表1　Intracystic papillary carcinomaの臨床的特徴および診断

症例	年齢・性	病悩期間（月）	部位	US 最大径（嚢胞mm）	US 最大径（充実内腫瘤mm）	US 充実腫瘤形状	MMG 腫瘤陰影	MMG 石灰化	MRI	FNA	CNB	術前病理診断
1	84・F	2	右A	22	5	不整型	辺縁不整	なし	／	／	／	なし
2	83・F	2	左D	11	6	整型	辺縁平滑	なし	／	class 5	／	DC
3	75・F	3	右A	22	7	不整型	辺縁不整	A	／	class 3	＋	なし
4	60・F	4	右B	36	10	整型	辺縁平滑	なし	／	class 2	＋	なし
5	43・F	3	左A	15	3	整型	辺縁平滑	なし	／	／	＋	なし
6	36・F	9	左C	34	17	不整型	はっきりせず	なし	／	／	＋	ICPC
7	57・F	4	左E	10	4	整型	辺縁平滑	なし	／	class 5	／	DC
8	70・M	6	左E	50	15	不整型	辺縁不整	なし	／	／	＋	ICPC
9	75・F	2	右A	28	20	整型	辺縁平滑	A	／	class 5	／	DC
10	48・F	3	左A	23	5	整型	辺縁平滑	P	／	class 2	＋	なし
11	74・F	8	左A	14	14	整型	／	／	／	／	＋	ICPC
12	82・F	24	右C	200	30	整型	／	／	BCP	class 2	＋	ICPC
13	81・F	2	右A	170	52	不整型	辺縁不整	なし	BCP	class 2	＋	ICPC
14	71・F	2	左E	60	21	不整型	辺縁平滑	なし	BCP	／	＋	ICPC

＊US：乳腺超音波検査．A：amorphous集簇．P：pleomrphic集簇．BCP：乳癌造影パターン
FNA：Fine needle aspiration．CNB：Core needle biopsy．DC：ductal carcinoma．

表2　手術・病理所見

症例	術式	嚢胞壁外浸潤	周囲DCIS	リンパ節転移	各種レセプター	p53	G	NG
1	Bp	なし	なし	郭清なし	ER 2 PgR 2 HER 2＋	－	1	1
2	Bp	なし	なし	郭清なし	ER 2 PgR 0 HER 2－	－	1	1
3	Bt＋sampling	なし	なし	0/2	ER 2 PgR 2 HER 2－	＋	2	2
4	Bq	なし	なし	郭清なし	ER 2 PgR 1 HER 2－	－	2	2
5	Bp＋Ax	なし	なし	0/11	ER 2 PgR 2 HER 2－	－	2	2
6	Bp＋Ax	なし	あり	0/22	ER 2 PgR 2 HER 2－	－	1	1
7	Bt＋Ax	なし	なし	0/20	ER 2 PgR 2 HER 2＋	－	2	2
8	Bp	なし	なし	郭清なし	ER 2 PgR 2 HER 2＋	2＋	2	2
9	Bt＋Ax	なし	なし	0/18	ER 1 PgR 1 HER 2－	－	2	3
10	Bq＋SLN	なし	なし	0/4	ER 1 PgR 2 HER 2－	－	1	1
11	Bp	あり	なし	郭清なし	ER 2 PgR 2 HER 2－	－	1	1
12	Bt＋SLN	なし	なし	1/5	ER 3 PgR 3 HER 2－	－	1	1
13	Bt＋SLN	なし	あり	0/5	ER 3 PgR 3 HER 2－	－	1	1
14	Bt＋SLN	あり	あり	0/3	ER 3 PgR 2 HER 2－	－	1	1

領域に1例で，E領域に3例に存在した．病悩期間は中央値5.2カ月（2～24カ月）であった．

2) 診断

超音波検査では1例は多房性の嚢胞であったが，他13例はすべて単房性の嚢胞であり，いずれの症例も内部に充実性成分を認めた．腫瘍径は中央値25.5mm（11～220mm）で，充実成分径は中央値12mm（3～52mm）であった．内部の充実成分の形状は整，不整とさまざまであった．

