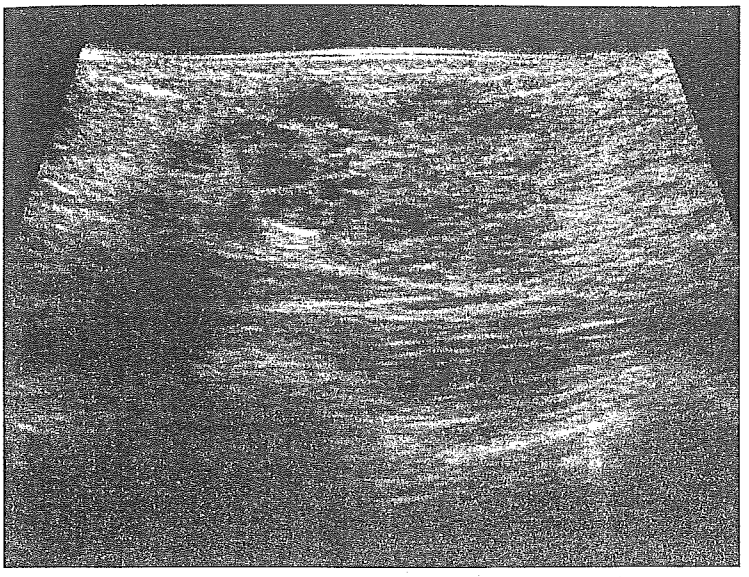


Fig. 4 Real-time sonogram (7.5MHz probe) showing a low echo area in the mammary gland with a multi-vesicular pattern.

ありFAが鑑別に挙げられるが，充実性成分はcollagenousな間質組織でFAに通常認める典型的なintracanalicular pattern，pericanalicular patternは見られないこと，多数の嚢胞，通常型の上皮過形成，アポクリン化生など多彩な像が認められ，スイスチーズを連想する肉眼的割面であったことからRosenが提唱したJPと診断した．

【症例2】22歳，女性．

【主訴】右乳房腫瘤を自覚．

【既往歴・家族歴】特記すべきことなし．

【現病歴】1週間前に右乳房腫瘤に気付き当院外来を受診した．

【初診時現症】身長155cm，体重42kg，右乳房CA領域に3cm大の境界やや不明瞭な硬い腫瘤を触知した．

【乳房超音波検査（Fig. 4）】小嚢胞が散見される背景乳腺．触知腫瘤部では乳腺内に低エコー域を認め，その内部には多数の小嚢胞が密に存在していた．DCISを第一に疑いカテゴリー4とした．

【マンモグラフィ（Fig. 5）】MLO像でU領域に局所的非対称性陰影を認める．構築の乱れ，石灰化の随伴は認めない．CC像では明らかな異常所見は指摘されなかった．カテゴリー3．

【右乳房MRI (Fig. 6)】Dynamic studyのT1強調脂肪抑制画像でCA領域の乳腺辺縁部に，早期相から粒状に造影される3cm大の領域が見られた．内部に小嚢胞を思わせる低信号域を数多く伴っている．造影効果のピークは2分で後期相では減弱しており，悪性が疑われる造影パターンであった．

【細胞診（Fig. 7）】筋上皮との二相性の保たれた異型のない上皮集塊と共に多数のアポクリン化生上皮の集塊が見られる．背景に嚢胞性病変を伺う泡沫細胞を伴っていた．

