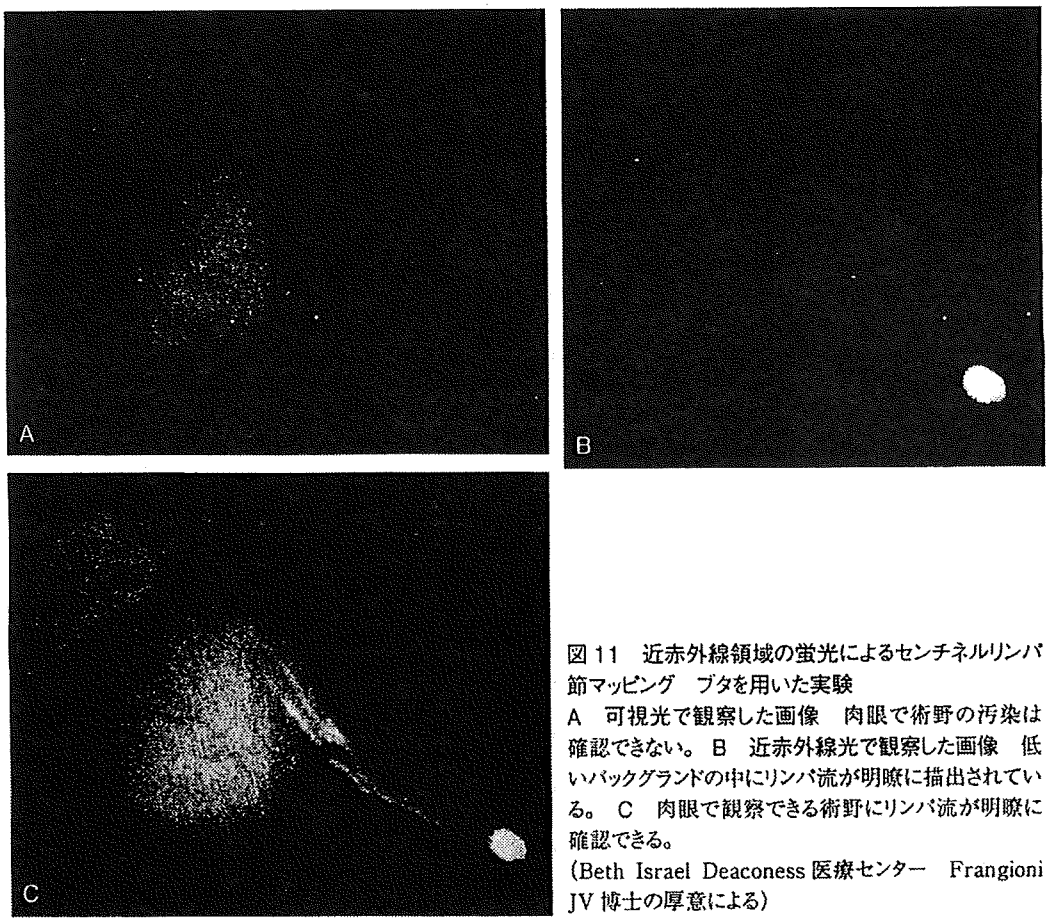

図11　近赤外線領域の蛍光によるセンチネルリンパ節マッピング　ブタを用いた実験
A　可視光で観察した画像　肉眼で術野の汚染は確認できない。B　近赤外線光で観察した画像　低いバックグランドの中にリンパ流が明瞭に描出されている。C　肉眼で観察できる術野にリンパ流が明瞭に確認できる。
(Beth Israel Deaconess 医療センター　Frangioni JV 博士の厚意による)

いが，詳細な解剖学的情報が得られるので，術中に描出された脈管との位置関係などを手がかりにしてセンチネルリンパ節の位置を確認することは可能である。

❹ 乳癌のセンチネルリンパ節の術中イメージング

センチネルリンパ節は径 1cm 前後の小さな構造物であり，周囲の構造物との区別が難しいのでトレーサーを使って同定する必要がある。術中は，術野を直接的にあるいは内視鏡などを通して間接的に観察できるので，情報量の多い視覚を利用するのが便利である。これまでも，リンパ移行性の高い青色色素を利用した方法が広く行われてきた。

最近，波長 700～900nm 程度の近赤外線光を照射すると発光するトレーサーを利用する方法が検討されている。この波長の光を照射した場合，生体からの自家蛍光が乏しく（"生体の窓"と呼ばれている），組織透過性が良好であるため，バックグランドからの信号を抑えて，高い感度で光信号を観察できる。Frangioni ら[33]は，ブタを用いた実験的検討により，近赤外線光を利用したセンチネルリンパ節マッピングが可能であることを確認し，近赤外線光と可視光を同時に観察することができる装置を開発し，臨床応用を目指している（図11）[34]。最近，内視鏡を用いた鏡視下手術が普及し，肉眼による直視ではなく，モニター上で観察しながら施行する術式に外科医がなれてきたこと，可視光で観察できる術野が色素により汚染されないことなどの理由により，この術式が実用化した場合，普及が期待できる。

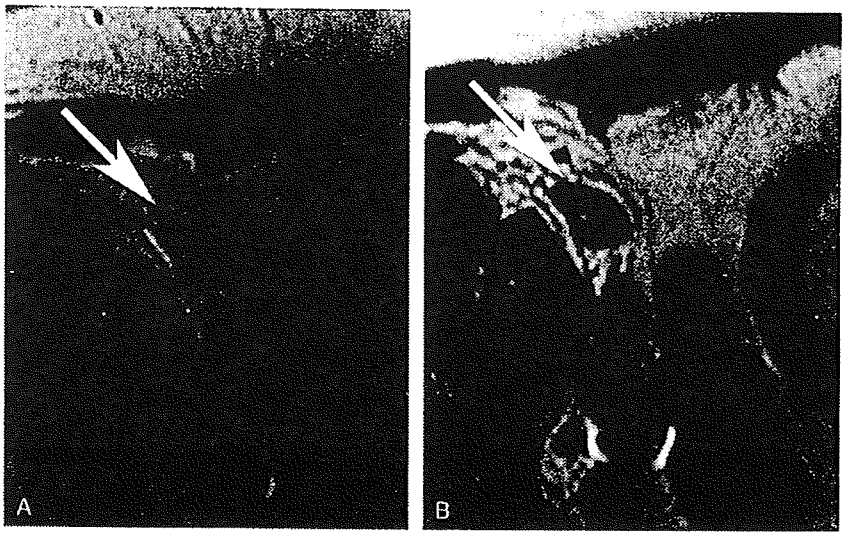

図 12　磁性体微粒子 MRI 造影剤を用いたリンパ節転移の診断
前立腺癌症例。転移リンパ節（→）内の信号は，造影剤投与前（A）はほぼ均一であるが，造影剤投与後（B）は，網内系組織の存在する非転移部位の信号が低下するため，リンパ節内の転移部位が高信号領域として観察できる。(Massachusetts 総合病院 Harisinghani MG 博士の厚意による)

❺ 小リンパ節転移のイメージング

上述のように，0.2mm 程度の小リンパ節転移病巣を確実に検出できるようになれば，乳癌症例におけるセンチネルリンパ節生検を省略できる可能性がある。この程度の大きさの転移は，リンパ節内の一部を占めるに過ぎず，リンパ節腫大を来すには至らない。このため，正常大のリンパ節の内部構造を観察する技術が求められることになる。Harisinghani ら[35]は，リンパ節内の網内系組織に貪食される性質を持つ磁性体微粒子を投与し，その後，MRI でリンパ節領域を高分解能撮像することにより，リンパ節内の転移病巣の有無を可視化する試みを報告しているが（図 12），この方法は問題解決のための足がかりになると考えられる。

■ ま と め

乳癌の適切な治療法の選択に正確なリンパ節転移診断が求められている。現在，多くの画像診断検査が利用されており，病変の糖代謝活性の評価が可能な FDG-PET 検査も活用されるようになったが，リンパ節転移診断の感度は中等度にとどまっている。このため，小リンパ節転移病変の評価にはセンチネルリンパ節生検が必須である。センチネルリンパ節の同定にもイメージング技術が貢献しているが，イメージング技術の進展により，0.2mm 程度の小リンパ節転移を *in vivo* で確実に診断できる技術が確立できれば，乳癌のセンチネルリンパ節生検自体も省略できる可能性があり，さらなる低侵襲治療が期待できる。

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非触知乳がん診断の進め方

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キーワード：乳がん，非浸潤性乳がん，非浸潤性乳管がん(DCIS)，非触知，微細石灰化，マンモグラフィ，石灰化強調(PEM)処理，ステレオガイド下マンモトーム生検

はじめに

乳がん検診にマンモグラフィが導入されて以来，非触知乳がんの発見が増加した．乳腺の画像診断における微細石灰化像は，非浸潤性乳がんを早期に発見する重要な手がかりとなる．本稿では，乳がんの診断に必要な疫学，解剖，病理を概観し，微細石灰化像をともなう非触知乳がんの画像診断を詳述する．

国立がんセンター東病院における乳がん診療

国立がんセンター東病院（以下，当院）はがん専門病院として，既に乳がんと診断されている，もしくは乳がんを疑われる紹介患者が多い．また，乳がん検診に対する精密検査施設でもあり，マンモグラフィ検診において要精査となった自覚症状のない患者も対象となる．

当院における年度別手術件数と乳房術式変遷（図1）および年度別病期の内訳（図2）を示す（国立がんセンターがん対策情報センターがん情報サービス参照（http://ganjoho.ne.jp/public/cancer/data/breast.html））．これによりここ数年は0期の非浸潤性乳がんと，腫瘍径が2 cmまでのⅠ期乳がんで約半数を占める．早期の乳がん数の増加や術前薬物治療の臨床応用にともない，乳房温存率の割合も増加し，現在では全手術症例の70-80%である．

