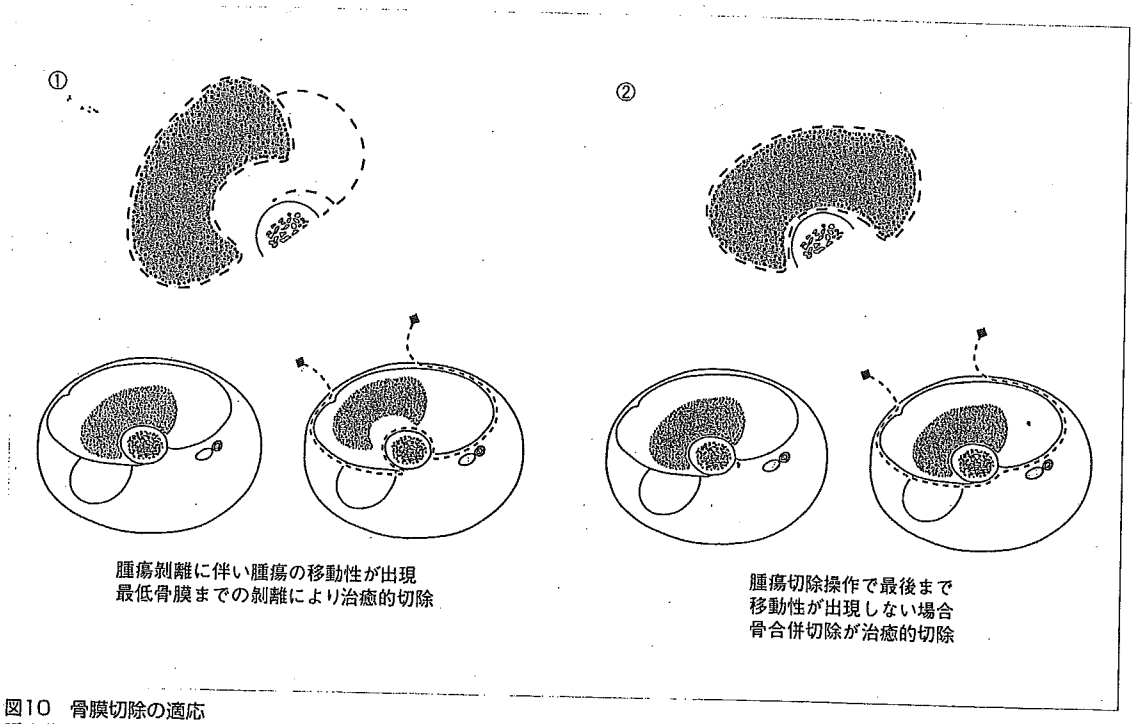


図10　骨膜切除の適応
腫瘍移動性を獲得できるか，否かによる．①骨膜が浸潤，癒着を受けていない場合，腫瘍の周辺の切離が進むにつれて，移動性がみられるようになる．このような状況で，骨膜剝離合併切除を追加すると十分な広範切除縁が確保できる．②一方，手術中も移動性が認められない場合は，腫瘍が強く骨膜と癒着を起こしているときや，骨近傍まで腫瘍が増大しているときで，もはや骨膜は安全なバリアとはいえない．骨合併切除が必要である．

が不可欠となり手術の手間は変わらない．

関節合併切除：関節，筋肉付着部，起始部では，骨膜は薄くバリアとならないことを銘記すべきである．関節包，筋肉付着部は骨膜と連続した組織で，さらに骨皮質へと連続しているので関節包や筋肉の付着部骨皮質の合併切除が基本である．ときには，関節面を切除縁として，関節包を起こし，周辺の靱帯，筋肉付着部を含む関節半側切除を施行する．

軟部処理のみの切除：関節近傍，周囲の腫瘍で，画像情報で関節包，周囲組織に接し切除縁は判別できない状況で，切除を進めるうちに関節包と腫瘍の間に，健常組織が存在して移動性が生じた場合は，関節周囲軟部の処理，関節包，関節周囲靱帯の合併切除で切除縁が確保される．

骨，関節合併切除：骨，関節に癒着し，関節包，筋肉付着部との連続性，術中腫瘍の移動性が確認できないとき，関節内に腫瘍浸潤を疑わせる所見を認める場合，骨関節内浸潤があると判断する．このときは，関節，骨片側切除，部分切除と関節周囲の軟部組織の合併切除が必要である．手技として，腫瘍から離れた関節包を起こし，関節周辺筋肉付着部を目安に骨皮質，骨組織とともにノミ，bone sawで合併切除する．特に，膝関節後方に局在した腫瘍の切除は，腓腹筋付着部，後方関節包を合併切除すると広範切除縁が確保できる．大腿部内転筋群の起始部に発生した軟部腫瘍は，骨盤に近接しているので，坐骨，恥骨の合併切除や，大腿骨，骨頭の合併切除が必要となる．骨膜，骨付着部を無理に剝離し，腫瘍を引き出す操作を行うと，腫瘍を被う軟部組織を破損し，局所再発の原因になる．切除に際して，血管神経が近接して，十分な展開が確保できない場合には，骨幹部で骨切りを行い，関節ごと腫瘍を翻転して血管神経を剝離すると切除，関節周辺の処置が確実となる（図11）．

悪性軟部腫瘍が，関節内，骨組織に浸潤した場合：積極的に関節外切除，骨幹部までの骨組織合併切除を行い，広範切除線を確保する．操作は増えるが，骨組織の移動で，視野は広がり

◎悪性軟部腫瘍を切除する基本技術は，切除縁の正確な確保と神経，血管を確実に処理する正確，丁寧な操作に集約される．

◎鋭的剥離，術後血腫，組織反応液貯留を防止，皮膚，組織壊死の発生防止などの術中，術後対策に配慮し，手術合併症の発生防止が重要である．

◎切除計画は十分に行い，確実な視野，展開を確保し無理な操作を極力避け，手術計画の正確な実践が安全性，確実性につながる．

処理も確実となるので，血管，神経に無理な牽引操作を加えずに切除が進められる．骨関節合併切除と強力な放射線療法の併用は勧められない．その理由は，静脈，リンパ管の還流が低下するため，下肢の循環不全が必発となるからである．術後の浮腫，広範な皮膚血行不全，皮膚壊死，感染発生が起こりやすくなるからである．特に会陰部での創には特に注意する必要がある．これらの合併症の危険性を回避するためには，関節周囲組織の合併切除後には，十分な健常な筋，皮下組織，皮膚組織による再建つまり筋膜，皮下組織を含めた局所回転皮弁，有茎皮弁，血管柄付き遊離筋皮弁の再建によるカバーリングが不可欠である．

骨盤，肩甲骨では，骨部分切除：骨盤，肩甲骨周辺の筋層は，菲薄で容易に浸潤を受けやすい．肩甲骨，支持性に関与する臼骨部から仙腸関節を除く腸骨，恥骨，坐骨は積極的に合併切除を計画して，より安全な切除縁を確保すべきである．足背，手背部，前腕部では，多くの小関節が存在し，関節周囲の組織が複雑に交差している．骨膜で切除操作を行うより，骨部分切除，骨皮質を削ぎとるように切離すると確実な切除が可能となる．

