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NINE CASES OF MAMMARY CARCINOMA CHARACTERIZED BY THE PRESENCE OF OSTEOCLAST-LIKE GIANT CELLS

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Mammary carcinoma containing osteoclast-like giant cells (OCGC) is an extremely rare tumor. We have encountered nine additional cases of this tumor, so we investigated is clinico-pathological and immunohistochemical characteristics. Four cases were in Stage I, three were in Stage II A, and two were in Stage II B. The tumor size varied from 1.5cm to 6.0cm. Lymph node metastasis was observed in four cases (44%). In all cases, histopathological examination revealed invasive ductal carcinoma containing OCGC among the tumor cell nests. The tumors were grade 2 in all cases, according to the modified Bloom-Richardson classification. Immunohistochemically, estrogen receptor, progesterone receptor and HER2 receptor were positive in five cases, six cases, and one case, respectively. One patient died of the disease five years and ten months after surgery while no signs of recurrence have been seen in the other cases. According to these results, it is possible that the prognosis of mammary carcinoma charaeterized by the piaeuce of OCGC is better than that of ordinary mammary carcinoma.

原著

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原発性乳がんに対するPrimary systemic therapy (PST)の適応—PST抵抗性乳がんを治療前に判定可能か？

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Clinicopathologic Features of Primary Breast Cancer Resisting Primary Systemic Therapy：Shien T[*1], Yoshida M[*1], Hojo T[*1], Shimizu C[*2], Kouno T[*2], Ando M[*2], Akashi-Tanaka S[*1], Seki K[*3], Katsumata N[*2], Fujiwara Y[*2] and Kinoshita T[*1] ([*1]Department of Surgery, [*2]Breast and Medical Oncology Division, [*3]Department of Pathology, National Cancer Center Hospital)

We evaluated the clinicopathologic and radiological features of patients with primary breast cancer resistant to PST to demonstrate the predictive factors of PST. Between 1998 and 2007, 443 PBC underwent curative surgical treatment after PST (anthracycline and/or taxane) at National Cancer Center Hospital (NCCH). We could evaluate 8 (2%) primary breast cancer patients who clearly judged clinical progressive disease (PD) with radiological examinations. Histological classifications were metaplastic carcinomas in 5 (63%) patients, but 2 of these patients were not correctly diagnosed before PST by core needle biopsy. All patients were triple negative (ER, PgR and HER2) by immunopathological examinations. On radiological examinations, the tumors were visualized as localized, round and non homogeneus masses. The clinicopathological and radiological features of PBC resistant PST were clear in this study. However, these features were similar to PBC with high sensitivity to PST. Another predictor is needed to accurately judge sensitivity to PST.

Key words：Breast cancer, Primary systemic therapy, Predictive features
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はじめに

現在乳がんに有効な抗がん剤の進歩に伴い，局所進行乳がんのみならず比較的早期の乳がんに対しても広くPrimary systemic therapy (PST) が行われるようになった．その，目的は[1]PSTにより原発腫瘍の完全消失（pCR）を得て予後を改善する．[2]原発腫瘍をできるだけ縮小させて切除範囲のできるだけ小さな乳房温存療法を可能にする．[3]原発腫瘍に対する抗がん剤の感受性を確認する．とされている[1]．しかし，治療前にPSTの効果を予測し効果にあわせたPSTの適応はいまだ議論されている最中である．

今回われわれは，PSTに抵抗性であった症例の臨床病理学的および画像的特徴を分類し，これらの症例を治療前に判定可能か検討した．

1．対象と方法

1998年5月から2007年9月までに国立がんセンター中央病院（NCCH）においてanthracyclineまたはtaxaneを含むPrimary systemic therapy (PST)を行った後治癒切除を行った原発性乳がん

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表1　患者背景および予後

症例	年齢	病期	PST	手術	再発・転移	DFS	死亡	OS
1	62	IIIB	AT	Bt+Ax	骨・肝	24	D	25
2	26	IIA	FECT	Bt+Ax	肺	14	D	21
3	42	IIIA	FECT	Bt+Ax	胸水	11	D	12
4	56	IIIB	ACT	Bt+Ax	局所	14	A	38
5	57	IIA	ACT	Bt+Ax	骨・肺	13	A	17
6	37	IIB	ACT	Bt+Ax	—	12	A	12
7	37	IIIB	ACT	Bt+Ax	肺	5	A	7
8	48	IIB	FECT	Bt+Ax	肺	6	D	9

AT：doxorubicin+Docetaxel. FECT：fluorouracil+epirubicin+cyclophosphamide followed by paclitaxel. ACT：doxorubicin+cyclophosphamide followed by paclitaxel. Bt：total mastectomy. Ax：axillary disection (level II). D：dead. A：alive

表3　画像所見

症例	組織型	画像所見
1	sq	限局性，境界明瞭，内部不均一
2	MPC	限局性，境界明瞭，内部不均一
3	sc	spiculaを伴う腫瘤
4	so	乳頭部に限局，境界明瞭
5	sq+sp	限局性，境界明瞭，内部不均一
6	so	限局性，境界明瞭，内部不均一
7	sp	限局性，境界明瞭，内部不均一
8	mix	限局性，境界明瞭，内部不均一

sq：squamous cell carcinoma. MPC：matrix producing carcinoma. so：solid tubular carcinoma
sc：scirrhous carcinoma. sp：adenocarcinoma with spindle cell metaplasia. mix：mixed epitherial metaplastic carcinoma.

患者は443名であった．そのうち，PSTに抵抗性で触診および画像上明らかに腫瘍の増大をみとめた症例8例（2％）について，病理学的特徴として治療前core needle biopsy (CNB) 検体および術後組織標本における，組織型，悪性度，リンパ節転移および免疫染色にてER, PgR, HER2, p53を比較検討した．また，治療前および術前画像結果から画像的特徴を検討した．

2．結　果

表1に8例の臨床的特徴を示す．年齢中央値は45歳（26～62歳）．臨床病期はStage IIA 2名，Stage IIB 2名，Stage IIIA 1名およびStage IIIB 3名であった．PSTのレジメンはいずれもanthracyclineおよびtaxaneをともに含むもで，AT (doxorubicin；50mg/m²/docetaxel；60mg/m²) 1名，FEC followed by paclitaxel (fluorouracil；500mg/m²，epirubicin；100mg/m²，cyclophosphamide；500mg/m²，paclitaxel；80mg/m²) 3名およびAC followed by paclitaxel (doxorubicin；60mg/m²，cyclophosphamide；600mg/m², paclitaxel；80mg/m²) 4名であった．Trastuzumabを投与された症例はなかった．手術は全例レベル2郭清を伴う乳房切除術が行われていた．予後についても同様に表1に示す．8例中7例で2年以内に再発を認めそのうち6例は遠隔臓器転移で1例は局所再発であった．また，再発した7例中3例は再発後1年以内に死亡していた．

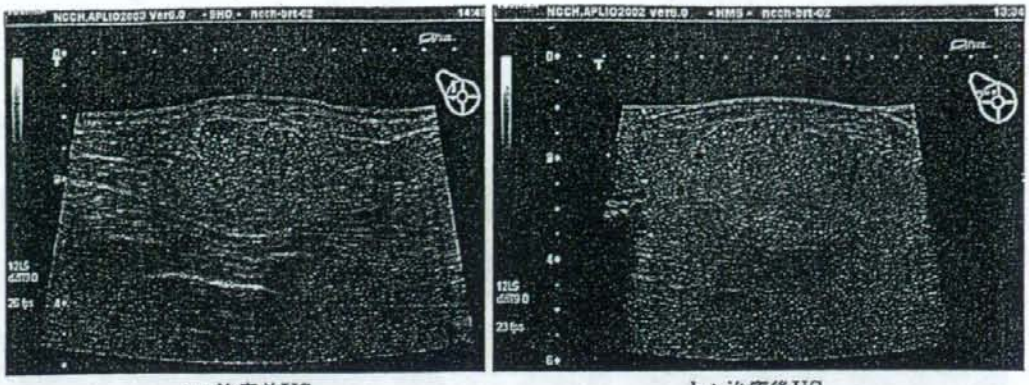
表2　免疫病理学的検査結果

症例	組織型(治療前CNB)	ER	PgR	HER2	G	p53	n
1	sq (sq)	0	0	0	3	2	21
2	MPC (so)	0	0	0	3	3	0
3	sc (sc)	0	0	0	3	3	19
4	so (so)	0	0	2+(0)	3	3	7
5	sq+sp (sq)	0	0	0	3	3	0
6	so (so)	0	0	0	3	3	2
7	sp (IDC)	0	0	0	3	3	1
8	mix (so)	0	0	0	3	3	3