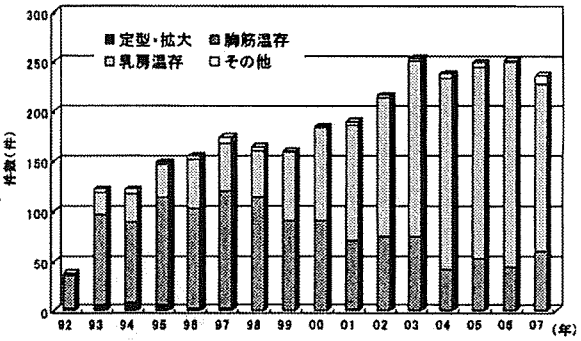

図1　年度別手術件数と乳房術式変遷

表1は当院の病期別健存率（治癒手術例に対する，

国立がんセンター東病院　放射線部　*国立がんセンター中央病院　放射線診断部　**国立がんセンター東病院　乳腺外科
別刷請求先：清水　薫　国立がんセンター東病院　放射線部　〒277-8577　千葉県柏市柏の葉6－5－1
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How to Diagnose Non-palpable Breast Cancer

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Key Words: breast cancer, non-invasive ductal carcinoma, DCIS, non-palpable, micro calcification, mammography, PEM, stereotactic vacuum-assisted breast biopsy

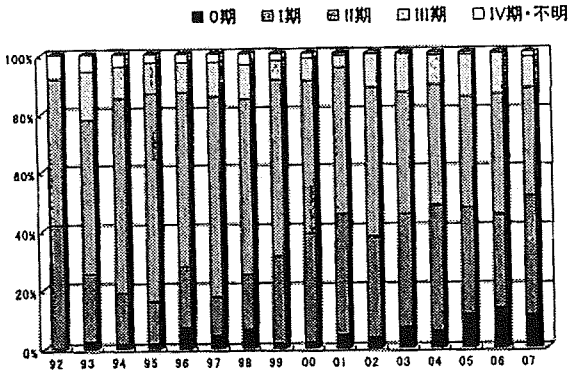


図2　年度別病期

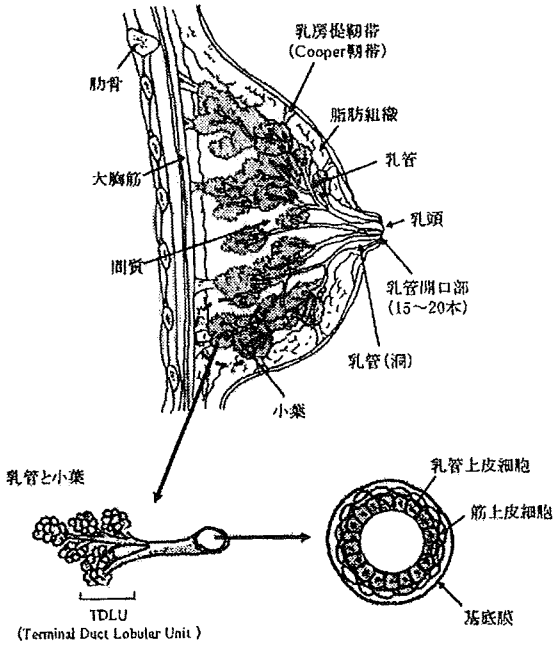


図3　乳腺の解剖[2]

再発を認めない生存例の率[1]より一部抜粋）・生存率を示したもので，病期が低いほど予後が良好であり，乳がんの早期発見・治療が予後に与える影響は大きい．

乳腺の解剖

乳腺は15-20個の腺葉とこれらを支える間質から形成される．各腺葉は乳頭を中心に放射状に配列し，末梢の小葉から発生する乳管は最終的に乳頭に開口する．腺葉末梢の小葉と小葉外終末乳管を合わせて，Terminal Duct Lobular Unit（TDLU）といい，乳がんの大部分がTDLUの乳管上皮細胞から発生する（homepage3.nifty.com/francis/data/13/horii.pdf：堀井　理絵：知っておきたい病理学の基礎-より正確な乳腺画像診断のために-）．

乳管は乳管上皮細胞と筋上皮細胞の2層から形成され，周囲は基底膜で覆われ，間質組織から隔離される（図3）．

表1　健存率と生存率

健存率	5年	10年
0期	98%	92%
I期	94%	91%
II期	81%	73%
III期	53%	47%
IV期	—	—

生存率	5年	10年
0期	100%	100%
I期	97%	93%
II期	89%	81%
III期	63%	49%
IV期	42%	24%

乳がんの組織分類と石灰化

1．非浸潤がんから浸潤がんへ

乳がんは組織学的に非浸潤がんと浸潤がん，Paget病の3型に分類される（図4）．

乳がんは，乳管および小葉の上皮細胞から発生し，次第に基底膜で囲まれた空間を満たすよう増殖する．がん細胞が乳管および小葉内にとどまるものを『非浸潤がん』といい，周囲組織への浸潤がないため，乳房内のがんを完全に切除できれば，理論上手術のみで根治が望める．これに対し，基底膜を破り間質や血管およびリンパ管など周囲組織への浸潤があるものを『浸潤がん』とよび，遠隔転移の要因となる．遠隔転移が臨床的に顕在化すると，がんの根治はきわめて困難になる（図5）．

非浸潤がんはある時点で基底膜を破って間質浸潤を開始し，浸潤がんへと移行すると考えられている．このため，非浸潤がんの段階での発見は良好な予後を得るため重要である．

2．非浸潤性乳管がん（DCIS）

非浸潤がんは，発生部位，構成細胞と増殖パターンにより，非浸潤性乳管がん：Ductal Carcinoma In Situ（DCIS）と非浸潤性小葉がん：Lobular Carcinoma In Situ（LCIS）に分類される．本稿ではおもに非浸潤性乳管がん（以下：DCIS）について述べる．

DCISは浸潤部分を認めず，乳管内で増殖進展をするが，その乳管腔内の組織形態によって以下のように亜分類される（表2）．大きく面疱型（Comedo

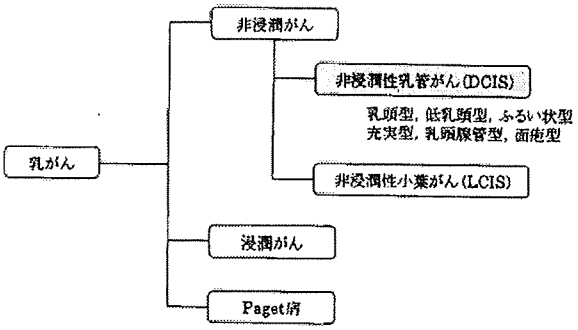


図4　乳がんの分類

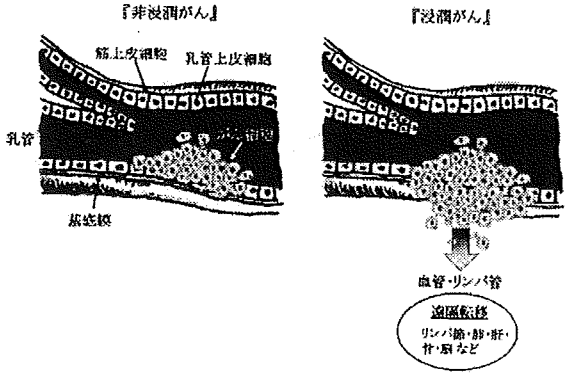


図5　非浸潤がんと浸潤がん

type）と非面疱型（Non-Comedo type）に分類する場合も多い．

3．乳がんの微細石灰化

乳がんの微細石灰化は，乳管内で増殖するがんの変性壊死物質や乳管内での分泌物の一部がカルシウムと反応して結晶化したものである．

よって病理組織像として石灰化を認める場所は主には，腫瘍化した乳管上皮に囲まれた管腔部分になる．

マンモグラフィで描出される乳がんの石灰化像は，乳管が非常に拡張していない限り微細，微小であることが多い．乳管腔が鋳型となり表現されるため，内腔の形態によって石灰化の形状が異なり，病理組織学的特徴を反映する．

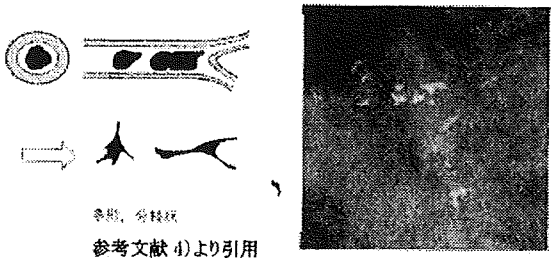
4．病理所見とマンモグラフィ石灰化像の特徴

1）面疱型（Comedo type）

がん細胞が増殖し乳管を満たすと，栄養の届かない中心部に壊死がおこり，カルシウムと反応して石灰化がおこる．微細石灰化像は腺腔に鋳型のように沈着する．マンモグラフィ上で見る面疱型の微細石灰化像の形状は微細線状，微細分枝状，多形性あるいは不均一な石灰化など奇異なパターンを呈する（図6）．非面疱型と比較し，圧倒的に微小浸潤をともなうことが多く，より悪性度が高い[3]．

表2　乳管腔内の組織形態分類

（1）面疱型　comedo type	
（2）ふるい状型　cribriform type	非面疱型（Non-Comedo type）
（3）乳頭型　papillary type	
（4）低乳頭型　low papillary type	
（5）充実型　solid type	
（6）乳頭腺管型　papillotubular type	



参考文献4)より引用

図6　微細石灰化像の成り立ちと画像（面疱型）

参考文献4)より引用

図7　微細石灰化像の成り立ちと画像（非面疱型）

2）非面疱型（Non-Comedo type）

非面疱型の石灰化の場合，うっ滞した分泌物内に生じるので点状や淡く不明瞭な石灰化となる．ふるい状型（cribriform type）の場合，がん細胞は密な小腺腔形成を示し，カルシウムは腺腔に部分的に沈着する．よって，微細石灰化像はより細かいものとなり，良性疾患との鑑別が困難になる（図7）．

このように，壊死の有無により微細石灰化像の形態は異なり，成り立ちや病態そのものを示す．ただし，微細石灰化像は乳腺症など良性疾患でもみられるため，良悪性の鑑別が必要になる．ここで，鑑別の手がかりとなるのが微細石灰化像の形態と分布である．マンモグラフィガイドライン[5]に記載されるカテゴリー分類のアルゴリズムを示す（表3）．

表3　良悪性の鑑別を必要とする石灰化のカテゴリー分類

		形態			
		微小円形	淡く不明瞭	多形性不均一	微細線状微細分枝状
分布	びまん性領域性	2	2	3	5
	集族性	3	3	4	5
	線状区域性	3・4	4	5	5

