なって初めて有力な手段となり，大規模比較試験ATACの中間報告によってこれまでのTamoxifenより効果が大であり，さらに子宮内膜癌の発生が少ないことが判明してきている．anti-aromatase agentは現在作用が可逆的なAnastrozole（Arimidex）と不可逆的に永続するsteroidal aromatase inactivatorのExemestane（Aromasin）2種が市販されていて，いずれnonstroidalのLetrozoleも含めて帰趨が定まってゆくであろう．欧米では閉経後の太った乳癌患者が多いため，このaromatase inhibitor/inactivatorの寄与が大きいかも知れない．

わが国では乳癌患者は平均50歳と欧米に比較すると中年好発であり，体形も肥満の著明な患者も多くないことなどを考えると，欧米で開発されてきた閉経後患者のホルモン療法は，日本人患者にとっては再考する必要もあり至適な薬剤と使用方法を息を永く見極めていかなければならない．

■■　放射線療法

乳癌は腺癌であっても，放射線に対する感受性は高いもので，再発進行乳癌でその奏効性が良く分かる．しかし，その補助療法については，これまで数多くの照射が行われてきたが，明らかな生命の延長に対して貢献したとの分析は得られていない．EBCTCGの照射に関するmetaanalysis[7]では，照射による延命効果を得ていないが，この分析として照射による延命効果と照射による心臓障害が相殺してしまって，結果として照射効果が認められないことになったとしている．補助照射のこの不安定さは，ひとえに照射を必要としている症例の選別の不徹底さ，たとえば，時代的な転移の画像診断不良，不安による照射，転移の多いものに対する隣接部照射などによるものと考える．現在では照射法の進歩，各種の画像診断による照射例の絞り込み，転移の多い症例に対する化学ホルモン療法の優先などがはかられ，補助照射でも奏効について効果を得ている．

乳房温存療法での照射は，癌が遺残している場所が残存乳房と限局されていて，遺残癌巣が微細である特殊条件下であって，照射効果は確実であり，温存療法は照射による残存乳房内照射を最小に抑えて，乳房切除に劣らぬ長期生存率を得ることに成功したのである．B Fisher等は乳房温存療法における照射を“rediscovering the worth of radiation therapy”と呼んでいる．

現在，照射にあたって必要とされている事項としては，

①画像診断，各種の針生検，手術時の生検による確認に基づく照射症例の絞り込み．

②X線あるいはCT simulationによる正確，確実な照射と隣接，前後の臓器の防護，

などが考えられる．

将来像としては，この確実な症例の限定，より厳密な照射域の確定と防護，さまざまに工夫された照射法，重粒子線照射などが期待される．

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特集　手術で役立つ臨床局所解剖の知識

乳癌手術

霞　富士雄*

はじめに

乳癌の手術は近年いちじるしく変化してきている。その変化とは，ひとえに縮小化であり，症例に応じた個別化とその標準化である。この傾向に伴って，病理，放射線科，オンコロジー，形成外科との協調が進んで，乳癌治療の一体化，緊密性がはかられてきて乳腺科(senology)という名称がふさわしくなっている。

I. 手術の変遷，縮小化（図1）[4)~6)]

2004年に行われた日本乳癌学会の主要施設での乳癌手術法の変遷をみると，2003年の時点で1990年代の後半より徐々に増加してきた乳房温存手術は48.4%，うち残存乳房照射率はほぼ77%であり，これに応じて乳房切除は減少し45.3%であった。

乳房温存手術はさらに増加を続け，おそらく現在では50%を超え，照射率も増加しているものと推定される。これは，温存手術の経験の積み重ねによる安全性の認識，乳房温存に対する希求の欧米化，次項で述べるSNBの浸透[1)]との相乗，乳癌の早期発見化などの要因によるものである。温存手術の場合，術前の画像診断ではMMG，USに造影MRIやCTも加わって，切除範囲の厳密化が進み，さらにN0の診断の信憑性も増してSNBが盛んに行われるようになった。初めの乳切+SNB転移（−）→バックアップ腋窩郭清の経験によって，Bp(q)+SNB転移→（−）郭清省略とする例が一段と増加した。

乳房切除[2)3)5)]は現在，大小胸筋ともに上，中間，下胸筋神経を残したBt+Ax，Auchincloss法一改変が行われている。さらに第2(3)肋間上腕神経を温存し，第2肋間上腕神経より尾側だけを郭清したり，胸背血管より外側にメスが及ばないようにしたり，尾側の第3肋間上腕神経を温存したりする縮小化が進んでいる。やむなくBtを行うにしてもSNBに従ってSNが転移（−）であれば腋窩郭清を省略するBt+SNBが盛んに行われるようになった。このため広範な石灰化例，TIでとくにa2，b1，b2，b5例，高齢者らには大きな福音になってきた。

縮小はさらに進んで，小腫瘍例に対し，ラジオ波[7)]やfocused USなどを照射して，メスによるBpに代えようとする試みがまだしっかりとした経験的なエビデンスは整っていないが，患者の許諾を得て行われ始めている。これにSNBによって腋窩郭清を省略すれば，メスをほとんど使用しないで原発性乳癌の根治手術が

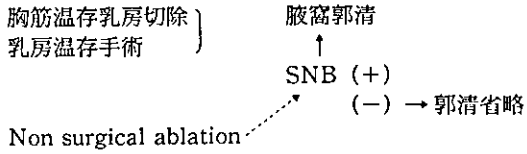

図1　乳癌手術縮小の現状

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図 2　乳房切除の皮切線の作図と使用メス
（電気メスと熱メス）

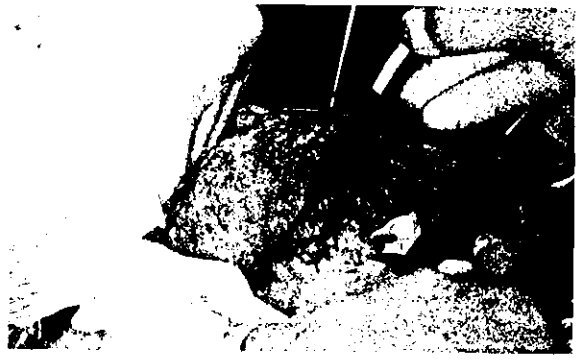

図 3　熱メスによる薄い脂肪を付けた
均一な皮弁の形成

終了する時代になりつつある。

II. 乳房切除術[2)3)5)]胸筋温存乳房切除術

温存手術後の照射への依存度にもよるが，温存手術の遂行は多くても全乳癌の 2/3 までで，それ以外の乳癌へは乳房切除を行わないわけにはいかない。局所進行乳癌，乳房内広汎進展例，多結節例で遠隔転移のない M 0 例に対しては根治的乳房切除術が施行される。腋窩リンパ節転移の認められる N（+）例には通常通り，レベル II までの郭清が行われ，腋窩上部まで転移が発見されればレベル III までの Kodama 法が行われる。いずれも大胸筋の機能を保ち，筋萎縮が起こらないように上，中間，下胸筋神経は温存する。Auchincloss の原法は下胸筋神経は切除したが，これを残し郭清がレベル II high point までのものを Auchincloss 法と呼んでいる。

乳房切除の場合でも画像診断の助力を借りて N 0 であれば積極的に，主として RI 法による SNB を行い，SN を 2 mm のスライスに分割して HE による迅速診断，サイトケラチン染色，RT-PCR，そのほかの方法などを駆使してこれによって転移（−）であれば腋窩郭清を省略する Bt＋SNB が日常的に行われている。広汎な石灰化例の場合で主として乳管内癌であろうが，一部浸潤部分もあるかもしれない症例など，N 0 であっても SNB を実施して SN 転移（−）を確認したあとに腋窩郭清の省略を行うのがよい。

1. 皮膚切除

癌が大きい場合や広汎な場合は原則として被蓋皮膚は切除するが乳房温存の世の中であり，創の大きさや障害は極力小さく留める配慮を行う。経験を積めばどのくらいの皮膚を切除しても primary closure を行って創縁が壊死になることが起こらないかが判断されるようになる。

2. 使用メス

筆者はこの皮膚切開以外の乳術中の切開・切離はすべて図 2 の熱メス（刃 # 10）[3)5)] と電気メスを用いて鋭的切開・切離を行う。切開・切離にあたっては，前立ち（第 1 助手）の牽引に対して術者の左手の牽引で答えて，両者のほどよい countertraction のなかでメスを走らせる。均一な層を選び，メスの腹で切離層の至適抵抗を感じながらゆっくりとメスを走らせる（図 3）。この極意のなか，鋏やほかの器具の介入は許されない。腋窩 SNB を行う予定の場合には，腋窩の上の皮弁形成は控え目とし大胸筋上腕骨起始部近くに近づくにつれて皮弁の厚さは 1 cm ほどに厚くして上下の皮弁を合流させる。

乳房切除は正中部頭側，すなわち鎖骨骨頭下より電気メスを用いて大胸筋筋膜を極力切除するように行う。できるだけ大胸筋の筋線維に平行にメスを走らせる。この際メスは大胸筋筋膜下を筋肉に食い込まないように迅速，颯爽と走