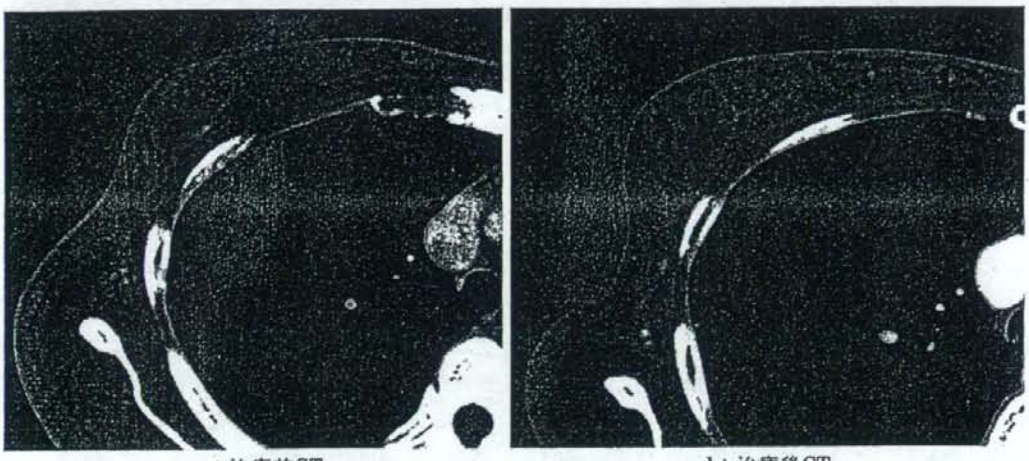
sq：squamous cell carcinoma. MPC：matrix producing carcinoma. so：solid tubular carcinoma
sc：scirrhous carcinoma. sp：adenocarcinoma with spindle cell metaplasia. IDC：invasive ductal carcinoma. mix：mixed epitherial metaplastic carcinoma. G：grade.
n：pathologically lymph node metastases

つづいて免疫病理学的検査結果を表2に示す．腫瘍の組織型は術後病理結果にて8例中5例（63％）でmetaplastic carcinomaの診断だった．しかし，そのうち2例は治療前CNBによる診断では浸潤性乳管癌であった．免疫組織学的検査結果ではホルモンレセプターはいずれも陰性でありHER2の発現は1例で2＋の結果であったもののFISH法にて陰性と判定されており，こちらも全例陰性の結果であった．つまり，8例ともtriple negativeであった．加えてp53は免疫染色にていずれも強陽性であり，組織学的悪性度はいずれもgrade 3（高悪性度）であった．リンパ節転移は8例中3例において7個以上（7～21個）の多数個認めたのに対してその他5例では3個以下（0～3個）と比較的転移個数は少なかった．

乳腺超音波またはCTによる画像検査結果を表3に示す．比較的リンパ節転移が多く組織型が硬癌の診断であった1例を除いていずれも比較的限局



a：治療前US　　b：治療後US



c：治療前CT　　d：治療後CT

図1　画像所見

症例5　57歳女性　AC 4コースでclinical CR後，paclitaxel 3週にて再増大組織型はSquamous cell and spindle cell metaplasia. USおよびCTにて限局性，境界明瞭および内部不均一な腫瘤を認める．

性，境界明瞭で内部は不均一なものであった（図1）．

3．考　察

近年抗がん剤治療の進歩および乳がん手術の縮小化に伴い，Primary systemic therapy (PST) は広く行われるようになった．当院においても，現在PST適応症例として治療前腫瘍径3 cm以上または治療前に明らかに腋窩リンパ節転移が疑われる症例としている．この理由は，腫瘍径3 cmにおいては乳房温存療法のガイドラインにおける温存療法の適応が腫瘍径3 cm以内である[2]ため，PSTを行って温存療法を可能にするためである．また，明らかに腋窩リンパ節転移陽性の症例については現在術後補助療法の指標とされているSt. Gallenのリスク分類[3]に従えば，術後必ず抗がん剤治療が行われることとなるために，PSTとして先に抗がん剤投与を行っても良いと考えられるためである．予後に関しては，基本的に同じ抗がん剤を手術前に行っても手術後に行っても腫瘍が完全消失するpCR症例以外予後は変わらないことが報告されている[4,5]．しかし，リンパ節転移に関しては近年PST後のリンパ節転移の個数がその後の予後を左右することが報告されており[6]，こういった面からも治療前にリンパ節転移陽性の症例がPSTにより転移個数が減少または消失した場合は良好な予後を得られる可能性があり，PSTの適応とされている．しかし，こういった適応を決める際に，腫瘍に対してPSTが予想しているような効果を挙げるかどうかは判定しておらず，PSTに

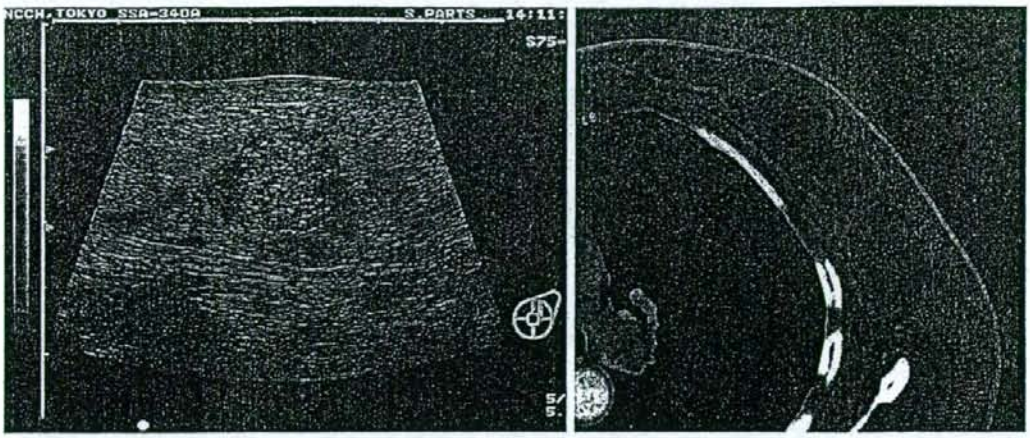


図2　pCR症例の画像所見
症例57歳女性．組織型は充実腺管癌．治療前CNBによる免疫組織学的検査結果はTriple negativeおよび組織学的悪性度grage 3
ACTによるPST効果はpCR（腫瘍の完全消失）．治療前画像所見では限局性，境界明瞭な腫瘤を認めた．

対する感受性は投与後に判定するのが現状である．

PSTの効果予測についてはさまざまな報告がある[7-10]が，いずれも決定的なものではなく，臨床に応用されているものは少ない．なかでもとくに有用とされ，コンセンサスを得られ始めているのは，PSTに非常に感受性があるとされるpCR症例の予測因子としてのホルモン陰性および組織学的高悪性度である．画像所見では，比較的限局性のものがびまん性に広がるものと比べて縮小効果が高いとされている[11,12]．ただし，これらの特徴のみでは適応を決めるまでにはいたっていない．