1：異常なし　2：良性
3：良性，しかし悪性を否定できず
4：悪性の疑い　5：悪性

＊表中の数字はカテゴリーを表す

デジタルマンモグラフィ

マンモグラフィで描出される乳がんを疑う所見は，主に腫瘤像や微細石灰化像である．とくに，マンモグラフィは乳管内の50-200μm 程度の微細石灰化像を描出することで，非触知の早期乳がんを検出できる．これが他のモダリティと比べ最大の利点である．

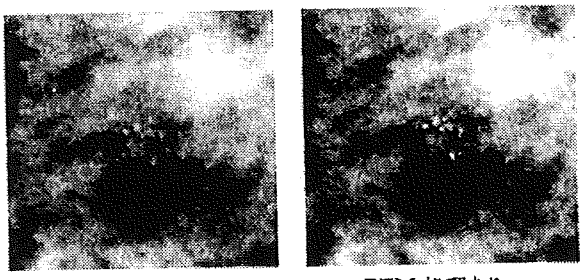
したがって，乳房内の微細な病変を描出する高い空間分解能がマンモグラフィには要求される．デジタルシステムにおいて空間分解能は画素サイズ（サンプリングピッチ）に依存する．画素サイズが大きいと，微細石灰化像の検出や形態診断に支障をきたす恐れがある[6]．

1．拡大スポット撮影

密着撮影において腫瘤像，微細石灰化像などが認められた場合，当院では拡大スポット撮影を追加する．病変を含む範囲を小さな圧迫板で圧迫，拡大撮影することにより周囲組織を圧排し，正常乳腺と病変とのコントラストを高めることができる[7]．とくに，微細石灰化像が認められた場合は，この拡大撮影が形態診断を行う上で非常に有益な情報を与えてくれる．

2．画像処理について

デジタルマンモグラフィの利点として画像処理が挙げられる．一般的には，階調処理・周波数処理・ダイナミックレンジ圧縮処理・石灰化強調処理などが用いられ，診断しやすい画像が提供される．



PEM 処理なし　　PEM 処理あり

図8　PEM 処理の有無での画像比較

表4　パラメータの種類および特性[8]

PRN	強調を行う周波数帯域を決めるパラメータ A:8Lp/mm　B:5.66Lp/mm　C:4.0Lp/mm D:2.83Lp/mm E:2.0Lp/mm
PTE	エッジ検出の感度を決めるパラメータ A—T（AからTになるに従い、エッジ検出の感度が下がる）
PTC	孤立点検出の感度を決めるパラメータ A—T（AからTになるに従い、孤立点検出の感度が下がる）
PRE	強調の程度を決めるパラメータ 0.0～16（値が大きい程、強調度が上昇）

しかし，これらの画像処理は原理と特性を十分理解した上で扱わないと擬画像を生じさせ，誤診の原因になりうるため注意して使用しなければならない．

1）石灰化強調処理（PEM 処理）

（Pattern Enhancement Processing for Mammography）

PEM 処理は，乳房画像中から微細石灰化像と思われる，急激な濃度勾配をもった点状の構造物にのみ強調処理を施すもので，微細石灰化像の検出率を向上させる（図8）．

PEM 処理には4つのパラメータがあり，PTE（エッジ検出感度）および PTC（孤立点検出感度）が石灰化と判断する閾値を決めるパラメータである（表4）[8]．

乳房画像中から処理を施す石灰化パターンを検出する際，石灰化パターンと背景のコントラストに注目し，ある閾値以上の信号かつ孤立した信号を石灰化パターンとする．背景とのコントラストに注目するため，画像全体のコントラストや背景に含まれるノイズの影響を受ける．適正な撮影条件の下得られ

た画像に対し，PTEおよびPTCの閾値を設定するため，IPへの到達線量が少ない画像やコントラストが高い画像が入力された場合，同感度で石灰化を検出することはノイズ成分まで検出することになり，擬似石灰化像を生み出す危険性がある．

PEM処理内部ではCR（Computed Radiography）のS値：50，L値：2.0となる画像を適正な撮影条件の下得られた画像と判断し，PTEおよびPTCを決定する．これが基準画像となる．S値とは画像データを読み取る際の読み取り感度の指標であり，撮影線量に依存する．また，L値とはコントラストの指標であり，撮影線質に依存する．実際は，S値：50，L値：2.0という基準画像に対し，入力された画像のS値およびL値からノイズ量を推定し，ノイズが多い画像が入力された場合，PTEおよびPTCの感度を下げるよう補正される．なお，基準画像に対しノイズが少ない画像では補正を行わない．

PEM処理は画像中の高周波数成分かつ点状構造物のみに施される処理であり，処理のかかる部分とかからない部分が極端に切り替わるような特殊な画像処理である．よって検出感度や強調度の調整が重要になるが，適切な撮影条件で得られた画像に施されることが大前提である．適切な撮影条件・画像処理条件が揃ってこそ，画像処理の効果を最大限に引き出せることを忘れてはならない．

ステレオガイド下マンモトーム

当院では，マンモグラフィでのみ発見された非触知病変の良悪性の鑑別診断に，マンモトーム：Mammotome®（図9）を用いた生検を行う．

マンモトームは90年代米国にて開発されたステレオガイド下吸引式乳房組織生検装置（Vacuum-assisted Breast Biopsy System）[9]で経皮的な針生検装置の一種である．主に11Gの針が使用されるが，乳房の厚さによっては8G，14Gも使用される[10]．腫瘤病変の生検に主に用いられるFNAC（Fine needle aspiration cytology）やCNB（Core needle biopsy）よりも多くの組織が採取できる（図10）．また，穿刺した針が360°回転することにより，多方向から切り組織を採取することが可能となる．しかし，石灰化の位置が照射野窓の端にある場合や，乳房を圧迫した際に乳房厚が十分でない場合，このマンモトーム生検ができない場合もある．マンモトーム生検ガイドライン[11]によるステレオガイド下マンモトームの適応を示す（表5）．

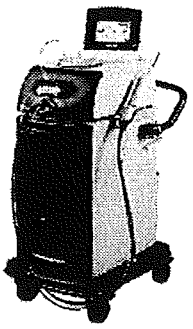


図9　マンモトーム装置
（ジョンソン・エンド・ジョンソン㈱提供資料）

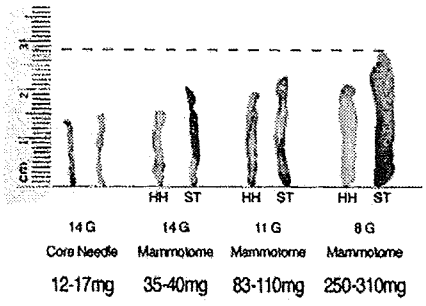


図10　採取した組織標本
（ジョンソン・エンド・ジョンソン㈱提供資料）

次にステレオガイド下マンモトームの検査法について述べる．通常の乳房撮影装置にステレオ装着を設置し，座位で検査するタイプと，専用テーブルを用いて腹臥位で検査するタイプの2種類に大きく分けられる．当院は精密検査施設であり，また設置スペースが十分に確保できたため腹臥位タイプのLORAD MultiCare® Platinum（図11）を2006年度より導入し使用している．

腹臥位マンモトームの検査手順

腹臥位マンモトームの検査手順について説明する．

(1) 丸い穴の開いた専用テーブルにうつぶせに寝てもらい，検側乳房を穴から下垂してもらう．（可能な限りストレスの少ない楽な姿勢にする）

(2) ポジショニングの後，スカウト撮影にて目的の石灰化が採取野の中央付近にあることを確認する（図12）．

(3) X線管球を左右各15°に振り，ステレオ撮影する．

表5　ステレオガイド下マンモトームの適応[11]

（1）悪性の疑いのある石灰化（カテゴリー4など）
（2）明らかに悪性と考えられるが組織診断を必要とする石灰化（カテゴリー5）
（3）良性と考えられるが組織診断を必要とする石灰化（カテゴリー3の一部など）
（4）石灰化以外の悪性を疑う病変（腫瘤、構築の乱れなどの超音波で描出できないもので組織診断を必要とする場合