図 4a　大胸筋筋膜を電気メスによって切除しつつ外縁上部に至り，下胸筋神経と伴行する胸筋外縁血管を温存する。

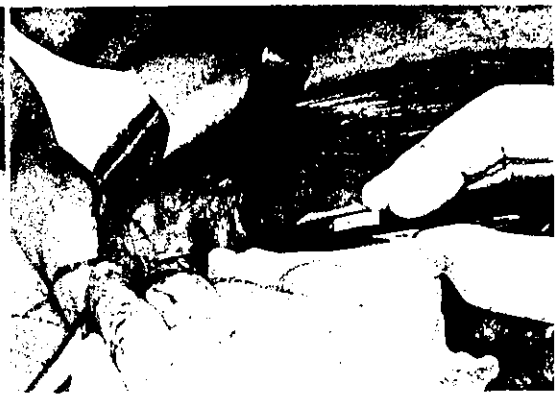

図 4b　腋窩静脈前面の露出と郭清，ときに熱メスの腹を，ときに先を使う。

図 5　第2肋間上腕神経の露出，中枢から行うが，ときに末梢からも行う。

図 6　長胸神経の露出，第2助手が肩胛下筋群を尾側に引いて長胸神経を伸展させると思わぬ損傷が防止できる。

らせる。

3．腋窩郭清

主として熱メスを用いて，一部電気メスを用いて郭清を行う（図4）。Auchinclossの主張した小胸筋裏のhigh pointまでの郭清を行い，第2肋間上腕神経を温存して（図5），通常レベルIIまでの郭清を行う。長胸神経，胸背血管・神経を温存し（図6），この血管より外側はいじらないようにする。可能であれば第3肋間上腕神経も残す。

SNB　N0，かつ現状ではT≦3.0 cm以内であればSNBは積極的に行い，SNに転移が認められない（パラフィン2 mm幅全割）場合には腋窩郭清は省略する（図7）。

III．乳房温存手術[1)~6)]

乳房温存手術は，創治癒後の残存乳房全体に照射を加えることを原則とする（この場合乳房温存療法と呼ぶ）。癌から離れて切除して局所切除の安全性を確保することと，切除範囲を小さめにして整容性を高めることは相反する。このため，あるところで線を引いてあとは残したとしても微細癌巣であれば残存乳房に対し対向

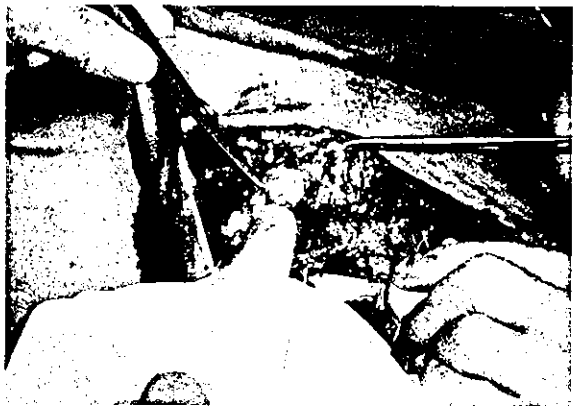

図 7　皮弁形成はSNBを行う予定であれば，SN meta（—）を想定して外上腋窩部分は浅く厚くしておく，ガンマープローブによるSNの同定は容易である。

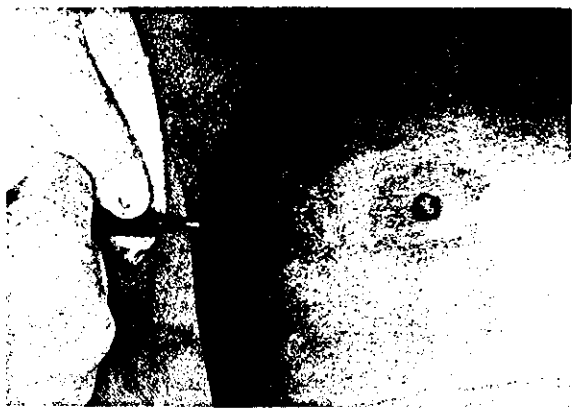

図 8　乳腺切離線と皮切線のスケッチと切離線に沿っての色素注入

2門のX線接線照射によって根治がはかられるというのが，乳房温存療法が歴史的に成立しえた所以である。こうすることによって乳房温存療法の術後成績は乳房切除術に劣らないことが実証されたのであるが，それでも少数例ではあるが残存乳房内再発を起こすこと，および大きめの切除になれば整容性が犯されることがこの療法の弱点である。このジレンマをそれぞれが自分流に克服するために，乳房温存療法では硬軟多数の態度が出てきてしまう。すなわち比較的限局型の癌だけを対象として，画像診断の示す癌の広がり全体をすべて局所切除しようとする態度と，触知される腫瘤だけを切除して乳管内進展くらいは残してもあとは照射がカバーするであろうとする両極端がある。前者は乳房内再発を最小にするためであるが，整容性が犯され，場合によっては乳房切除になってしまう。また，術中組織診や細胞診をはじめ，術後の検体の検査などに，ひと，もの，かねの努力と出費がかさんでしまう。しかしこれによってもし，安全に切除しきれたと判断されれば照射は不要のものになる。一方，後者の方式では温存乳房内の再発は増えるが，照射効果は著明なものがあって，みるみる増えるわけではないが，効きの悪いアクセルを踏むように乳房内再発が増加してくる。

1．局所切除・色素注入

原則的には，安全性と整容性を満足させられると判断される症例を選び，最新のMMG，US所見に従ってその教える範囲を局所切除するが，切離線を入れる正確性を確保するために図8のように皮膚面にピオクタニンで作図し，ツベルクリン針と2ccの注射器を使用してピオクタニンに同量のキシロカインゼリーを混ぜ，よく撹拌した液体を約1.5cmおきに乳腺深く刺入し抜きながら注入しておく。

2．皮弁形成

術後照射を行う予定であれば，あるいは癌が皮膚から深い場合には，乳癌直上の皮膚切除はしないでよいが，浅くてdimpleがあるような場合は，心配のある直上の皮膚は切除しておくほうが無難であり，さらに皮弁形成の第一刃は注意深く癌に接近しないようにする。

皮弁形成は，皮下に脂肪層を1〜2mm均一に残すように広く皮弁形成を行う（図9）。あとで乳腺切離した空隙を埋める際に皮膚の変形ができないようにするため，初めから適度の皮弁形成を作っておいたほうがよい。

3．乳線切離

色素注入点は少々拡散してしまうが，この中心を澪標（みおつくし）として，かつ腫瘍縁を指で触知しな

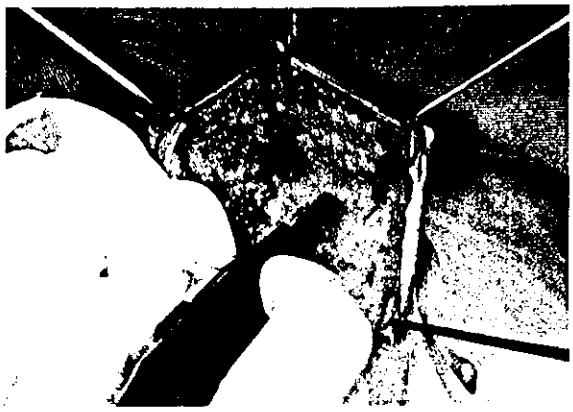

図 9　皮弁形成を均一に十分に行っておく。

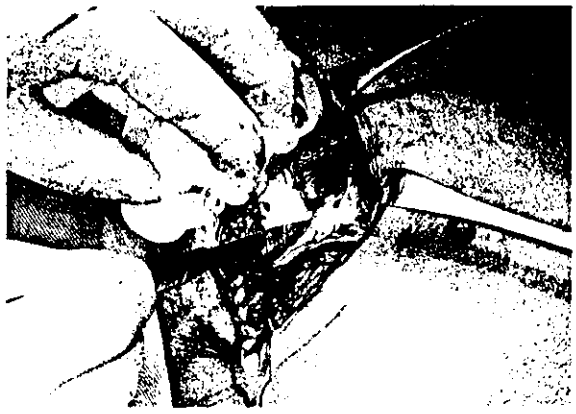

図 10　腫瘍縁を触れながら，改めて色素注入点を確かめながら，皮下脂肪層を熱メスで，乳腺に至ったら大円刃の通常メスで切離する。

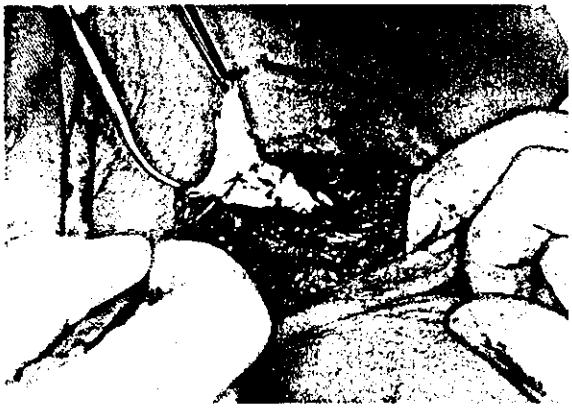

図 11　乳腺切離端を薄く切除して迅速診断へ提出

図 12　円状乳房部分切除を終了する。標本を降ろす前に，腫瘍が中央にあるかを改めて確認し，後に標本撮影 specimen radiography を行う。

がら安全域を保ちつつ，メスを胸壁に垂直に走らせて平面を保ちながら切離する。図 10 では筆者は切離面を病理検索のために保護する目的で通常の大円刃メスで切離している。

