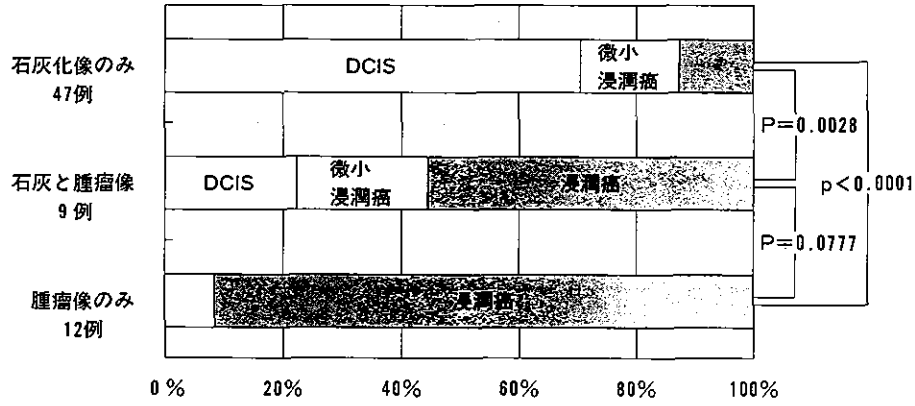


図1　マンモグラフィ所見と組織所見との比較

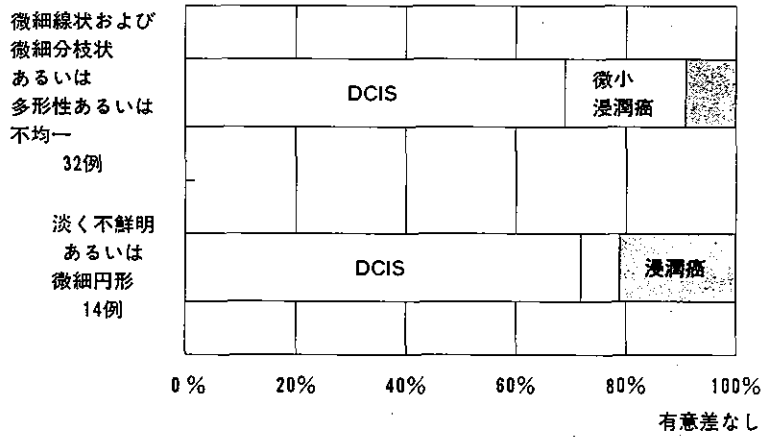


図2　石灰化像のみの症例での石灰の形態と組織像の比較

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DCIS15例，微小浸潤癌5例，浸潤癌2例，淡く不鮮明でDCIS1例，微小浸潤癌1例，浸潤癌1例，微細円形でDCIS9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）．