マンモグラフィー（MMG）は12例に施行，7例が辺縁平滑で，4例は辺縁不整の腫瘤陰影として描出され，1例はMMG上腫瘤陰影を認めなかった．amorphousおよびpleomorphicな集簇する石灰化を3例にみとめた．MRIは3例に施行，嚢胞内容液はいずれも血性所見を呈した．ダイナミックスタディーでは3例（100%）ともに乳癌の造影パターンを示した．また嚢胞壁外進展を1例（症例14）に認めた．8例にFine needle aspiration施行，class5が3例，class3が1例，class2が4例であった．class5であった3例はいずれもductal carcinoma疑いという結果であった．Fine needle aspirationの細胞診陽性率は8例中3例（37.5%）であった．class3以下の5例にはCore needle biopsy 追加施行した．また5例はFine needle biopsy施行せずに，はじめからCore needle biopsyを施行．計10例のCore needle biopsyを施行，

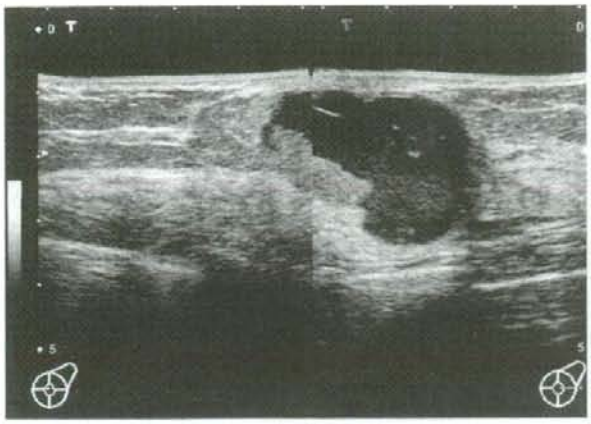

図1　超音波所見
後方エコーの増強を伴った50×43×26 mmの嚢胞と，嚢胞壁の一部から内腔に突出する21×18×7 mm大の乳頭状腫瘍を認めた．

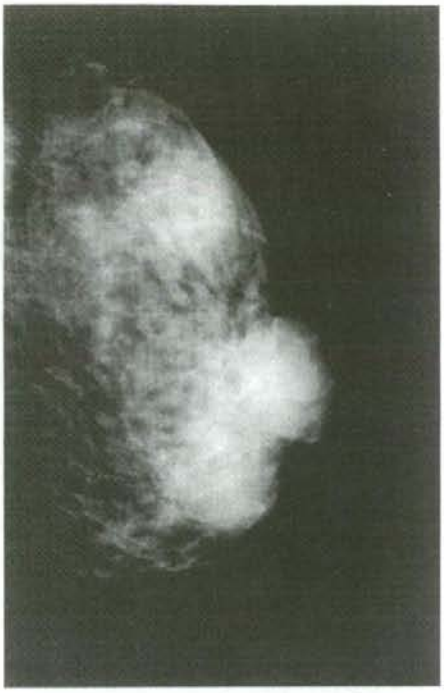

図2　マンモグラフィー所見
medio-lateral viewでE領域に辺縁平滑で，ほぼ均一な腫瘤陰影を認めた．石灰化は認めなかった．

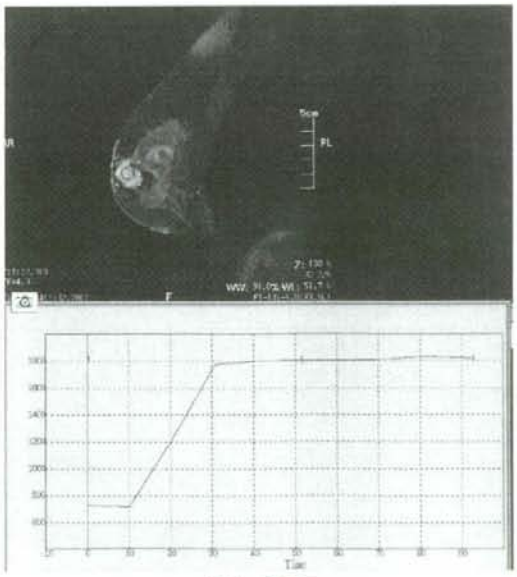

図3　MRI
ダイナミックスタディーにて乳癌の造影パターンを示した．

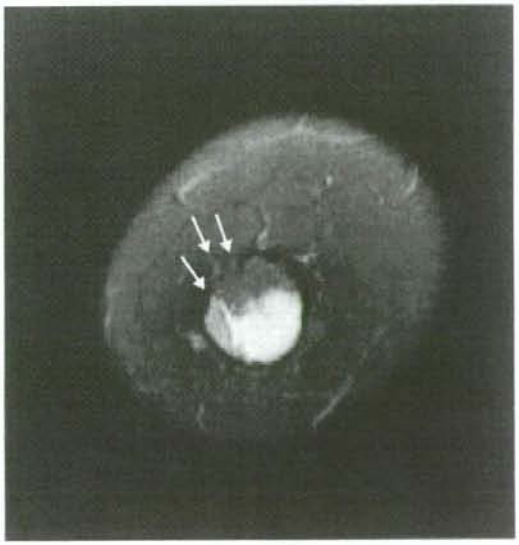

図4　MRI
T2W1において嚢胞壁と考えられる低信号域の断裂が認められ，MRI上，腫瘍の嚢胞壁外進展がみられた．