今回われわれは，当院において経験したPST症例のうち明らかにPSTに対して抵抗性で腫瘍の増大を認めた8例に絞って検討を行った．組織学的にはmetaplastic carcinoma症例が多かった．これまでにも，metaplastic carcinomaが治療抵抗性であり予後が悪いことは当院からも報告している[13,14]．しかし，今回の症例においても示されているとおり，CNB検体にて組織診断が必ず可能かどうかは不明である．これにはCNBの精度も関係するが，腫瘍内部の細胞が均一ではないことが考えられ，PSTによりPSTの効果のある腫瘍細胞は死滅するが，抵抗性の腫瘍は増大し最終的に残存する可能性も考えられるためである．とくに，これらの症例においてはこれまでの報告によりEGFRの発現や筋上皮への分化が示されているものもあり[13]，こういった症例を治療前に判定する上で新たな因子を検討する必要があると考える．

免疫学検査結果では全例ホルモンレセプター陰性およびHER2陰性であるいわゆるTriple negativeの症例であった．さらに組織学的悪性度も全例grade 3であった．さらに画像検査所見では，限局性，境界明瞭なものがほとんどであった．これらの因子は，上記のこれまでの報告や実臨床においてにおいても比較的PSTが良く効くと考えられている特徴とほぼ同一である（図2）．

Triple negativeに関しては抗がん剤に対する感受性が特殊であることから近年注目を集めている．それは，今回提示した症例のように抗がん剤に対して非常に抵抗性であるものと，逆に抗がん剤に対して著効を示すものがあるためである．当院における術前化学療法403例の検討においても，Triple negative症例のpCR達成率は15%であり，それ以外の症例の7%に比べて非常に高かった．Triple negative症例の中で今回提示したような症例が，Basal-like typeといわれる治療抵抗性の症例分類と同一かどうかは今回の検討では明らかではないが，現在日常的に行われている組織学的検査およびホルモンレセプターとHER2といった免疫学的検査だけではPSTの適応を決定することは非常に困難であり，これらとは別の因子の検討が必要と考えた．

今回PSTの適応を検討するため，とくにPSTに抵抗性である症例を除外することが可能かどうか検討した．結果いくつかの因子の中で，とくに有用な因子としてMetaplastic carcinomaの組織型が明らかとなった．しかし，治療前に確実にこの組織型を判定することは困難と考えられ，今後更なる症例の集積と新たな因子の検討が必要と考えた．

結　語

PSTに対してPDであった症例は，metaplastic carcinomaの組織型を持つものが多く，免疫染色でtriple negativeおよび画像所見では限局性，境界明瞭で内部不均一といった特徴があった．こういった症例はPSTの適応外と考えられたが，これらの特徴はPSTに非常に感受性のある症例と類似しており，治療前に全て診断するためには更なる検討および新しい予測因子が必要と考えた．

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原著

2008.2.5受付

80歳以上の超高齢者乳癌の治療

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Treatment for The Elderly Breast Cancer Patients Older Than 80 Years: Shien T[*1], Kinoshita T[*1], Yoshida M[*1], Hojo T[*1], Shimizu C[*2], Kouno T[*2], Ando M[*2], Akashi-Tanaka S[*1], Katsumata N[*2] and Fujiwara Y[*2] ([*1]Department of Surgery, National Cancer Center Hospital, [*2]Breast and Medical Oncology Division, National Cancer Center Hospital)

We examined the clinicopathological features and prognosis of elderly breast cancer patients over 80 years old to d define the optimad treatment strategy for these patients. Between 1966 and 2006, 117 primary breast cancer patients over 80 years of age at diagnosis underwent surgery in the National Cancer Center Hospital (NCCH). The median age was 82 (range 80-94). Operations were partial resection in 30 (27%), total resection 73 (62%), axillary lymph node dissection (ALND) in 64 (52%) and sentinel lymph node biopsy in 11 (9%) patients. On pathological diagnosis, the median tumor diameter was 2cm (range 0.2-5). Histological types were invasive ductal carcinoma in 73 (62%) and mucinous carcinoma in 16 (14%). Estrogen receptor (ER) and Progesteron receptor (PgR) were positive in 66 (57%) and 44 (38%) patients, respectively. Twenty-nine (44%) of 66 patients with ER-positive tumors received adjuvant hormone therapy and 10 (33%) of 30 patients who underwent partial resection received radiation therapy. The median overall survival time was 70 months. Clinical staging, distant and/or local metastasis and the number of axillary lymph node metastases were important predictors of overall survival (OS). ALND and/or SLNB were not important predictors of OS. In N0 patients with ER-positive tumors, the adjuvant hormone therapy was not an important predictor of OS. In elderly breast cancer patients over 80 years of age, the predictor of OS was not ALND but the number of ALN metastases, similar to that in young age. Adjuvant hormone therapy did not affect OS in N0 patients.

Key words: The elder breast cancer, Hormonal therapy, Prognosis
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はじめに

わが国の女性における臓器別のがん年齢調整罹患率は現在胃がんを抜いて乳癌が第1位でありその割合は今後もさらに上昇傾向にある．また日本人の平均寿命も年々延長しており高齢者乳癌症例は増加しており，日本乳癌学会による2004年次全国乳癌患者登録調査においても80歳以上の乳癌患者は全体の約5％と報告されている．現在乳癌が他の固形癌とくらべて比較的予後が良いことや，日常生活に不利益となる機能的な障害や症状をあまりきたさないことから，高齢者の乳癌治療は手術において低侵襲化し，放射線，薬物療法においても消極的になってきている．そういった流れにおいて，エビデンスが示されている部分はいまだ少なく議論の余地がある点が多い．さらに，近年アロマターゼ阻害剤などのホルモン療法薬剤の進

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歩に加えて，抗がん剤においても経口フッ化ピリミジンの普及など比較的高齢者においても投与しやすい副作用が少なく効果のある薬剤が増加している．

今回われわれは，国立がんセンター中央病院(NCCH)においてこれまで経験した80歳以上の超高齢者乳癌の治療をretrospectiveに検討して，これらの症例に対する今後の治療方針決定に参考となるよう比較検討した．

1. 対象と方法

1996年6月から2006年5月までにNCCHにおいて手術を伴う治療を行った初診時80歳以上の原発性乳癌117症例を対象としてretrospectiveな検討を行った．これらの症例において，手術より得られた検体の病理組織学的検査結果を検討し高齢者乳癌の臨床的特徴を明らかにするとともに，臨床病理学的予後因子を検討した．さらにこれらの症例に対して行われた手術方法，術後ホルモン療法について予後との相関を検討した．治療方針は今回検討した症例の治療期間が40年と長く，また院内でも確固たる治療方針が決定していない症例群のため，それぞれの担当医の独自の判断で行われていた．エストロゲンレセプター(ER)はEIA法において10fmol/mgP以上またはIHC法において10%以上陽性の場合を陽性と判定した．また，生存率はKaplan-Meier法を使用してLog-rank testにより検定した．

2. 結　果

今回検討した初診時80歳以上の原発性乳癌117例の臨床病理学的特徴を表1に示した．年齢中央値は82歳(範囲80～94歳)．80例(68%)の症例が既往歴を持ちうち19例(16%)が他がんの既往を持っていた．主訴はしこりを触知したものが103例(93%)と多く，検診発見や乳頭の症状などは少なかった．初診時の臨床病期はcStage I, II, III, IVがそれぞれ40例(34%)，68例(58%)，6例(5%)，3例(3%)であった．cStage IVの3例について転移部位はいずれも骨転移であり，初期治療として原発巣の切除が3例とも行われていた．手術検体における病理組織学的検査結果も表1に

表1　患者背景 (n=117)