残した乳腺切断面から薄く乳腺端を切離して迅速病理検索する（図 11）。

部分切除完成（図 12）。SNB で SN を 2 mm 幅で細切りし迅速診断で転移（−）である場合，腋窩郭清を暫定的に省略するために腋窩脂肪織の切除はほとんど行わないが，小胸筋外縁の腋窩篩板までを切除する程度に行っておくほうが術後腋窩脂肪が突出して醜くなるのを防ぐことができる。術中はリンパ節を 2 mm 幅で迅速診を行って（−）であっても術後パラフィンチェックで 5% 程度が（+）になってしまい問題が起こる。これも false negative の一部となる。

4. SNB

これまでの処理が終了しているとガンマープローブの当て方，SNB の同定，摘出は容易である（図 13）。プローブのカウント値が高いリンパ節を摘出し患者から離してもう一度プローブを当ててカウント値を確認し，SN と同定する（図 14）。SN の 2 mm 幅の全割（図 15），各切片の stamp cytology（図 16）を各切片毎

図 13　部分切除後に SNB を行う。SN の同定に難点があることはまずない。

図 14　切除した SN をガーゼに乗せて患者から離した位置で，改めて高カウントであることを確認する。

図 15　SN は 2 mm 幅で分割する。

図 16　2 mm 幅の各片の stamp smear も提出する。

図 17　SN 1-a，1-b，1-c として迅速診へ。

に迅速提出する（図 17）。

5．乳腺切離部縫合

この症例は切離端をそのまま縫合することですまされた。癌の占居部位が外上方であると，図 12 のような大きさを切除しても乳房の歪みはあまり分からないように整形できるものである（図 18）。この症例のように欠損部の直接縫合はもっとも単純であるが，これは初めに行っておいた広い皮弁形成によって目立った変形なしに直接縫合が可能となる。直接縫合ができない場合は，上下の乳腺外縁に切開線を入れて減張・縫合したり，乳腺切離面に大胆に 5 cm ほどの切開線を入れて，できた半島状の突起で欠

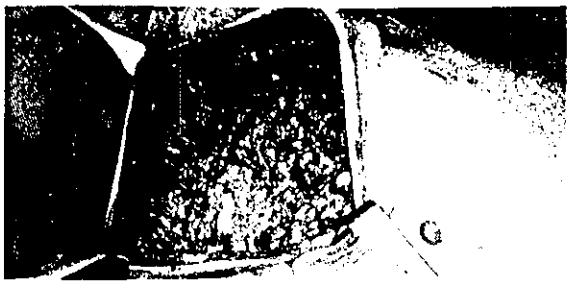

図 18　SN に meta がなければ郭清を省略して手術を終了する。乳腺部分切除部欠損はそのまま縫合閉鎖してある。皮膚は埋没縫合し，縫合線はカラヤヘッシブで被覆した。

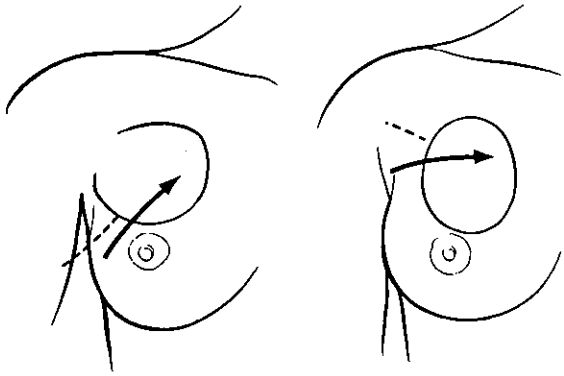

図 19　乳頭内上（c 領域）1.0×1.0 cm の癌。切除後，切開線の入れ方

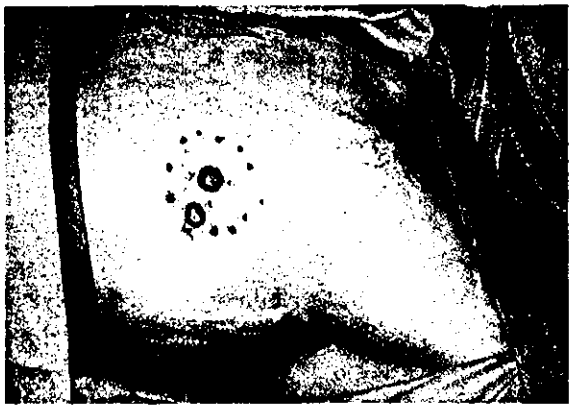

図 20　乳頭切除を予定し 1.5 cm の安全域を付けて点墨

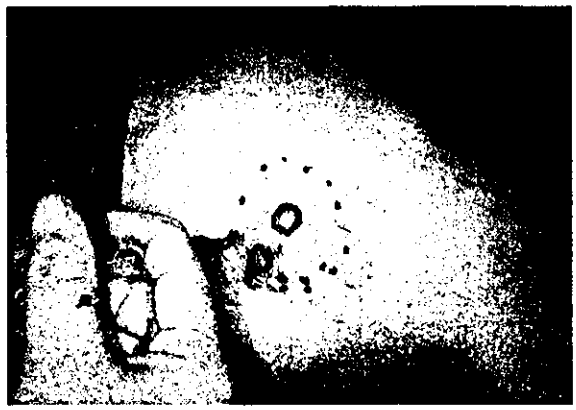

図 21　SN は皮膚面より脂肪織の中を垂直に入り，α プローブを当てて SN を同定する。

損部を覆い，乳房下縁線を新たに作製する（図19)。

外上部以外に占居する癌の場合は，それだけで術後の整容性は満足されなくなる。乳腺外の脂肪弁を授動あるいは回転させて充塡させたり，no でありそうであれば支配血管である vasa thoracica lateratis を残した，lateral tissue flap 法を用いるのもよい。LDMC あるいは LDMF flap まで行うのはいきすぎであり，それ以前の諸問題で解決を図るべきである。

6．小腫瘍の場合の部分切除と SNB による腋窩郭清の省略[6]

図 20 に示すような小腫瘍 10×10 mm の場合は，前述したように色素注入し（図 21)，乳頭方向に向かって乳管内進展があることを予想して乳頭直下で乳腺切離し，1.5 cm の安全域を確保した。N 0 に対して SNB を行い（図 22)，一つの SN をガンマープローブで同定し切除した（図 23)。この症例は手術前日入院，夕方ないし手術当日早朝 RI・コロイド注射，手術施行，翌日退院の 2 泊 3 日の短期入院ですませ，標本は固定後全割検索し，切離端に癌の波及がみられないで，SN も 2 mm おきの検索で（−）のため照射を追加せず，このままで根治手術の終了となった（図 24)。