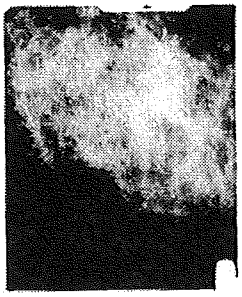


図12　スカウト画像

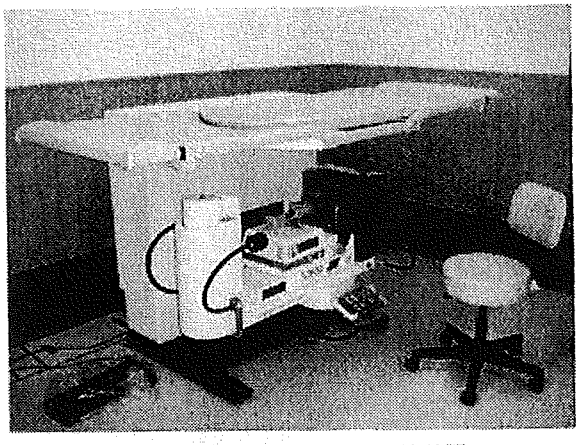


図11　腹臥位式ステレオ生検装置
LORAD MultiCare® Platinum

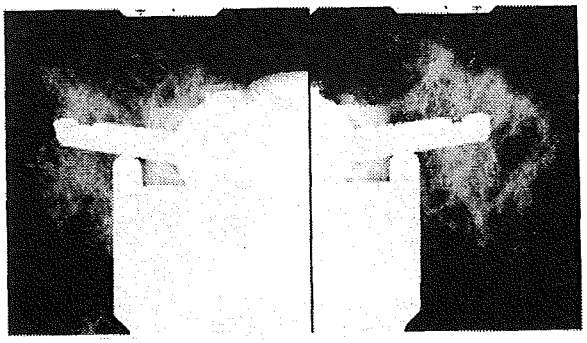


図13　ステレオ画像

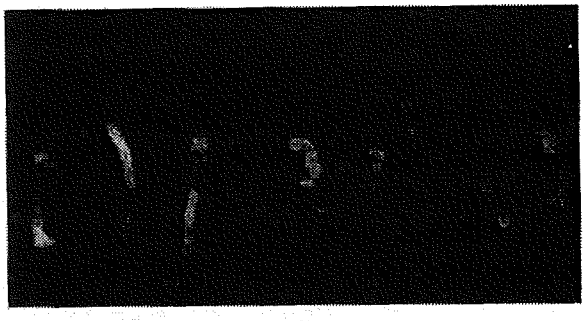


図14　採取した組織標本撮影

(4)　2枚の画像上で同一の石灰化をターゲッティングし3次元座標を算出する．
(5)　皮膚を消毒後，皮下麻酔薬（1%キシロカインE20ml）を注入し局所麻酔をする．
(6)　位置のずれがないか，再度ステレオ撮影する．
(7)　皮膚に約4mmの小切開をし，目的の石灰化の手前（−2mm）まで針の先端を挿入していく．
(8)　先端が石灰化の手前にあるか確認するため，再びステレオ撮影する．
(9)　確認後，ボタンを押して外筒を発射する．
(10)　外筒と石灰化の位置を確認するため，再びステレオ撮影する（図13）．
(11)　マンモトームのスイッチを入れ，組織を採取する．スイッチを入れると吸引とカッター付き内筒が高速回転され，開口部から外筒部に引き込まれた組織を内筒がカットして中に取り込む．外筒は留置したまま内筒を戻すと内筒の中に吸引された組織が回収される[10]．
(12)　採取した組織を乳房撮影装置にて拡大撮影し，石灰化の有無を確認する（図14）．

場合によっては，生検位置や手術位置の目印として，2mm程度のステンレス製クリップ(MicroMark II Clip®）を埋め込む場合がある．手術の場合クリップごと乳腺を切除する．経過観察で乳腺内に留置となった場合でも，身体には影響はない．
(13)　10分程度圧迫止血をしてテープで固定．さらにベッドで2時間安静にしてもらう．

検査時間は慣れてくると30分ぐらいで終了する．

乳房の厚さが薄い場合はAir Gap法を用いて乳房厚を加算する場合もある（図15）．

当院では，病理結果が良性の場合，定期的（6カ月もしくは1年後）に経過観察している．悪性の場合は手術となる．手術を行う場合，非触知で病変部位の同定が困難となるため，マンモグラフィにてマーキングを行い手術部位の特定を行う．鉛片を病変

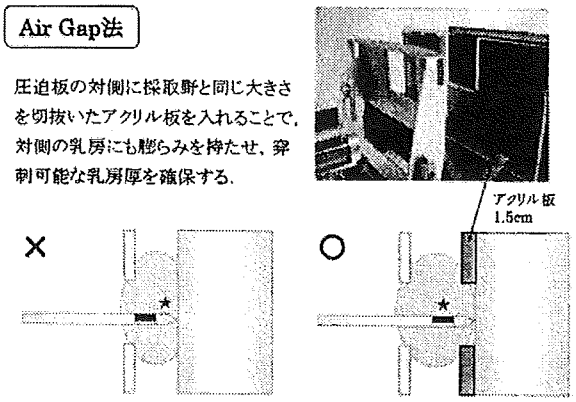
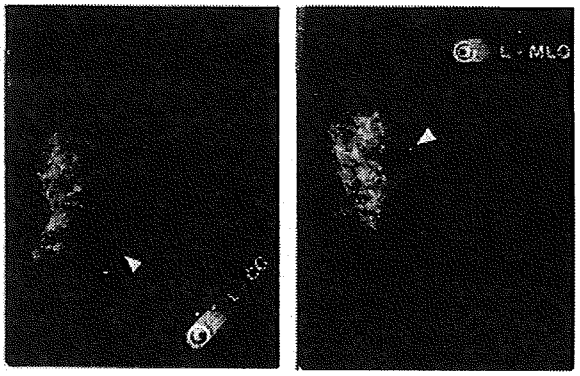


図15　Air Gap 法の概要



頭部方向　　側面方向

図16　術前マーキング撮影

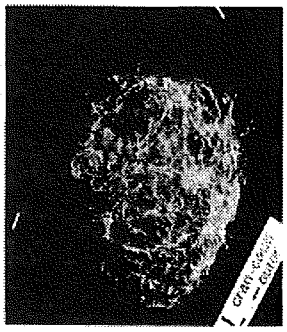


図17　術中標本撮影

部位皮膚にマークし，頭尾方向（CC-view），側面方向（ML-view）の2方向で撮影する（図16）．乳腺外科医はこのマークを切除範囲の決定に役立てている．また，手術中に切除した検体をマンモグラフィにて拡大撮影し，標的となる微細石灰化が中心にあり，すべての石灰化病変が切除範囲内にあるか確認する（図17）．

おわりに

本稿では，微細石灰化像をともなう非触知乳がんの発生から精密検査法について，画像診断を中心に詳述してきた．乳がん検診にマンモグラフィが導入され，さらに2004年4月の診療報酬改定において「乳腺腫瘍画像ガイド下吸引術」が保険適応になり，ますますマンモグラフィやマンモトーム生検は増加している．現在，乳がんは増加傾向にあり，早期のうちに発見・治療することが乳がん患者のQOLの向上につながる．われわれ放射線技師は，マンモグラフィ装置やマンモトーム装置などのデジタルシステムの利点と併せもつ危険性をよく理解し，診断価値の高い画像を提供できるよう努めなくてはならない．

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Original contribution

Histopathologic factors significantly associated with initial organ-specific metastasis by invasive ductal carcinoma of the breast: a prospective study☆

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Bone;
Breast cancer;
Fibrotic focus;
Liver;
Lung

Summary The purpose of this study was to identify histologic factors significantly associated with initial organ-specific metastasis by 1044 invasive ductal carcinomas (IDCs) of the breast with and without adjuvant therapy, separately, according to nodal status and pathologic TNM stage status. The following histologic factors were prospectively analyzed by multivariate analyses for distant organ metastasis and bone metastasis in patients with IDC who did not receive adjuvant therapy, and for distant organ metastasis, bone metastasis, liver metastasis, and lung metastasis in patients with IDC who received adjuvant therapy: (1) invasive tumor size, (2) histologic grade, (3) tumor necrosis, (4) fibrotic focus (FF), (5) lymphatic invasion, (6) blood vessel invasion, (7) adipose tissue invasion, (8) skin invasion, (9) muscle invasion, (10) age, (11) estrogen (ER)/progesterone (PR) status, and (12) nodal status. The results showed that FF diameter greater than 8 mm and FF fibrosis grade 1 were the factors that most accurately predicted distant organ metastasis and bone metastasis in patients with IDC who did not receive adjuvant therapy. In patients with IDC who received adjuvant therapy, FF diameter greater than 8 mm was the factor that most accurately predicted bone metastasis, and the presence of tumor necrosis and ER−/PR− were very important predictive factors for metastasis to the lung. Ten or more nodal metastases (N3) were the factor that most accurately predicted liver metastasis. Based on these findings, FF characteristics can be concluded to be the most important histologic factors for predicting metastasis

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to the bone, the presence of tumor necrosis and ER−/PR− for predicting metastasis to the lung, and N3 for predicting metastasis to the liver.

1. Introduction

Several studies have attempted to identify the factors that are specifically associated with organ-specific tumor recurrence of breast cancer [1-9], but most have been retrospective and did not carefully consider the kind of breast carcinoma (ductal carcinoma, lobular carcinoma, etc), tumor status (eg, nodal status, pathologic TNM [pTNM] stage, or adjuvant therapy status), or number of cases investigated. The pattern of metastatic spread by lobular carcinoma is known to be different from that of ductal carcinoma [10], and the hormone receptor status of the primary tumor and pattern of tumor recurrence have been found to be in some way related [11]. Thus, these studies have not provided adequate information to accurately predict organ-specific tumor recurrence in patients with invasive ductal carcinoma (IDC) of the breast. Although no studies have ever attempted to precisely identify histologic factors that accurately predict organ-specific tumor recurrence in patients with IDC, it is very important to identify them, because histopathologic examination of IDCs can be routinely performed in any hospital, and it is a very useful method for following patients with IDC clinically.

We have already reported that IDCs with a fibrotic focus (FF) are associated with a significantly higher frequency of nodal metastasis, a significantly higher frequency of lymph vessel invasion, a higher histologic grade, a significantly higher frequency of presence of tumor necrosis, a significantly larger invasive tumor size, and a significantly higher pTNM stage than IDCs without an FF [12,13]. We have also reported that presence of an FF in patients with IDCs is of prognostic significance [13,14], and that finding has been confirmed by others [15-17]. In addition, we have pointed out that the presence of an FF may be an important specific histologic indicator of tumor recurrence in bone in patients with IDC [18].

The purpose of the present study was to identify histopathologic factors that are significantly associated with organ-specific tumor recurrence in patients with IDC who have received adjuvant therapy and who have not received adjuvant therapy, according to nodal status and pTNM stage status.

2. Materials and methods

2.1. Cases

The subjects of this study consisted of 1044 consecutive cases of IDC of the breast surgically treated at the National Cancer Center Hospital East between July 1992 and November 2003. The IDCs were diagnosed by aspiration cytology, mammography, or ultrasonography before surgery. Clinical information was obtained from the patients' medical records after complete histologic examination of all IDCs. All patients were Japanese women, and they ranged in age from 28 to 78 years (mean, 51 years). All had a solitary lesion; 440 patients were premenopausal and 604 were postmenopausal. Partial mastectomy had been performed in 460, modified radical mastectomy in 560, and standard radical mastectomy in 24. Level I and II axillary lymph node dissection had been performed in all patients, and some of the patients had been treated by level III axillary lymph node dissection. None of the patients had received radiotherapy or chemotherapy before surgery, but 804 patients had received adjuvant therapy, which consisted of chemotherapy in 240 patients, endocrine therapy in 276 patients, and combined chemoendocrine therapy in 288 patients. The chemotherapy regimens used were anthracycline based with or without taxane in 214 patients and non–anthracycline based in 320 patients. The endocrine therapy regimens used were tamoxifen with or without a gonadotropin-releasing hormone agonist or tamoxifen with or without an aromatase inhibitor in 525 patients, an aromatase inhibitor alone in 33, and a gonadotropin-releasing hormone agonist alone in 8 patients. There were no cases of inflammatory breast cancer in this series. All tumors were classified according to the pTNM classification [19]. Estrogen receptors (ERs) and progesterone receptors (PRs) in the cytosol fractions were determined by enzyme immunoassay (Otsuka Assay Laboratory, Tokushima, Japan) or immunohistochemistry.