Parameter	No. of patients (%)
年齢中央値（範囲）	82 (80～94)
既往歴	
あり	80 (68)
なし	37 (32)
他がんの既往	
あり	19 (16)
主訴	
しこり	109 (93)
検診発見	6 (5)
乳頭分泌	1 (1)
乳頭びらん	1 (1)
臨床病期	
cStage I	40 (34)
cStage II	68 (58)
cStage III	6 (5)
cStage IV	3 (3)
病理腫瘍径cm（範囲）	2 (0.2～5)
病理組織型	
浸潤性乳管癌	71 (61)
浸潤性小葉癌	5 (4)
非浸潤性乳管癌	10 (9)
粘液癌	16 (14)
リンパ節転移個数	
0	61 (52)
1 <n< 3	16 (14)
4 <n< 9	4 (3)
n>10	8 (7)
不明	28 (24)
ER陽性	67 (57)
PgR陽性	45 (38)
手術	
Bt+Ax	71 (60)
Bp+Ax	5 (4)
Bt+SLNB	10 (9)
Bp+SLNB	1 (1)
Bt	4 (3)
Bp*	24 (20)
Biopsy	1 (1)
術後治療	
Hormone therapy	42 (63)
Chemotherapy	4 (3)

表2　センチネルリンパ節生検 (n=11)

	結果
方法	全例色素法
リンパ節個数（範囲）	平均 2.2個（1～4）
迅速病理結果	全例陰性
同定率	100%
再発・転移症例	0

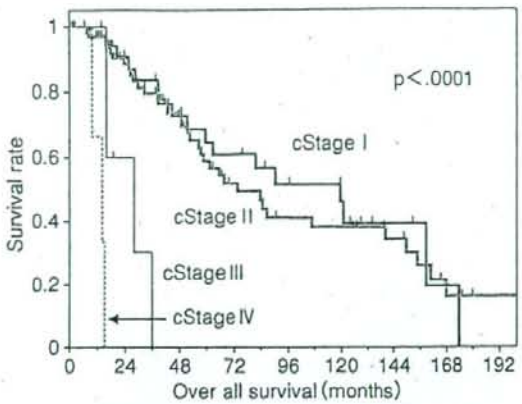

図1　cStage分類による全生存率の比較

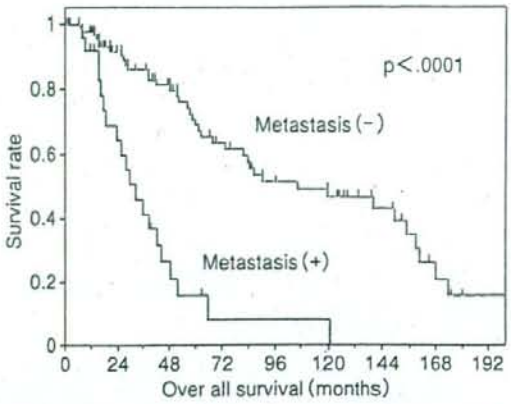

図2　遠隔転移・再発の有無による全生存率の比較
Metastasis：distant and/or local metastasis

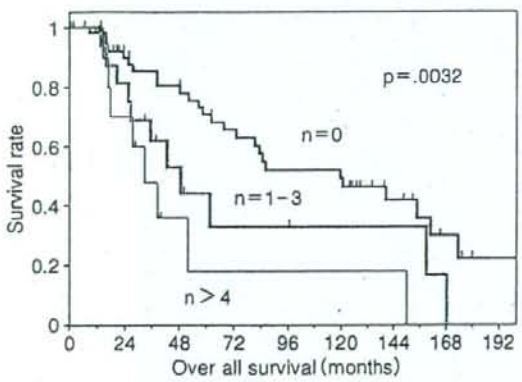

図3　腋窩リンパ節転移個数による全生存率の比較
(n=89)

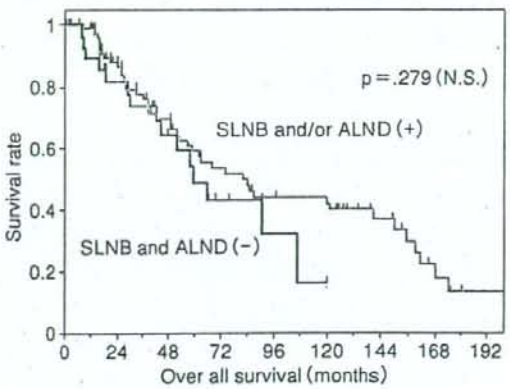

図4　腋窩手術の有無による全生存率の比較
SLNB：sentinel lymph node biopsy, ALND：axillary lymph node dissection

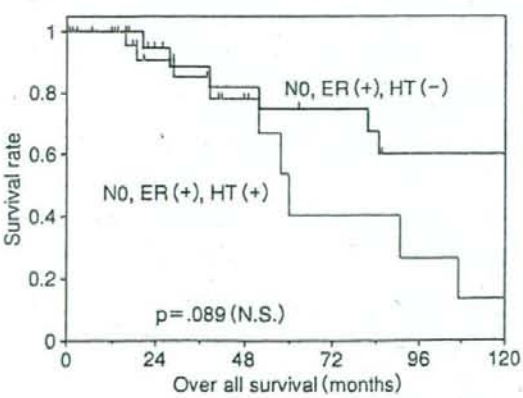

図5　N0症例における術後ホルモン療法の有無による全生存率の比較 (n=54)
N0：clinical lymph node negative, ER (+)：estrogen receptor positive,
HT：adjuvant hormone therapy.

示した．腫瘍径は中央値2 cm（範囲0.2～5 cm）で病理組織型は浸潤性乳管癌71例(61%)，浸潤性小葉癌5例（4%），非浸潤性乳管癌10例（9%）に対して粘液癌が16例（14%）とやや多かった．リンパ節転移個数は1～3個陽性16例(14%)，4～9個陽性4例（3%），10個以上8例（7%）で転移なしが61例（52%）であった．28例（24%）は腋窩手術を行っておらず不明であった．免疫病理検査結果ではER陽性67例(57%)，PgR陽性45例(38%)だった．手術は郭清を伴う全乳房切除71例(60%)，郭清を伴う乳房温存療法は5例（4%），原発巣のみの切除は部分切除のみ24例(20%)，全乳房切除のみ4例（3%）でセンチネルリンパ節生検（SLNB）を伴う手術は11例（10%）に行われた．術後のホルモン療法はER陽性だった67例中42

例に行われ，術後補助化学療法としてCMF療法が3例に行われていた．また，当院フォローアップ中に再発をきたした症例は初診時遠隔転移を認めた3例も含めて26例（22%）あった．うち2例がannthracyclineを含む抗がん剤治療を施行されていたが，他はホルモン療法また放射線療法のみであった．抗がん剤を投与された症例はいずれも全身状態が良好な症例で重篤な副作用はなかった．SLNBを伴う手術が行われた11例の生検結果を表2に示した．1%パテントブルーまたは1%メチレンブルー約3 m*l*を使用した色素法で行われていた．摘出されたセンチネルリンパ節（SLN）の個数は平均2.2個で迅速病理検査の結果は全例陰性であった．SLNの同定率は100%で，これらの症例に今のところ腋窩再発を含む再発症例は認められていない．

続いて予後における検討を示す．全症例の全生存期間（OS）の中央値は70カ月であった（data not shown）．OSにおいて臨床病期は有意な予後因子であった（p<.0001）．とくにcStage III以上の症例で予後が悪かった（図1）．また，再発の有無とリンパ節転移個数はOSにおける非常に有意な予後因子であった（p<.0001，p=.0032）（図2，3）．

手術方法とくに腋窩操作（郭清またはSLNB）の有無によってOSに差はなかった（図4）．最後に術後補助ホルモン療法の有無のOSにおける検討を図5に示した．今回の対象症例においては，前述の通り治療方針は担当医の判断に任されておりとくに追加治療の有無にはばらつきがあるため，ER陽性の症例のうち臨床的にリンパ節転移の認められなかったN0症例（54例）に絞って術後補助ホルモン療法を行った24例（44%）と行わなかった30例（51%）についてOSとの相関を検討した．結果，補助ホルモン療法の有無はOSにおいて有意な因子ではなかった．