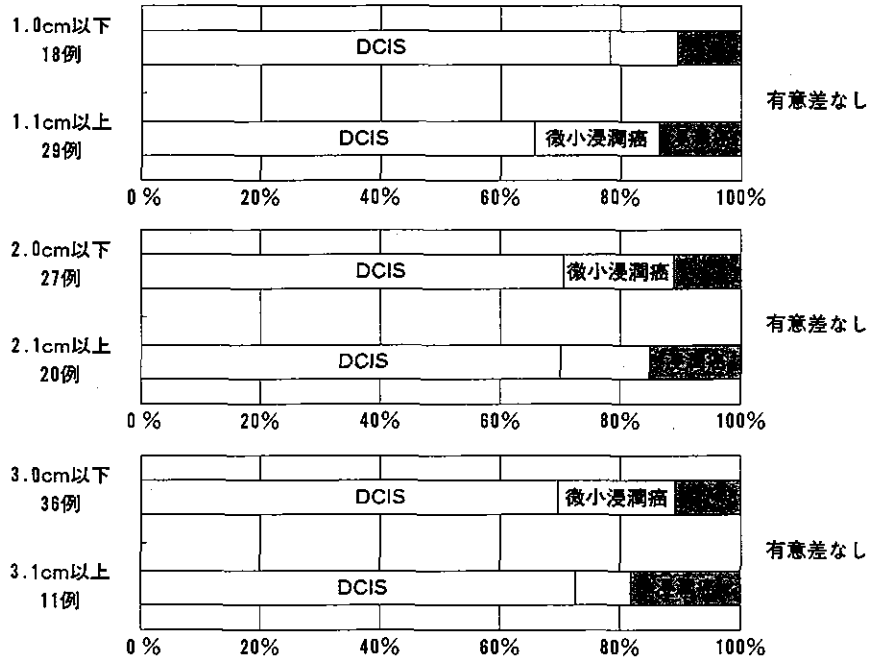


図3　石灰化像のみの症例での石灰の範囲と組織像との比較

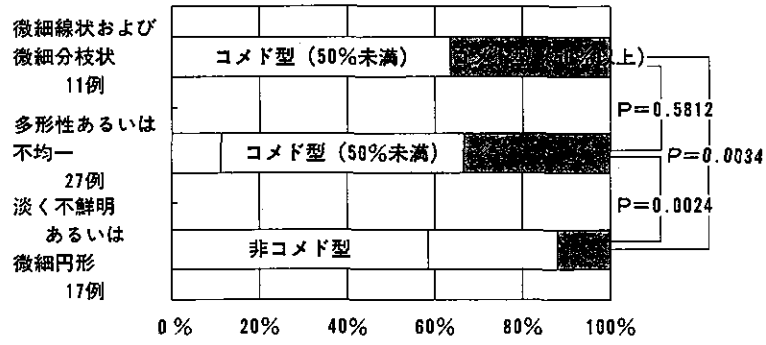


図4　石灰の形態と乳管内癌の亜分類との比較

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

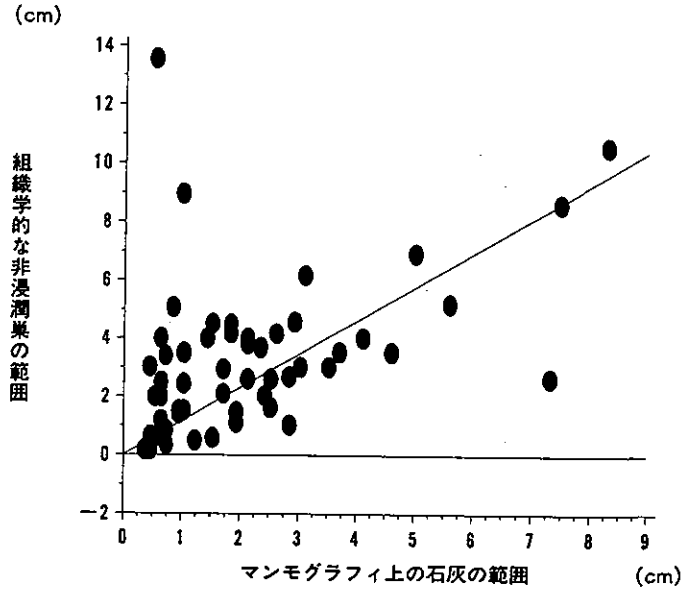


図5　マンモグラフィの石灰と組織学的非浸潤巣の範囲の比較

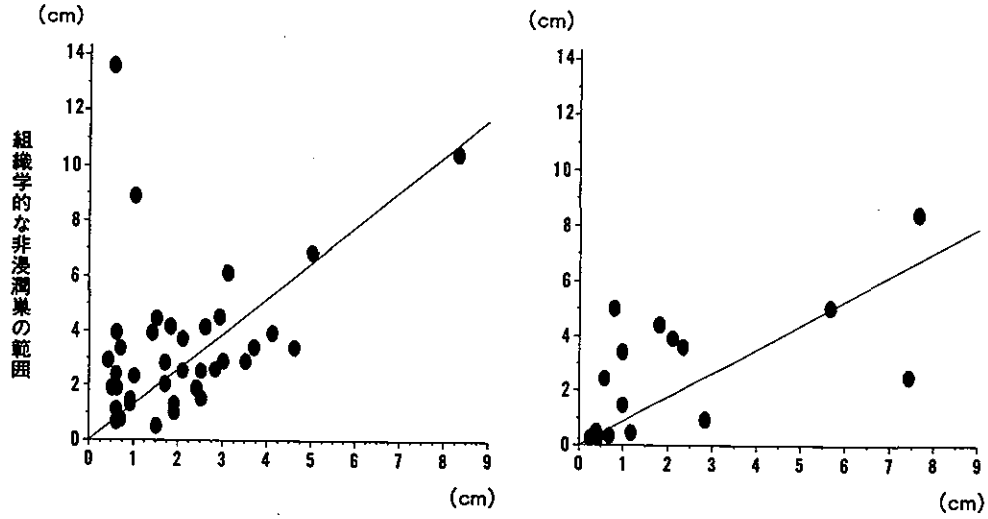


図6　マンモグラフィの石灰と組織学的非浸潤巣の範囲の比較

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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# Randomized clinical trial comparing level II and level III axillary node dissection in addition to mastectomy for breast cancer

T. Tominaga, S. Takashima and M. Danno on behalf of the Modified Radical Mastectomy Study Group

Breast Cancer Centre, Toyosu Hospital, Showa University School of Medicine, 4-1-18 Toyosu, Koutou-ku, Tokyo 135-8577, Japan
*Correspondence to:* Dr T. Tominaga (e-mail: t-tominaga@hkg.odn.ne.jp)

**Background:** In addition to mastectomy, level II and level III axillary node dissection procedures are performed widely in Japan. A randomized clinical trial was performed to determine which procedure was more effective.

**Methods:** One group of women had resection of the pectoralis minor muscle and dissection of level I, II and III axillary lymph nodes (level III dissection). In a second group, the pectoralis minor muscle was left intact and level III axillary lymph node dissection was not performed (level II dissection). A total of 1209 women with stage II breast cancer were enrolled in the study and randomly assigned to one of the two groups.

**Results:** The 10-year cumulative survival rate was 86·6 per cent after level II and 85·7 per cent after level III axillary dissection (hazard ratio (HR) 1·02; $P = 0·931$, log rank test). The 10-year disease-free survival rate was 73·3 and 77·8 per cent respectively (HR 0·94, $P = 0·666$). Overall survival and disease-free survival rates in the two groups were similar after both procedures. The duration of surgery was significantly shorter ($P < 0·001$) and blood loss was significantly less ($P = 0·001$) after level II dissection. In a survey of patients' symptoms on follow-up, no significant differences were found between the two procedures.

**Conclusion:** The addition of pectoralis minor muscle resection and level III axillary lymph node dissection to mastectomy for stage II breast cancer did not improve overall or disease-free survival rates.

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## Introduction

Operations for breast cancer have undergone several changes, from the radical mastectomy described by Halsted through modified radical mastectomy to breast-conserving surgery, as a result of randomized clinical trials investigating the outcomes of different operations[1–7].

When modified radical mastectomy is required, the axilla may be cleared to level II[8,9] or level III[10]; both procedures are performed in Japan[11]. No studies have been published to indicate which of these operations is better. The present study was undertaken to determine the clinical value of pectoralis minor muscle resection and level III axillary lymph node dissection with modified radical mastectomy for stage II breast cancer. Level III dissection was defined as resection of the pectoralis minor muscle together with axillary lymph nodes from levels I, II and III. Level II dissection was defined by leaving pectoralis minor muscle and level III axillary lymph nodes intact.