ICPCの術前病理学的診断を得た症例は計6例(60%)であり，残りの4例はCore needle biopsyでも確定できず切除生検にて乳癌の診断を得た．なお1例はFine needle aspirationおよびCore needle biopsyをともに施行せずに切除生検を行った．

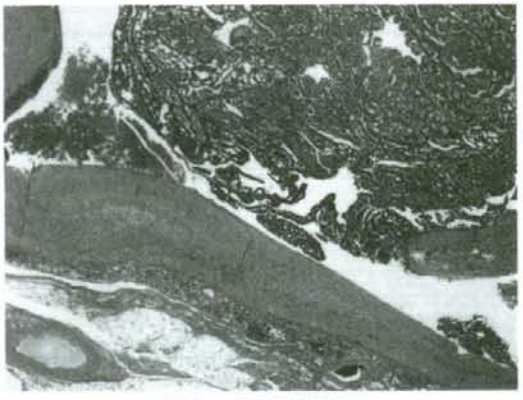

図5　病理組織所見
径5cm大の嚢胞内に2cm大の乳頭状隆起性病変を認め，嚢胞液は暗赤色であった．この隆起性病変は中等度の核異型，核分裂像を有する腫瘍細胞が乳頭状，cribriform patternを呈して増殖．

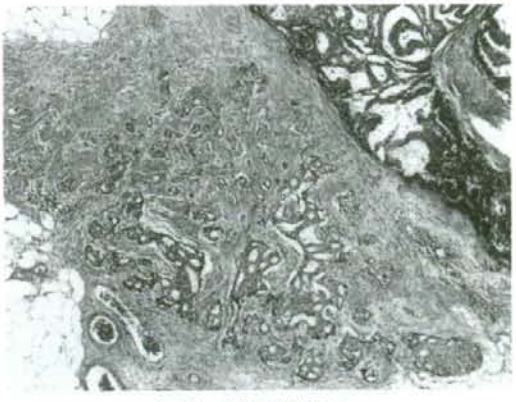

図6　病理組織所見
腫瘍細胞の間質への浸潤が認められた．

3) 手術・病理（表2）

5例に腋窩郭清を伴う乳房切除術および乳房部分切除術を施行，4例は腋窩郭清を伴わない乳房部分切除術を施行した．さらに2004年以降の4例はセンチネルリンパ節生検を伴う乳房切除術および乳房部分切除術を施行した．嚢胞内容液の性状はいずれもきわめて淡い血性から濃い暗赤色を呈し，14例のうち2例（14.2%）に間質浸潤を認めた．また3例に嚢胞壁外にDCISを認め，1例に腋窩リンパ節転移を認めた．G1とG2がそれぞれ8例（57%）6例（43%），NG1とNG2とNG3がそれぞれ8例（57%）5例（36%）1例（7%）であった．またホルモンレセプターはERが全例（100%），PgRは13例が陽性（92.8%）で，HER2は3例（21.4%），p53は2例（14.2%）が陽性であった．

4) リンパ節転移症例

ICPC14例のうち1例に腋窩リンパ節転移を認めた．本症例は82歳女性，病悩期間が24カ月，腫瘍径が20cmであった．Core needle biopsyでICPCの診断を得，乳房切除術およびセンチネルリンパ節生検を施行，術中迅速病理診断にてセンチネルリンパ節転移はなかったが，永久標本にてリンパ節1個にmicrometastasisを認めた．ER，PgRはともに陽性，HER2，p53はいずれも発現していなかった．作成標本上，嚢胞壁外への浸潤はみとめていない．