3．考　察

80歳を越える超高齢者の乳癌の臨床病理学的特徴は今回の検討においては，しこりを主訴とし組織学的には粘液癌の割合が比較的多いというものであった．文献的にも粘液癌やアポクリン癌の割合が多いとされ，またホルモンレセプター陽性率が高いとされている[1,2]．アポクリン癌に関しては今回の症例では認められなかったが，ホルモンレセプターは58%が陽性であった．さらに腫瘍径は中央値2 cmと比較的小さめで限局しているものが多い傾向にあった．

手術に関しては，多くの患者が治療中の既往歴を有していたが手術・麻酔による肺梗塞等致命的な合併症を起こした症例はなかった．術式をみると，まず乳房において術後放射線治療を行うことの煩雑さや局所再発を避ける患者・家族の希望から近年まで全乳房切除を行うことが多かった．しかし，乳房温存術が安全に行われる症例が増加したことより超高齢者に対しても徐々に温存を行うことが増えてきた．これには，70歳以上のホルモン陽性患者に対して温存療法後の残存乳房への放射線治療は不要といった報告[3]も影響しており，今回の症例においても温存療法を行った患者のうち術後に放射線療法を行ったものは10例のみで他の症例は行っていない．温存療法後の局所のみの再発症例は今回の症例中1例のみであった．腋窩郭清においては，初期では標準的郭清を行っていた症例もあったが，近年センチネルリンパ節生検を行う症例が少しずつ増加してきた．高齢者ではセンチネルリンパ節の同定率が低下するため注意が必要であるが，今回われわれが行った11症例では同定できなかった症例はなかった．腋窩リンパ節郭清の意義は現在予後因子として補助療法を決定するリンパ節転移個数を確認することとされている．今回の検討においても腋窩郭清の有無は予後には影響していなかった．そのことから，術後に補助療法を何らかの理由で行わない症例においては郭清の意義が損なわれることになり腋窩郭清は必要がないと考えられる．

当院におけるこれまでの超高齢者に対する治療方針は年代ごとにやや異なりそのつど詳細に決められているものではないが，術後は他の年代の患者とは異なってリスクにあわせた術後補助化学療法は行われずホルモン療法剤が担当医の判断で追加されるかまたは何もせずに経過のみ観察するというものであった．そのために，手術によりリンパ節転移が陽性であった症例ではホルモン療法剤

が投与されている症例が多く，これらの症例でホルモン療法剤がOSに寄与しているかどうかは検討できなかった．しかし，逆にN0症例に対しては必ずしも投与されておらず，今回検討を行ったところホルモン療法剤の有無はOS延長に有意な因子ではなかった．これらのことから，再発リスクの少ないリンパ節転移陰性の症例では術後のホルモン療法は不要ではないかと考えられた．しかし，リンパ節転移の個数は他の年代同様に80歳以上の高齢者においても重要な予後因子であり，リンパ節転移があるハイリスクの症例については術後ホルモン療法の効果がある可能性は十分にあり，また投与を安全に行ってよい効果を得たといった報告[4-6]も認められることから，今後詳細な検討が必要と考える．

術後補助療法としての抗がん剤の投与の有用性に関しては今回の検討では明らかにはならなかった．しかし，経口フッ化ピリミジンなどのコンプライアンスの非常に高く，しかも効果のある薬剤が報告されるようになっている[7,8]．これらの薬剤の術後補助療法としてのエビデンスはいまだ少ないが，今後高齢者の治療に有用される可能性は十分にあると考える．また，現在広く使用されているタキサンにおいても高齢者に対して安全に使用したという報告も多い[9]．それに対して，高齢者においては他の年代よりも副作用の出現率が高いとする報告もある[10]．80歳以上の超高齢者においても他の年代同様にリンパ節転移個数や遠隔転移の有無がOSを左右することは今回の検討でも明らかであり，今後これらの症例に対して安全にしかも有効に抗がん剤を使用することを目標とする検討が必要と考える．

4. 結　語

今回われわれは80歳以上の超高齢者乳癌の治療方針についてretrospectiveな検討を行った．これらの症例におけるエビデンスはまだ少なく，確固たる治療方針は明らかとなっていないが平均寿命の延長に伴って，これらの症例は増加しこれまで以上に適切な治療が求められてくるのは明らかであり，ホルモン療法剤や抗がん剤の進歩に伴うコンプライアンスの上昇，および乳癌手術の低侵襲化にあわせた高齢者に対する適切な治療方針の決定が必要であると考えた．

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Review Article

Sentinel Lymph Node Biopsy is Feasible for Breast Cancer Patients after Neoadjuvant Chemotherapy

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Background: Despite the increasing use of both sentinel lymph node (SLN) biopsy and neoadjuvant chemotherapy (NAC) in patients with operable breast cancer, information on the feasibility and accuracy of sentinel node biopsy following neoadjuvant chemotherapy is still quite limited. Therefore, we investigated the feasibility and accuracy of sentinel lymph node biopsy for breast cancer patients after NAC.

Methods: A total of 104 patients with Stage II and III breast cancers, previously treated by NAC, were enrolled in the study. All patients were clinically node-negative after NAC. The patients underwent SLN biopsy, which involved a combination of an intradermal injection of radiocolloid and a subareolar injection of blue dye over the tumor. This was followed by completion axillary lymph node dissection (ALND).

Results: SLN could be identified in 97 of 104 patients (identification rate, 93.3%). In 93 of the 97 patients (95.9%), the SLN accurately predicted the axillary status. Four patients' SLN biopsies were false negative, resulting in a false-negative rate of 10.0%. The SLN identification rate tended to be lower among patients with T4 primary tumors prior to NAC (62.5%).

Conclusion: The SLN identification and false-negative rates were similar to rates in non-neoadjuvant studies. The SLN accurately predicted metastatic disease in the axilla of patients with tumor response following NAC.

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Key words: Sentinel node biopsy, Neoadjuvant chemotherapy, Breast cancer, Intradermal injection

Introduction

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

Recent studies report identification rates greater than 90% and 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 have been established, including T3 or T4 tumors, multicentric or multifocal lesions, a large biopsy cavity, previous axillary surgery, previous chest-wall irradiation, and NAC[4,5].

The application of SLN biopsy in NAC patients may identify, as in non-neoadjuvant chemotherapy groups, patients who do not necessarily require an ALND. Several studies have evaluated the use of SLN biopsy in patients with breast cancer after NAC, but the results have been varied and inconclusive[6-14].

Recently, the American Society of Clinical Oncology panel concluded that there are insufficient data to recommend SLN biopsy for patients receiving preoperative therapy, although SLN biopsy after preoperative systemic chemotherapy is technically feasible[15]. It is possible that the tumor response to chemotherapy may alter or

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Abbreviations:
SLN, Sentinel lymph node; NAC, Neoadjuvant chemotherapy; ALND, Axillary lymph node dissection

interrupt the lymphatic drainage, thus causing lower SLN identification rates and higher false-negative rates than in non-neoadjuvant studies. We hypothesize that the lymphatic flow within the skin lesion overlying the tumor is less damaged by chemotherapy than that in the parenchyma surrounding the tumor, except in T4 tumors. Thus, the usefulness of SLN biopsy with intradermal radiocolloid injection for patients with NAC-treated breast cancer has yet to be established.

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

Patients and Methods

Between May 2003 and October 2005, 104 patients with T2-4N0-2 breast cancer underwent NAC with SLN biopsy plus ALND performed by a single surgeon. The pathologic diagnosis was established by core needle biopsy in all patients prior to NAC.

Patients under 65 of age received four cycles of 5FU (500mg/m^2) / epirubicin (100mg/m^2) / cyclophosphamide (500mg/m^2) (FEC), plus twelve weekly cycles of paclitaxel (80mg/m^2). Patients over 65 years of age received twelve weekly cycles of paclitaxel (80mg/m^2) alone. After NAC, we enrolled the 104 clinically node-negative patients into this study.