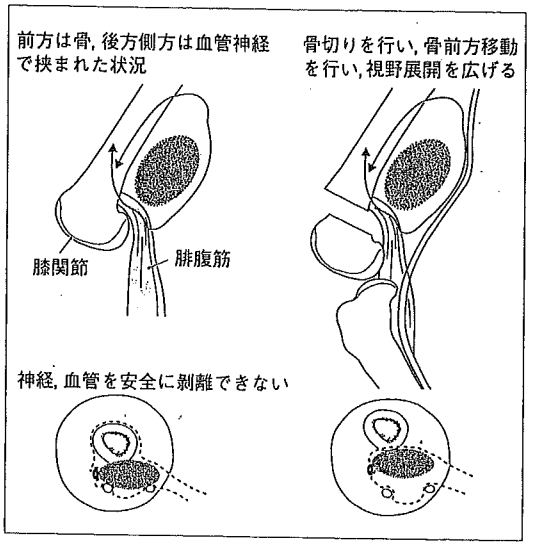


図11　骨切り，移動による展開（膝窩部）

文献
1) 整形外科・病理：悪性軟部腫瘍取扱い規約．日本整形外科学会　骨・軟部腫瘍委員会編，金原出版株式会社，2002
2) Fleming, ID et al : Soft tissue sarcoma. In Fleming ID, Cooper JS, Henson DE, et al. AJCC Cancer staging manual. American Joint Committee on Cancer, 5th ed, Lippinocott-Raven, pp149-188, 1997
3) 川口智義：軟部肉腫の治療－1．腫瘍の切除法．整形外科 50：655-661，1999
4) 川口智義：軟部肉腫の治療－2．手術の補助療法と組織の処理再建法．整形外科 50：780-786，1999
5) Enneking, WF : Staging musculoskeletal tumors. Musculoskeletal tumor surgery, ed by Enneking WF, Churchill Livingstone, New York, pp69-88, 1983
6) Kawaguchi, N et al : New method of evaluating the surgical margin and safety margin for musculoskeletal sarcoma, analysed on the basis of 457 cases. J Cancer Res Clin Oncol 121：555-563，1995
7) Manabe, J : Analysis of safety margins based on registration of surgical challenges for musculoskeletal sarcomas. ed by Surgical Society for Musculoskeletal Sarcoma. Japanese Foundation Cancer Research 3：333-344，2003
8) Brennan, MF et al : Soft tissue sarcoma. In DeVita, VT, Hellman, S and Rosenberg, SA (eds). Cancer : principles and practice of oncology. Lipponcott-Raven Publishers, New York, pp1738-1788, 1997
9) Brennan, MF et al : Diagnosis and Management of Soft Tissue Sarcoma, Martin Dunitz Ltd, London, pp153-166, 2002

# 緊急を要する脊椎除圧固定術の適応決定

ONE POINT ADVICE

国立がんセンター中央病院整形外科
中馬広一

■はじめに

がん患者の再発，末期の骨転移は，患者の生活の質，日常生活活動性を急速に低下させるので，末期緩和治療の大きなテーマである．特に脊椎転移は，高度体動時痛，麻痺を発生させ，緩和的化学療法，放射線療法を行うための大きな障害となる．緊急手術に際して最小限の情報を収集する方法，放射線治療と緊急緩和的脊椎除圧の適応の決定について述べる．

■脊椎腫瘍，脊髄麻痺に対する手術療法に必要な情報

麻痺，高度体動時痛が発生した患者を治療するために必要な情報は，麻痺の程度，麻痺の進行速度，画像所見，全身状態，内科治療や放射線治療による麻痺改善の反応性などであり，これらを総合的に判断する．

運動神経麻痺，痛覚の低下を評価するフランケルCからBのレベルまで低下すると，術後の運動神経の回復が不完全となり，回復まで数ヵ月から半年の集中リハビリが必要となる．軽度運動知覚麻痺が出現するか，歩行不能となり始めた軽微な段階で手術に踏み切るべきである．患者，他科の担当医への適応，ベネフィットについて十分に説明してほしい．

血液凝固系，高Ca血症などの電解質異常，臓器転移（特に縦隔リンパ管，がん性リンパ管炎，肝臓転移），多発，びまん性骨髄転移などの所見は，腫瘍量が非常に多い状況を示すもので致命的な臓器，血液障害が発生していると考える．肺がん，胃がんで起こりやすいが，胆管，大腸がんなどの消化器系のがんの末期，比較的経過が長いと考えられる乳がん，前立腺がん，頭頸部がん，腎臓がんでも組織悪性度の高い症例で観察され，周術期の合併症，短期死亡の原因となる．予後不良症例であり手術の適応はない．

■脊椎固定術，脊髄除圧などの緩和的脊椎手術の適応

緊急手術の適応を集約すると4つのケースがある（図1）．

(a) 急激な麻痺の発症と高度な麻痺に遭遇したとき

がんの既往があっても，初回再発か，全身の腫瘍が十分にコントロールされて，普通の社会活動を営んでいた患者が，突然，高度な疼痛と麻痺を発症した場合は，緊急手術の対象となる．このような症例では，麻痺は高度で，急速増悪期にあり，緩和的な放射線治療，大量ステロイド療法，緊急化学療法などでは麻痺の改善が望めず，時間の経過とともに脊髄の障害は進行する．早急に除圧，脊椎固定が不可欠である．最低限の検査は，全身麻酔，一般的手術の術前検査，全身の造影CT，脊椎，骨盤のMRI検査である．単発性再発の患者，十分に全身状態がコントロールされている患者，麻痺発生前に高い肉体，精神的活動性が保たれ術後早期に離床し，社会生活に復帰できる患者が手術の対象となる．担当医は長期予後が見込まれ，有望な内科的治療があり，患者もその治療を望んでいることを確認する必要がある．近年，分子標的治療薬剤が導入され，組織細胞の増殖因子の有無がその後の治療の選択に重要な情報となってきているので，緩和的椎弓切除，後方固定の際に，組織採取，生検を行うことの重要性が増している．生命予後の判定では，がんの種類に応じた平均的予後のスコアリングが判断の参考となり，6ヵ月以上の予後が期待されるときは手術療法が薦められる．

(b) 放射線治療抵抗性の麻痺

脊椎転移に対して放射線療法を開始したものの，麻痺が進行する場合は，緩和的椎弓切除，脊椎固定の適応となる．多くの場合は，麻痺増悪は急激で緊急手術が不可欠で，あまりだらだらと経過を観察しないことが望まれる．麻痺の増悪に伴う回復までの期間は，かなり必要でなるべく早い段階での決断が必要となる．

(c) 高度な疼痛，体動時痛

病巣がさまざまな治療に抵抗性で，高度な脊柱変形や椎体変形による高度な痛みが発生している症例に対して後方固定が有効となる．予防的に広範囲に脊椎固定を行うと，長期間脊椎の安定を保つことが可能である．麻痺の発生がなくても，脊椎の安定性確保によって，長期間の日常生活活動性を保つことが可能になる．部分的な椎体変形や不安定性に伴う疼痛に対しては，椎体形成術，セメント注入も一つの有効な治療法となり，局所麻酔下で行えるので試みてよい方法である．内臓転移を起こし状態不良な症例にも試行可能で，治療のモダリティーを広げることになる．

(d) 未診断の原発不明がんの脊椎転移腫瘍，脊椎腫瘍

がんの既往のない患者が，頑固な背部痛，麻痺で初めて発症した脊椎腫瘍は，緊急な対応が必要である．単発脊椎腫瘍，数個転移，多発びまん性転移，骨髄症などと骨転移の病状，進行度はさまざまなので，血液凝固系異常，代謝異常の有無，MRI画像，全身のCT画像を行って，全身の病状を判断する．骨髄症やびまん性転移を呈する症例では，骨髄穿刺，骨髄生検で組織診断，がん細胞が確定できることが



S)