5) 補助療法・予後

13例にTAM投与，温存術8例中3例に残存乳房に対する術後照射を行った．男性症例の1例の他因死を除き，13例すべて再発の所見なく生存中である．次に代表的な1例（症例14）を提示する．

症　例：71歳，女性．

家族歴：特記事項なし．

既往歴：特記事項なし．

現病歴：2006年10月，左乳房腫瘤に気づき前医受診し，当科紹介となる．

入院時血液検査所見：末梢血，生化学検査ともに正常範囲内で，腫瘍マーカー（CEA 0.9ng/ml，CA15-3 14U/ml，ST439<1.0）の上昇もみられなかった．

入院時現症：左乳房E領域を中心にBD領域に及ぶ60mm大のやや弾性硬の腫瘤を認めた．胸筋，皮膚への固定は認めなかった．乳頭分泌なく，腋窩リンパ節も触知しなかった．

超音波所見（図1）：後方エコーの増強を伴った60×43×26mmの嚢胞と，嚢胞壁の一部から内腔に突出する21×18×7mm大の乳頭状腫瘍を認めた．

MMG所見（図2）：E領域に辺縁平滑で，ほぼ均一な腫瘤陰影を認めた．石灰化は認めなかった．

MRI：ダイナミックスタディーにて乳癌の造影パターンを示した（図3）．また，T2W1において嚢胞壁と考えられる低信号域の断裂が認められ，

MRI上，腫瘍の嚢胞壁外進展がみられた（図4）．

経　過：以上の所見より，2006年11月Core needle biopsy施行し，ICPCの診断を得て，乳房切除術＋センチネルリンパ節生検を施行した．術中迅速病理診断にてセンチネルリンパ節に転移は認めなかった．

病理組織所見：径5 cm大の嚢胞内に2 cm大の乳頭状隆起性病変を認め，嚢胞液は暗赤色であった．この隆起性病変は中等度の核異型，核分裂像を有する腫瘍細胞が乳頭状，cribriform patternを呈して増殖（図5），一部間質への浸潤が認められた（図6）．リンパ節転移は認めず(0/3)，G2，NG2および免疫組織学的検索にてER，PgRはともに陽性，HER2，p53はいずれも発現していなかった．