## Patients and methods

Between May 1991 and April 1993, patients having a mastectomy for breast cancer and who met the following criteria were enrolled before operation into a multicentre trial organized by the Modified Radical Mastectomy Study Group. All women had a histological diagnosis of stage II breast cancer (T2 N0 or T2 N1a, excluding N1b) according to the tumour node metastasis (TNM) classification system[12]. All were aged less than 76 years, did not have bilateral or inflammatory breast cancer, and were not pregnant or lactating. None had evidence of synchronous or metachronous cancer, and none required preoperative treatment for breast cancer, or postoperative

radiotherapy or oophorectomy. All had adequate organ function: lymphocyte count at least 4000 per $mm^3$, platelet count 100 000 per $mm^3$ or more; aspartate and alanine aminotransferase levels less than twice the upper limit of normal range. Preoperative consent was obtained from all women.

Women were randomly assigned to one of the two groups by a central registration system accessed by telephone. Patients in group 1 had a mastectomy with level I and II axillary lymph node dissection, but without resection of the pectoralis minor muscle. Those in group 2 had a mastectomy with pectoralis minor muscle resection and level I–III axillary lymph node dissection.

Women in both groups were treated for 2 years after surgery with oral tamoxifen 20 mg/day and 1-hexylcarbamoyl-5-fluorouracil (HCFU) 300 mg/day, starting from the second postoperative week. Adjuvant therapy was similar in the two groups. HCFU is an oral chemotherapeutic agent developed as a masked compound of 5-fluorouracil (5-FU) for oral use and has been available in Japan since 1980. It is converted into 5-FU via a non-enzymatic process[13], and had a high response rate of 33·3 per cent against advanced breast cancer in a phase II study[14]. HCFU also improves disease-free survival in women with lymph node-positive breast cancer[15]. Tamoxifen is also widely used as postoperative adjuvant therapy for breast cancer[16].

A follow-up questionnaire concerning the presence of arm pain, motor function of the arm, and social functioning was completed 6, 12, 18 and 24 months after surgery. Additionally, the presence of pectoralis major muscle atrophy was evaluated by physicians during follow-up. In the questionnaire survey, arm pain was scored according to four grades: 1, acute pain requiring medication; 2, constant pain; 3, occasional pain; 4, no pain. Motor function was also scored according to four grades: 1, arm could not be raised to horizontal level; 2, arm could be raised above horizontal level but to an angle of less than 45°; 3, arm could be raised above an oblique angle of 45° but less than vertically; 4, arm could be raised vertically. Social functioning was scored according to four grades: 1, no association with other people; 2, little association with other people; 3, same as before surgery; 4, social life improved after surgery. Pectoralis major muscle atrophy was scored according to three grades: 1, atrophy in the upper half of pectoralis major; 2, atrophy in the lower half of pectoralis major; 3, no atrophy. The mean score for each item was calculated for each postoperative questionnaire survey.

The study conformed to the Japanese rules for reporting cancer survival and end-results[17]. $\chi^2$ and Mann–Whitney *U* tests were used to determine the uniformity of preoperative clinical factors. Overall and disease-free survival rates were estimated using the Kaplan–Meier method and analysed with the log rank test[18]. All calculations were performed using the SAS® life test procedure program (SAS Institute, Cary, North Carolina, USA).

## Results

Between May 1991 and April 1993, 1209 women were enrolled in the study: group 1 (level II dissection), 604 patients; group 2 (level III dissection), 605 patients. Of these, 36 women (3·0 per cent) were ineligible for the following reasons: benign disease (18 patients), stage 1 (ten), N1b (one), N2 (two), bilateral breast cancer (one), two tumours (two), informed consent not obtained (one) and operation refused (one). Consequently, 585 procedures in group 1 and 588 procedures in group 2 were eligible for analysis.

The operation was changed in a total of 61 women (5·0 per cent): 41 (6·8 per cent) in group 1 and 20 (3·3 per cent) in group 2. In the level II group, level III dissection was performed in 26 women and breast-conserving surgery in five; Halsted radical mastectomy was carried out in eight women and two had extended operations. In the level III group, level II dissection was performed in 11 women, Halsted radical mastectomy in eight, and one woman had extended surgery. Converted operations were classified as incomplete. Consequently, 544 patients in group 1 and 568 in group 2 were analysed as eligible complete cases.

There were no significant differences in preoperative clinical factors such as age, menopausal status, tumour diameter, lymph node metastasis, histological classification and hormone receptor status in all enrolled patients in the two groups (*Table 1*). One woman in group 1 was node stage N2 because her operation was changed to a level III dissection. A similar comparison of preoperative clinical factors was performed for all eligible women and for all those who completed the study as randomized; there were no differences in either analysis.

For the eligible complete procedures, the mean(s.d.) duration of surgery was significantly shorter for level II than for level III axillary dissection (133(51) *versus* 145(53) min; $P < 0·001$). Mean(s.d.) blood loss was also significantly less for level II than for level III dissections (216(159) *versus* 250(175) ml; $P = 0·001$).

Compliance with adjuvant therapy was similar between the two groups. Regarding HCFU, the proportion of women who completed more than 80 per cent of the medication regimen was 68·7 per cent in group 1 and 70·4