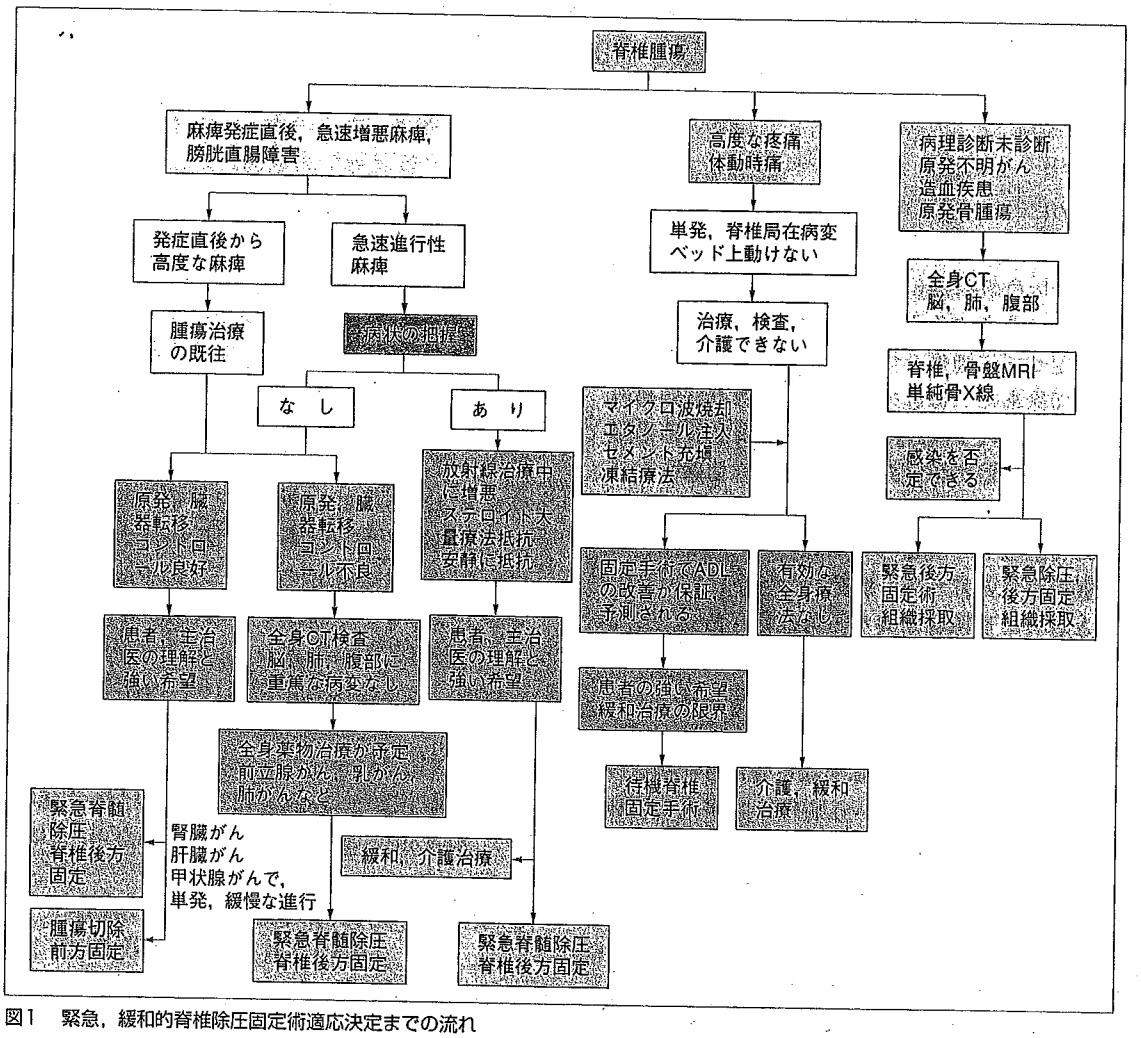


図1　緊急，緩和的脊椎除圧固定術適応決定までの流れ

多く，病状も不安定で，内科的治療が最優先となる．成人発生の多発転移は，原発不明がん骨転移の症例が多いが，腫瘍マーカーを含めた血液検査，全身CT検査，細胞診，コアーニードルで採取された小組織片でがんであることの診断は十分可能である．単発性脊椎腫瘍においては，造血性腫瘍，原発性骨腫瘍，比較的まれな腫瘍など，組織診断による情報が不可欠である．また，消化器造影検査，内視鏡検査など多くの画像検査や，PET検査は，患者輸送や体動が制限されている状況では行いにくく，患者の苦痛や負担も大きくなる．腫瘍組織採取，生検をかねて脊髄除圧を行い，脊椎の安定性を確保して麻痺，高度体動時痛を緩和する目的で脊髄除圧後方固定を行うことは大きな支援療法となる．内科的緩和的治療を行うにしても，麻痺や疼痛で動けない患者の化学療法や緩和治療はきわめて困難である．骨，脊椎合併症は，患者生活，社会活動，闘病生活をきわめて制限することになる．病理組織診断の生検術をかねた緩和的脊椎固定，脊髄除圧を初めに行う外科的治療はきわめてメリットが高い．注意する点は，感染症と麻痺の増悪の危険性を如何に軽減するかである．放射線療法や化学療法を併用することが多いがんの治療では，感染の併発がきわめて大きな治療障害因子となり十分に注意すべき合併症である．

Reprinted From

The American Journal of Surgery

FEBRUARY 2006 VOLUME 191, NUMBER 2

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

Takayuki Kinoshita, M.D.[a], Miyuki Takasugi, M.D.[a], Eriko Iwamoto, M.D.[a], Sadako Akashi-Tanaka, M.D.[a], Takashi Fukutomi, M.D.[a], Shoji Terui, M.D.[b]

[a]*Division of Surgical Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji Chuo-ku, Tokyo 104-0045, Japan*
[b]*Division of Nuclear Medicine, National Cancer Center Hospital, Tsukiji Chuo-ku, Tokyo, Japan*

pp. 225-229

Excerpta Medica

The American Journal of Surgery*

The American Journal of Surgery 191 (2006) 225–229
Scientific papers–International

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

Takayuki Kinoshita, M.D.[a,*], Miyuki Takasugi, M.D.[a], Eriko Iwamoto, M.D.[a], Sadako Akashi-Tanaka, M.D.[a], Takashi Fukutomi, M.D.[a], Shoji Terui, M.D.[b]

[a]*Division of Surgical Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji Chuo-ku, Tokyo 104-0045, Japan*
[b]*Division of Nuclear Medicine, National Cancer Center Hospital, Tsukiji Chuo-ku, Tokyo, Japan*

Manuscript received February 10, 2005; revised manuscript June 22, 2005

**Abstract**

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

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

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

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

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

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

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

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

* Corresponding author. Tel.: +81-3-3542-2511; fax: +81-3-3542-3815.
*E-mail address:* takinosh@ncc.go.jp

0002-9610/06/$ – see front matter 
doi:10.1016/j.amjsurg.2005.06.049

Table 1
Patient demographics

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

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

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

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

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

## Methods

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

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

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

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

## Results

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

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

Table 2
Results of sentinel node biopsy examination

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

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

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

False-negative rate = 11.1%.

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

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

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

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

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

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

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

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

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

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

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

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

## Comments

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

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

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

Table 7
Studies of SLN biopsy procedures after NAC

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

NS = not specified.

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

It has been speculated that among patients who have their axillary lymph node status downstaged by NAC, tumors also typically respond to NAC and shrink, so that damage to and alteration of the lymphatic flow from tumor tissues to the axillary basin are more likely to occur. This may cause an increase in the false-negative rate for SLN biopsy examination and a decreasing identification rate for SLN biopsy examination. Our hypothesis is that the lymphatic flow around the skin lesion is rich and less influenced by the effect of chemotherapy and tumor size than that in the parenchyma around the tumor. Our results were not significantly influenced by tumor size, tumor response, or nodal status before NAC.

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

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

## References

[1] Cody HS 3rd. Clinical aspects of sentinel node biopsy. Breast Cancer Res 2001;3:104–8.
[2] Cody HS, Borgen PI. State-of-the-art approaches to sentinel node biopsy for breast cancer: study design, patient selection, technique and quality control at Memorial Sloan-Kettering Cancer Center. Surg Oncol 1999;8:85–91.
[3] Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer—a multicenter validation study. N Engl J Med 1998;339: 941–6.
[4] Anderson BO. Sentinel lymphadenectomy in breast cancer: an update on NCCN Clinical Practice Guidelines. J Natl Compr Cancer Network 2003;1(Suppl 1):S64–70.
[5] Reintgen D, Giuliano R, Cox C. Lymphatic mapping and sentinel lymph node biopsy for breast cancer. Cancer J 2002;8(Suppl 1):S15–21.
[6] Breslin TM, Cohen L, Sahin A, et al. Sentinel lymph node biopsy in accurate after neoadjuvant chemotherapy for breast cancer. J Clin Oncol 2000;18:3480–6.
[7] Miller AR, Thompson VE, Yeh IT, et al. Analysis of sentinel lymph node mapping with immediate pathologic review in patients receiving preoperative chemotherapy for breast carcinoma. Ann Surg Oncol 2002;9:243–7.
[8] Stearns V, Ewing CA, Slake R, et al. Sentinel lymphadenectomy after neoadjuvant chemotherapy for breast cancer may reliable represent the axilla except for inflammatory breast cancer. Ann Surg Oncol 2000;9:235–42.