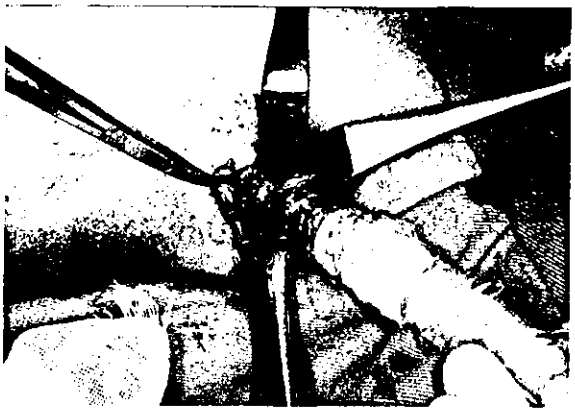

図 22　出血させないよう，血管，皮膚神経を損傷させないよう十分注意する。

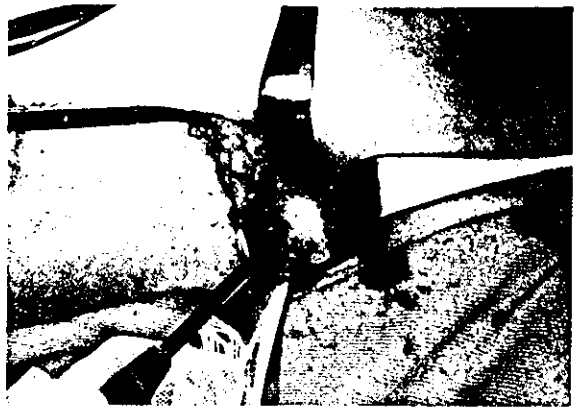

図 23　SN に meta がなかったので，これで手術を終了した。ドレーンは入れない。現在，最小の乳癌根治手術である。

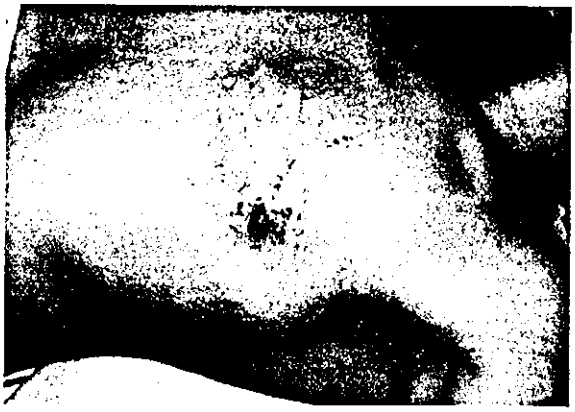

図 24　手術終了

IV. Non surgical ablation[7]

内外の文献報告があり，日本でも少数例の報告がある。多くは肝臓癌用のラジオ波照射用の電極を US ガイド下に腫瘍の中心部に刺入，US 観察下に照射して蛋白変性を US の shadow 形成で察知する。ラジオ波照射後の局所切除あるいは乳房切除の所見によると，多くは癌が焼灼壊死しているが，周辺に癌巣が認められることもあるという。ラジオ波焼灼後はそのままとして壊死巣部分の切除を行わないで経過観察をしている報告もあるが，形成された壊死硬結の将来，焼灼の確実度と X 線照射の必要性，電極刺入経路の播種など解決しなければならない課題が多いし，何より情報開示の時代であって，現在ではまだ実験台とならざるをえないので，志望者の確実な同意と，各施設の倫理委員会の認知を受けなければならない。しかし，この non surgical ablation は乳癌治療の終局であって US で同定される極小癌や石灰化の集簇巣に対しての将来性は十分にあり，さらに SNB の施行腋窩郭清の省略も可能である。

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Changes in Findings of Mammography, Ultrasonography and Contrast-enhanced Computed Tomography of Three Histological Complete Responders with Primary Breast Cancer Before and After Neoadjuvant Chemotherapy: Case Reports

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We report the changes in the findings of imaging examinations (mammography, ultrasonography and contrast-enhanced computed tomography) of three patients with primary breast cancer before and after neoadjuvant chemotherapy, who obtained histologically complete responses after the chemotherapy. The neoadjuvant chemotherapy consisted of four cycles of doxorubicin and docetaxel. All patients were clinically judged as partial responders, because of the remaining tumorous lesions in the imaging examinations. However, these tumorous lesions could be related to the chemotherapy-induced fibrosis and tumor necrosis or the remaining fibrocystic changes. In this study, it was considered very difficult to estimate the extent of residual tumors accurately in patients with primary breast cancer after neoadjuvant chemotherapy by any type of imaging examination.

Key words: breast cancer – histological assessment – neoadjuvant chemotherapy – computed tomography – complete response

INTRODUCTION

There has been considerable interest in the use of neoadjuvant chemotherapy for primary breast carcinoma. The clinical response rates of this type of chemotherapy were reported to be ~60–80% (1–3). However, a histologically complete response, which is defined here as no microscopic evidence of residual cancer cells in the invasive or intraductal component, is extremely rare (1–3). It would be very useful to select patients by imaging examinations who have obtained a histologically complete response and need not undergo surgery after chemotherapy. We report here three histologically complete responders with primary breast carcinoma after neoadjuvant chemotherapy, with regard to the changes in the findings of imaging examinations (mammography, ultrasonography and contrast-enhanced computed tomography).

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CASE REPORTS

The neoadjuvant chemotherapy consisted of four cycles of doxorubicin (adriamycin, ADM) and docetaxel (taxotere, TXT). After fully informed consent, the patients received 50 mg/m^2 of ADM and 60 mg/m^2 of TXT intravenously on day 1 of each cycle every 3 weeks. They underwent surgery 3–4 weeks after the termination of chemotherapy. Evaluation of efficacy was performed prior to surgery. The details of the three cases are given below.

CASE 1

A 67-year-old postmenopausal woman with a right primary breast carcinoma (T4bN1M0) received the above neoadjuvant chemotherapy. She had no past or family history of malignancies. Physical examination showed an ill-defined mass with skin redness, located in the upper outer quadrant of her right breast. The tumor size was 6.0 × 6.0 cm in diameter at the first consultation. As for the diagnostic procedures, mammography (MMG: Mammomat 3, Siemens, Germany) revealed an ill-defined tumor shadow with microcalcification in the right breast, the size of which was 5.8 × 5.3 cm in diameter. An irregular hypoechoic-tumorous lesion could be detected in the right breast by ultrasonography (US: EUB-515 with a 7.5 MHz

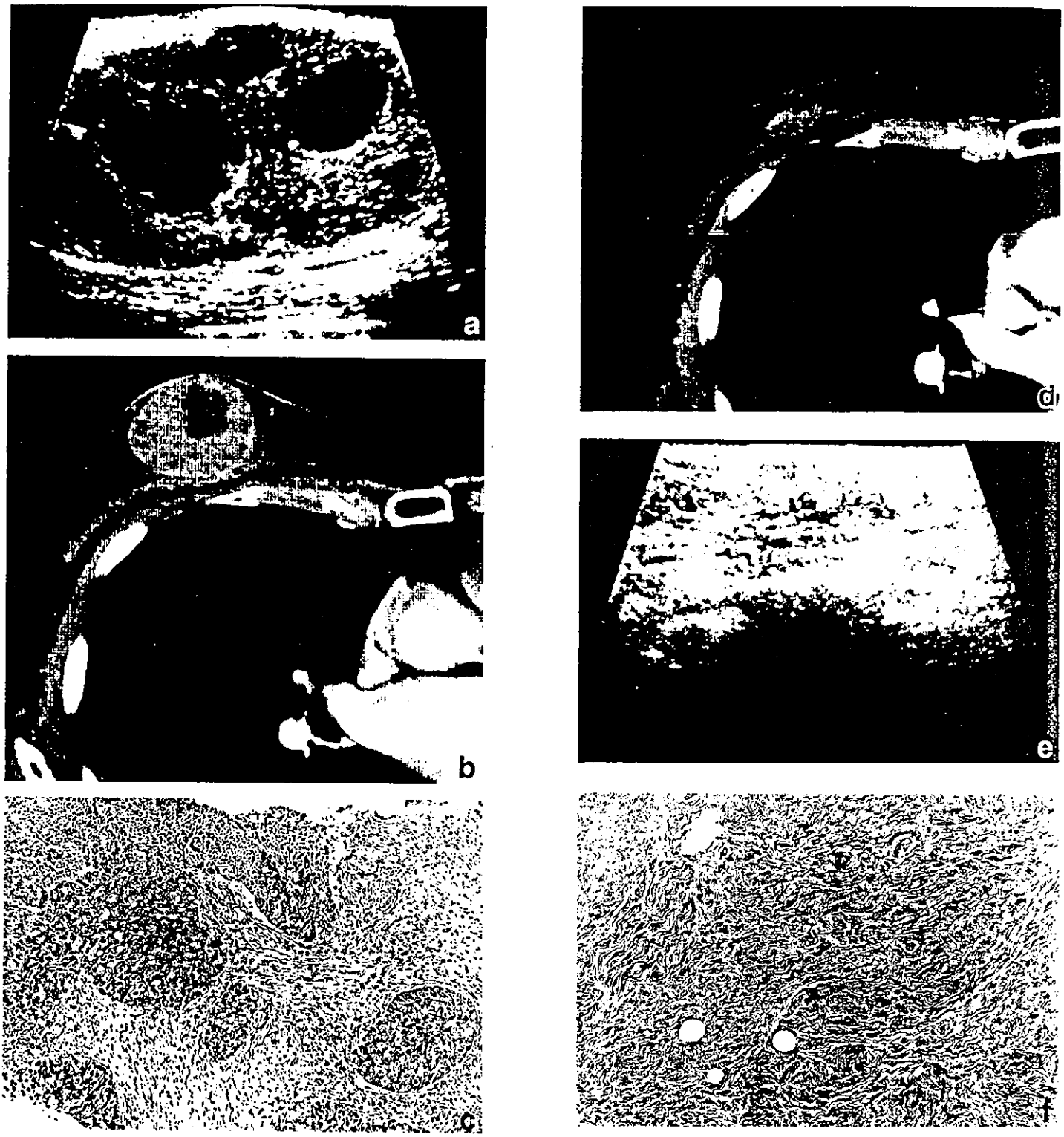

Figure 1. Case 1: a 67-year-old postmenopausal woman presented with a right primary breast carcinoma (T4bN1M0). (A) Ultrasonography revealed an irregular hypoechoic–tumorous lesion in the right breast, the size of which was 6.3 × 5.0 cm. (B) A well-defined tumorous lesion also could be detected in a contrast-enhanced CT scan, the size of which was 4.5 × 3.9 cm in diameter. (C) Core needle biopsy revealed an invasive ductal carcinoma, histological grade 3 (HE). (D) The tumor size was 2.2 × 0.6 cm on CT after the chemotherapy. In addition, the low-density area disappeared on CT. (E) US indicated that the lesion had completely disappeared and only ductal structure was detected after the chemotherapy. (F) Histopathological examination revealed that the right breast tumor had completely disappeared at the initial site of the tumor after the chemotherapy. Only foamy changes with lymphocytic infiltration and stromal hyalinization could be observed in the resected specimen (HE).