Lymphatic mapping was performed using a 3 ml combination of blue dye (Patent blue V®, TOC Ltd., Tokyo, Japan) and 30-80 megabecquerels of technetium-99m-labeled Phytate (Daiichi RI Laboratory, Tokyo, Japan). One day prior to surgery, the radiotracer was intradermally injected into the area overlying the tumor, while blue dye was intraoperatively injected into the subareolar site. For nonpalpable lesions, injections were performed using mammographic or ultrasonic needle localization. Sentinel lymph nodes were identified as blue stained, radioactive, or both. SLN biopsy was then followed by a standard level I/II ALND. For 32 patients, lymphscintigraphy was also performed prior to NAC, and was compared to lymphatic mapping after NAC.

All sentinel nodes were histologically evaluated by creating 3-5 mm serial sections and staining with hematoxylin and eosin (H&E). Lymph nodes submitted as part of the axillary dissection were submitted in their entirety and evaluated using standard H&E staining.

Table 1. Patient demographics

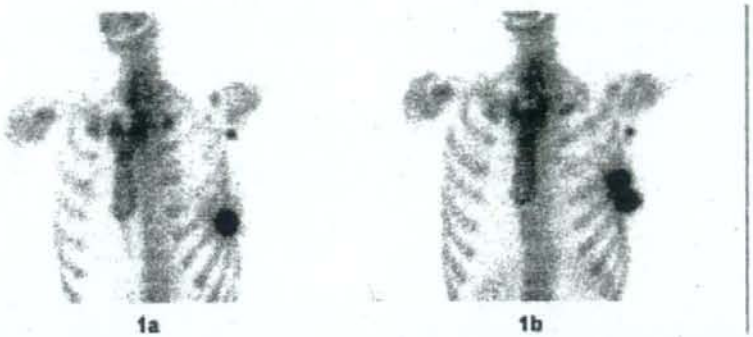
	Number of patients
Age (years)	
Mean	50.2
Range	27-77
Clinical tumor size (cm)*	
Mean	4.89
Range	2.5-12
Tumor classification*	
T2	61 (58.7%)
T3	35 (33.6%)
T4	8 (7.7%)
Lymph node status*	
N0	54 (52.0%)
N1	40 (38.5%)
N2	10 (9.5%)
Tumor type	
Invasive ductal	102 (98.1%)
Invasive lobular	2 (1.9%)
Type of NAC	
FEC plus paclitaxel	100 (96.2%)
paclitaxel alone	4 (3.8%)
Clinical response of the tumor	
CR	55 (52.9%)
PR	41 (39.4%)
SD	8 (7.7%)
Pathological response of the tumor	
pCR	23 (22.1%)
pINV	81 (77.9%)
Pathological nodal status	
Negative	60 (57.7%)
Positive	44 (42.3%)

*Before NAC.
pCR = pathological complete response; pINV = pathological invasive.
CR = Complete response; PR = Partial response; SD= Stable disease

Results

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

Based on lymphscintigraphy studies before and after NAC, the results of lymphatic mapping were quite similar in 30/32 patients, as shown in Fig 1. SLN were not detected in two cases with a



1a 1b

Fig 1. Lymphscintigraphy before and after NAC (1a and 1b, respectively) revealed one sentinel node at the axilla. The bone scintigram was performed simultaneously to detect bone metastasis.

Table 2. Results of sentinel node biopsy

	Number of patients
Total no. of patients	104
SLN identified	97 (93.4%)
SLN positive	36 (34.6%)
SLN was only positive lymph node	16 (44.4%)
SLN identification method	
Radiocolloid and blue dye	91 (87.5%)
Blue dye only	13 (12.5%)

Table 3. Comparison of lymph node status of SLNs and non-SLNs (n=97)

	Non-SLN status	
SLN status	Positive	Negative
Positive	20	16
Negative	4	57

False-negative rate, 10%; overall accuracy, 96%; negative predictive value, 93%; positive predictive value, 100%

T4d primary tumor.

As seen in Table 2, the overall SLN identification rate was 93.4% (97 of 104). Of the 97 patients in whom an SLN could be identified, 36 (34.6%) had positive SLNs. In 16 of these patients (44.4%), the SLN was the only positive node. SLNs were identified by both radiocolloid and blue dye in 91 patients (87.5%) and by blue dye alone in 13 patients (12.5%).

The pathological status of the SLNs and non-SLNs is outlined in Table 3.

The SLNs accurately predicted axillary status in 93/97 patients (95.9%). Four patients had false-negative SLN biopsies, a false-negative rate of 10.0% (4/40). Fifty-seven patients had pathologically negative SLN or non-SLN.

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

	T2 (n=59)		T3/T4 (n=38)	
	Non- SLN status			
SLN status	Positive	Negative	Positive	Negative
Positive	7	7	13	9
Negative	2	43	2	14
	SLN identified, 59/61 (97%) False-negative rate, 13%		SLN identified, 38/43 (88%) False-negative rate, 8%	

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

In T2 tumors before NAC, the SLN identification rate was 97% (59 of 61), and 2 patients had false-negative SLN biopsies, or a false-negative rate of 13%. In T3 and T4 tumors, the results were 88.4% (38 of 43) and 8%, respectively (Table 4). The SLN identification rate tended to be higher in patients with a T2 primary tumor before NAC than in those with T3/T4 primary tumor before NAC, but the difference was not statistically significant.

In the SLN biopsy results, there was no significant difference between nodal status prior to NAC.

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

	N0 (n=52)		N1/N2 (n=45)	
	Non- SLN status			
SLN status	Positive	Negative	Positive	Negative
Positive	4	8	16	8
Negative	2	38	2	19
	SLN identified, 52/54 (96%) False-negative rate, 14%		SLN identified, 45/50 (90%) False-negative rate, 7%	

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

	CR (n=50)		PR/SD (n=47)	
	Non- SLN status			
SLN status	Positive	Negative	Positive	Negative
Positive	6	5	14	11
Negative	2	37	2	20
	SLN identified, 50/55 (91%) False-negative rate, 15%		SLN identified, 47/49 (96%) False-negative rate, 7%	

Table 7. Success rate of sentinel node identification according to tumor characteristics

	No. of Attempted	Success Rate (%)	P
Tumor classification			
T2	61	97 %	*N.S.*
T3	35	94 %	
T4	8	63 %	
Clinical nodal status			
Negative	54	96 %	*N.S.*
Positive	50	90 %	
Clinical tumor response			
CR	55	91 %	*N.S.*
PR/SD	49	96 %	
Pathological tumor response			
pCR	23	91%	*N.S.*
pINV	81	94 %	

In the patients with clinically negative lymph nodes (N0) before NAC, the SLN identification rate was 96.3% (52 of 54), and two patients had a false-negative SLN biopsy, a false-negative rate of 14%. In the patients with clinically positive lymph nodes (N1/N2), the results were 90% (45 of 50) and 7%, respectively (Table 5). In the SLN biopsy results, there was no significant difference between nodal status prior to NAC.

For patients with complete tumor response (CR) after NAC, the SLN identification rate was 91.0% (50/55) and two patients had false-negative SLN biopsies, resulting in a false-negative rate of 15%. For patients with partial tumor response (PR) and stable disease (SD), the results were 96.0% (47/49) and 7%, respectively (Table 6). The SLN identification rate tended to be lower, although the difference was not statistically significant, after NAC in patients with CR after NAC as compared to those with PR and SD.

There was no significant difference in the false-negative rate according to the tumor classification before NAC, the clinical lymph node status before NAC, or the tumor responses after NAC.

There was also no significant difference in the success rate of SLN identification according to tumor classifications before NAC, the clinical lymph node status before NAC, the clinical response of the tumor after NAC, or the pathological response of the tumor after NAC, although the success rate tended to be lower in patients with a T4 primary tumor (Table 7).