[9] Haid A, Tausch C, Lang A, et al. Is sentinel lymph node biopsy reliable and indicated after preoperative chemotherapy in patients with breast cancer? Cancer 2001;92:1080–4.
[10] Julian TB, Patel N, Dusi D, et al. Sentinel node biopsy after neoadjuvant chemotherapy for breast cancer. Am J Surg 2001;182:407–10.
[11] Julian TB, Dusi D, Wolmark N. Sentinel node biopsy after neoadjuvant chemotherapy for breast cancer. Am J Surg 2002;184:315–7.
[12] Tafra L, Verbanac KM, Lannin DR. Preoperative chemotherapy and sentinel lymphadenectomy for breast cancer. Am J Surg 2001;182:312–5.
[13] Nason KS, Anderson BO, Byrd DR, et al. Increased false negative sentinel node biopsy rates after preoperative chemotherapy for invasive breast carcinoma. Cancer 2000;89:2187–94.
[14] Shimazu K, Tamaki Y, Taguchi T, et al. Sentinel lymph node biopsy using periareolar injection of radiocolloid for patients with neoadjuvant chemotherapy-treated breast carcinoma. Cancer 2004;100:2555–61.
[15] Bedrosian I, Reynolds C, Mick R, et al. Accuracy of sentinel lymph node biopsy in patients with large primary breast tumors. Cancer 2000;88:2540–5.
[16] O'Hea BJ, Hill AD, El-Shirbiny AM, et al. Sentinel lymph node biopsy in breast cancer: initial experience at Memorial Sloan-Kettering Cancer Center. J Am Coll Surg 1998;186:423–7.
[17] Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from the National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 1997;15:2483–93.
[18] Smith IC, Heys SD, Hutcheon AW, et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol 2002;20:1456–66.
[19] Mamounaus E, Brown A, Smith R, et al. Accuracy of sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: update results from NSABP B-27. Proc Am Soc Clin Oncol 2002;21:36a.
[20] Gianni L, Baselga H, Eiermann W, et al. First report of European Cooperative Trial in operable breast cancer (ECTO): effect of primary systemic therapy (PST) on local-regional disease. Proc Am Soc Clin Oncol 2002;21:34a.

The Breast (2005) 14, 322–324

ELSEVIER

THE
BREAST

www.elsevier.com/locate/breast

CASE REPORT

# Intracystic papillary carcinoma of the breast in a male patient diagnosed by core needle biopsy: a case report

Takayuki Kinoshita[a,*], Takashi Fukutomi[a], Eriko Iwamoto[a], Miyuki Takasugi[a], Sadako Akashi-Tanaka[a], Tadashi Hasegawa[b]

[a]*Surgical Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan*
[b]*Pathology Division, National Cancer Center Research Institute, Japan*

Received 17 August 2004; received in revised form 29 November 2004; accepted 15 December 2004

The Breast (2005) 14, 322–324

ELSEVIER

THE BREAST

www.elsevier.com/locate/breast

CASE REPORT

# Intracystic papillary carcinoma of the breast in a male patient diagnosed by core needle biopsy: a case report

Takayuki Kinoshita[a,*], Takashi Fukutomi[a], Eriko Iwamoto[a], Miyuki Takasugi[a], Sadako Akashi-Tanaka[a], Tadashi Hasegawa[b]

[a]*Surgical Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan*
[b]*Pathology Division, National Cancer Center Research Institute, Japan*

Received 17 August 2004; received in revised form 29 November 2004; accepted 15 December 2004

KEYWORDS
Intracystic papillary carcinoma;
Male breast carcinoma;
Core needle biopsy

**Summary** We report a case of intracystic papillary carcinoma (IPC) of the breast in a 71-year-old man in whom diagnosis was made by core needle biopsy. He came to our hospital complaining of a left subareolar mass. Imaging diagnosis was a cyst with an intracystic component. Since aspiration biopsy cytology was interpreted as a borderline lesion, the decision was made to proceed with core needle biopsy.

Pathological examination of the specimen revealed the intracystic component to be non-invasive papillary carcinoma. So the patient underwent simple mastectomy without axillary node biopsy. From the final pathological result, no invasion was identified.


## Introduction

Male breast cancer is an uncommon disease with an incidence of approximately 1% of all breast cancers.[1] Intracystic papillary carcinoma (IPC) forms a small subgroup of breast carcinomas with a favorable prognosis.[2,3] Core needle biopsy has been increasingly utilized as initial approach for the diagnosis of mammographic abnormalities and palpable breast lesions. In this report, we describe a case of mammary IPC diagnosed in a 71-year-old man by core needle biopsy. We discuss the clinicopathological features of cystic breast cancer in the male and review the literature and the present case.

## Case report

A 71-year-old man, complaining of a round mass in his subareolar region with bloody nipple discharge,

*Corresponding author. Tel.: +81 3 3542 2511; fax: +80 3 3542 3815.
*E-mail address:* takinosh@ncc.go.jp (T. Kinoshita).

0960-9776/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.breast.2004.12.003

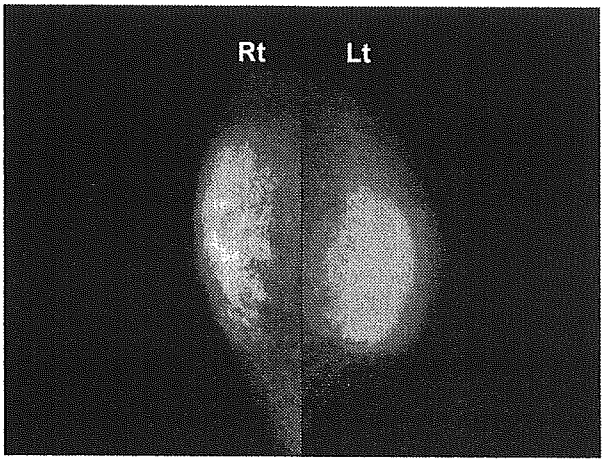


**Figure 1** Mammogram revealed a 6 cm lobulated mass in his left breast and subareolar gynecomastia in his right breast.

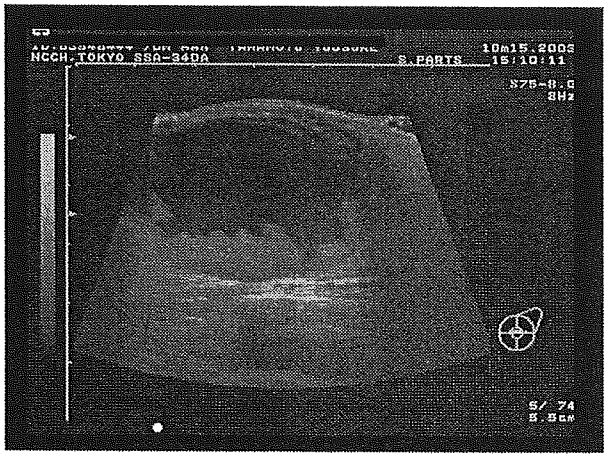

**Figure 2** Ultrasound studies showed a cystic lesion with an intracystic component.

visited the National Cancer Center Hospital in October 2003. He had a past history of lung cancer and gastric cancer. There was no reported history of breast trauma. He had gynecomastia in his right breast. The tumor was $6 \times 5\,cm^2$ in size with a smooth surface and clear margin. No overlying skin retraction and no palpable axillary lymph nodes were noted.

Mammogram revealed a 6 cm lobulated mass in his left breast and subareolar gynecomastia in his right breast (Fig. 1). Ultrasound studies showed a cystic lesion with an intracystic component (Fig. 2).

We diagnosed intracystic papilloma or carcinoma from the radiological appearance of the intracystic lesion. So, the decision was made to proceed with core needle biopsy. Three passes with 16-gauge biopsy gun were performed. The diagnosis of non-invasive papillary carcinoma was made on core needle biopsy (Fig. 3). Finally, we diagnosed the

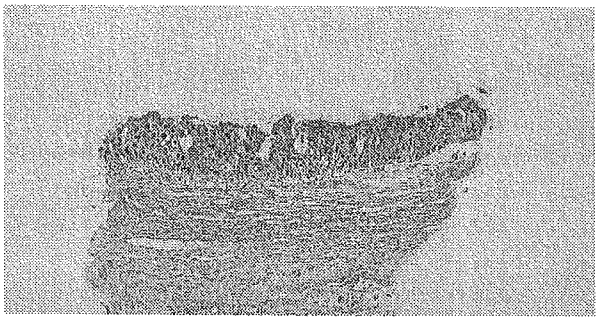

**Figure 3** Core needle biopsy demonstrates a solid epithelial proliferation composed of papillary structures with fibrovascular cores lined by a uniform population of neoplastic cuboidal cells. No invasion was identified.

tumor as intracystic carcinoma from these combined informations. The patient underwent simple mastectomy without axillary lymph node biopsy. Because the role of adjuvant therapy is not clearly defined for this type of tumor, no other treatment was performed.

## Pathologic findings

The specimen consisted of a simple mastectomy with an overlying ellipse skin with nipple. A $4.1 \times 2.0\,cm^2$ well-circumscribed, partially hemorrhagic cystic mass was identified under the areola. At lower-power magnification, the cyst wall was lined by multilayered flat epithelial cells, and papillary epithelial lesions with a fibrous stalk present in the wall (Fig. 4A).