transducer, Hitachi, Japan), the size of which was 6.3 × 5.0 cm in diameter (Fig. 1A). An irregular tumorous lesion also could be detected in a contrast-enhanced computed tomographic scan (CT: X-Vigor, Toshiba, Japan), the size of which was 4.5 × 3.9 cm in diameter (Fig. 1B). Core needle biopsy revealed an invasive ductal carcinoma, histological grade 3, of the right breast (Fig. 1C). Estrogen receptor (ER) of the right tumor was negative but progesterone receptor (PgR) was positive by

immunohistochemistry. Negative p53 nuclear immunoreaction (RSp53, Nichirei, Tokyo, Japan) and negative c-erbB-2 overexpression (Nichirei) by immunohistochemical staining were observed in this tumor. She received the neoadjuvant chemotherapy to completion and toxicities were tolerable. After the termination of chemotherapy, the tumor size was 2.5 × 2.5 cm by palpation (tumor shrinkage rate: 83%). The imaging examinations (MMG, US and CT) were also re-evaluated prior to surgery. The tumor sizes were 3.7 × 3.3 cm (60%) on MMG and 2.2 × 0.6 cm (92%) on CT (Fig. 1D). The tumor shadow remained but became vague on MMG. The low-density area disappeared on CT. However, on US, the lesion had completely disappeared and only a ductal structure was detected after the chemotherapy (Fig. 1E). In brief, a partial response was obtained clinically. A wide resection of the right breast was carried out 28 days after the termination of neoadjuvant chemotherapy. Histopathological examination revealed that the tumor had completely disappeared with negative lymph node metastasis (0/14). Only foamy changes with lymphocytic infiltration and stromal hyalinization could be observed in the resected specimen (Fig. 1F). The effect of neoadjuvant chemotherapy was therefore evaluated as a histologically complete response. Postoperative adjuvant chemotherapy consisting of two cycles of ADM plus TXT was given to the patient. She is currently disease free 6 months after surgery.

CASE 2

A 61-year-old postmenopausal woman with a left primary breast carcinoma (T3N0M0) received the above neoadjuvant chemotherapy. She had no past or family history of malignancies. Physical examination showed an ill-defined, stony-hard mass located in the upper inner quadrant of her left breast. The tumor size was 5.5 × 4.0 cm in diameter at the first consultation. MMG revealed an ill-defined tumor shadow without microcalcification in the left breast, the size of which was 3.3 × 2.8 cm in diameter. An irregular hypoechoic-tumorous lesion could be detected by US, the size of which was 3.1 × 3.0 cm in diameter. A lobulated tumorous lesion also could be detected on CT, the size of which was 3.0 × 2.5 cm in diameter. Core needle biopsy revealed an invasive ductal carcinoma of the left breast, histological grade 3. ER and PgR were both negative. Positive p53 nuclear immunoreaction but negative c-erbB-2 overexpression were observed in this tumor. She received the neoadjuvant chemotherapy to completion and toxicities were tolerable. After the termination of chemotherapy, the tumor size was 3.0 × 2.5 cm (66%). The imaging examinations (MMG, US and CT) were also re-evaluated prior to surgery. MMG illustrated a reduction in tumor size (2.1 × 1.6 cm: 64%). On US, whereas the lesion had been longer than wide before the chemotherapy, it was oval-shaped, horizontally oriented after the chemotherapy (1.5 × 0.9 cm: 85%). In addition, the internal echo changed from heterogeneous to homogeneous after the chemotherapy. Echogenic rim and bilateral retrotumoral shadowing were also evident after the chemotherapy. With regard to CT, the irregular tumorous lesion became smaller but still remained after the chemotherapy (2.0 × 1.5 cm: 60%). Therefore, a partial response was obtained clinically. A modified radical mastectomy (Auchincloss mode) was carried out 27 days after the termination of neoadjuvant chemotherapy. Histopathological examination revealed that the tumor had completely disappeared but without lymph node metastasis (0/13). With regard to the initial site of the tumor, only inflammatory changes with foamy macrophages and hemosiderin deposits could be observed in the resected specimen. The effect of neoadjuvant chemotherapy was therefore evaluated as a histologically complete response. Postoperative adjuvant chemotherapy consisting of two cycles of ADM plus TXT was given to the patient. She is currently disease free 8 months after surgery.

CASE 3

A 67-year-old postmenopausal woman with a right primary breast carcinoma (T3N0M0) received the above neoadjuvant chemotherapy. She had no past or family history of malignancies. Physical examination showed an ill-defined, stony-hard mass incompletely fixed to the skin, located in the upper outer quadrant of her right breast. The tumor size was 5.2 × 5.2 cm in diameter at the first consultation. MMG revealed an ill-defined spiculated tumor shadow with microcalcification in the right breast, the size of which was 3.0 × 3.0 cm in diameter (Fig. 2A). An irregular hypoechoic–tumorous lesion could be detected by US, the size of which was 4.0 × 4.0 cm in diameter. An irregular tumorous lesion also could be detected on CT, the size of which was 3.0 × 2.5 cm in diameter. Core needle biopsy revealed an invasive ductal carcinoma of the right breast, histological grade 3. ER and PgR were both negative. Positive p53 nuclear immunoreaction and positive c-erbB-2 overexpression were observed in this tumor. She received the neoadjuvant chemotherapy to completion and toxicities were tolerable. After the termination of chemotherapy, the tumor size was 2.5 × 2.5 cm (77%). The imaging examinations (MMG, US and CT) were also re-evaluated prior to surgery. On MMG, the lesion became smaller (2.0 × 1.5 cm: 67%) and the tumor spiculation became vague but microcalcification was unchanged (Fig. 2B). US illustrated a definite reduction in tumor size after the chemotherapy (1.5 × 0.9 cm: 92%). It could not be differentiated from fibrocystic changes, e.g. adenosis. With regard to CT, the irregular tumorous lesion became smaller but still remained after the chemotherapy (2.0 × 1.5 cm: 60%). Therefore, partial response was obtained clinically. A wide excision was carried out 27 days after the termination of neoadjuvant chemotherapy. Histopathological examination revealed that the right breast tumor had completely disappeared without lymph node metastasis (0/13). With regard to the initial site of the tumor, only fibrocystic changes with an aggregate of foamy and hemosiderin-laden macrophages and an inflammatory cell infiltrate could be observed in the resected specimen. The effect of neoadjuvant chemotherapy was therefore evaluated as a histologically complete response. Postoperative adjuvant