DCISの否定は完全にはできないが，細胞診で明らかな悪性像を認めなかったため，USでの多数の小嚢胞が密に存在する特異な所見からJPを疑った．

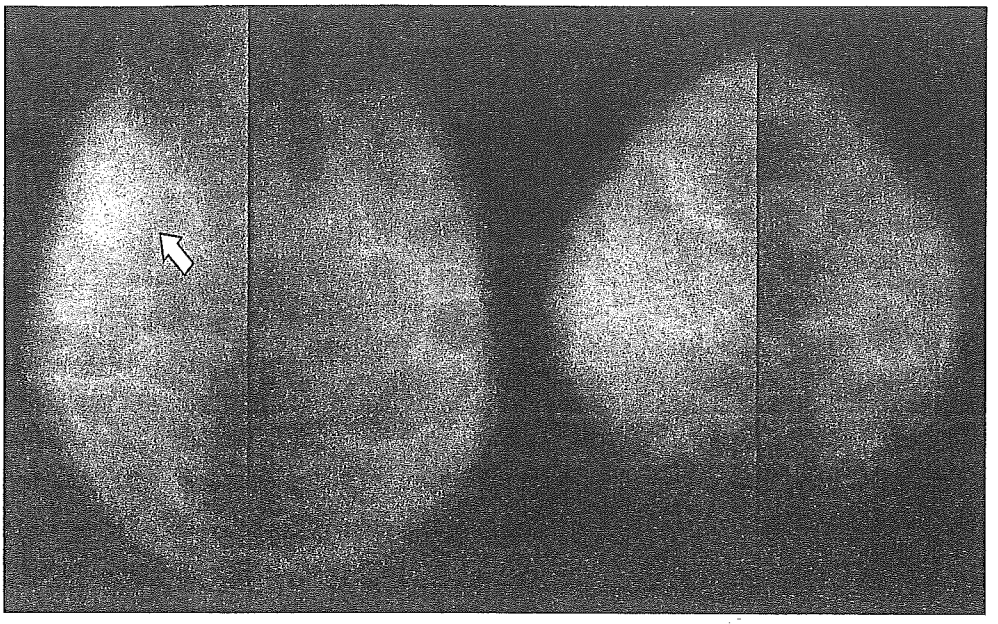
【手術所見】全麻下にprobe lumpectomy（Tm）を行った．

【切除標本肉眼所見】数mm大の嚢胞や充実性小結節が多発していた．

【病理組織学所見（Fig. 8）】直径2～3mmの嚢胞が多発しスイスチーズ様である．嚢胞を覆う上皮に異型はなく，アポクリン化生，乳頭状アポクリン化生が見られる．この他に末梢性乳頭腫，線維腺腫様過形成，中等度の通常型上皮過形成を認める．悪性像は認めず，JPとして矛盾のない所見であった．

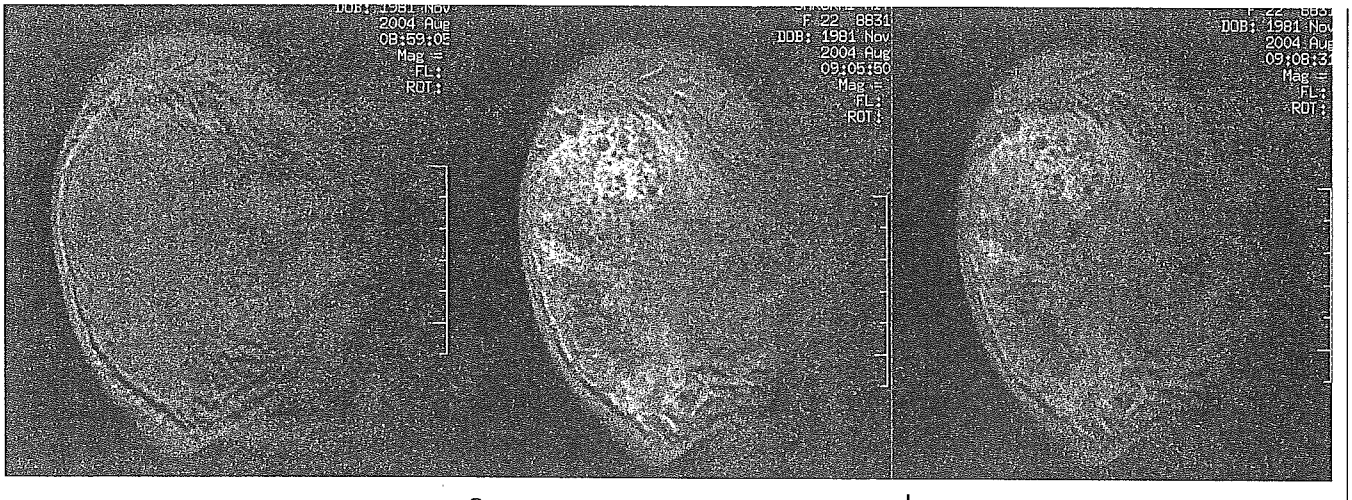
考察

若年性乳頭腫症（Juvenile papillomatosis）は嚢胞状乳管拡張，上皮過形成が特徴的である腫瘤形成性の良性増殖性病変であり，通常30歳以下の若年女性に見られる．組織学的には嚢胞と上皮過形成が常に見られ，アポクリン化生，硬化性腺症，線維腺腫様過形成などを伴うことがある．本性の一部に見られる上皮過形成は，内腔へ向かう上皮の増殖であるが，血管結合組織性の間質を伴うものではない．「乳頭腫」という用語の使われ方に



a b

Fig. 5 (a) Mediolateral oblique view of a mammogram of the right breast showing a lesion with focal asymmetric density. (b) Craniocaudal view showing no abnormality.



a b c

Fig. 6 Using dynamic MRI (coronary view) with T1-weighted images, the lesion was enhanced markedly in the early phase. (a) Plain image. (b) Early phase (2 min). (c) Late phase (5 min).