At higher magnification, this solid papillary proliferation is composed of neoplastic cells with mild nuclear atypia and a high mitotic index (Fig. 4B). Since no evidence of stromal invasion was found, the lesion was diagnosed as IPC, high grade.

The immunohistological examination for cancer cells revealed positive for estrogen and progesterone receptor, and negative for HER-2 and p53 protein.

## Discussion

IPC of the breast in the male is a very rare disease and it also shows a good prognosis. IPC represents a small subgroup of breast cancers and accounts 0.5–2% of breast cancer in women.[2] Some studies have suggested that they form a higher percentage in men, with an incidence range of 5–7.5%.[4,5] Furthermore, increased risk in men with gynecomastia has been reported.[6] Pacelli,[7] in a recent review of the literature, reported that nine

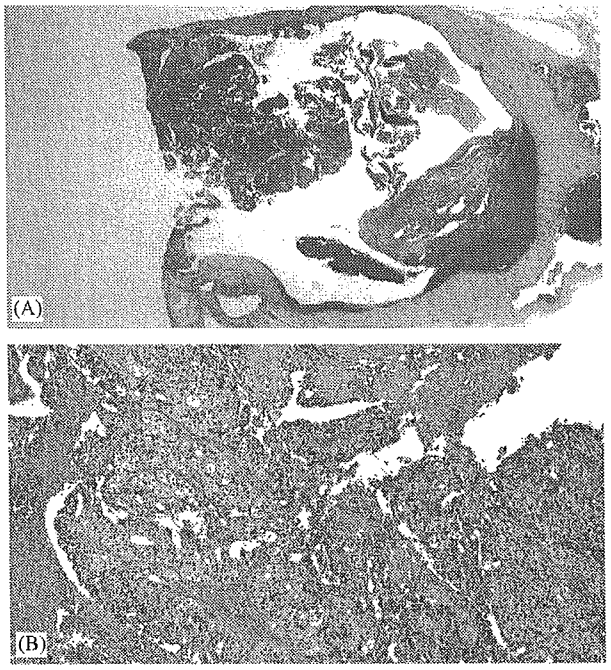


**Figure 4** (A) Microscopic feature of the cystic lesion. The cyst wall was lined by multilayered flat epithelial cells, and a papillary epithelial lesion with a fibrous stalk is present in the wall. (B) At higher magnification, this solid papillary proliferation is composed of neoplastic cells with mild nuclear atypia and a high mitotic index. Since no evidence of stromal invasion was found, the lesion was diagnosed as IPC, high grade.

patients underwent fine-needle aspiration, but only four cases were positive for malignant cells. In the remaining patients, fine-needle biopsy gave either negative (two cases), or borderline results (three cases). Imoto,[8] in a review of Japanese literature, also stated that the difficulty in obtaining a definite diagnosis of malignancy by fine-needle aspirate can attributed to the cystic and hemorrhagic nature of these lesions. Only one case was reported that was diagnosed by core needle biopsy.[7] Fine-needle aspiration cytology in male breast lesions is a useful technique and has been shown to be highly sensitive and specific with good cytohistologic correlation.[9,10] However, many institutions have chosen core needle biopsy as alternative to fine-needle aspiration cytology due to the level complexity involved in the interpretation of breast cytology.[11] In our case, core needle biopsy was very useful in decision of operating procedure because of a favorable prognosis of this tumor.

The majority of the reports confirm excellent prognosis associated with pure IPC. The low frequency of axillary node metastases with pure IPC does not justify axillary lymph node dissection.[12] The role of sentinel node biopsy has not been evaluated in this disease, but sentinel node biopsy may be an excellent alternative to full axillary dissection in patients with IPC and associated invasive carcinoma. Lumpectomy is an option for pure IPC. However, the role of radiotherapy in these patients remains undefined. The majority of patients with IPC will have associated DCIS or invasive cancer, or both, and should be treated on the basis of this associated pathology.

Our case report demonstrates that the ICP can be accurately diagnosed by core needle biopsy and the radiological feature of the tumor in a male patient. Because of a favorable prognosis of this tumor, histologic finding is very important in decision of operating procedure.

## References

1. Haagensen CD. *Disease of the breast*. Philadelphia: WB Saunders; 1986.
2. Czernobilsky B. Intracystic carcinoma of female breast. *Surg Gynecol Obstet* 1967;**124**:93–8.
3. Carter D, Orr SL, Merino M. Intracystic papillary carcinoma of the breast after mastectomy, radiotherapy or excision biopsy alone. *Cancer* 1983;**52**:14–9.
4. Heller KS, Rosen PP, Schottenfeld D, Ashikari R, Kenne DW. Male breast cancer: clinicopathologic study of 97 cases. *Ann Surg* 1978;**188**:60–5.
5. Wolff M, Renis MS. *Breast cancer in males: clinicopathologic study of 40 patients*. New York: Masson Publishing; 1981.
6. Liechty RD, Davis J, Gleysteen J. Cancer of the male breast: forty cases. *Cancer* 1967;**20**:1617–24.
7. Pacceli A, Bock BJ, Jensen EA, et al. Intracystic papillary carcinoma of male breast in a male patient diagnosed by ultrasound-guided core biopsy. *Breast J* 2002;**8**:387–90.
8. Imoto S, Hasebe T. Intracystic papillary carcinoma of the breast in male: case report and review of the Japanese literature. *Jpn J Clin Oncol* 1998;**28**:517–20.
9. Joshi A, Kapila K, Verma K. Fine needle aspiration cytology in the management of male breast masses. Nineteen years experience. *Acta Cytol* 1999;**43**:334–8.
10. Dei Tos AP, Della Giustina D, Bittesini L. Aspiration biopsy cytology of malignant papillary breast neoplasms. *Diagn Cytopathol* 1992;**8**:580–4.
11. Masood S. Fine-needle aspiration biopsy of nonpalpable breast lesions. Challenges and promises. *Cancer Cytolpathol* 1998;**84**:197–9.
12. Carmen CS, Lavinia PM, Kelly KH, et al. Treatment and outcome with intracystic papillary carcinoma of the breast. *Am J Surg* 2002;**184**:364–8.

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

## *Risk Factors and Impact on Distant Metastases*

**Yoshifumi Komoike, M.D.**[1]
**Futoshi Akiyama, M.D.**[2]
**Yuichi Iino, M.D.**[3]
**Tadashi Ikeda, M.D.**[4]
**Sadako Akashi-Tanaka, M.D.**[5]
**Shozo Ohsumi, M.D.**[6]
**Mikihiro Kusama, M.D.**[7]
**Muneaki Sano, M.D.**[8]
**Eisei Shin, M.D.**[9]
**Kimito Suemasu, M.D.**[10]
**Hiroshi Sonoo, M.D.**[11]
**Tetsuya Taguchi, M.D.**[12]
**Tsunehiro Nishi, M.D.**[13]
**Reiki Nishimura, M.D.**[14]
**Shunsuke Haga, M.D.**[15]
**Keiichi Mise, M.D.**[16]
**Takayuki Kinoshita, M.D.**[17]
**Shigeru Murakami, M.D.**[18]
**Masataka Yoshimoto, M.D.**[19]
**Hideaki Tsukuma, M.D.**[20]
**Hideo Inaji, M.D.**[1]

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

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

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

[1] Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan.

[2] Department of Breast Pathology, Cancer Institute Hospital, Tokyo, Japan.

[3] Department of Emergency and Critical Care Medicine, Gunma University Faculty of Medicine, Gunma, Japan.

[4] Department of Surgery, Kelo University School of Medicine, Tokyo, Japan.

[5] Division of Breast Surgery, National Cancer Center Hospital, Tokyo, Japan.

[6] Department of Surgery, National Shikoku Cancer Center, Ehime, Japan.

[7] Third Department of Surgery, Tokyo Medical University, Tokyo, Japan.

[8] Department of Surgery, Niigata Cancer Center Hospital, Niigata, Japan.

[9] Department of Surgery, National Osaka Hospital, Osaka, Japan.

[10] Department of Surgery, Saitama Cancer Center, Saitama, Japan.

[11] Department of Breast and Thyroid Surgery, Kawasaki Medical School, Okayama, Japan.

[12] Department of Surgical Oncology, Osaka University Graduate School of Medicine, Osaka, Japan.

[13] Department of Surgery, Mitsui Memorial Hospital, Tokyo, Japan.

[14] Department of Surgery, Kumamoto City Hospital, Kumamoto, Japan.

[15] Department of Surgery, Tokyo Women's Medical University Daini Hospital, Toyko, Japan.

[16] Kodama Clinic, Fukuoka, Japan.