3．考　察

ICPCは嚢胞内腔へ乳頭状に突出し発育する乳癌で，乳癌全体の約2％弱[1]といわれている．一般的にductal carcinoma *in situ*の範疇で浸潤を伴うことはほとんどなく，現在の乳癌取扱い規約によれば，病巣が嚢胞内に限局し，非浸潤性嚢胞内乳癌とすることが記載されている．しかし，組織学的にも嚢胞壁外への浸潤や乳管内で広く進展を示す例[3]や，同時性肝転移例[4]などの報告もあり，定義についてはいまだコンセンサスを得られていない．したがって今回われわれは，浸潤の有無を問わず病理学的検索にて，ICPCと診断された14例を検討した．通常の乳癌と比較すると，平均年齢65歳（範囲34～92歳）[1]と高齢者に多いとされ，今回の14例でも中央値72.5歳（36～82歳）であり通常乳癌より高齢であった．また病悩期間も長いことも報告[2,5]されており，今回も中央値5カ月（1～24カ月）であった．腫瘍の性質として通常乳癌より発育が緩徐で，潰瘍を形成せずにGradeが低いため，放置されやすいと考えられる．良悪性の鑑別として，嚢胞内乳頭腫と鑑別は困難である．鑑別点としては嚢胞内乳頭腫の平均年齢は40.7～47歳で低く，60歳以上の嚢胞内腫瘍では，癌は81％に認めたという報告がある[7,8,9]．また腫瘍径は悪性であれば良性より大きい傾向にあるが，良悪性鑑別において診断的価値は低い[7,8]と報告されている．超音波検査は良悪性の鑑別検査としてあげられるが，嚢胞内腫瘤部分の辺縁など良悪性とも不整なものが多く鑑別にあまり有用でないといわれている[8,9]．通常乳癌における良悪性の鑑別としてMRIは有用であり，MRI所見が乳癌病理組織像を反映するという報告もある[10]．われわれは症例12以降の3例においてMRIを施行しいずれもダイナミックスタディーにて悪性を示す造影パターンを呈した．ICPCにおいても良悪性鑑別のため画像診断の1つとしてMRIは重要であると考えられる．またさらに，症例14においてMRIで腫瘍の嚢胞壁外浸潤を認めたように，MRIは進展度診断にも有用であり，嚢胞壁進展の評価にもきわめて有効である．以上より，少しでも悪性が疑われる場合はFine needle aspirationを行い，さらにCore needle biopsyをエコーガイド下に充実性部分を確実に穿刺することが必要である．しかし本検討症例においてもそうであるが，嚢胞内充実成分への針生検は難しく，Fine needle aspirationおよびCore needle biopsyにても診断の得られない症例では積極的に切除生検を考慮するべきと思われる．治療は原則として非浸潤性乳管癌(DCIS)治療に沿って行うことが可能である．しかし，嚢胞壁外浸潤を示す例[3]や，同時性肝転移例[4]などの報告もあることを把握しておく必要がある．報告によると浸潤癌はまれではなく，乳管内進展についても嚢胞壁より2 cm以上超えて乳管内を進展するものも報告されている[6]．今回の14例中2例に浸潤部分を認め，さらに別の1例に作成標本には浸潤部は認めなかったが，リンパ節転移を認め，標本作成外に浸潤部分が存在したことが推察された．このように切除範囲決定には，MRIによる進展度評価を参考にし，広範な腫瘍進展を念頭において断端陰性となることが重要である．術前化学療法，術後化学療法の報告はなく，統一された指針はないが，第一選択治療は切除療法と考える．リンパ節転移に関しては0～25％と報告に幅があるが，通常の乳癌より頻度は低いとされている[8,9]．われわれは2004年以降よりセンチネルリンパ節生検を開始し，4例にセンチネルリンパ節生検を伴う乳房切除，乳房部分切除術を施行した．通常乳癌と同様，郭清省略には慎重であるべきで，センチネルリンパ節生検はよい適応と思われる．

今回14例すべてホルモン感受性を認め，乳房部分切除は8例に施行した．補助療法としては，明確な指針はないがDCIS治療にしたがって，症例を選びホルモン療法，残存乳房放射線照射などを考慮する必要があると思われる．

4. 結　語

ICPCの14例につき臨床病理学的検討を加え報告した．良悪性の鑑別は困難であり，Fine needle aspiration, Core needle biopsyに加え切除生検が必要である．切除範囲決定には，MRIによる進展度評価を参考に，広範な腫瘍進展を念頭において断端陰性となることが重要である．また，腋窩リンパ節の評価は病変の大きさに関わらず必要であり，現在広く施行されているセンチネルリンパ節生検は腋窩リンパ節転移の少ないICPCによい適応と考えられる．

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

Risk Factors and Impact on Distant Metastases

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

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

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

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

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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 ($P < 0.0001$).

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 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 ($P < 0.0001$).

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.

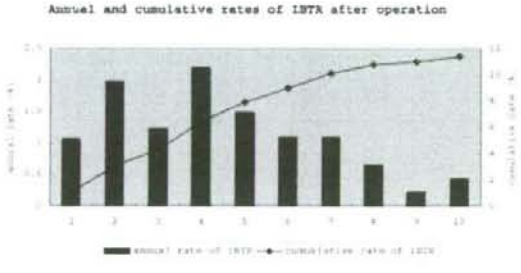

FIGURE 1. Annual and cumulative rates of ipsilateral breast tumor recurrence (IBTR) after primary operation are represented. The bar graph shows annual rates of IBTR. It was 1 to 2% up to 7 years from primary operation. After that, the incidences decreased slightly, but they did not reach zero. The incidence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

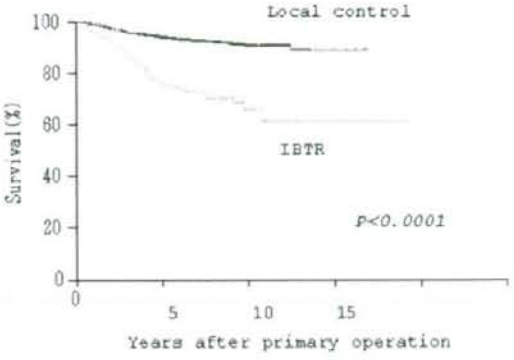

FIGURE 2. Distant-free survival after primary operation is shown according to local relapse. The distant-free survival curve shows that patients with IBTR are more likely to develop subsequent distant metastases. There was a statistically significant difference between the two groups ($P < 0.0001$). 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.