For pathologic examination, the surgically resected specimens were fixed in 10% formalin overnight at 4°C. The size and gross appearance of the tumors were recorded, and their size was confirmed by comparison with tumor size on histologic slides.

2.2. Histologic examination

Serial sections of each tumor area were cut from paraffin blocks. One section from each case was stained with hematoxylin and eosin, and examined histologically to confirm the diagnosis, and another section was subjected to elastica staining to assess blood vessel invasion. The following histologic factors were evaluated in each IDC approximately 7 to 10 days after the operation: (1) invasive tumor size (≤20, >20 to ≤50, >50 mm), (2) histologic grade (1, 2, 3) [20], (3) tumor necrosis (absent, present) [21], (4) FF size [12-14] (absent, FF diameter ≤8 mm, FF diameter greater than 8 mm) (Fig. 1A-C), (5) FF fibrosis grade [12-14] (absent; fibrosis grade 1, large number of fibroblasts with a

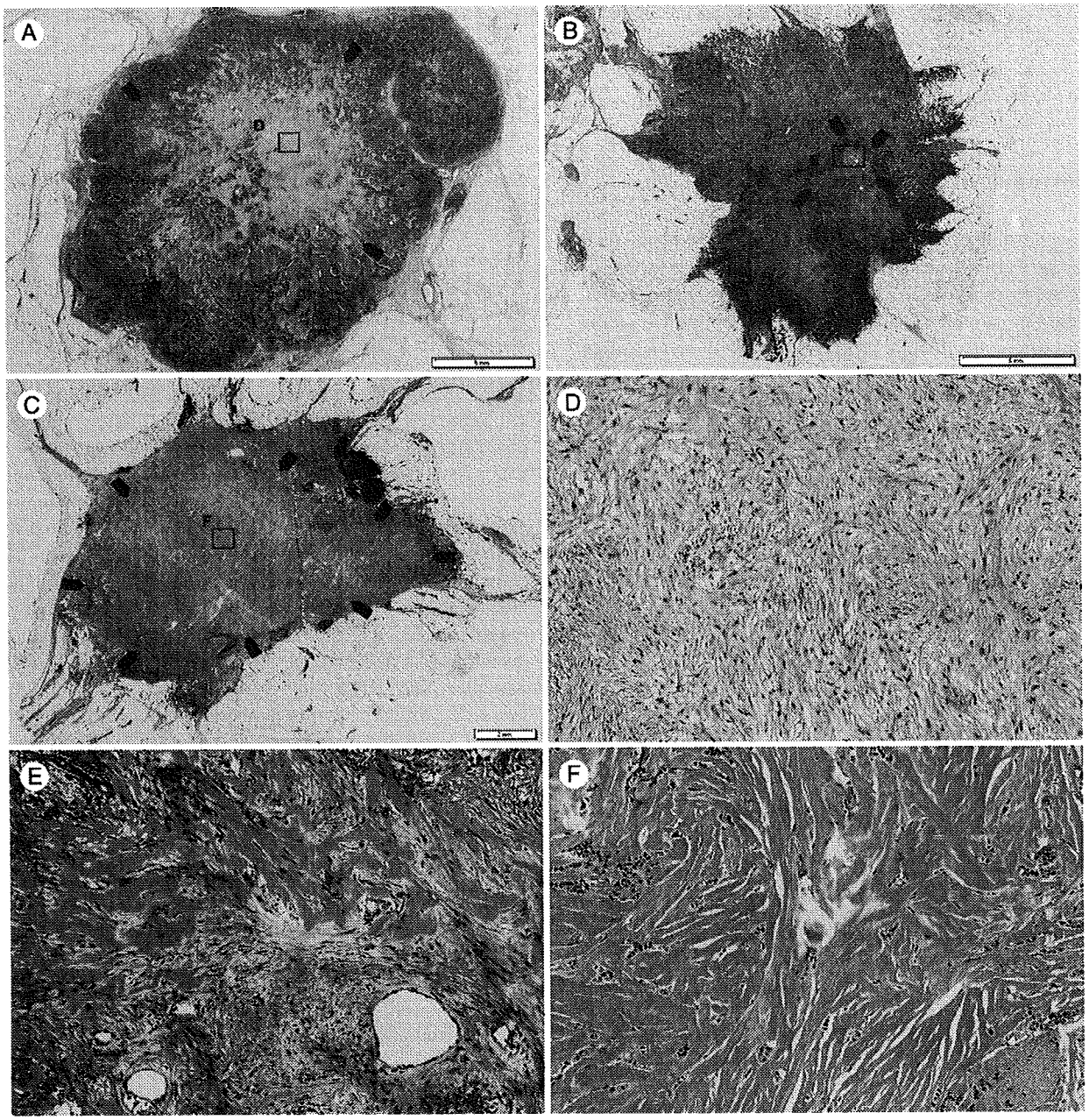

Fig. 1 IDCs with FFs. A, An FF measuring 15.2 × 13.8 mm is observed within the tumor (panoramic view) (arrowheads). The FF shows a scar-like feature and has a moth-eaten appearance, and is surrounded by IDC cells. Several residual tumor islands of various sizes are observed within the FF. B, A small FF measuring 4.0 × 2.5 mm is observed within the tumor (panoramic view) (arrowheads). The FF shows a scar-like feature but there are no residual tumor islands. C, An FF measuring 12.8 × 8.4 mm is observed within the tumor (panoramic view) (arrowheads). The FF has the appearance of a radiating fibrosclerotic core and is surrounded by IDC cells. D, The FF area consists of fibroblasts arranged in a storiform pattern (fibrosis grade 1). E, The FF consists of fibroblasts (upper half) and hyalinized collagen fibers (lower half) in a storiform arrangement (fibrosis grade 2). F, The FF consists of hyalinized collagen fibers in a storiform arrangement intermingled with invasive tumor cells (fibrosis grade 3).

small amount of collagen fibers; fibrosis grade 2, intermediate between grade 1 and 3, with fibroblasts and collagen fibers intermingled in various ratios; fibrosis grade 3, mainly collagen fibers, mostly hyalinized) (Fig. 1D-F), (6) lymphatic invasion (absent, present), (7) blood vessel invasion (absent, present), (8) adipose tissue invasion (absent, present), (9) skin invasion (absent, present), and (10) muscle invasion (absent, present). We classified IDC cases with muscle invasion and/or skin invasion as class T4 in the pTNM stage classification independent of the degree of muscle invasion or skin invasion by the tumor. Thus, IDCs with a slight degree of muscle or skin invasion and IDCs with

a moderate to severe degree of muscle or skin invasion were lumped together into pTNM stage class T4, and many IDCs with muscle invasion in this study had a slight degree of muscle invasion that was probably not apparent clinically.

All tumors were classified according to the guidelines of the World Health Organization [22]. One author (TH) routinely assessed all of the histologic parameters, and one of 2 other authors (TY or GI) immediately identified the characteristics of all the IDCs to confirm the IDC characteristics recorded by TH. Whenever there was a discrepancy, TH and either TY or GI reexamined the slides to reach a consensus.

2.3. Patient outcome and statistical analysis

Patient survival was evaluated by follow-up for a median period of 82 months (range, 16-173 months) until March 2006. At that time, 845 patients were alive and well, and 126 had an initial distant-organ metastasis (bone, liver, lung, or brain). The measurements of initial distant-organ metastasis-free survival started at the time of surgery. Tumor relapse was considered to have occurred whenever there was evidence of metastasis. Initial distant-organ metastasis was observed in the following organs: (1) bone, in 59 cases; (2) lung, in 44 cases; (3) liver, in 31 cases; and (4) brain, in 6 cases.

We prospectively analyzed the predictive power of the 10 histologic factors listed above and age (≤39 and >39 years), ER/PR status (ER/PR both positive, ER positive and PR negative, and ER/PR both negative), and nodal status (no nodal metastasis, N0; 1-3 nodal metastases, N1; 4-9 nodal metastases, N2; and 10 or more nodal metastases, N3) [19] for initial distant-organ metastasis, bone metastasis, liver metastasis, and lung metastasis according to nodal status and pTNM stage [19] separately in the cases that had received and had not received adjuvant therapy. Different kinds of adjuvant therapy (endocrine therapy, chemotherapy, and chemoendocrine therapy) were analyzed as prognostic predictive factors for the patients with IDC who had received adjuvant therapy. The factors significantly associated with outcome in the univariate analyses were then entered together into the multivariate analyses using the Cox proportional hazard regression model [23], and the step-down method was applied until all of the remaining factors were significant at a P value less than .05. As diameter and fibrosis grade are both histologic characteristics of an FF and are closely correlated with each other, to be able to accurately assess the prognostic value of each of them in the multivariate analyses, their mutual influence on outcome had to be avoided by analyzing the prognostic predictive power of the diameter of an FF and the fibrosis grade of an FF separately (model 1, diameter of an FF; model 2, fibrosis grades of an FF). As there were fewer than 10 patients with tumor recurrence in the lung and fewer than 10 patients with recurrence in the liver in the no–adjuvant-therapy IDC group, we were unable to perform multivariate analyses for tumor recurrence in the lung and liver in these IDC groups. Similarly, as there were fewer than 10 patients with tumor recurrence in the lung and fewer than 10 with recurrence in the liver in the node-negative IDC group, it was impossible to perform multivariate analyses for lung metastasis and liver metastasis in the node-negative IDC group. We also calculated the median intervals between surgery and the detection of the initial organ metastasis according to the factors that were significantly associated with organ metastasis in the multivariate analyses in the group that had received and the group that had not received adjuvant therapy. Survival curves were drawn by the Kaplan-Meier method [24]. All analyses were performed with Statistica/Windows software (StatSoft, Tulsa, Okla).