[17] Department of Surgery, National Tokyo Medical Center Hospital, Tokyo, Japan.

[18] Department of Breast Oncology, National Kyushu Cancer Center 1, Kyoto, Japan.

[19] Department of Breast Surgery, Cancer Institute Hospital, Tokyo, Japan.

[20] Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan.

Supported by a Grant-in-Aid for research of cancer treatment from the Ministry of Health, Labour and Welfare of Japan (No.13-9).

Address for reprints: Yoshifumi Komoike, Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan; Fax: (011) 81-6-6981-8055; E-mail: komoike-yo@mc.pref.osaka.jp

Received June 29, 2004; revision received June 16, 2005; accepted July 19, 2005.


DOI 10.1002/cncr.21551
Published online 6 December 2005 in Wiley InterScience (www.interscience.wiley.com).

developed IBTR, initial lymph node metastases and short interval to IBTR were significant risk factors for subsequent distant metastasis.

**CONCLUSIONS.** Young age, positive surgical margin, and omission of radiation therapy seemed to be important factors in relation to local control. The authors' results also indicated that IBTR is significantly associated with subsequent distant metastasis. Patients with positive nodal status at primary operation or with short interval from primary operation to IBTR are at especially high risk of distant metastasis. It remains unclear, however, whether IBTR is an indicator or a cause of subsequent distant metastases. *Cancer* **2006;106:35–41.**


**KEYWORDS: breast cancer, breast-conserving treatment, ipsilateral breast tumor recurrence, distant metastases.**

A long time has passed since breast-conserving therapy (BCT) became the standard treatment modality for early stage breast cancers.[1–2] The increasing number of patients treated with BCT resulted in a corresponding increase of ipsilateral breast tumor recurrence (IBTR). The main concern for both physicians and patients is, therefore, the risk of IBTR in the preserved breast.

Postoperative irradiation to the remaining breast has significantly reduced the incidence of IBTR.[1–5] The results of the recent National Surgical Adjuvant Bowel and Breast Project (NSABP) B-21, showed that radiation therapy was so effective that it would even benefit early breast cancers at minimal risk for IBTR.[6] Therefore, postoperative irradiation was thought to be an important part of standard procedure for BCT.

In addition to radiation therapy, some factors were reported to have an influence on IBTR. For example, young women were generally thought to have a higher frequency of local recurrence.[7–11] Kroman et al. recently reported a relation between young age and increasing risk of IBTR, from a study of BCT with over 2000 patients.[12] The European Organization for Research and Treatment of Cancer (EORTC) trial also confirmed the impact of age.[13]

The presence or absence of cancer cells at the resection margin, and their quantity, are also major factors affecting IBTR.[14–19] Park et al. reported that the 8-year accrued rate of IBTR was 7% in patients with negative and close margins, 14% in those with focally positive margins, and 27% in those with extensively positive margins.[14] Although the definitions of positive margin are obscure, the importance of pathologic margin status in relation to the risk of IBTR has been shown.

Many studies have shown that IBTR is associated with subsequent distant metastases (DM) and worse survival.[20–28] Whether IBTR is an indicator or a cause of subsequent DM is debatable.[26,29–33] It has been proposed that IBTR is not the cause but is simply a significant indicator of subsequent DM. Other groups have recently suggested that IBTR may be a cause of DM.[32,34,35]

In the current study, we summarized the long-term follow-up results of BCT for Japanese women with breast cancer, and we focused on IBTR, particularly its incidence, risk factors, and predictive significance for subsequent DM. In Japan, BCT was adopted later than in western countries. Therefore, there are few studies summarizing the results of BCT for Japanese women.[36,37] This is the first long-term report of large-scale results of BCT in this ethnic group.

## MATERIALS AND METHODS

Included in this study were 1901 patients with unilateral breast cancer ≤ 3 cm in diameter who underwent BCT at 18 major institutes from 1986 to 1993. Patients who had received primary systemic therapy, and those with past history of breast cancer, were excluded. Postoperative irradiation or adjuvant therapy were not exclusion criteria. The surgical procedure consisted of wide excision or quadrantectomy plus axillary lymph node dissection.

Questionnaire forms were sent to the members of this study in November 2001 to collect clinical patient data. The questionnaire asked for data as follows: age at primary operation, menopausal status, date of primary operation, initial tumor size by palpation, histologic type, pathologic lymph node status, histologic margin status, lymphovascular invasion, nuclear grade, extensive intraductal component (EIC), estrogen receptor status (ER), progesterone receptor status (PgR), adjuvant endocrine therapy, adjuvant chemotherapy, postoperative irradiation, boost radiation, date of IBTR, method of salvage operation, systemic therapy after IBTR, secondary local recurrence and its date, distant metastases, date of distant metastases, contralateral breast cancer, death, cause of death, and date of death or last visit. Serial sections of resected specimens were meticulously examined at all institu-

tions. Margins ≤ 5 mm from the cut edge of the specimen were usually regarded as positive margins. Measurement methods and cutoff levels of the hormone receptors were not standardized, and they varied between institutions.

IBTR was defined as all events which occurred in the remaining breast after BCT. No distinction was made between recurrence because of residual cancer cells or because of new primary cancer.

Local-free, disease-free, distant disease-free, and overall survival rates were calculated using the Kaplan–Meier method. The statistical differences of local, distant, disease-free rates, and overall survival were proved using a log-rank test for univariate analysis. Multivariate analyses for local free and distant disease-free rates were performed using the Cox proportional hazards model. In univariate and multivariate analysis, age was dealt with as a serial variable and was not categorized at a certain point, such as ≤ 35 years or older. All statistical analyses were performed with Stat View 5.0 software (SAS Institute, Cary, NC).

## RESULTS

### Systemic Recurrence and IBTR

There were 1901 patients available for analysis of survival and recurrence rates. The median follow-up period was 107 months(range, 2–184 mos). Patient characteristics are shown in Table 1. There were 172 patients who developed IBTR, and 179 patients had recurrences in distant organs or regional lymph nodes. During follow-up, 182 patients died; of these, 128 patients died of their breast cancers. The 10-year overall and cause-specific survival rates were 83.9% and 92.2%, respectively. The 10-year distant disease-free survival was 77.8%. The 10-year cumulative rate of IBTR was 9.6% (8.5% in the group with postoperative irradiation and 17.2% in the group without RT). There was a significant difference between these two groups ($P < 0.0001$).

### Risk Factors for IBTR

Factors influencing IBTR are shown in Table 2. In a univariate analysis, younger age at primary operation, tumor size, positive margin status, high nuclear grade, EIC, PgR, omission of endocrine therapy, and omission of postoperative irradiation were significantly associated with IBTR. Of these, younger age, positive margin status, and omission of postoperative irradiation were independently associated with IBTR on a multivariate Cox proportional hazards model analysis.

### Time Course of IBTR and Distant Metastasis

The annual rate and cumulative incidence of IBTR after primary operation is shown in Figure 1. The peak of IBTR was seen at 3 to 4 years after primary operation, and the annual rate decreased gradually thereafter. Figure 2 shows the clinical outcome of patients with and without IBTR. Patients who developed IBTR had a significantly greater risk of developing DM ($P < 0.0001$).

TABLE 1
Patient Characteristics

| Characteristic | No. of patients |
|---|---|
| Age, yrs | |
| Median | 49 |
| Range | 21–89 |
| ≤ 35 | 135 |
| > 36 | 1766 |
| Clinical tumor size, cm | |
| Median | 17 |
| Range | 0–30 |
| Lymph node metastasis | |
| Positive | 380 |
| Negative | 1476 |
| Unknown | 45 |
| ER status | |
| Positive | 779 |
| Negative | 482 |
| Unknown | 640 |
| PgR status | |
| Positive | 510 |
| Negative | 430 |
| Unknown | 961 |
| Surgical margin | |
| Positive | 263 |
| Negative | 1503 |
| Uncertain | 135 |

ER: estrogen receptor; PgR: progesterone receptor.

### Risk Factors for Distant Metastasis

Both distant disease-free and overall survival rates were significantly lower in the IBTR group. To determine whether IBTR is related to DM and patient prognosis, we verified risk factors for DM. Univariate analysis showed that initial age, lymph node metastases, margin status, lymphovascular invasion, nuclear grade, EIC, PgR, and IBTR were all significantly correlated with DM (Table 3). In a multivariate analysis, IBTR was independently associated with DM as well as with lymph node metastases. The hazard ratio (HR) associated with distant metastasis was 3.93 (95% confidence interval [CI], 2.676–5.771) in IBTR, and 3.34 (95% CI, 2.365–4.724) in node-positive patients (Table 3).