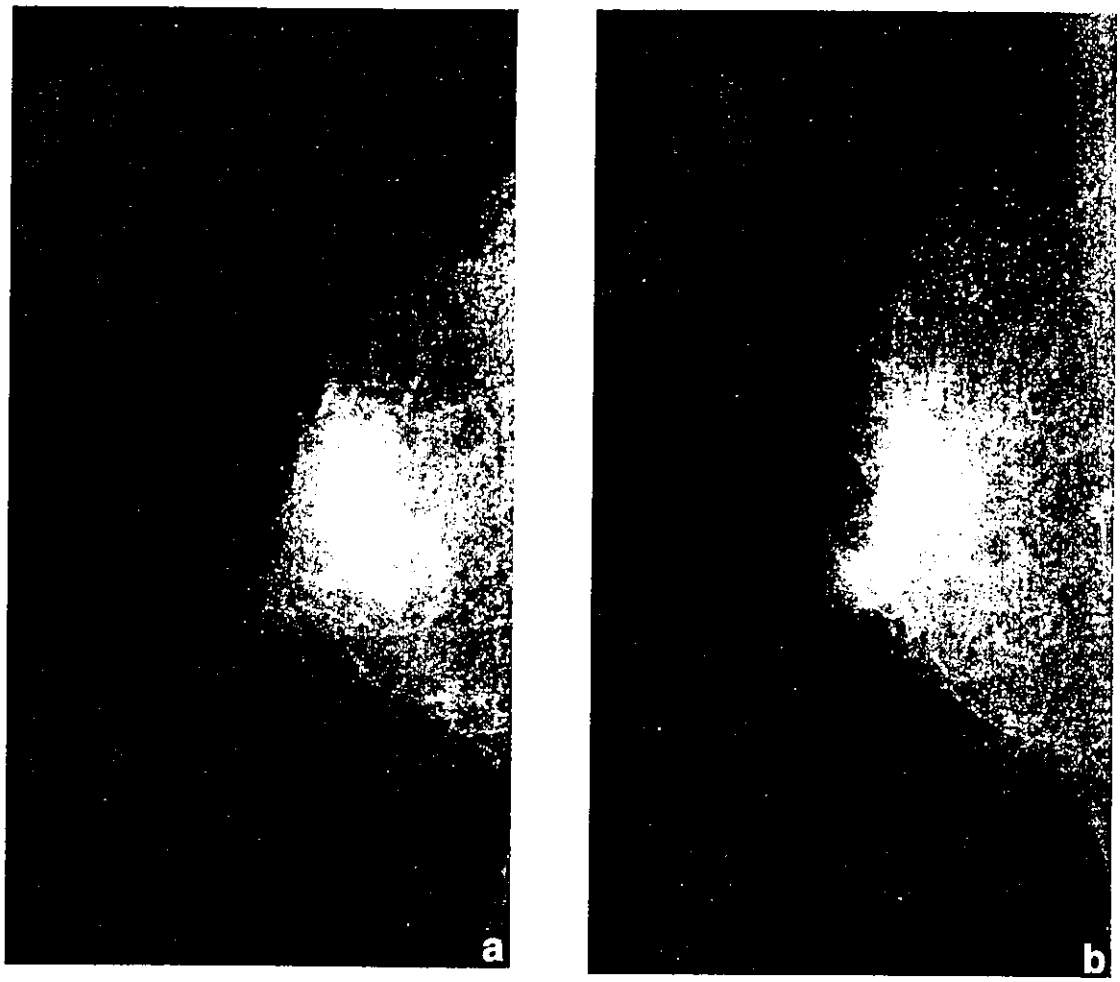

Figure 2. Case 3: a 67-year-old postmenopausal woman presented with a right primary breast carcinoma (T3N0M0). (A) MMG revealed an ill-defined spiculated tumor shadow with microcalcification, the size of which was 3.0 × 3.0 cm in diameter. (B) MMG indicated that the lesion had become smaller (2.0 × 1.5 cm) and the tumor spiculation had become vague, but microcalcification was unchanged.

chemotherapy consisting of two cycles of ADM plus TXT was given to the patient. She is currently disease free 10 months after surgery.

DISCUSSION

In these three cases with primary breast carcinoma after neoadjuvant chemotherapy, the resected specimen showed no microscopic evidence of residual cancer cells including an intraductal component in the primary lesions. There was histological evidence of tumor regression in each specimen. All patients were judged clinically as partial responders, because of the remaining tumorous lesions in the imaging examinations. However, these tumorous lesions could be related to the chemotherapy-induced fibrosis and tumor necrosis or the remaining fibrocystic changes.

Helvie et al. (4) documented that MMG was more sensitive than clinical examination in the prediction of residual carcinoma after chemotherapy. However, it was very difficult to evaluate the clinical meaning of the remaining microcalcifications after chemotherapy as in case 3. We previously reported that CT scanning was useful for evaluating histological tumor extension of breast carcinomas (5). Several authors have documented that contrast-enhanced magnetic resonance imaging could identify the residual disease in patients with breast cancer after neoadjuvant chemotherapy (6,7). Recently, the RECIST Working Group reported that US should not be used for the evaluation of cancer treatment (8). In this study, it was considered very difficult to estimate the extent of residual tumors accurately in patients with primary breast cancer after neoadjuvant chemotherapy by any type of imaging examination. In all specimens, chemotherapy-induced diffuse fibrosis and tumor necrosis were evident. The remaining tumorous lesion or microcalcification on the imaging examinations prior to surgery was not related to the cancerous changes but mainly to fibrosis or granulomatous changes due to tumor necrosis. These were the main reasons why imaging examinations tended to overestimate the residual tumor cells after chemotherapy.

The evaluation of the residual mass on the imaging examinations requires further studies. This will allow the selection of patients who may not need additional surgery.

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Accuracy of Contrast-Enhanced Computed Tomography in the Prediction of Residual Breast Cancer after Neoadjuvant Chemotherapy

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SUMMARY **Determination of the extent of residual disease after neoadjuvant chemotherapy is sometimes inaccurate by conventional diagnostic methods. The purpose of this study was to evaluate the accuracy of contrast-enhanced computed tomography (CE-CT) in depicting the extent of residual carcinomas. Fifty-seven patients with breast carcinomas of 3 cm diameter or more received neoadjuvant chemotherapy with four cycles of AT (doxorubicin and docetaxel). Before surgery, the patients underwent clinical examination, mammogram (MMG), ultrasonography (US), and CE-CT. Thirteen patients were not evaluated by CE-CT before surgery. Enhancement patterns on CE-CT were classified into multiple spots, tumor and spots, solid tumor type, and no enhancement. When all types of cancers were included in the analysis, clinical examination showed the best correlation with the pathology of the extent of residual carcinomas. However, except in invasive lobular carcinoma (ILC) and inflammatory breast carcinoma (IBC), CE-CT showed the best correlation ($R^2 = 0.537$). More than half of the residual microcalcifications on MMG after neoadjuvant chemotherapy suggested residual viable tumor. In conclusion, CE-CT is the most accurate noninvasive technique for identifying the extent of the residual carcinoma after neoadjuvant chemotherapy if cases of IBC and ILC are excluded.** *Int. J. Cancer (Radiat. Oncol. Invest.) 96, 66–73 (2001).* **© 2001 Wiley-Liss, Inc.**

Key words: CT scan; breast cancer; neoadjuvant chemotherapy; breast-conserving surgery; diagnostic x-ray

INTRODUCTION

The use of neoadjuvant chemotherapy has been extended to operable breast cancer. A large randomized clinical trial has confirmed the efficacy of neoadjuvant chemotherapy in downstaging and permitting lumpectomies [1], although no survival advantage has been demonstrated. The dilemma in the management of breast cancer after neoadjuvant chemotherapy is in defining the extent of residual disease so that appropriate surgery may be undertaken. Some reports have suggested that physical examination and mammogram (MMG) are complementary in the assessment of primary tumor response [2,3], whereas other reports have concluded that sonographic measurements correlate best with pathological findings [4]. Clinical measurements of breast masses are often inaccurate, and substantial

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interindividual variation exists among examiners [5]. Chemotherapy-induced fibrosis impairs evaluation of residual tumors by means of clinical examination, MMG, and ultrasonography (US) [6].

We have reported excellent results with contrast-enhanced computed tomography (CE-CT) in demonstrating the extensive intraductal component (EIC) and small invasive foci of breast carcinoma [7,8]. The purpose of this study was to evaluate the accuracy of CE-CT in depicting the extent of residual carcinomas after neoadjuvant chemotherapy.

MATERIALS AND METHODS

Patients

Fifty-seven patients with breast carcinoma of 3 cm diameter or more underwent neoadjuvant chemotherapy at our hospital from May 1998 to January 2000. The treatment protocol comprised four cycles of AT (doxorubicin, docetaxel) at a dose of 50 and 60 mg/m^2 with a cycle length of 21 days, followed by mastectomy or breast-conserving surgery. The eligible women had initial pathologic confirmation of breast carcinoma by core needle biopsy. Complete staging in the form of chest x-ray, liver ultrasonography, and bone scan was performed in all patients at the beginning of neoadjuvant treatment. After the final chemotherapy cycle, patients were evaluated by palpation and imaging, including MMG, US, and CE-CT. Thirteen patients were not evaluated by CE-CT before surgery.

Imaging Examinations

Helical CT scanning was performed using an X-Vigor (Toshiba, Japan) at 300 mA. The patients underwent one single spiral acquisition during deep inspiratory apnea for up to 30 sec in the supine position. The first step was identification of the main tumor by a non-contrast-enhanced CT scan from the cranial end of the sternum to the inframammary fold. Subsequently, enhanced zoomed scanning was planned from 50 mm above to 50 mm below the main tumor with a collimation of 5 mm and a pitch of 1 mm. One hundred milliliters of non-ionic contrast material (300 mg I/g) was injected at a rate of 2 ml/sec. The time between the administration of the bolus injection of contrast material and the initiation of scanning was 60 sec. The reconstruction interval was 5 mm.

For mammographic examination, a Mammomat 3000 (Siemens, Germany) was used. In addition to standard oblique and cranio-caudal projections, cranio-caudal or medio-lateral spot views (5 cm in diameter) without magnification were obtained in most cases. Whole-breast US was performed using a model SSA340A device (Toshiba) with an annular array transducer. Tumor diameters were measured in a transverse direction with all modalities in this study. We measured the extent of tumor shadows and microcalcifications evident on MMG [9], low echoic masses and irregularly dilated ducts on US [10], and enhanced masses and spotty nodular enhancements on CE-CT [8] to determine the extent of residual carcinomas.

Surgical specimens were sectioned at about 7–10-mm intervals in a transverse direction and analyzed by breast pathologists. The classification of response to neoadjuvant chemotherapy was defined according to the general rules for clinical and pathological recording of breast cancer [11]: grade 0, no response was observed; grade 1a, slight degenerative change in any range of area or severe degenerative change in one-third of cancerous cells was observed; grade 1b, severe degenerative change was observed in one-third to two-thirds of cancerous cells; grade 2, more than two-thirds of cancerous cells were degenerated; and grade 3, complete response, no cancerous cells were observed. These slices were compared with the area of CE-CT abnormality and with the cranio-caudal view of the MMG and US.