3. Results

3.1. Univariate analyses for distant organ metastasis, bone metastasis, lung metastasis, and liver metastasis according to adjuvant therapy status

In the IDC group that did not receive adjuvant therapy, the factors in the univariate analyses that were significantly associated with distant organ metastasis were age, blood vessel invasion, lymph vessel invasion, FF diameter, FF fibrosis grade, histologic grade, invasive tumor size, and pTNM stages (Table 1). All of the above factors, except age and blood vessel invasion, were also significantly associated with bone metastasis in the univariate analyses, and muscle invasion was significantly associated with bone metastasis.

In the group that received adjuvant therapy, all of the factors except blood vessel invasion were significantly associated with distant organ metastasis in the univariate analyses, and age, lymph vessel invasion, muscle invasion, skin invasion, FF diameter, FF fibrosis grade, invasive tumor size, nodal status, and pTNM status were also significantly associated with bone metastasis (Table 2). ER/PR status, lymph vessel invasion, skin invasion, tumor necrosis, FF diameter, histologic grade, invasive tumor size, nodal status, and pTNM stage were significantly associated with lung metastasis in the univariate analyses. The univariate analyses also showed that ER/PR status, FF diameter, FF fibrosis grade, histologic grade, invasive tumor size, nodal status, and pTNM stage were significantly associated with liver metastasis.

3.2. Multivariate analyses for distant organ metastasis and bone metastasis according to nodal status and pTNM stage in the IDC group that did not receive adjuvant therapy

The hazard rate (HR) and 95% confidence interval (CI) values of the factors in the upper row were obtained by the multivariate analyses in model 1 (FF diameter), and those of

Table 1 Association of clinicopathologic factors with distant-organ metastasis and bone metastasis in patients with IDC who did not receive adjuvant therapy

Factors	Total cases (N = 240)	No. of patients(%)			
		Distant organ metastasis		Bone metastasis	
		+ (n = 18)	− (n = 222)	+ (n = 13)	− (n = 227)
Age, y			0.025		0.207
≤39	7	2 (29)	5 (71)	1 (14)	6 (86)
>39	233	16 (7)	217 (93)	12 (5)	221 (95)
ER/PR status			0.290		0.130
+/+	115	7 (6)	108 (94)	4 (3)	111 (97)
+/−	54	4 (7)	50 (93)	3 (6)	51 (94)
−/−	71	7 (10)	64 (90)	6 (8)	65 (92)
Adipose tissue invasion			0.231		0.391
Absent	38	1 (3)	37 (97)	1 (3)	37 (97)
Present	202	17 (8)	185 (92)	12 (6)	190 (94)
Blood vessel invasion			0.048		0.378
Absent	158	9 (6)	149 (94)	8 (5)	150 (95)
Present	82	9 (11)	73 (89)	5 (6)	77 (94)
Lymph vessel invasion			0.049		0.024
Absent	189	11 (6)	178 (94)	7 (4)	182 (96)
Present	51	7 (14)	44 (86)	6 (12)	45 (88)
Muscle invasion			0.074		0.029
Absent	236	17 (7)	219 (93)	12 (5)	224 (95)
Present	4	1 (25)	3 (75)	1 (25)	3 (75)
Skin invasion			0.141		0.490
Absent	229	16 (7)	213 (93)	12 (5)	217 (95)
Present	11	2 (18)	9 (82)	1 (9)	10 (91)
Tumor necrosis			0.119		0.914
Absent	202	13 (6)	189 (94)	11 (5)	191 (95)
Present	38	5 (13)	33 (87)	2 (5)	36 (95)
FF, diameter (mm)			<0.001		<0.001
Absent	147	2 (1)	145 (99)	1 ()	145 (99)
≤8	48	4 (8)	44 (92)	4 (8)	44 (92)
>8	45	12 (27)	33 (73)	8 (18)	37 (82)
FF, fibrosis grade			0.001		0.005
Absent	147	2 (1)	145 (99)	1 (1)	145 (99)
1	6	3 (50)	3 (50)	3 (50)	3 (50)
2	38	6 (16)	32 (84)	4 (11)	34 (89)
3	49	7 (14)	42 (86)	5 (10)	44 (90)
Histologic grade			<0.001		<0.001
1	107	2 (2)	105 (98)	1 (1)	106 (99)
2	92	7 (8)	85 (92)	4 (4)	88 (96)
3	41	9 (21)	32 (78)	8 (20)	33 (80)
Invasive tumor size (mm)			<0.001		0.002
≤20	147	6 (4)	141 (96)	4 (3)	143 (97)
>20-≤50	89	9 (10)	80 (90)	7 (8)	82 (92)
>50	4	3 (75)	1 (25)	2 (50)	2 (50)
UICC pN category			0.086		0.621
N0	213	14 (7)	199 (93)	11 (5)	202 (95)
N1	14	2 (14)	12 (86)	1 (7)	13 (93)
N2	6	1 (17)	5 (83)	1 (17)	5 (83)
N3	7	1 (14)	6 (86)	0	7 (100)
pTNM stages			0.005		0.007
I	136	5 (4)	131 (96)	3 (2)	133 (98)
II	81	9 (11)	72 (89)	7 (9)	74 (91)
III	23	4 (17)	19 (83)	3 (23)	20 (86)

Abbreviations: +, present; −, absent; UICC, International Union Against Cancer; pN, pathologic regional lymph node.

Table 2 Association of clinicopathologic factors with distant-organ metastasis, bone metastasis, liver metastasis, and lung metastasis in patients with IDC who received adjuvant therapy

Factors	Total cases (N = 804)	No. of patients (%)							
		Distant organ metastasis		Bone metastasis		Lung metastasis		Liver metastasis	
		+ (n = 108)	− (n = 696)	+ (n = 46)	− (n = 758)	+ (n = 39)	− (n = 765)	+ (n = 28)	− (n = 776)
Age, y			0.005		0.003		0.536		0.183
≤39	742	92 (12)	650 (88)	37 (5)	705 (95)	35 (5)	707 (95)	24 (3)	718 (97)
>39	62	16 (26)	46 (74)	9 (15)	53 (85)	4 (7)	58 (93)	4 (7)	58 (94)
ER/PR status			<0.001		0.987		<0.001		0.003
+/+	406	37 (9)	369 (91)	21 (5)	385 (95)	11 (3)	395 (97)	8 (2)	398 (98)
+/−	176	23 (13)	153 (87)	15 (9)	161 (91)	5 (3)	171 (97)	5 (3)	171 (97)
−/−	222	48 (22)	174 (78)	10 (5)	212 (95)	23 (10)	199 (90)	15 (7)	207 (93)
Adjuvant therapy			0.007		0.126		0.410		0.069
Endocrine	276	16 (6)	260 (94)	10 (4)	266 (96)	5 (2)	271 (98)	4 (1)	272 (99)
Chemotherapy	240	48 (20)	192 (80)	15 (6)	225 (94)	23 (10)	217 (90)	11 (5)	229 (95)
Chemoendocrine	288	44 (15)	244 (85)	21 (7)	267 (93)	11 (4)	277 (96)	13 (5)	275 (95)
Adipose tissue invasion			0.048		0.182		0.571		0.358
Absent	103	7 (7)	96 (93)	3 (3)	100 (97)	4 (4)	99 (96)	2 (2)	101 (98)
Present	701	101 (14)	600 (86)	43 (6)	658 (94)	35 (5)	666 (95)	26 (4)	675 (96)
Blood vessel invasion			0.133		0.620		0.356		0.289
Absent	371	47 (13)	324 (87)	46 (6)	758 (94)	17 (5)	354 (95)	11 (3)	360 (97)
Present	433	61 (14)	372 (86)	24 (6)	409 (94)	22 (5)	411 (95)	17 (4)	416 (96)
Lymph vessel invasion			<0.001		0.004		0.015		0.390
Absent	458	42 (9)	416 (91)	17 (4)	441 (96)	15 (3)	443 (97)	14 (3)	444 (97)
Present	346	66 (19)	280 (91)	29 (8)	317 (92)	24 (7)	322 (93)	14 (4)	332 (96)
Muscle invasion			<0.001		<0.001		0.080		0.396
Absent	788	100 (13)	688 (87)	41 (5)	747 (95)	37 (5)	751 (95)	27 (3)	761 (97)
Present	16	8 (50)	8 (50)	5 (31)	11 (69)	2 (12)	14 (88)	1 (6)	15 (94)
Skin invasion			<0.001		0.031		<0.001		0.175
Absent	715	83 (12)	632 (88)	37 (5)	678 (95)	28 (4)	687 (96)	23 (3)	692 (97)
Present	89	25 (28)	64 (72)	9 (10)	80 (90)	11 (12)	78 (88)	5 (6)	84 (94)
Tumor necrosis			<0.001		0.551		<0.001		0.060
Absent	622	71 (11)	551 (89)	35 (6)	587 (94)	22 (4)	600 (96)	18 (3)	604 (97)
Present	182	37 (20)	145 (80)	11 (6)	171 (94)	17 (9)	165 (91)	10 (5)	172 (95)
FF, diameter (mm)			<0.001		<0.001		0.005		0.020
Absent	382	29 (8)	353 (92)	10 (3)	372 (97)	12 (3)	370 (97)	9 (2)	373 (98)
≤8	169	23 (14)	146 (86)	11 (7)	158 (93)	8 (5)	161 (95)	5 (3)	164 (97)
>8	253	56 (22)	197 (78)	25 (10)	228 (90)	19 (8)	234 (92)	14 (6)	239 (94)
FF, fibrosis grade			<0.001		<0.001		0.059		0.017
Absent	382	29 (8)	353 (92)	10 (3)	372 (97)	12 (3)	370 (97)	9 (2)	373 (98)
1	19	3 (16)	16 (84)	1 (5)	18 (95)	2 (10)	17 (90)	0	19 (100)
2	226	37 (16)	189 (84)	15 (7)	211 (93)	15 (7)	211 (93)	7 (3)	219 (97)
3	177	39 (22)	138 (78)	20 (11)	157 (89)	10 (7)	167 (97)	12 (6)	165 (94)
Histologic grade			<0.001		0.186		0.003		0.010
1	161	10 (6)	151 (94)	4 (2)	157 (98)	5 (3)	156 (97)	2 (1)	159 (99)
2	395	53 (13)	342 (87)	28 (7)	367 (93)	16 (4)	379 (96)	12 (3)	383 (97)
3	248	45 (18)	203 (82)	14 (6)	234 (96)	18 (7)	230 (93)	14 (6)	234 (94)
Invasive tumor size (mm)			<0.001		<0.001		0.002		0.011
≤20	345	25 (7)	320 (93)	10 (3)	335 (97)	10 (3)	335 (97)	6 (2)	339 (98)
>20-≤50	409	63 (15)	346 (85)	27 (7)	382 (93)	23 (6)	386 (94)	19 (5)	390 (95)
>50	50	20 (40)	30 (60)	9 (18)	42 (82)	6 (12)	44 (88)	3 (6)	47 (94)
UICC pN category			<0.001		<0.001		<0.001		<0.001
N0	381	24 (6)	357 (94)	12 (3)	369 (97)	8 (2)	373 (98)	4 (1)	377 (99)
N1	267	33 (12)	234 (88)	13 (5)	254 (95)	15 (6)	252 (94)	9 (3)	258 (97)
N2	85	17 (20)	68 (80)	10 (12)	75 (88)	5 (6)	80 (94)	4 (5)	81 (95)
N3	71	34 (48)	37 (52)	11 (15)	60 (84)	11 (15)	60 (85)	11 (15)	60 (85)
pTNM stages			<0.001		<0.001		<0.001		<0.001
I	190	7 (4)	183 (96)	3 (2)	187 (98)	2 (1)	188 (99)	2 (1)	188 (99)
II	388	32 (8)	356 (92)	12 (3)	376 (97)	13 (3)	375 (97)	9 (2)	379 (98)
III	226	69 (31)	157 (69)	31 (14)	195 (86)	24 (11)	375 (89)	17 (8)	209 (92)

