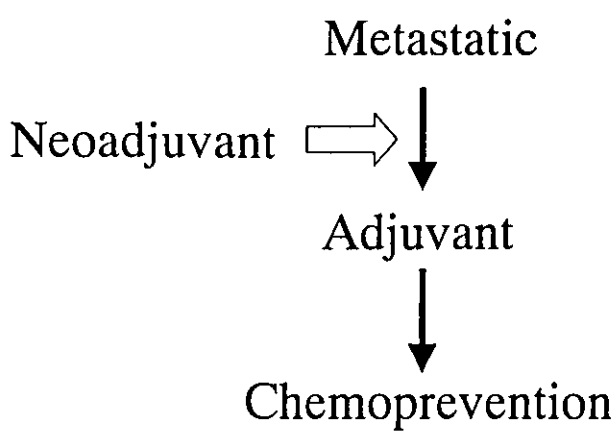

Fig 2. Place of neoadjuvant chemotherapy in drug development. The place of neoadjuvant chemotherapy in drug development is between metastatic disease and adjuvant chemotherapy.

Obviously there are many ongoing issues in neoadjuvant chemotherapy, but the benefit usually outweights the disadvantages given the same overall survival rate. It is essential to develop more effective regimens for the most sensitive group of patients.

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調査研究

2003.5.17受付

乳がん薬物療法の現状(内分泌療法)

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In 2001, the Japanese Society of Clinical Oncology conducted a survey of physicians specializing in breast cancer. The survey asked the specialists about their preferred approach to the chemo-endocrine treatment of breast cancer. A questionnaire was mailed in August and September 2001 to those who mainly treated breast cancer patients, and in principle replies were returned anonymously. The main questionnaire items pertaining to endocrine therapy were the following：the types of endocrine agents in daily use, sequence of endocrine therapy, schedule, duration of treatment and preferable endocrine regimens in the clinic a setting. In order to provide standardized therapy for breast cancer in Japan, high quality evidence from clinical trials should be classified. In addition, we need to consider medical insurance, the role of co-medicals in clinics and ethnic differences between Japanese and Caucasian populations. The results of the survey of daily practices may be useful to select standardized therapies for breast cancer patients in Japan.

Key words：Questionnaire, Endocrine therapy, Breast cancer
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はじめに

第39回日本癌治療学会総会では，標準的な治療を目指して乳がん薬物療法のわが国の実態と，世界の動向が示された．わが国の乳がん薬物療法は，臨床腫瘍学領域におけるevidence based medicine（EBM：エビデンス・ベースド・メディスン）の普及とともに国際的な標準化の渦に巻き込まれつつある．しかし，乳がん薬物療法におけるエビデンスのほとんどが日本人以外を対象とした臨床

試験結果であり，わが国の治療の現場に必ずしも応用できないエビデンスも認められる．現在，厚生労働省の委託事業として乳がんの診療ガイドライン，日本乳癌学会，日本癌治療学会臨床腫瘍データベース委員会などがガイドラインの作成を行っているが，EBMの手法に則った作業が中心であり，わが国の医療の現状（行政・施設・人員）を考慮するならば，乳がん専門医のみならず，患者および行政の立場を代表する人たちの意見を加味してガイドラインを作成する必要がある．そのために，わが国で実施され，乳がん専門医が標準的であると考えている乳がん薬物治療を調査する必要があり，既に化学療法については報告した．今回，平成13年の日本癌治療学会前にわが国で乳がんの診断・治療の専門家を対象にアンケートを送付し，内分泌療法についての結果をまとめたので報告する．

期間と方法

平成13年8月から9月にかけて，わが国で乳がん治療を専門に実施している医師宛てにアンケートを郵送し，原則無記名で回収した．アンケートの質問事項は，回答者の背景，補助療法の適応条件，補助化学療法の対象患者，種類，用法，用量，

表1　回答者の背景

項目		回答者数	%
専門			
	外科	184	95.8
	内科	8	4.2
年齢			
	31～40	25	13.0
	41～50	98	51.0
	51～60	53	27.6
	61≦	16	8.3
施設形態			
	大学病院	85	44.3
	大学附属病院を除く総合病院	62	32.3
	がん専門病院	30	15.6
	診療所	10	5.2
	その他	5	2.6
乳癌学会の専門医			
	認定医	37	19.7
	専門医	105	55.9
	認定医かつ専門医	42	22.3
	その他	4	2.1
専任医師数			
	0人	3	1.6
	1人	36	18.8
	2～3人	87	45.3
	4人以上	66	34.4
年間の新患数（原発性乳がん）			
	10人以下	2	1.0
	11～ 50人	48	25.0
	51～100人	69	35.9
	101～150人	29	15.1
	151～200人	15	7.8
	201～300人	15	7.8
	それ以上	14	7.3
化学療法を担当しているか？			
	している	180	4.7
	していない	3	93.8
	他の専門医に依頼する	9	1.6