Of 1901 patients, 172 developed IBTR, and 51 developed subsequent DM after IBTR; 27 of these patients developed distant metastases within 1 year after IBTR.

TABLE 2
Factors Influencing Ipsilateral Breast Tumor Recurrence (IBTR), Results of Univariate and Multivariate Analysis

| Variable | Univariate analysis *P* value | Multivariate analysis HR | *P* value | 95% CI |
|---|---|---|---|---|
| Age | < 0.0001 | 0.943 | < 0.0001 | 0.917–0.970 |
| Size | 0.0257 | 1.017 | 0.2557 | 0.988–1.047 |
| Histologic type | | | | |
| DCIS/IDC/special | 0.6053 | | | |
| Lymph node metastasis | | | | |
| +/− | 0.141 | | | |
| Surgical margin | | | | |
| +/− | < 0.0001 | 2.849 | 0.0004 | 1.587–5.012 |
| ly +/− | 0.8768 | | | |
| v +/− | 0.5236 | | | |
| Nuclear grade | | | | |
| 3/1, 2 | 0.0650 | | | |
| EIC +/− | 0.0106 | 1.422 | 0.1857 | 0.847–2.398 |
| ER −/+ | 0.0493 | 0.696 | 0.1464 | 0.427–1.135 |
| PgR −/+ | 0.0036 | | | |
| Chemotherapy | | | | |
| −/+ | 0.0878 | | | |
| Endocrine therapy | | | | |
| −/+ | 0.0180 | 1.543 | 0.0824 | 0.397–1.057 |
| Radiation therapy | | | | |
| −/+ | < 0.0001 | 3.861 | < 0.0001 | 0.155–0.433 |

HR: hazard ratio; CI: confidence interval; DCIS: ductal carcinoma in situ; IDC: invasive ductal carcinoma; Special: lobular carcinoma, medullary carcinoma, squamous cell carcinoma, etc.; ly: lymphatic invasion; v: vascular invasion; EIC: extensive intraductal component; ER: estrogen receptor; PgR: progesterone receptor.

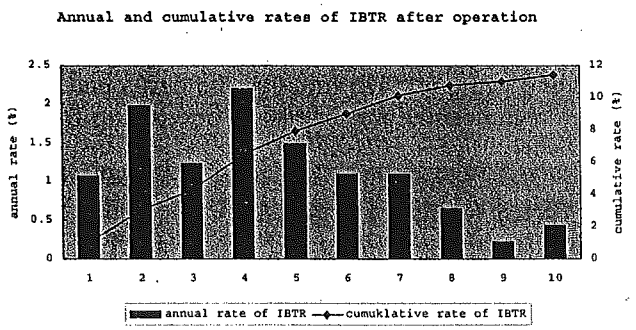


**FIGURE 1.** Annual and cumulative rates of ipsilateral breast tumor recurrence (IBTR) after primary operation are represented. The bar graph shows annual rates of IBTR. It was 1 to 2% up to 7 years from primary operation. After that, the incidences decreased slightly, but they did not reach zero. The incidence was highest at 4 to 5 years after primary operation. The line graph shows cumulative incidence of IBTR. It was linear to 7 years and a little flattened thereafter.

Factors associated with distant metastases among patients who developed on IBTR were analyzed. Univariate analysis showed that nodal status, lymphovascular invasion, and period to IBTR were potential risk factors for DM. Initial nodal status and interval to IBTR were independent risk factors for DM by Cox proportional hazard model (Table 4). Annual rates of DM for primary operation in patients with or without IBTR were compared (Fig. 3). The incidences of DM in the group of patients with IBTR were higher than those in the group of patients without IBTR regardless of the time after operation. More interestingly, the annual rates of distant metastases in the group of patients with IBTR showed two

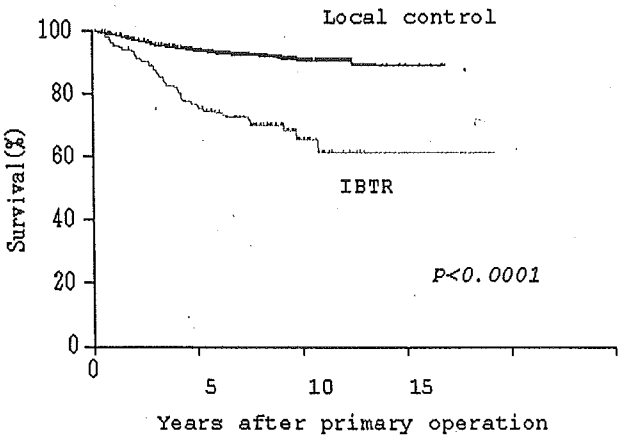


**FIGURE 2.** Distant-free survival after primary operation is shown according to local relapse. The distant-free survival curve shows that patients with IBTR are more likely to develop subsequent distant metastases. There was a statistically significant difference between the two groups ($P < 0.0001$). The actuarial distant-free survival rate at 10 years was 89.7% in the local control group and 70.3% in the IBTR group.

TABLE 3
Risk Factors for Distant Metastases After Breast Conserving Surgery, Results of Univariate and Multivariate Analysis

| Variable | Univariate analysis HR | *P* value | Multivariate analysis HR | *P* value | 95% CI |
|---|---|---|---|---|---|
| Age | 0.979 | 0.004 | 0.99 | < 0.30 | 0.978–1.008 |
| Size | 1.013 | 0.10 | | | |
| Lymph node metastasis | | | | | |
| +/− | 3.55 | < 0.0001 | 3.34 | < 0.0001 | 2.365–4.724 |
| Surgical margin | | | | | |
| +/− | 1.46 | 0.03 | 1.30 | 0.20 | 0.873–1.926 |
| ly +/− | 2.16 | < 0.0001 | | | |
| v +/− | 1.98 | 0.002 | | | |
| Nuclear grade | | | | | |
| 3/1, 2 | 3.32 | 0.006 | | | |
| EIC +/− | 0.57 | 0.03 | | | |
| ER −/+ | 0.79 | 0.16 | | | |
| PgR −/+ | 0.64 | 0.01 | | | |
| IBTR +/− | 3.72 | < 0.0001 | 3.93 | < 0.0001 | 2.676–5.771 |

HR: hazard ratio; CI: confidence interval; ly: lymphatic invasion; v: vascular invasion; EIC: extensive intraductal component; ER: estrogen receptor; PgR: progesterone receptor; IBTR: ipsilateral breast tumor recurrence.

TABLE 4
Risk Factors for Subsequent Distant Metastases After IBTR, Results of Univariate and Multivariate Analysis

| Variable | Univariate analysis *P* value | Multivariate analysis HR | *P* value | 95% CI |
|---|---|---|---|---|
| Age | 0.1724 | | | |
| Size | 0.5618 | | | |
| Lymph node metastasis +/− | < 0.001 | 2.68 | 0.008 | 1.291–5.574 |
| Surgical margin +/− | 0.3113 | | | |
| ly +/− | 0.0161 | 1.21 | 0.599 | 0.888–2.506 |
| v +/− | < 0.0001 | | | |
| Nuclear grade 3/1, 2 | NE | | | |
| EIC +/− | 0.2134 | | | |
| ER −/+ | 0.4057 | | | |
| PgR −/+ | 0.2230 | | | |
| DFI | < 0.0001 | 0.99 | 0.008 | 0.999–1.000 |

HR: hazard ratio; CI: confidence interval; ly: lymphatic invasion; v: vascular invasion; EIC: extensive intraductal component; ER: estrogen receptor; PgR: progesterone receptor; DFI: disease free interval.

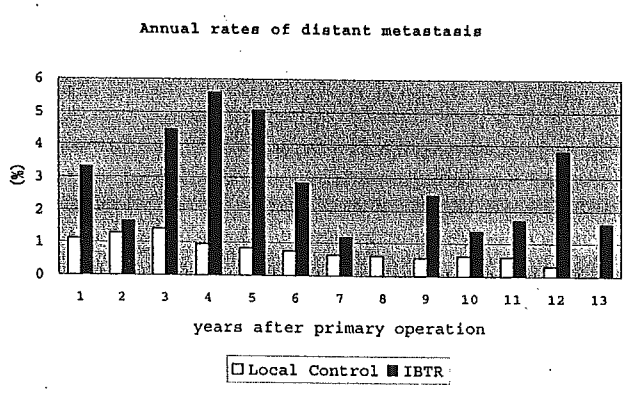


**FIGURE 3.** The time distribution of distant metastases after primary operation compares the local control group (LC) and IBTR group. In the group of patients without IBTR, the incidence of DM was high at 2 to 4 years after primary operation, and it gradually decreased thereafter. By contrast, in the group of patients with IBTR, the annual rates of distant metastases showed two peaks, 4 to 5 years and 12 to 13 years after primary operation. The proportion of DM after 9 years was remarkably high.

peaks, and the incidence of DM after 9 years was remarkably high. By contrast, in the group of patients without IBTR, the incidence of DM was high at 2–4 years after primary operation and subsequently decreased.