the HRs and 95% CIs in the lower row were obtained by the multivariate analyses in model 2 (FF fibrosis grade).

FF diameter greater than 8 mm, FF fibrosis grade 1 (Fig. 2A), age 39 years or younger, histologic grade 2, and histologic grade 3 significantly increased the HRs for distant-organ metastasis in the N0 IDC group and the stages I and II IDC group (Table 3). Muscle invasion and FF fibrosis grade 3 significantly increased the HRs for distant-organ metastasis in the N0 IDC group and the stages I and II IDC group, respectively.

FF diameter greater than 8 mm, FF fibrosis grade 1, and histologic grade 3 significantly increased the HRs for bone metastasis in the N0 IDC group and the stages I and II IDC group (Table 3). Muscle invasion significantly increased the HRs for bone metastasis in the N0 IDC group, and FF fibrosis grade 3 significantly increased the HR for bone metastasis in the stages I and II IDC group.

Many factors that were significantly associated with organ metastasis in the multivariate analyses were associated with an 18- to 24-month interval between surgery and detection of the initial organ metastasis, and presence of muscle invasion was associated with the shortest median interval between surgery and detection of the initial distant-organ metastasis and bone metastasis, independent of nodal status and pTNM stage, and it was followed by histologic grade 3 and characteristics of FF (Table 4).

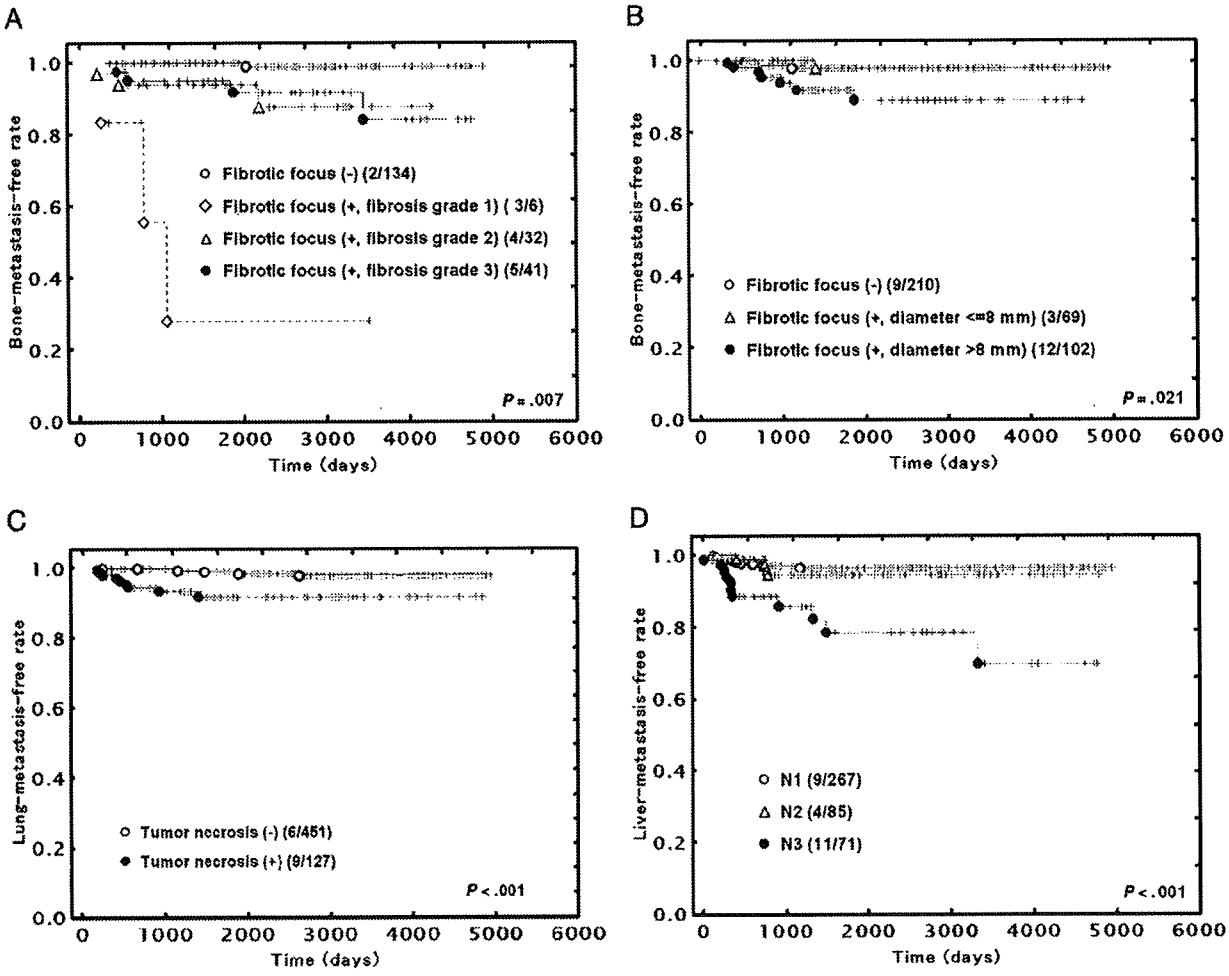

Fig. 2 Survival curves of patients with IDC with bone metastasis (A and B), lung metastasis (C), and liver metastasis (D). A, Among the patients with IDC who did not receive adjuvant therapy and had no nodal metastasis, the patients with FF fibrosis grade 1 IDC have a significantly shorter bone metastasis–free survival curve than any of the other groups of patients. B, Among the patients with IDC who received adjuvant therapy and had no nodal metastasis, the patients with IDC with an FF greater than 8 mm in diameter have a significantly shorter bone metastasis–free curve than the patients with IDC without an FF and the patients with IDC with an FF 8 mm or less in diameter. C, Among the patients with stages I and II IDC who received adjuvant therapy, the patients with tumor necrosis had a significantly shorter lung metastasis–free curve than those without tumor necrosis. E, Among the patients with IDC who received adjuvant therapy and have nodal metastasis, the patients with IDC with 10 or more nodal metastases (N3) have a significantly shorter liver metastasis–free curve than the patients with IDC classified as N1 (1-3 nodal metastases) or N2 (4-9 nodal metastases).

Table 3 Factors in the multivariate analyses that significantly increased the HR for organ-specific metastasis according to nodal status and pTNM stage in patients with IDC who did not receive adjuvant therapy

Groups of patients with IDC according to nodal status and pTNM stage	N0	Stages I and II
Distant-organ metastasis		
FF, diameter >8 mm (*vs* FF, absent)	13.9/4.5-43.2	20.4/4.4-92.6
FF, fibrosis grade 1 (*vs* FF, absent)	22.3/4.1-119.8	43.7/8.0-250.8
Age, ≤39 y (*vs* age, >39 y)	–/– 11.1/2.2-56.6	–/– 10.0/2.0-48.8
Histologic grade 2 (*vs* histologic grade 1)	–/– 13.5/1.6-115.2	–/– 6.7/1.3-35.4
Histologic grade 3 (*vs* histologic grade 1)	–/– 16.0/1.9-142.0	–/– 7.0/1.2-39.0
Muscle invasion, present (*vs* muscle invasion, absent)	17.2/2.0-149.3 –/–	NA NA
FF, fibrosis grade 3 (*vs* FF, absent)	–/–	4.3/1.3-14.5
Bone metastasis		
FF, diameter >8 mm (*vs* FF, absent)	8.0/1.9-32.5	27.6/3.3-225.2
FF, fibrosis grade 1 (*vs* FF, absent)	13.3/2.9-60.3	32.2/5.8-189.5
Histologic grade 3 (*vs* histologic grade 1)	4.0/1.0-15.4 6.6/1.7-25.1	–/– 4.3/1.1-16.7
Muscle invasion, present (*vs* muscle invasion, absent)	22.4/2.2-228.7 24.4/2.3-220.3	NA NA
FF, fibrosis grade 3 (*vs* FF, absent)	–/–	5.3/1.1-24.0

Note: Models 1 and 2: values are shown as HR/95% CI.
Abbreviations: –/–, not significant; NA, not available.