Discussion

Although the use of SLN biopsy has dramatically increased over the past several years, and some experienced surgeons are performing this procedure without completing axillary dissection, it is unlikely that SLN biopsy will become the generally accepted standard of care in axillary staging until results from ongoing randomized trials

Table 8. Studies of SLN biopsy after NAC

	No. of patients	Stage	Tumor size (cm)	No (%) of successful SLN biopsies	False negative (%)
Breslin et al.2000 [6]	51	II or III	5.0	43 (84.3)	3 (12)
Miller et al., 2002 [7]	35	T1-3N0	3.5	30 (86.0)	0 (0)
Stearns et al.2000 [8]	34	T3-4, any N	5.0	29 (85.0)	3 (14)
Haid et al.2001 [9]	33	T1-3, any N	3.3	29 (88.0)	0 (0)
Julian et al.2002 [10]	31	I or II	NS	29 (93.5)	0 (0)
Tafra et al.2001 [12]	29	Any T, N0	NS	27 (93.0)	0 (0)
Nason et al.2000 [13]	15	T2-4, N0	NS	13 (87.0)	3 (33)
Shimazu et al.2004 [14]	47	II or III	4.5	44 (93.6)	4 (12)
Current study	104	T2-4, any N	4.9	97 (93.0)	4 (10)

demonstrate the equivalence of this procedure with axillary dissection in terms of axillary recurrence and overall survival. At the same time, it is unlikely that the value of sentinel node biopsy following NAC will be established[1]. The main reason for this is that only a small proportion of operable breast cancer patients currently receive NAC, making a randomized trial quite difficult. Another reason is that when the results from the ongoing randomized trials are disclosed, if they are favorable towards the SLN biopsy procedure, the majority of surgeons will extrapolate the applicability of these results to patients who have received NAC. Thus, it is quite possible that demonstrating the feasibility and efficacy of SLN biopsy after NAC will depend on the retrospective data of single-institution experiences.

NAC can reduce tumor size and significantly increase the ability to perform breast-conserving therapy[16-18]. After NAC, axillary downstaging is similarly affected. NAC with anthracycline/cyclophosphamide-containing regimens has been shown to neutralize the involved axillary nodes in about 30% of patients[16]. The addition of taxanes to anthracycline/cyclophosphamide-containing regimens has increased the conversion rate to around 40%[19, 20]. With the number of patients receiving NAC increasing, the question arises as to whether SLN biopsy is an option for these patients. We summarize the studies regarding SLN biopsy after NAC in Table 8, but they are inconclusive[6-14]. Breslin *et al.*[6] reported a study of 51 patients who underwent SLN biopsy after NAC and concluded that SLN biopsy following NAC is accurate. They had an identification rate of 84.3% and a false-negative rate of 12.0%. Nason *et al.*[13] reported a smaller number of patients who hard received NAC, and their identification and false-negative rates were 87.0% and 33.3%, respectively. They concluded that SLN biopsy resulted in an unacceptably high false-positive rate. However, in these small series, even 1 or 2 patients with false-negative SLNs can greatly affect the conclusions in a different direction. We report here a study of 104 patients who received NAC and had an identification rate of 93.4% and false-negative rate of 10.0%. We conclude in our study that SLN biopsy after NAC is accurate and feasible even for large tumors and patients with positive axillary nodal status before NAC without inflammatory breast cancer.

It has been speculated that among patients who have had 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 might then cause an increased false-negative rate for SLN biopsy and a decreased identification rate of SLN biopsy. However the hypothesis of the present study is that the lymphatic flow around skin lesions is rich and less influenced by the effects of chemotherapy and tumor size than that in the parenchyma surrounding the tumor. The lymph-scintigraphy in this study results before and after NAC demonstrated that the effect of NAC did not at all change the lymphatic flow of the breast.

The results of our study suggest that SLN biopsy after NAC using intradermal injection of radiocolloid is feasible and can accurately predict axillary lymph node status for patients with clinically negative lymph node status following NAC. This procedure could help patients who have had their

axillary lymph node status downstaged from positive to negative and patients with large tumors qualify as appropriate candidates for SLN biopsy.

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

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Case Report

Brain Metastases after Achieving Local Pathological Complete Responses with Neoadjuvant Chemotherapy

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Background: We encountered two patients with inflammatory breast carcinoma who developed symptomatic brain metastases after achieving local pathological complete responses (pCR) with neoadjuvant chemotherapy (NAC).

Case presentations: The first patient is a 39-year-old woman (Case 1), who underwent NAC with AC (doxorubicin + cyclophosphamide) followed by weekly paclitaxel. After achieving a clinical CR (cCR), we conducted a modified radical mastectomy. Pathological evaluation confirmed no residual malignant cells within the breast tissue or lymph nodes. However, she developed neurological symptoms from brain metastases one month postoperatively. The second patient is a 44-year-old woman (Case 2). Again, no residual malignant cells were detected within the breast tissue or lymph nodes following NAC, but the patient developed symptomatic brain metastases eight months postoperatively. When primary breast tumors are locally advanced, it may be worthwhile to rule out brain metastases even if pCR is obtained after NAC.

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Key words: Brain metastasis, Pathological complete response, Breast cancer

Introduction

Neoadjuvant chemotherapy (NAC) is a standard treatment option for patients with locally advanced and/or inflammatory breast cancers. The outcomes of patients achieving pCR of their primary tumors are significantly better than those with residual disease[1-3]. Here, we introduce two patients who developed symptomatic brain metastases shortly after documented pCRs following NAC and surgery.

Case Report

Case 1

A 39-year-old premenopausal woman sought medical attention for erythematous induration of her left breast. With a working diagnosis of inflammatory breast cancer, fine needle aspiration cytology revealed adenocarcinoma. The patient was referred to the National Cancer Center Hospital for further treatment in February 2005. Physical examination revealed an indistinct 12 cm mass in the upper area of the left breast, and the surface of this lesion exhibited a peau d'orange appearance. Axillary and supraclavicular lymph nodes were palpable and measured 4 and 2 cm in diameter, respectively. The axillary lymph node was fixed to the surrounding tissue. Ultrasonography (US) revealed a 7 cm breast mass with dermal thickening, edematous subcutaneous tissue, and enlarged lymph nodes (Fig 1a). These findings were also observed on computed tomography (CT) and magnetic resonance imaging (MRI).

Core needle biopsy led to a pathological diagnosis of invasive ductal carcinoma (grade 3, nuclear grade 3, and HER-2 negative) (Fig 2a). The tumor was negative for both estrogen and progesterone receptors. Chest X-ray, bone scintigraphy, abdominal US, and chest and abdominal CT revealed no distant metastases. Due to the presumed low incidence of brain metastases at this clinical stage, brain imaging was not done at

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Abbreviations:
pCR, Pathological complete response; NAC, neoadjuvant chemotherapy; US, ultrasonography; CT, Computed tomography; MRI, Magnetic resonance imaging

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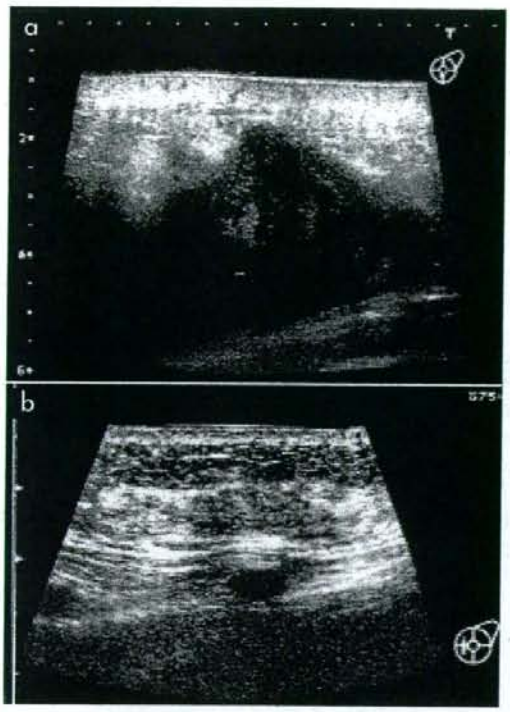

Fig 1. (a) US reveals a 7 cm breast mass with overlying skin thickening, edematous subcutaneous tissue. (b) US reveals no residual tumor following neoadjuvant chemotherapy.