**Table 1** Distribution of preoperative clinical factors in all enrolled women

| | Level II ($n = 604$) | Level III ($n = 605$) | Total ($n = 1209$) | $P^*$ |
|---|---|---|---|---|
| Type of operation | | | | |
| Level II dissection | 553 | 11 | 564 | |
| Level III dissection | 26 | 575 | 601 | |
| Breast-conserving surgery | 5 | 0 | 5 | |
| Halsted radical mastectomy | 8 | 8 | 16 | |
| Extended surgery | 2 | 1 | 3 | |
| Unknown | 10 | 10 | 20 | |
| Age (years) | | | | 0·909 |
| ≤ 40 | 56 | 59 | 115 | |
| 41–50 | 223 | 224 | 447 | |
| 51–60 | 152 | 161 | 313 | |
| 61–70 | 133 | 120 | 253 | |
| ≥ 71 | 34 | 37 | 71 | |
| Unknown | 6 | 4 | 10 | |
| Menopausal status | | | | 0·218 |
| Premenopausal | 279 | 288 | 567 | |
| Postmenopausal | 310 | 310 | 620 | |
| Unknown | 15 | 7 | 22 | |
| Tumour stage | | | | 0·181 |
| T1a | 4 | 7 | 11 | |
| T2a | 584 | 587 | 1171 | |
| T2b | 10 | 3 | 13 | |
| Unknown | 6 | 8 | 14 | |
| Node stage | | | | 0·987 |
| N0 | 443 | 446 | 889 | |
| N1a | 152 | 151 | 303 | |
| N1b | 2 | 1 | 3 | |
| N2 | 1 | 1 | 2 | |
| Unknown | 6 | 6 | 12 | |
| Lymph node metastasis | | | | 0·843 |
| n0 | 389 | 398 | 787 | |
| n1 | 180 | 172 | 352 | |
| n2 | 20 | 23 | 43 | |
| Unknown | 15 | 12 | 27 | |
| Tumour diameter (cm) | | | | 0·259 |
| ≤ 2·0 | 178 | 164 | 342 | |
| 2·1–3·0 | 283 | 319 | 602 | |
| 3·1–4·0 | 77 | 64 | 141 | |
| 4·1–5·0 | 22 | 24 | 46 | |
| ≥ 5·1 | 0 | 0 | 0 | |
| Unknown | 44 | 34 | 78 | |
| Histological findings | | | | 0·673 |
| Invasive ductal carcinoma | 521 | 527 | 1048 | |
| Other | 64 | 64 | 128 | |
| Unknown | 19 | 14 | 33 | |
| Oestrogen receptor status | | | | 0·123 |
| Positive | 338 | 303 | 641 | |
| Negative | 173 | 196 | 369 | |
| Unknown | 93 | 106 | 199 | |
| Progesterone receptor status | | | | 0·512 |
| Positive | 238 | 223 | 461 | |
| Negative | 224 | 224 | 448 | |
| Unknown | 142 | 158 | 300 | |

*$\chi^2$ test.

per cent in group 2. For tamoxifen, the proportions were 74·1 and 78·2 per cent respectively.

The mean overall length of follow-up was 86 months. On the basis of intention to treat (1209 patients), the 5-year cumulative survival rate was 92·5 per cent after level II and 92·1 per cent after level III axillary dissection ($P = 0·915$, log rank test); the 10-year cumulative survival rates were 86·6 and 85·7 per cent respectively (hazard ratio (HR) 1·02; $P = 0·931$, log rank test) (*Fig. 1*). The 5-year disease-free survival rate was 84·1 per cent after level II and 84·5 per cent after level III axillary dissection ($P = 0·756$); 10-year disease-free survival rates were 73·3 and 77·8 per cent respectively (1209 patients) (HR 0·94; $P = 0·666$) (*Fig. 2*). No significant differences were observed between the two groups.

Among the eligible women (1173 patients), the 10-year cumulative survival rate was 86·4 per cent after level II and 85·5 per cent after level III axillary clearance (HR 1·01; $P = 0·947$); the 10-year disease-free survival rates were 73·0 and 77·4 per cent respectively (HR 0·95; $P = 0·690$). No significant differences were observed between the groups.

Among the 1112 'eligible complete' women, the 10-year cumulative survival rate was 87·8 per cent after level II and 85·5 per cent after level III axillary clearance (HR 1·13; $P = 0·516$), and 10-year disease-free survival rates were 74·1 and 77·6 per cent respectively (HR 1·02; $P = 0·908$).

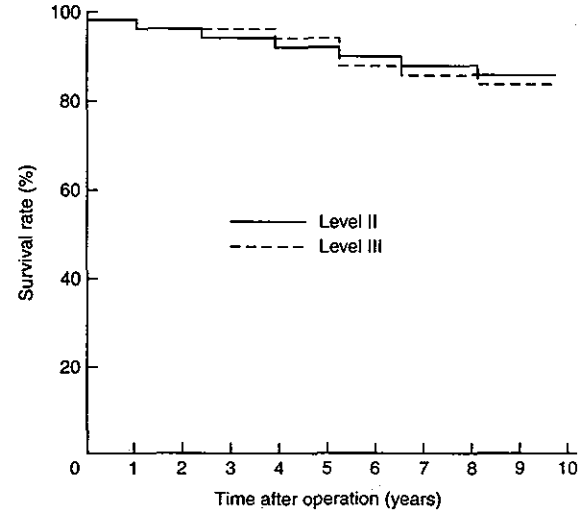


**Fig. 1** Kaplan–Meier survival curves for all 1209 enrolled women. There were no differences in overall survival between the groups: $P = 0·915$ at 5 years; $P = 0·931$ at 10 years, hazard ratio 1·02 (log rank test)

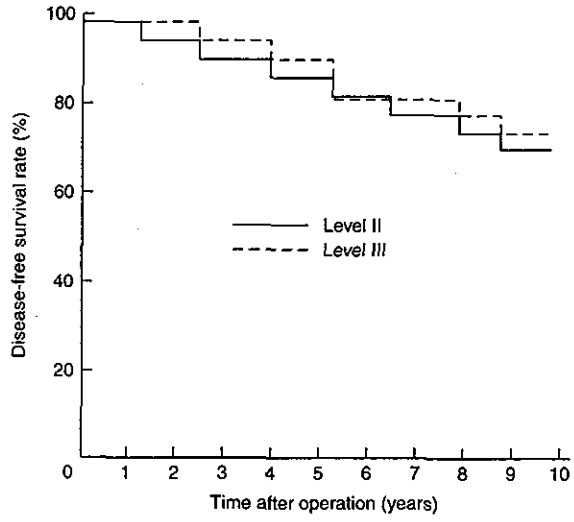


**Fig. 2** Disease-free survival for all 1209 enrolled women. There were no differences between the groups: $P = 0{\cdot}756$ at 5 years; $P = 0{\cdot}666$ at 10 years, hazard ratio 0·94 (log rank test)

Again, no significant differences were observed between the two groups.