Table 1. Patient and Tumor Characteristics at Entry to Neoadjuvant Chemotherapy*

Parameter	No. of patients (no. evaluated by CE-CT)
Total	57 (42)
Median age in years	48
(range)	(29–69)
Primary tumor status	
T2	21 (20)
T3	16 (12)
T4a–c	14 (8)
T4d	6 (2)
Pathology	
Invasive ductal carcinoma	50 (35)
Invasive lobular carcinoma	5 (5)
Other	2 (2)

CE-CT = contrast-enhanced computed tomography.

RESULTS

At the time of this evaluation, 57 patients had finished chemotherapy. Fifty-five patients underwent surgery, one rejected surgery, and another ended chemotherapy in the second cycle because of progressive disease. Forty-two patients were evaluated by CE-CT before surgery. The characteristics at entry of this protocol of 57 patients are shown in Table 1. Overall clinical response rate by clinical examination (cCR +cPR) was 86.0% (49/57). Six

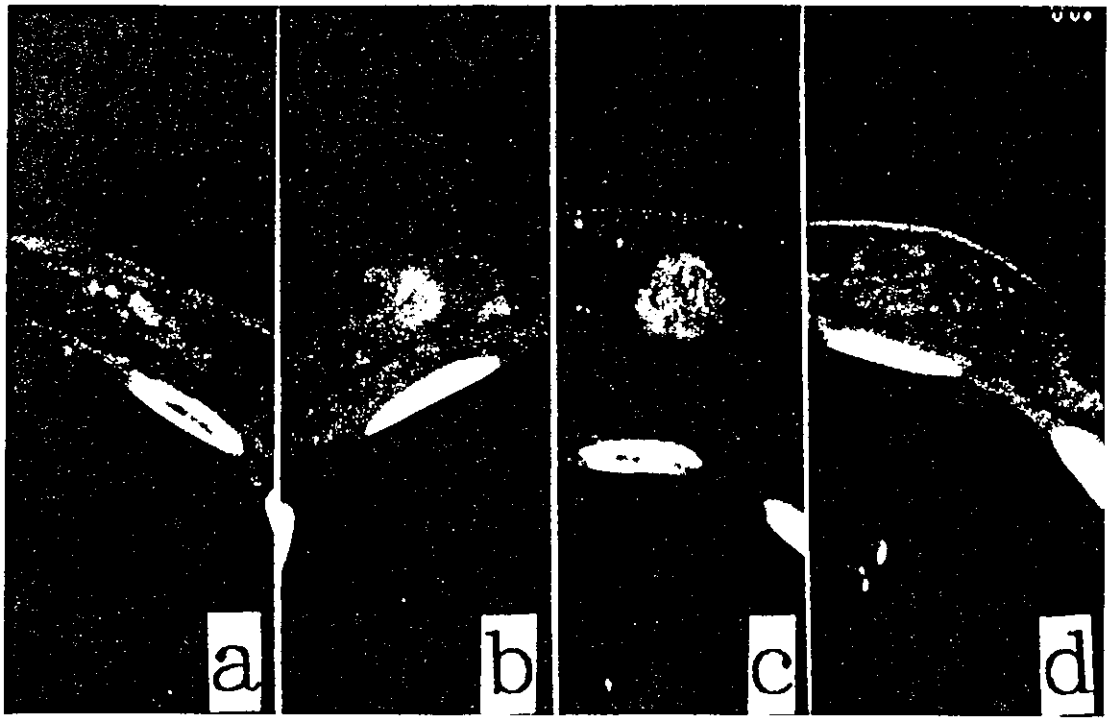

Fig. 1. Examples of patterns of enhancement on contrast-enhanced computed tomography (CE-CT): (**a**) multiple spots type, (**b**) tumor and spots type, (**c**) solid tumor type, and (**d**) no enhancement.

patients (10.5%) achieved cCR, and 43 patients (75.4%) achieved cPR. Three tumors (3/55: 5.5%) displayed pathological grade 3 response, 18 (18/55: 32.7%) grade 2 response, 24 (24/55: 43.6%) grade 1b response, 9 (9/55: 16.4%) grade 1a response, and 1 (1.8%) displayed no response.

The patterns of enhanced lesions on CE-CT were classified into multiple spots, tumor and spots, solid tumor type, and no enhancement, as shown in Figure 1. The correlations between residual invasive and/or intraductal components and enhanced patterns are shown in Table 2. The multiple spots type was related to residual intraductal components. Although no residual cancer was present, two patients appeared to have solid tumors by CE-CT as well as by MMG and US because of a cyst with fibrosis and an adenosis adjacent to the primary cancer. Cases that showed no enhancement on CE-CT included one case of inflammatory carcinoma (IBC), two cases of invasive lobular carcinoma (ILC), three cases of tiny residual cancer (under 3 mm), and one case of pathological complete response.

The correlations between the clinical, sonographic, mammographic, and CT measurements with pathological measurement of residual tumor diameters are presented in Figures 2–5. The coefficients of correlation between pathological size and types of evaluation were 0.333, 0.311, 0.156, and 0.181, respectively (Table 3). The discrepancies in size in CE-CT for IBC and ILC were marked, as shown in Figure 5. If cases of ILC and IBC are excluded, then CE-CT showed the best correlation ($r^2 = 0.537$) with pathology of the extent of residual carcinomas.

After neoadjuvant chemotherapy, widespread calcifications on MMG could be seen in 13 patients, even if the tumor shadows had disappeared or become smaller on MMG. In five cases, viable residual cancer cells were present within almost the same extent of microcalcification. In eight cases, the extent of the tumors was much smaller than that of the microcalcifications on MMG and almost equal to that of CE-CT enhancement (Fig. 6).

DISCUSSION

Neoadjuvant chemotherapy permits more breast-conserving surgery, particularly in patients with large tumors [1]. With the newer chemotherapeutic agents, the response of breast carcinoma to preoperative chemotherapy may be dramatic. In some patients, the tumor is no longer visible on either MMG or US. Thus, the rate of ipsilateral breast tumor recurrence was greater in women who were initially candidates for a mastectomy but who subsequently underwent a lumpectomy than in those who were initially considered candidates for lumpectomy [1]. This suggests that a more accurate modality for evaluating residual tumors is needed.

To our knowledge, only one study has been reported that evaluated CT for assessing the effect

Table 2. Relationship Between Enhancement Patterns on CE-CT and Residual Cancer Components*

Type	Residual cancer component				
	DCIS or mainly intraductal[a]	Invasive ductal cancer with EIC	Invasive carcinoma	No. tumor	Total
Multiple spots	2	1			3
Tumor and spots	2	3	5		10
Solid tumor	2	4	14	2	22
No enhancement	1		5	1	7
Total	7	8	24	3	42

*CE-CT = contrast-enhanced computed tomography; DCIS = ductal carcinoma in situ; EIC = extensive intraductal component.
[a]Tumors in which more than 80% of the area was occupied by an intraductal component.

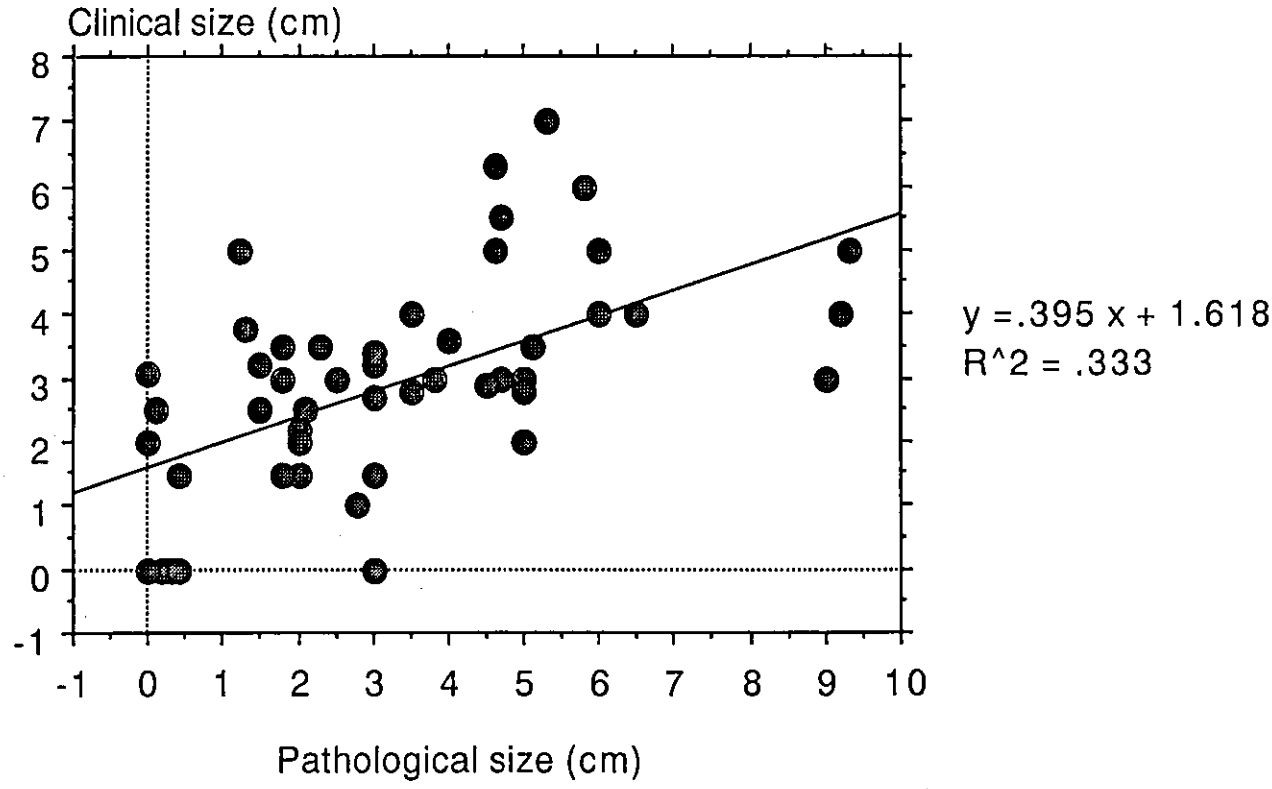

Fig. 2. Correlation between clinical sizes and pathological measurements.

of chemotherapy [12]. Lluch et al. [12] performed CT examinations in 44 patients and concluded that CT was a sensitive and accurate noninvasive technique for assessing axillary involvement after neoadjuvant chemotherapy in breast cancer and that clinical examination remains the best method for estimating primary tumor size.