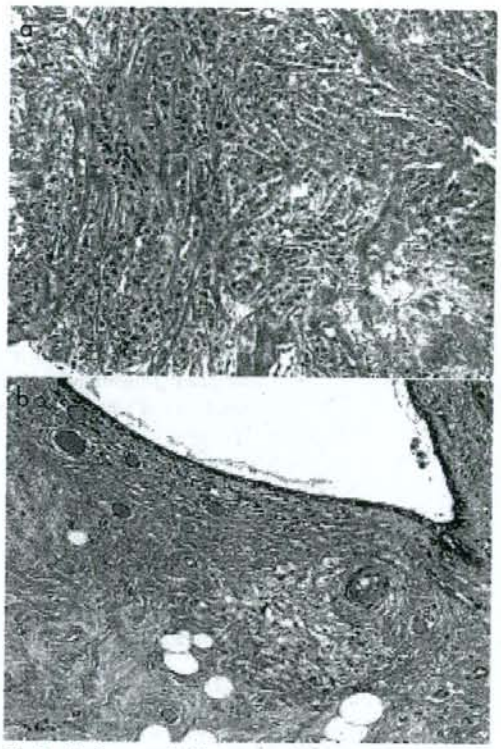

Fig 2. (a) Core needle biopsy reveals invasive ductal carcinoma, grade 3, nuclear grade 3. (b) No residual tumor is detected. The presence of inflammatory cells surrounding a duct with an increased number of enlarged capillary vessels, typical after tumor disappearance, is observed. (hematoxylin-eosin staining, ×100).

this point. Inflammatory breast cancer of the left breast was initially diagnosed, T4dN3M0, Stage IIIC, according to the general rules for clinical and pathological grading of breast cancers[4]. She received NAC from February to July consisting of doxorubicin and cyclophosphamide (60/600 mg/m^2) 4 times every 3 weeks, followed by paclitaxel (80 mg/m^2) weekly for 12 weeks. Following NAC, only induration of her left breast was apparent upon physical examination, and no breast masses or axillary lymph nodes were detected by US (Fig 1b) and CT. Additionally, serum levels of tumor markers (CEA, CA 15-3, ST 439) remained within normal limits before and after chemotherapy. We subsequently conducted a modified radical mastectomy in August, and no malignant cells were detected in the resected breast tissue and dissected axillary lymph nodes (Fig 2b). However, the patient presented with vertigo and severe headache prior to the initiation of radiotherapy to the left chest wall in September. Brain MRI revealed multiple metastatic lesions in her right frontal lobe, temporal lobe, and bilateral cerebellum (Fig 3). To control her symptoms, whole-brain radiotherapy with a total dose of 30 Gy/10 fractions was incorporated in October. However, her condition deteriorated, and she expired in December.

Case 2

A 44-year-old premenopausal woman was seen at a nearby hospital with a chief complaint of an erythematous enlarged right breast. Inflammatory breast cancer was suspected, so she was referred to our institution in December 2004.

On initial examination, the right breast was firm, erythematous, and edematous with a thickened dermis. Axillary and supraclavicular lymph nodes were palpable and measured 5 cm and 1 cm

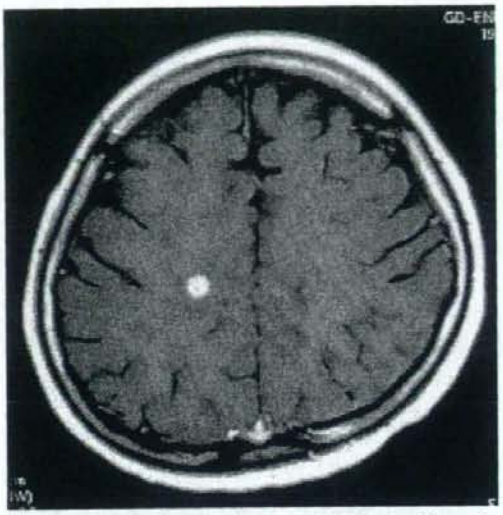

Fig 3. The metastatic lesions exhibited high signal intensity in the right temporal lobe by T1 weighted MRI.

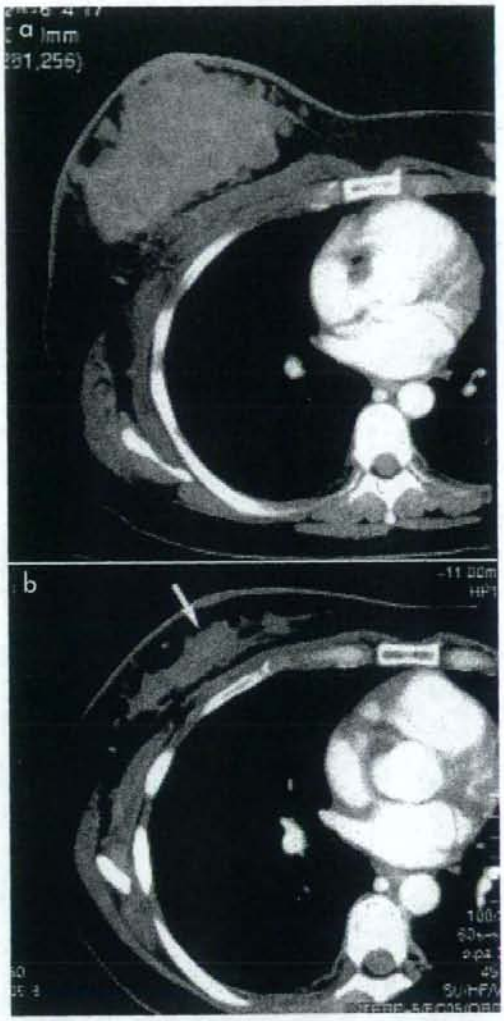

Fig 4. (a) CT shows a large right breast mass with overlying edematous subcutaneous tissue and thickened skin. This is not the early phase but late phase scan of breast CT, because only chest CT without an early phase scan was performed to detect distant metastasis instead of breast CT. (b) CT scan reveals a mass-like lesion measuring 3 cm, without enhancement, in the right breast.

in diameter, respectively. CT showed a large right breast mass with an edematous dermis and subcutaneous tissue.Additionally, the axillary and supraclavicular lymph nodes were enlarged (Fig 4a). The specimen obtained by the core needle biopsy was consistent with an invasive ductal carcinoma (solid tubular type, grade 3, nuclear grade 3, HER-2 negative, estrogen and progesterone receptor negative) (Fig 5a). No metastatic lesions were detected by bone scintigraphy, chest X-ray, chest CT, or abdominal US, though diagnostic brain imaging was not performed at that time. Serum tumor markers were elevated, with a CEA of 52.4 ng/ml, CA 15-3 of 279 U/ml, and NCC-ST 439 of 910 U/ml. Inflammatory breast cancer, T4dN3M0, Stage IIIC[4] was diagnosed. She underwent NAC from December to May 2005, using the same treatment regimen as Patient 1. Following NAC, physical examination revealed only induration of the right breast with slight thickening of the overlying skin. CT revealed a slightly enhanced, 3-cm lesion in the breast (Fig 4b) without enlarged lymph nodes. All tumor markers were within normal limits after chemotherapy. We performed a modified radical mastectomy in July, and no tumor cells were pathologically detected in the breast tissue and axillary lymph nodes (Fig 5b). Following surgery, we performed local radiotherapy with a total dose of 60 Gy/30 fractions from August through October. However, the patient developed headache and ambulatory disturbance in early December. Brain CT and MRI scans performed in March 2006 detected a tumor measuring 5 cm in diameter in her right temporal lobe with surrounding edema (Fig 6). A right frontotemporal craniotomy followed by whole-brain radiotherapy of 37.5 Gy/15 fractions was carried out from