## DISCUSSION

The current study was conducted to clarify the risk factors for IBTR, as well as the impact of IBTR on distant metastases in patients with early stage breast cancer treated with BCT. We first summarized the results of BCT cases in Japan with long-term follow-up. As previously reported,[36,37] the survival rates and local control rates of BCT in Japan were favorable. Risk factors of IBTR were younger age, positive margin status, and omission of postoperative irradiation. These results were consistent with previous reports.

The 10-year cumulative rates of IBTR were 8.5% and 17.2% in patients with and without radiation therapy, respectively. On a Cox proportional hazards model, postoperative irradiation decreased the risk of IBTR by about one-fourth (HR, 0.259, 95% CI, 0.214–0.431, $P < 0.0001$). This result is similar to the result of Early Breast Cancer Trialists' Collaborative Group (EBCTCG) metaanalysis.[38]

In the current study, positive surgical margins were also associated with an increased risk of IBTR as previously reported.[14–18] However, definitions of margin status are not standardized. Some researchers defined it only as "positive" or "negative".[16,20] Other studies have assessed surgical margin according to distance from the cut edge,[17] but these distances varied by < 1 mm, < 2mm, or < 10mm.[14,19,39] In the current study, the majority of close margins (≤ 5 mm from the cut edge of the specimen) were regarded as positive margins. Although judgment of margin status depends on each institution, meticulous histologic assessment was done in all institutions. (The removed specimens are examined by expert pathologists at each institute, by using 5 mm sections.)

The influence of young age on the risk of IBTR is striking. It has been supported by many previous studies.[7–11] Jobsen et al. reported that age < 40 years was the only significant predictor of IBTR for women treated with BCT with pathologic T1 tumors and negative lymph node status.[10] Harrold et al. showed a correlation with young age and IBTR by using a cut-point age of 40 years.[40] Freedman et al. also found age to be a risk factor of IBTR, but their cut-point age was 55 years.[9] Fourquet et al. categorized patients into 4 age groups (< 32, 32–45, 46–55, > 55).[7] In our series, age was analyzed as a serial variable. The results are that the younger the patient, the higher the risk of IBTR. It was noteworthy that younger age was a risk factor of IBTR regardless of age cut-point.

Our results also showed that IBTR was significantly correlated with DM, as shown by several other reports.[19–24] The HR was 3.93 by multivariate analysis. This ratio was very similar to that of NSABP B-06.[20] When compared with the relative risk (3.34) of lymph node metastasis for distant metastasis, IBTR has almost the same impact on DM.

One of the aims of this study was to clarify what type of IBTR is likely to develop subsequent DM. Univariate analysis showed that initial lymph node metastases,

lymphovascular invasion, nuclear grade, and the interval from primary operation to IBTR were significantly associated with DM. Short DFI was reported to be highly correlated with subsequent DM.[21,25,26,31,41–44] These risk factors appear to reflect the inherent aggressive characteristics of primary tumors.[38,39] Thus the risk of developing DM would be predetermined before treatment, with local recurrence being a manifestation of this risk.

The time distribution of annual rates of DM among patients with IBTR showed a noteworthy pattern. Two peaks in the incidence of DM were observed; 4 to 5 years and 12 to 13 years after primary operation. In patients without IBTR, a peak of incidence was seen 3 to 4 years after primary operation, with a gradual decrease thereafter. Our results agreed with the long-term results of NSABP B-06 and some other studies.[32,33] Some groups have presumed that the second peak of DM was due to IBTR.[28,29] Considering that late distant metastases are not likely to develop so frequently after mastectomy, IBTR may be a cause of DM in such cases. Up to now, many investigators thought that IBTR was only a marker for DM[19,20,23,24] because many cases of IBTR that subsequently developed DM had more aggressive primary tumor characteristics. Recently, however, it appears that additional radiation may lead to a survival benefit, suggesting IBTR may, in part, be a cause of DM, especially in cases of IBTR who develop late DM.[45]

Classifying IBTR into true recurrence (TR) or new primary tumor (NP) is one of the concerns. The finding that cumulative incidence of IBTR is linear to 7 years and flattens slightly thereafter (Table 1. line graph) suggests that not a few cases of late recurrence may be NP recurrence. In the current study, we did not distinguish a second primary breast cancer from true recurrence because it is difficult to correctly diagnose. Some studies suggest the prognostic significance of IBTR from this viewpoint. True recurrence is generally thought to have worse prognosis than a new primary tumor.[46–48] Haffty and colleagues speculated that a certain portion of IBTR contained new primary tumor and biologic behaviors were quite different.[48,49] So it is noteworthy that IBTR represent two distinct entities, and classifying IBTR may help our understanding of the complicated behavior of IBTR.

In summary, young age, positive surgical margin, and omission of radiation therapy are independent risk factors for IBTR, and IBTR was certainly correlated with subsequent DM. Initial nodal status and the interval to IBTR were significantly associated with DM after IBTR. It remains unclear whether IBTR is an indicator of DM or a cause of it. Further study is needed to solve this question.

## REFERENCES


1. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002;347:1233–1241.
2. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med.* 2002;347:1227–1232.
3. Clark RM, Whelan T, Levine M, et al. Randomized clinical trial of breast irradiation after lumpectomy and axillary dissection for node-negative breast cancer: an update. *J Natl Cancer Inst.* 1996;88:1659–1664.
4. Liljegren G, Holmberg L, Adami HO, et al. Sector resection with or without postoperative radiotherapy for stage I breast cancer: five-year results of a randomized trial. Uppsala-Orebro Breast Cancer Study Group. *J Natl Cancer Inst.* 1994; 86:717–722.
5. Forrest AP, Stewart HJ, Everington D, et al. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. Scottish Cancer Trials Breast Group. *Lancet.* 1996;348:708–713.
6. Fisher B, Bryant J, Dignam JJ, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in woman with invasive breast cancers of one centimeter or less. *J Clin Oncol.* 2002;20: 4141–4149.
7. Fourquet A, Campana F, Zafrani B, et al. Prognostic factors of breast recurrence in the conservative management of early breast cancer: A 25-year follow-up. *Int J Radiat Oncol Biol Phys.* 1989;17:719–725.
8. Locker AP, Ellis IO, Morgan DAL, et al. Factors influencing local recurrence after excision and radiotherapy for primary breast cancer. *Br J Surg.* 1989;76:890–894.
9. Freedman GM, Hanlon AL, Fowble BL, et al. Recursive partitioning identifies patients at high and low risk for ipsilateral tumor recurrence after breast-conserving surgery and radiation. *J Clin Oncol.* 2002;20:4015–4021.
10. Jobsen JJ, van der Palen J, Meerwaldt JH. The impact of age on local control in women with pT1 breast cancer treated with conservative surgery and radiation therapy. *Eur J Cancer.* 2001;37:1820–1827.
11. Arriagada R, Le MG, Contesso G, et al. Predictive factors for local recurrence in 2006 patients with surgically resected small breast cancer. *Ann Oncol.* 2002;13:1404–1413.
12. Kroman N, Holtveg H, Wohlfahrt J, et al. Effect of breast-conserving therapy versus radical mastectomy on prognosis for young women with breast carcinoma. *Cancer.* 2004;15: 688–693.
13. Vrieling C, Collette L, Fourquet A, et al. Can patient-, treatment- and pathology-related characteristics explain the high local recurrence rate following breast-conserving therapy in young patients? *Eur J Cancer.* 2003;39:932–944.
14. Park CC, Mitsumori M, Nixon A, et al. Outcome at 8 years after breast-conserving surgery and radiation therapy for invasive breast cancer: influence of margin status and systemic therapy on local recurrence. *J Clin Oncol.* 2000;18: 1668–1675.
15. Renton SC, Gazet J-C, Ford HT, et al. The impact of the resection margin in conservative surgery for breast cancer. *Eur J Surg Oncol.* 1996;22:17–22.