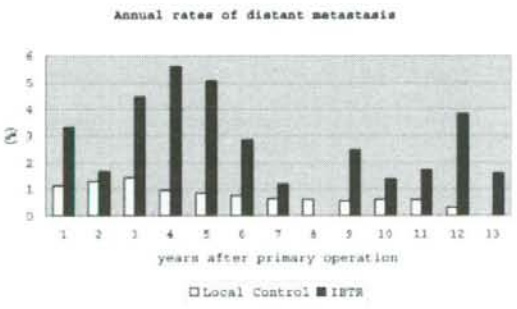

FIGURE 3. The time distribution of distant metastases after primary operation compares the local control group (LC) and IBTR group. In the group of patients without IBTR, the incidence of DM was high at 2 to 4 years after primary operation, and it gradually decreased thereafter. By contrast, in the group 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.

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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

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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

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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.

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Breast Cancer
Vol. 13 No. 1 January 2006

Case Report

A Case of Mucinous Carcinoma of the Breast that Demonstrated a Good Pathological Response to Neoadjuvant Chemotherapy Despite a Poor Clinical Response

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A 30-year-old woman presented with a right breast tumor. Mucinous carcinoma was diagnosed by core needle biopsy (T2: 5 cm N1 M0). Despite receiving a neoadjuvant anthracycline and taxane regimen, the patient demonstrated no clinical response (NC). Based on the patient's strong preference, we performed breast-conserving surgery. On histological examination, we observed widespread mucus and a few viable malignant cells, a Grade 2 therapeutic response. Neither optimal management procedures nor guidelines for chemotherapy for primary mucinous carcinoma of the breast have been established. It is a reasonable assumption, however, that discordance between the clinical response and therapeutic response to neoadjuvant chemotherapy may occur in cases of mucinous carcinoma.

Breast Cancer 13:100-103, 2006.

Key words: Breast cancer, Mucinous carcinoma, Therapeutic response, Neoadjuvant chemotherapy

Neoadjuvant chemotherapy results in significant regression of primary breast carcinomas, thus allowing breast-conserving surgery. While a variety of imaging modalities are useful to estimate the extent of residual tumor[1,2], chemotherapy-induced fibrosis, tumor necrosis, and remaining fibrocystic changes make it difficult to evaluate the residual tumor load accurately. As far as we know, no reports have evaluated the responses to chemotherapy and neoadjuvant chemotherapy of mucinous carcinoma of the breast. In this report, we describe a case of breast mucinous carcinoma that demonstrated a pathological Grade 2 response, according to the histopathological response criteria of the Japanese Breast Cancer Society[3], despite a poor clinical response to neoadjuvant chemotherapy.

Case Report

A 30-year-old premenopausal woman was referred to our hospital with a lump in her breast. Physical examination revealed a hard elastic mass measuring 5 × 4.5 cm in diameter located in the upper outer quadrant of her right breast. An enlarged lymph node was also palpable in the right axilla. Mammography (MMG) displayed a well-circumscribed and high-density tumor shadow with microcalcifications (Fig 1A). The tumor measured approximately 5 cm in diameter by MMG. Ultrasonography (US) revealed an irregularly shaped hypoechoic lesion in the right breast, measuring over 5 cm in diameter (Fig 1B). The swollen lymph node was 1.5 cm in diameter, which was highly suggestive of lymph node metastasis. Serum levels of multiple tumor markers were normal; CEA levels were 2.0 ng/ml (normal: <5.0), CA15-3 was 6 U/ml (nl: <28), and ST439 was <1.0 U/ml (nl: <7.0). A core needle biopsy revealed mucinous carcinoma. Immunohistochemical analysis revealed no reactivity for either Estrogen receptor (ER) or Progesterone receptor (PgR). We did not observe immunoreactivity for p-53 or c-erbB-2 overexpression in this tumor.