All enrolled women were stratified according to the main factors considered to influence prognosis, and overall and disease-free survival rates were calculated. However, no significant differences were found between the groups (*Table 2*).

Finally, the women in group 1 who wrongly had level III clearance were added to the 'eligible complete' women in group 2, and those in group 2 who had a level II clearance were added to the 'eligible complete' women in group 1; a comparison was made of the prognosis for all women who had a level II clearance (555 patients) and for all those who had a level III axillary clearance (594). There were no differences in background clinical factors in these women. The 10-year cumulative survival rate was 87·9 per cent for level II and 84·6 per cent for level III clearance ($P = 0{\cdot}257$, log rank test); the 10-year disease-free survival rates were 74·1 and 76·6 per cent respectively ($P = 0{\cdot}619$). No significant differences were observed between the two types of operation.

Breast cancer recurrence rates were similar in both groups for all the enrolled women. In particular, there were no differences in the sites of recurrence between the two groups (*Table 3*).

The results of the quality of life survey varied slightly according to the time at which the survey was completed. The proportion of completed surveys for women enrolled in group 1 was 48·5–66·5 per cent, whereas that in group 2 was 47·9–62·9 per cent. There were no significant differences with respect to arm pain, motor function, social functioning or pectoralis major muscle atrophy between the two procedures at 6, 12, 18 or 24 months after surgery (*Fig. 3*).

**Table 2** Ten-year overall and disease-free survival rates by stratification of prognostic factors in all 1209 enrolled women

| | No. of patients | 10-year survival rate (%) | P* | 10-year disease-free survival rate (%) | P* |
|---|---|---|---|---|---|
| Premenopausal | | | 0·628 | | 0·559 |
| Level II | 279 | 83·8 | | 67·7 | |
| Level III | 288 | 84·8 | | 77·1 | |
| Postmenopausal | | | 0·583 | | 0·881 |
| Level II | 310 | 88·8 | | 77·3 | |
| Level III | 310 | 86·8 | | 78·0 | |
| Oestrogen receptor ($ER^-$) | | | 0·846 | | 0·778 |
| Level II | 173 | 85·7 | | 75·9 | |
| Level III | 196 | 81·2 | | 75·7 | |
| Oestrogen receptor ($ER^+$, unknown) | | | 0·873 | | 0·343 |
| Level II | 431 | 87·1 | | 71·6 | |
| Level III | 409 | 88·4 | | 79·3 | |
| Lymph node metastasis ($n^-$) | | | 0·696 | | 0·417 |
| Level II | 389 | 93·5 | | 83·4 | |
| Level III | 398 | 93·9 | | 86·8 | |
| Lymph node metastasis ($n^+$) | | | 0·610 | | 0·893 |
| Level II | 200 | 72·7 | | 53·3 | |
| Level III | 195 | 69·1 | | 59·5 | |

*Log rank test.

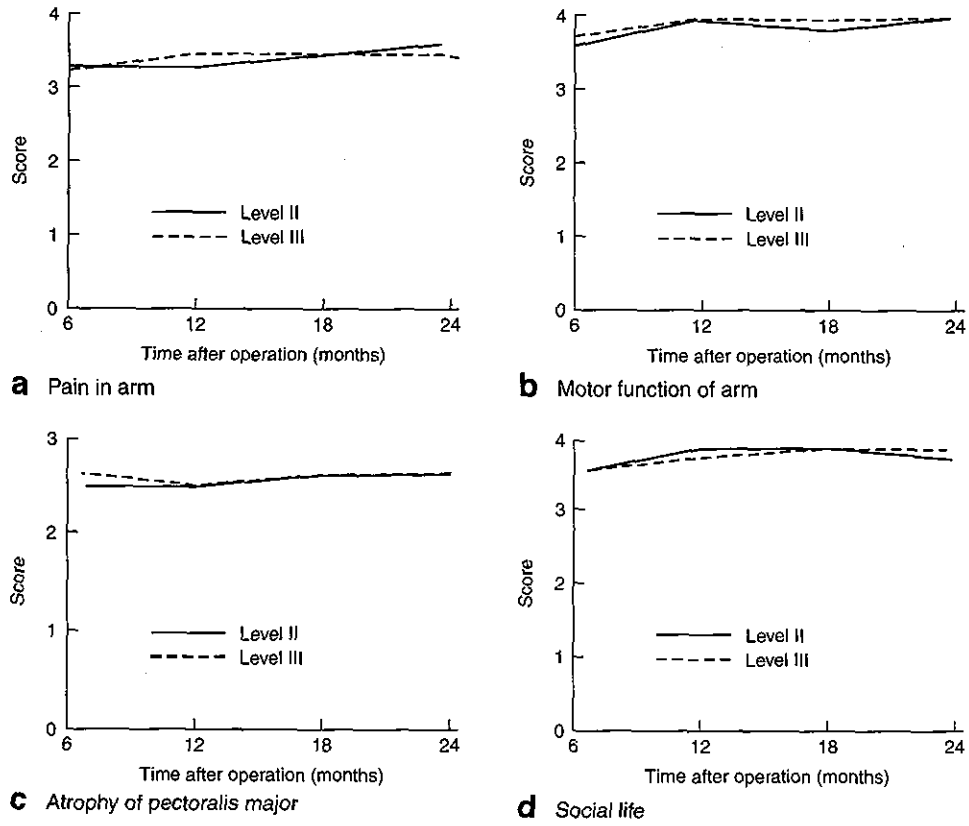


**Fig. 3** Changes in mean scores of questionnaire survey over time. **a** Arm pain: grade 1, acute pain requiring medication; 2, constant pain; 3, occasional pain; 4, no pain. **b** Motor function of arm: grade 1, arm could not be raised to horizontal level; 2, arm could be raised above horizontal level but less than 45° obliquely; 3, arm could be raised more than 45° obliquely; 4, arm could be raised vertically. **c** Pectoralis major muscle atrophy: grade 1, atrophy in upper half of muscle; 2, atrophy in lower half of muscle; 3, no atrophy. **d** Social functioning: grade 1, no association with other people; 2, little association with others; 3, same as before surgery; 4, improved. There were no differences between the groups