3.3. Multivariate analyses for distant organ metastasis, bone metastasis, lung metastasis, and liver metastasis according to nodal status and pTNM stage in the IDC group that received adjuvant therapy

FF diameter greater than 8 mm significantly increased the HRs for distant organ metastasis in all IDC groups in the multivariate analyses, and N3 significantly increased the HRs for distant organ metastasis in the N+ group and the stage III IDC group (Table 5). Tumor necrosis significantly increased the HRs for distant organ metastasis in the N0, N+, and stages I and II IDC groups in the multivariate analyses. FF fibrosis grades 2 and 3 significantly increased the HRs for distant organ metastasis in the N+ group and stages I and II IDC group in the multivariate analyses. Age 39 years or younger significantly increased the HRs for distant organ metastasis in the N+ group and stage III IDC group.

FF diameter greater than 8 mm significantly increased the HRs for bone metastasis in all IDC groups in the multivariate analyses (Table 5) (Fig. 2B). Age 39 years or younger and FF fibrosis grade 3 significantly increased the HRs for bone metastasis in the N+ group and the stage III IDC group in the multivariate analyses.

Tumor necrosis significantly increased the HRs for lung metastasis in the N+ group and stages I and II IDC group (Table 5) (Fig. 2C). ER−/PR− significantly increased the HRs for lung metastasis in the N+ group and the stage III IDC group.

N3 significantly increased the HRs for liver metastasis in the N+ group and the stage III IDC group in the multivariate analyses (Table 5) (Fig. 2D). ER−/PR− and FF fibrosis grade 3 significantly increased the HRs for liver metastasis in the multivariate analyses.

Many factors that were significantly associated with organ metastasis in the multivariate analyses were associated with an 18- to 24-month interval between surgery and detection of the initial metastasis, and some factors were associated with an interval of more than 10 years (Table 6). When the median interval between surgery and the detection of the initial metastasis in the cases as a whole was used as the standard median interval, the presence of muscle invasion, the presence of tumor necrosis, histologic grade

Table 4 Intervals between surgery and detection of the initial tumor metastasis according to factors that were significantly associated with organ-specific metastasis in patients with IDC who did not receive adjuvant therapy, according to nodal status and pTNM stage

Factors	N0	Stages I and II
Median interval between surgery and detection of the initial distant-organ metastasis (mo)		
Cases as a whole	30 (7-112)	30 (9-112)
Muscle invasion, present	7	NA
Histologic grade 3	19	25
FF, fibrosis grade 1	25	25
FF, diameter >8 mm	27	27
Age, ≤39 y	30	30
Histologic grade 2	32	32
FF, fibrosis grade 3	–/–	26
Median intervals between surgery and detection of the initial bone metastasis (mo)		
Cases as a whole	25 (7-112)	29 (9-112)
Muscle invasion, present	7	N/A
FF, diameter >8 mm	18	27
Histologic grade 3	19	25
FF, fibrosis grade 1	25	25
FF, fibrosis grade 3	–/–	40

Note: Values in parentheses are ranges.

3, N3, and age 39 years or younger tended to be associated with shorter median intervals (Table 6), whereas the characteristics of FF and ER/PR status tended to be associated with longer median intervals independent of nodal status or pTNM stage.

4. Discussion

The data for the factors that significantly increased the HRs for distant-organ metastasis and bone metastasis in the IDC group that did not receive adjuvant therapy and in

Table 5 Factors in the multivariate analyses that significantly increased the HR for organ-specific metastasis according to nodal status and pTNM stage in patients with IDC who received adjuvant therapy

Groups of patients with IDC according to nodal status and pTNM stage				
	N0	N+	Stages I and II	Stage III
Distant-organ metastasis				
FF, diameter >8 mm (*vs* FF, absent)	2.8/1.2-6.3	2.1/1.3-3.2	2.6/1.3-4.9	2.0/1.3-3.1
N3 (*vs* nodal status, N0,	NA	4.4/2.8-6.9	NA	2.8/1.8-4.5
in stage III status;	NA	4.2/2.6-6.8	NA	2.9/1.8-4.6
vs nodal status, N1, in N+ status)				
Tumor necrosis, present	–/–	1.6/1.0-2.6	2.6/1.4-5.0	–/–
(*vs* tumor necrosis, absent)	3.2/1.4-7.2	–/–	3.0/1.6-5.7	–/–
FF, fibrosis grade 2 (*vs* FF, absent)	–/–	1.9/1.1-3.3	2.2/1.0-4.7	–/–
FF, fibrosis grade 3 (*vs* FF, absent)	–/–	2.5/1.4-4.3	3.0/1.3-6.7	–/–
Age, ≤39 y (*vs* age, >39 y)	–/–	2.5/1.3-4.7	–/–	2.7/1.4-5.4
	–/–	2.5/1.3-4.7	–/–	2.5/1.3-5.0
Other factors	Muscle invasion, present	ER+/PR-		
		ER-/PR-		
		Skin invasion, present		
		Histologic grade 3		
Bone metastasis				
FF, diameter >8 mm (*vs* FF, absent)	3.7/1.1-12.0	3.1/1.5-6.3	4.9/1.5-16.0	2.4/1.2-5.0
Age, ≤39 y (*vs* age, >39 y)	–/–	5.1/2.1-12.6	–/–	6.8/2.8-16.3
	–/–	5.3/2.2-13.1	–/–	6.9/2.9-16.6
FF, fibrosis grade 3 (*vs* FF, absent)	–/–	2.8/1.4-5.6	–/–	2.5/1.2-5.1
Other factors	Muscle invasion, present	Invasive tumor size, >50 mm		
	FF, fibrosis grade 2	Nodal status, N2		
		Nodal status, N3		
Lung metastasis				
Tumor necrosis, present		2.2/1.1-4.7	5.3/1.8-15.3	–/–
(*vs* tumor necrosis, absent)		2.2/1.1-4.7	6.0/2.1-17.1	–/–
ER-/PR- (*vs* ER+/PR+)		2.8/1.2-6.4	–/–	2.8/1.1-7.0
		2.8/1.2-6.4	–/–	2.8/1.1-7.0
Other factors		Skin invasion, present		Lymph vessel invasion, present
		N3		
Liver metastasis				
N3 (*vs* nodal status, N0,		5.4/2.4-12.5	NA	7.6/1.6-34.4
in stage III status;		5.9/2.6-14.1	NA	7.6/1.6-34.4
vs nodal status, N1, in N+ status)				
ER-/PR- (*vs* ER+/PR+)		3.8/1.5-9.6	8.2/1.0-65.2	–/–
		3.3/1.3-7.7	11.0/1.4-86.3	–/–
FF, fibrosis grade 3 (*vs* FF, absent)		2.6/1.2-6.1	4.3/1.3-14.1	–/–
Other factors		ER+/PR-		
		FF, diameter >8 mm		
		Histologic grade 3		

Note: Models 1 and 2: values are shown as HR/95% CI.

Table 6 Interval periods for initial tumor metastasis from operation of factors that were significantly associated with organ-specific metastasis according to nodal status and pTNM stage in patients with IDC who received adjuvant therapy

Factors	N0	N+	Stages I/II	Stage III
Median intervals between surgery and detection of the initial distant-organ metastasis (mo)				
Cases as a whole	25 (7-86)	18 (5-122)	24 (4-122)	18 (5-110)
Muscle invasion, present	17	–/–	NA	–/–
Tumor necrosis, present	19	11	17	–/–
Histologic grade 3	–/–	11	–/–	–/–
N3	NA	14	NA	14
Skin invasion, present	–/–	14	NA	–/–
Age, ≤39 y	–/–	15	–/–	15
FF, fibrosis grade 2	–/–	18	38	–/–
FF, diameter >8 mm	24	20	25	17
FF, fibrosis grade 3	–/–	25	15	–/–
ER+/PR–	–/–	27	–/–	–/–
ER–/PR–	–/–	37	–/–	–/–
Median intervals between surgery and detection of the initial bone metastasis (mo)				
Cases as a whole	24 (11-61)	26 (8-122)	31 (8-122)	24 (9-90)
Muscle invasion, present	17	–/–	NA	–/–
Age, ≤39 y	–/–	17	–/–	19
N2	NA	25	NA	–/–
N3	NA	26	NA	–/–
FF, fibrosis grade 2	24	–/–	–/–	–/–
FF, diameter >8 mm	25	30	36	26
Invasive tumor size, >50 mm	–/–	36	NA	–/–
FF, fibrosis grade 3	–/–	39	–/–	30
Median intervals between surgery and detection of the initial lung metastasis (mo)				
Cases as a whole		27 (6-110)	17 (6-88)	28 (6-110)
Tumor necrosis, present		10	27	–/–
N3		16	NA	–/–
Skin invasion, present		17	NA	–/–
ER–/PR–		44	–/–	20
Lymph vessel invasion, present		–/–	–/–	26
Median intervals between surgery and detection of the initial liver metastasis (mo)				
Cases as a whole		13 (5-109)	18 (4-51)	13 (5-109)
Histologic grade 3		11	–/–	–/–
N3		11	NA	11
FF, diameter >8 mm		14	–/–	–/–
FF, fibrosis grade 3		14	10	–/–
ER–/PR–		25	16	–/–
ER+/PR–		33	–/–	–/–

Note: Values in parentheses are ranges.

the IDC group that received adjuvant therapy are shown in Figs. 3 and 4, respectively. The factors are ranked in decreasing order of contribution to accurate prediction of metastasis to each of the organs according to nodal status and pTNM stage. Factors that significantly increased the HRs for metastasis to each distant organ in models 1 and 2 in all the tumor status categories are marked by an asterisk.

Fig. 3 shows that FF diameter greater than 8 mm and FF fibrosis grade 1 were the most important of the 7 distant-organ metastasis predictive factors and of the 5 bone-metastasis predictive factors, and that FF fibrosis grade 3 ranked third. Thus, the diameter and fibrosis grade of an FF can be concluded to be very important histologic factors of primary invasive IDCs for accurate prediction of distant-organ metastasis and bone metastasis by the IDCs of patients who did not receive adjuvant therapy. FF diameter also had strong organ-metastasis predictive power for distant-organ metastasis and bone metastasis in patients with IDC who received adjuvant therapy, and it was more accurate than N3 in predicting bone metastasis among patients with IDC who received adjuvant therapy, independent of nodal status or pTNM stage (Fig. 4A). FF fibrosis grades 2 and 3 ranked within the 3 most accurate predictive factors for distant-organ metastasis and bone metastasis. It can therefore be