We have reported excellent results of CE-CT in detecting EIC and small invasive foci and the usefulness of CE-CT in determining the extent of resection when performing CT of the breast [7,8]. In this study also, CE-CT depicted residual cancerous lesions after preoperative chemotherapy most accurately among conventional diagnostic methods. As shown in Figure 5, almost all the dots except for those of IBC and ILC fell between $y = x - 2$ and $y = x + 2$. The precise location of enhancement can be estimated easily by the combination of the number of slices from the nipple cephalocaudally and the distance from the sternum or the nipple transversally. This may suggest that a wide excision determined by CE-CT with 2 cm of free margin is the optimal excision extent.

Some studies using magnetic resonance imaging (MRI) reported its potential role in defining the extent of residual disease [13–16]. The pharmacokinetics of CT iodinated contrast agents is similar to that of nonselective Gd-chelates used as intrave-

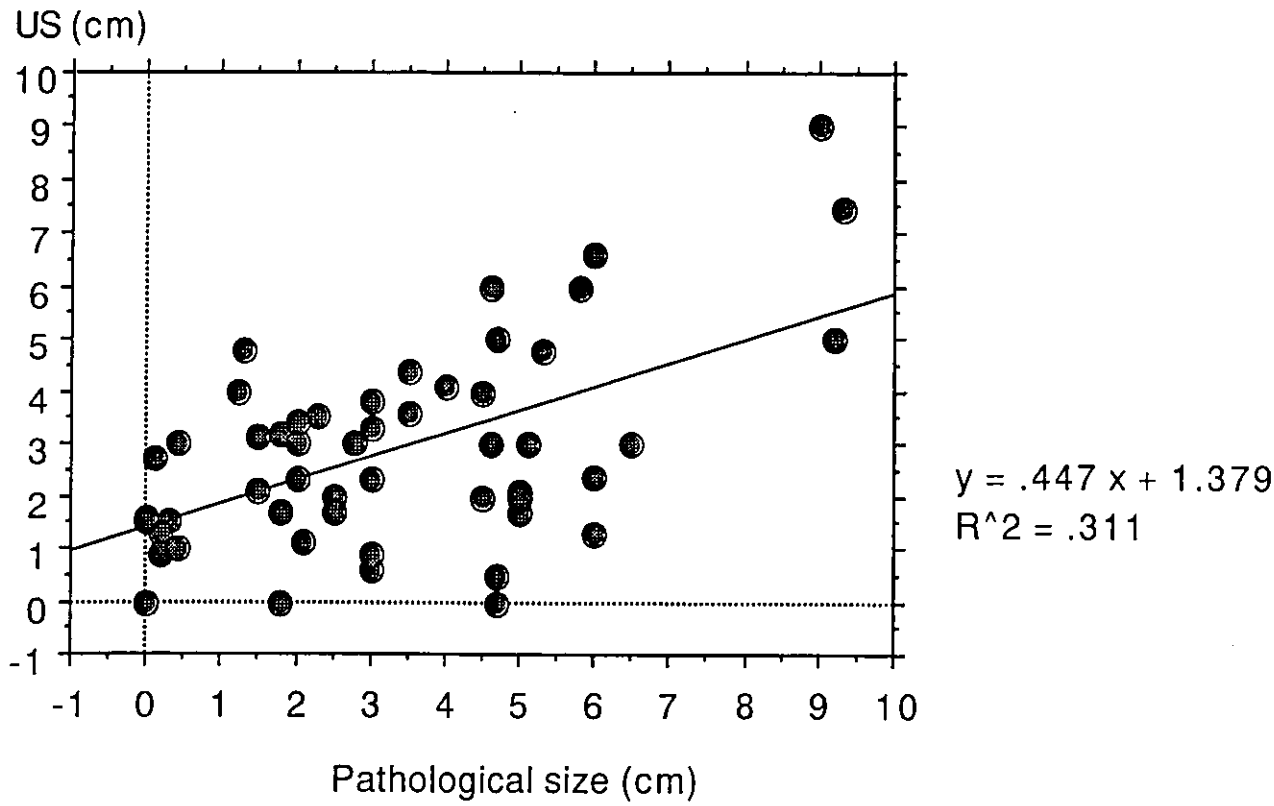

Fig. 3. Correlation between ultrasonographic (US) sizes and pathological measurements.

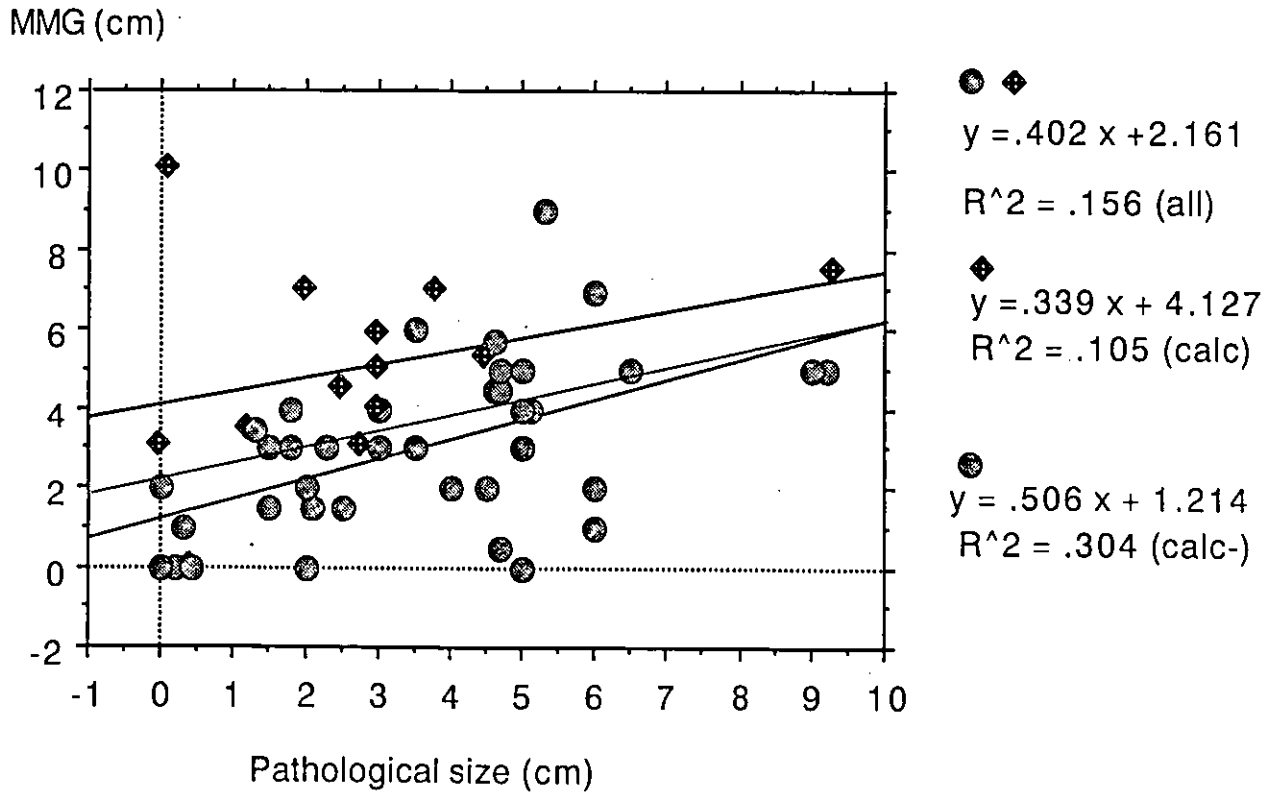

Fig. 4. Correlation between mammographic (MMG) sizes and pathological measurements. Circles, tumor without microcalcifications; diamonds, tumor with microcalcifications.