**Table 3** Sites of breast cancer recurrence in all enrolled women

| | Level II ($n$ = 604) | Level III ($n$ = 605) | Total ($n$ = 1209) | $P^*$ |
|---|---|---|---|---|
| Recurrence free | 490 (81·1) | 497 (82·1) | 987 (81·6) | |
| Women with recurrence | 114 (18·9) | 108 (17·9) | 222 (18·4) | 0·646 |
| Site of recurrence | | | | |
| Soft tissue | 43 (7·1) | 34 (5·6) | 77 (6·4) | 0·141 |
| Opposite breast | 3 (0·5) | 2 (0·3) | 5 (0·4) | 0·653 |
| Skin | 21 (3·5) | 18 (3·0) | 39 (3·2) | 0·622 |
| Lymph node | 19 (3·1) | 14 (2·3) | 33 (2·7) | 0·375 |
| Bone | 32 (5·3) | 33 (5·5) | 65 (5·4) | 0·904 |
| Viscera | 34 (5·6) | 34 (5·6) | 68 (5·6) | 0·994 |
| Lung | 23 (3·8) | 19 (3·1) | 42 (3·5) | 0·526 |
| Brain | 1 (0·2) | 0 (0·0) | 1 (0·1) | 0·317 |
| Liver | 8 (1·3) | 8 (1·3) | 16 (1·3) | 0·997 |
| Other | 2 (0·3) | 7 (1·2) | 9 (0·7) | 0·095 |
| Other | 5 (0·8) | 7 (1·2) | 12 (1·0) | 0·564 |

Values in parentheses are percentages. *$\chi^2$ test.

## Discussion

Modified radical mastectomy is an operation in which the breast and axillary lymph nodes are dissected *en bloc* and the pectoralis major muscle is left intact. This operation was first performed by Patey[10] and continues to be used widely in Japan today. Compared with radical mastectomy, it has the advantages of a good postoperative cosmetic appearance, maintained motor activity in the arm, a low rate of postoperative arm oedema and easy postoperative breast reconstruction.

This study was a randomized comparison of level II and level III dissection for removal of axillary lymph nodes in women with stage II breast cancer. In Japan, when this study was conducted, dissection to level III was performed for almost all patients with fixed, palpable axillary nodes (stage 1b); therefore, patients with these tumours were excluded from the study. There were no significant

differences in 5- and 10-year cumulative or disease-free survival rates between the two axillary procedures, nor in the sites of cancer recurrence.

While some unknown prognostic factor may have masked possible differences, the background factors of the women were well matched and there were no significant primary factors that could have influenced the results. The possibility that operations that deviated from protocol created a bias was ruled out, as there were no significant differences in the results when these operations were excluded from the analysis. Additionally, comparison of the actual operations performed did not identify differences in overall and disease-free survival rates. It is unlikely that the adjuvant therapy used exerted an influence, because both groups received the same postoperative adjuvant therapy and no difference in compliance was found between the groups.

Duration of operation and blood loss were significantly less for level II axillary dissection, but this did not influence the clinical results. With respect to symptoms reported during follow-up, there were no differences in arm pain, pectoralis major muscle atrophy, motor function of the arm, or social functioning.

In this randomized clinical trial comparing two variations of modified radical mastectomy for stage II breast cancer, there were no significant differences in the 10-year cumulative and disease-free survival rates. There was no benefit from resection of the pectoralis minor muscle and dissection of level III axillary nodes. Level II axillary node dissection is preferable for these patients.

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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

Hiroyuki Takei*1, Kimito Suemasu*1, Masafumi Kurosumi*2, Kazuhiro Uchida*1, Kiyomi Igarashi*1, Jun Ninomiya*1, Rin Naganuma*1, Tomoyuki Kusawake*1,3, Noritaka Sugamata*1,4, Hiroshi Matsumoto*1, and Yasuhiro Higashi*1

*1*Division of Breast Surgery, *2*Department of Pathology, Saitama Cancer Center, *3*Tamamura Chuo Clinic, and *4*Mammoexas Sugamata Clinic, Japan.*

***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

Reprint requests to Hiroyuki Takei, Division of Breast Surgery, Saitama Cancer Center, 818 Ina-machi, Kitaadachi, Saitama 362-0806, Japan.
E-mail: h-takei@cancer-c.pref.saitama.jp

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 $\mu$m 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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原著

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# 腫瘤径31-50mmの乳癌に対する乳房温存療法の成績

五十嵐 清美[*1]　武井寛幸[*1]　末益公人[*1]　黒住昌史[*2]　内田和宏[*1]
二宮　淳[*1]　長沼りん[*1]　井上賢一[*3]　田部井敏夫[*3]　東　靖宏[*1]

**Outcome of Breast-Conserving Treatment in Patients with Invasive Breast Cancer Measuring 31 to 50mm** : Igarashi K[*1], Takei H[*1], Suemasu K[*1], Kurosumi M[*2], Kazuhiro U[*1], Ninomiya J[*1], Naganuma R[*1], Inoue K[*3], Tabei T[*3] and Higashi Y[*1] ([*1]Division of Breast Surgery, [*2]Department of Pathology, [*3]Division of Breast Oncology Saitama Cancer Center).