The patient received neoadjuvant chemotherapy consisting of four cycles of 5FU (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (500 mg/m^2) every three weeks, followed by 12 cycles of paclitaxel (80 mg/m^2) weekly. The che-

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Received January 7, 2005; accepted July 27, 2005

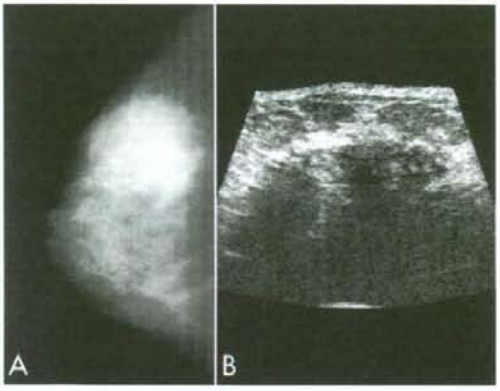

Fig 1. Mammography (MMG) showed a well-circumscribed, high-density tumor shadow with microcalcifications (A), while ultrasonography (US) revealed an irregularly shaped hypoechoic lesion in the right breast, measuring over 5 cm in diameter (B).

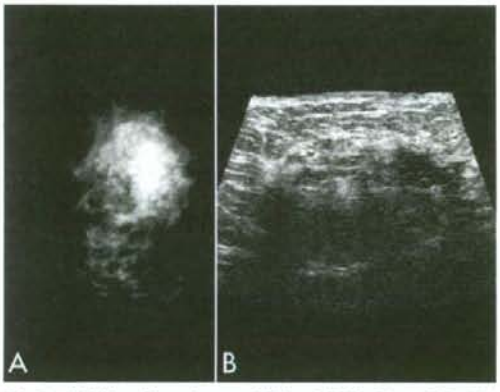

Fig 2. Additional imaging modalities (MMG (A) and US (B)) also revealed a tumor with similar size and features to that observed prior to the chemotherapy.

motherapeutic course was completed and the toxicities were tolerable. After the termination of chemotherapy, however, the tumor size remained unchanged. The tumor measured 4.5 × 4 cm in diameter by palpation, and the axillary lymph node was still palpable. The imaging examinations (MMG and US) also revealed a tumor of the same size with similar features as those seen prior to chemotherapy (Fig 2). Contrast-enhanced computed tomography (CE-CT) of the breast revealed an irregularly shaped faintly enhanced tumor shadow approximately 5 cm in diameter (Fig 3). Considering these features, we evaluated the clinical

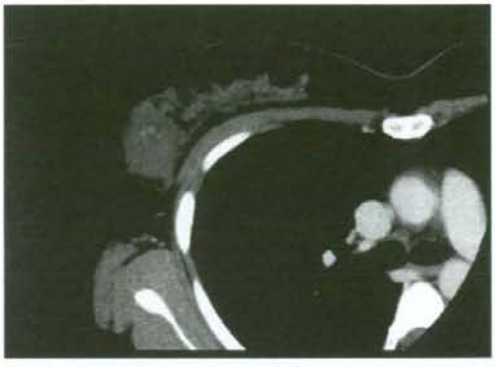

Fig 3. Contrast-enhanced computed tomography (CE-CT) of the breast revealed an irregularly shaped tumor shadow, which faintly enhanced and measured about 5 cm in diameter.

response to chemotherapy as no change (NC).

According to the patient's preference, we performed a wide resection of the tumor in the right breast with a level II lymph node dissection (Bp+Ax). The cut margin of the specimen was negative (free margin: 2 cm). Histologically, the tumor exhibited a pure infiltrating mucinous carcinoma, with no infiltrating ductal carcinoma component. The pathological tumor size was 5.0 cm in diameter and histological cut margin was also negative. Despite widespread mucus in the breast tumor, we recognized only a few viable malignant cells. The majority of the remaining tumor cells were necrotic (Fig 4A, 4B). According to the histopathological response criteria of the Japanese Breast Cancer Society, the pathological assessment of the therapeutic response was Grade 2[3]. We also recognized two swollen lymph nodes filled with mucus, but devoid of malignant cells.

Postoperatively, she received radiotherapy. She remains disease-free five months after the operation.

Discussion

Neoadjuvant chemotherapy has become standard therapy for patients with locally advanced or large operable breast cancers. This procedure makes breast-conserving surgery possible. In this report, we present a case of mucinous carcinoma, demonstrating a Grade 2 pathological response to neoadjuvant chemotherapy, despite no clinical response.