In 1999 the Japanese Breast Cancer Society proposed guidelines for breast-conserving treatment (BCT), in which one of the criteria for patient selection is a tumor size of 30mm or smaller. To determine whether BCT is reasonable for patients with invasive breast cancer (IBC) measuring 31mm or larger, we compared the outcome of BCT on 173 patients with IBC measuring 31 to 50mm (group A) with that on 322 patients with IBC measuring 21 to 30mm (group B). Median follow-up period was 27 and 33 months in groups A and B, respectively. The local recurrence rate was 2.3% and 2.2% in groups A and B, respectively, showing no significant difference. Relapse-free survival (RFS) and overall survival (OS) were not significantly different between groups A and B, although both seemed to be slightly worse in group A than in group B. Multivariate analysis using Cox proportional hazard regression model demonstrated that breast radiotherapy and estrogen receptor status were independently predictive for local recurrence, while nodal status and ER status were independently predictive for both RFS and OS.

In conclusion, there was no significant difference in local recurrence rates based on the tumor size itself. Therefores the decision in patient selection for BCT should not be based solely on tumor size.

**Key words** : Breast-conserving treatment, Tumor size,Local recurrence, Prognosis
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## はじめに

乳房温存手術は，1970年代にFisherやVeronesiらにより臨床試験が開始され[1,2]，1990年代になると日本でも多くの施設で導入された．日本乳癌学会のアンケート調査によると，2000年乳癌手術症例のうち乳房温存手術の占める割合は41%であった[3]．

1999年に日本乳癌学会学術委員会が作成した乳房温存療法ガイドライン[4]によれば，乳房温存療法の適応基準の一つに，「腫瘤の大きさが3.0cm以下であること」との記載がある．但し書きとして，「腫瘤の大きさが3.1cm以上で患者が本療法を強く希望する場合，術前・術後治療を十分検討し，実施することが望ましい」とある．しかし，腫瘤径の基準を3.0cmとした理由は明らかでなく，また，欧米の乳房温存療法のガイドラインには，「腫瘍径は乳房温存療法の絶対的禁忌でない」[5]とある．

当科では1991年から乳房温存療法を開始し，当初，腫瘤径，腫瘤乳頭間距離を適格基準に入れていたが，最近では，腫瘤の完全切除が可能で整容

*1 埼玉県立がんセンター乳腺外科
*2 埼玉県立がんセンター病理科
*3 埼玉県立がんセンター内分泌科

性が保たれれば，腫瘤径にこだわらず乳房温存療法を施行している．このような乳房温存療法の適応拡大には，術前画像診断の進歩により腫瘍の広がりを的確に評価できるようになったことが大きく寄与している．

今回われわれは，乳房温存療法ガイドラインによると適応外症例である，腫瘤径31mm以上の乳癌に対する乳房温存療法の妥当性を検討するために，腫瘤径31mm以上のT2乳癌症例に対する乳房温存療法の成績を，30mm以下のT2乳癌症例と比較検討したので報告する．

## 対象と方法

1991年1月から2001年12月までに当センターで乳房温存手術が施行され，非浸潤性乳癌症例，術前化学療法施行症例，術前乳房照射施行症例，異時両側乳癌の第2癌症例を除外した，T2,N0-1乳癌，495症例を対象とした．このうち，腫瘤径が31mm以上50mm以下の173症例をA群，21mm以上30mm以下の322症例をB群とし，両群間で臨床病理学的因子および予後について比較検討した．

検討項目は，年齢，腫瘤径，組織型，腋窩リンパ節転移，ホルモンレセプター（エストロゲンレセプター：ER，プロゲステロンレセプター：PR），切除断端（5mm以内に癌のあるものを陽性），腋窩郭清の有無，術後照射の有無，術後補助療法，乳房内無再発生存率，健存率および全生存率であった．

両群間の統計学的比較は$\chi^2$検定，t-検定を，また生存率の算出，検定にはKaplan-Meier法，log-rank検定を用い，臨床病理学的因子の予後に及ぼす影響については，Coxの比例ハザードモデルを用いた単変量解析を行い，有意差を有する因子ではさらに多変量解析を行った．

## 結　果

### 1）臨床病理学的背景因子（表1）

平均年齢では，A群が52.2歳，B群が54.5歳でA

**表1　乳房温存術が施行されたT2 N0,1乳癌症例の腫瘍径別臨床病理学的特徴**

| | | A群(31-50mm) | | B群(21-30mm) | | P値 |
|---|---|---|---|---|---|---|
| 症例数 | | 173 | | 322 | | |
| 平均年齢 | | 52.2(25-82)歳 | | 54.5(25-81)歳 | | 0.028 |
| 平均腫瘤径 | | 37.0mm | | 24.7mm | | <0.0001 |
| N | 0 | 107 | 62% | 260 | 81% | |
| | 1 | 66 | 38% | 61 | 19% | <0.0001 |
| 組織型 | 乳頭腺管癌 | 33 | 19% | 74 | 23% | |
| | 充実腺管癌 | 60 | 35% | 71 | 22% | |
| | 硬癌 | 63 | 36% | 149 | 46% | 0.016 |
| | その他 | 17 | 10% | 28 | 9% | |
| リンパ節転移個数 | 0 | 101 | 58% | 199 | 62% | |
| | 1-3 | 45 | 26% | 88 | 27% | |
| | 4- | 26 | 15% | 28 | 9% | 0.10 |
| | 非郭清 | 1 | 1% | 7 | 2% | |
| ホルモンレセプター | ERまたはPR陽性 | 104 | 60% | 231 | 72% | |
| | ER，PRともに陰性 | 67 | 39% | 85 | 26% | 0.017 |
| | 不明 | 2 | 1% | 6 | 2% | |
| 断端 | 陽性 | 56 | 32% | 82 | 25% | |
| | 陰性 | 117 | 68% | 240 | 75% | 0.10 |
| 腋窩郭清 | あり | 101 | 58% | 191 | 59% | |
| | なし | 1 | 1% | 7 | 2% | 0.37 |
| | SLNBのみ | 71 | 41% | 124 | 39% | |
| 術後照射 | あり | 148 | 86% | 266 | 83% | |
| | なし | 25 | 14% | 56 | 17% | 0.40 |
| 補助療法 | ホルモン療法 | 96 | 55% | 198 | 61% | 0.19 |
| | 化学療法 | 77 | 45% | 131 | 41% | 0.41 |
| | なし | 21 | 12% | 41 | 13% | 0.85 |

ER：エストロゲンレセプター，PR：プロゲステロンレセプター，SLNB：センチネルリンパ節生検

群のほうが若年であった(P=0.028). 平均腫瘤径は, A群, 37mm, B群, 25mmで, A群のほうが大きく, 有意差を認めた (P<0.0001). 腋窩リンパ節転移では, A群でN1症例が38%認められ, B群の19%に比べ有意に多かった (P<0.0001). 病理学的リンパ節転移陽性例, 転移個数ともA群で多い傾向が見られたが, 有意差は認められなかった. 組織型についてみると, 乳頭腺管癌, 硬癌では両群間に有意差はなかったが, 充実腺管癌がA群において有意に多かった(P=0.016). ホルモンレセプターでは, ER, PRともに陰性の症例がA群において有意に多かった (P=0.017). 切除断端では, 断端陽性率がA群32%, B群25%と, A群に断端陽性例が多い傾向がみられたが, 有意差はなかった. 腋窩郭清施行の有無, 乳房照射の有無および術後補助療法については, 両群間に有意差はなかった.

**2) 予　後**

腫瘤径別予後を検討すると, 観察期間中央値は, A群, 27 (6-132) カ月, B群, 33 (6-134) カ月で, A群で有意に短かった(表2). これは乳房温存療法適応拡大の時期のずれによるものと思われる. 乳房内再発をみると, A群では4例(2.3%), B群では7例 (2.2%) に認められ, 有意差はなく (表2), これら再発症例すべてにサルベージ手術が行われた. 遠隔再発はA群12例 (6.9%), B群14例 (4.3%) に認められ, 乳癌死は, A群5例 (2.9%), B群6例 (1.9%) に認められ, A群のほうが遠隔再発, 乳癌死ともに多い傾向であったが, 有意差はなかった (表2).

Kaplan-Meier法により健存率, 生存率を算出し, log-rank testによる有意差検定を行った. 5年乳房内無再発生存率はA群95.9%, B群96.8%で, 両群間に有意差はなかった (P=0.70) (図1a). 術後乳房照射の有無による, 5年乳房内無再発生存率は照射群97.7%, 非照射群90.7%で, 照射を施行した患者で有意に良好であった (P=0.011) (図1b). また, ERの陽性と陰性では, ER陽性群98.2%, 陰性群93.6%で, ER陽性症例で有意に良好であった(図1c). 腫瘤径別の5年健存率はA群84.8%, B群90.3%とA群でやや不良であったが, 有意差はなかった (P=0.13) (図2). 5年全生存率についてみると, A群94.6%, B群97.7

表2　乳房温存術が施行されたT2 N0,1乳癌症例の腫瘤径別予後

| | A群(31-50mm) | | B群(21-30mm) | |
|---|---|---|---|---|
| 観察期間中央値 | 27カ月 | | 33カ月 | |
| 乳房内再発 | 4例 | 2.3% | 7例 | 2.2% |
| 遠隔再発 | 12例 | 6.9% | 14例 | 4.3% |
| 乳癌死 | 5例 | 2.9% | 6例 | 1.9% |

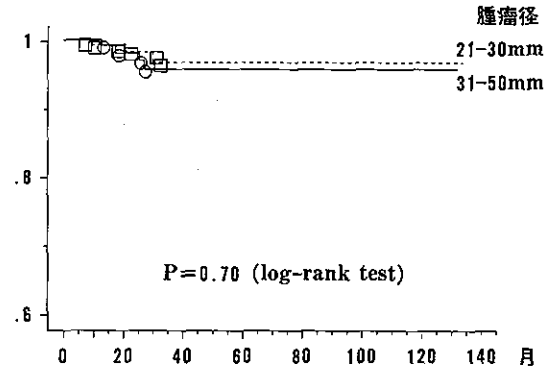


図1a　腫瘤径別の乳房内無再発生存率

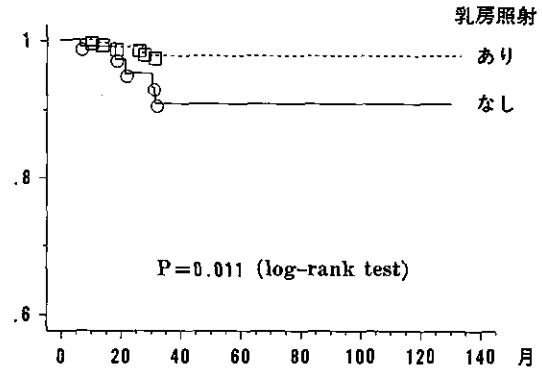


図1b　乳房照射有無による乳房内無再発生存率

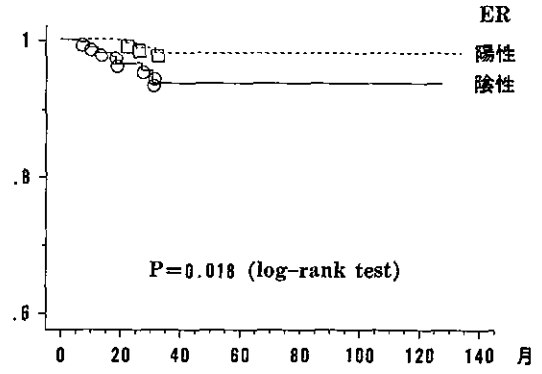


図1c　ER陽陰性別の乳房内無再発生存率