The reported incidence of mucinous carcino-

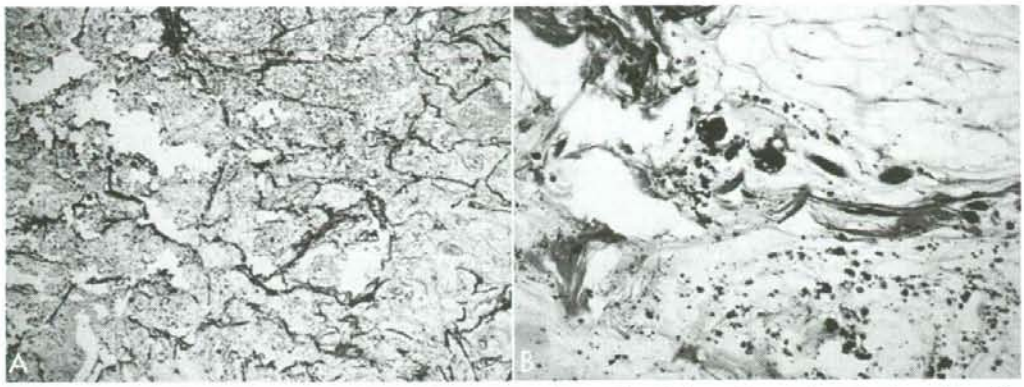

Fig 4. A: Despite widespread mucus in the primary breast tumor, microscopic analysis could recognize only a few viable malignant cells. The majority of these tumor cells were necrotic (hematoxylin and eosin [H&E] stain, original magnification, ×40), B: Viable malignant cells (H&E stain, original magnification, ×200).

ma has varied from 1% to 6% of all breast malignancies. Mucinous carcinoma has a better prognosis than infiltrating ductal carcinomas[4-6]. Komenaka *et al.* reported that the number of involved axillary lymph nodes was the only significant predictor of death from disease; the size of the lesion was not a significant prognostic factor in mucinous carcinoma, because the mucin comprised the majority of the tumor volume[5]. Pure mucinous carcinoma of the breast is suitable for breast-conserving therapy, even for large tumors of up to 5 cm in diameter, because these tumors have a low incidence of extensive intraductal spreading[6]. There have not been, however, any reports detailing the typical responses to chemotherapy or neoadjuvant chemotherapy for mucinous carcinoma of the breast. Mucinous carcinomas tend to be identified early, when the tumors are small in size and neoadjuvant chemotherapy is often unnecessary. According to multiple studies, tumors with aggressive biological markers, such as high histological grade, overexpression of HER-2, reactivity for p-53, and negative hormone receptor status, exhibited better pathological responses[7-9]. In mucinous carcinomas, estrogen and progesterone receptor positivity have been reported in approximately 60-90% of the tumors, while HER2/neu oncoprotein overexpression and p53 protein accumulation are not normally seen. These biological features suggest that mucinous carcinomas may not respond well to neoadjuvant chemotherapy. Fortunately, this estimation did not fit this case; the negative hormone receptor status of this tumor may be associated with a good response to neoadjuvant chemotherapy.

Categorization of the clinical response to chemotherapy depends on an accurate measurement of residual tumor size, but is complicated by variable histopathologic changes that can occur within the tumor bed. The remaining tumorous lesions may be related to chemotherapy-induced fibrosis, tumor necrosis, or fibrocystic changes. These secondary processes can result in clinical and macroscopic overestimation of the residual tumor size[10, 11]. Rajan *et al.* reported that chemotherapy in some tumors can dramatically reduce cellularity, but only minimally affects the overall tumor size[12]. In this case, chemotherapy was profoundly effective against the tumor cells themselves, but the large amounts of extacellular mucus were not sensitive to chemotherapy; thus, the remaining mucus made up a significant portion of the residual tumor. This phenomenon resulted in a discordance between the residual tumor size and the effectiveness of chemotherapy. Meanwhile, we observed five patients with pure type mucinous carcinoma that received neoadjuvant chemotherapy at our hospital (Table 1). The pathological assessments of the therapeutic responses of these tumors were Grade 1a (two cases), Grade 1b (two cases) and Grade 2 (this case) according to the percentage of necrotic malignant cells. Interestingly, in the two Grade 1b cases, approximately two-thirds of the tumor cells were necrotic, but large amounts of mucus remained. Due to the small number and varied responses, we could not