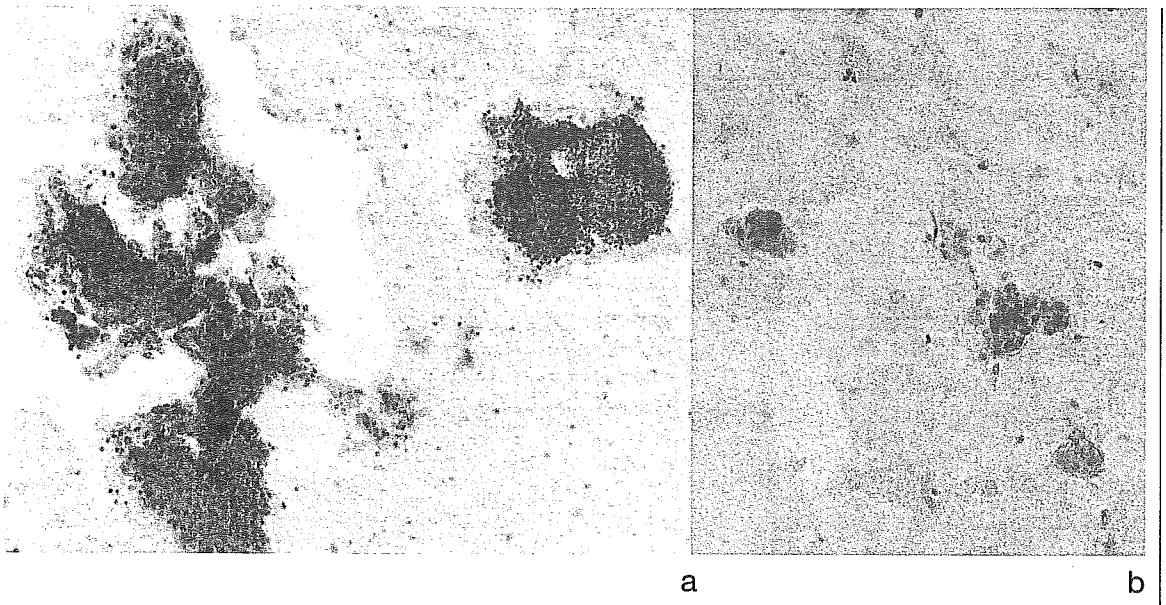


Fig. 7 (a) Benign epithelial hyperplasia and apocrine metaplasia×100. (b) With foam cells suggesting cystic change Papanicolaou stain×200.

は多少の混乱があり，本来上皮過形成と呼ぶべき病変が含まれている場合がある．厳密には「乳頭腫」という場合には血管結合組織の支持を有する上皮の内腔への増殖を意味するので，JPという病名はその本質を的確に表現するものではない．このような用語や病名の混乱のため，本来多発性乳頭腫というべき病変などがJPとして報告されていることもある[2]．JPの組織像に特異性はないが，肉眼像は特徴的で，周囲と明瞭に区別された腫瘤でありながら大小の嚢胞を示している[1)-3)]．

欧米ではRosenが1985年に180例という多数の症例を集積，報告しているが[4]，1990年にはさらに長期間経過観察できた41例に関して検討を行っている[5]．一方，わが国では症例報告が散見される程度である[6)-9)]．

臨床的には硬い限局した腫瘤として触知され，これが主訴となることが多い．

Kersschotら[10]によるとUS像は境界不明瞭な腫瘤影を示し，内部エコーは不均質で，幾つもの小円形の無エコーに近いエリアをもっており，それらは比較的腫瘤の辺縁部に配置していたと報告している．我々の第1例では嚢胞の数は際立って多いとは言えず，FAの所見に類似した境界明瞭な腫瘤像を呈しており若干異なる所見を呈していたが，第2例ではほぼ同様の所見を示している．このような内部に小嚢胞が多発する限局した腫瘤像は，乳腺症，DCISが最初の鑑別診断に上がると思われるが，JPを疑うことのできる有力な手がかりであると考える．

JPは若年者が多いためマンモグラフィの実施例が少ないが，報告例では病変を指摘することができないか，局所的非対称性陰影もしくは境界不明瞭な腫瘤影として認識されている[4),10),11)]．

JPのMRI像は，Mussurakisらの報告[11]による

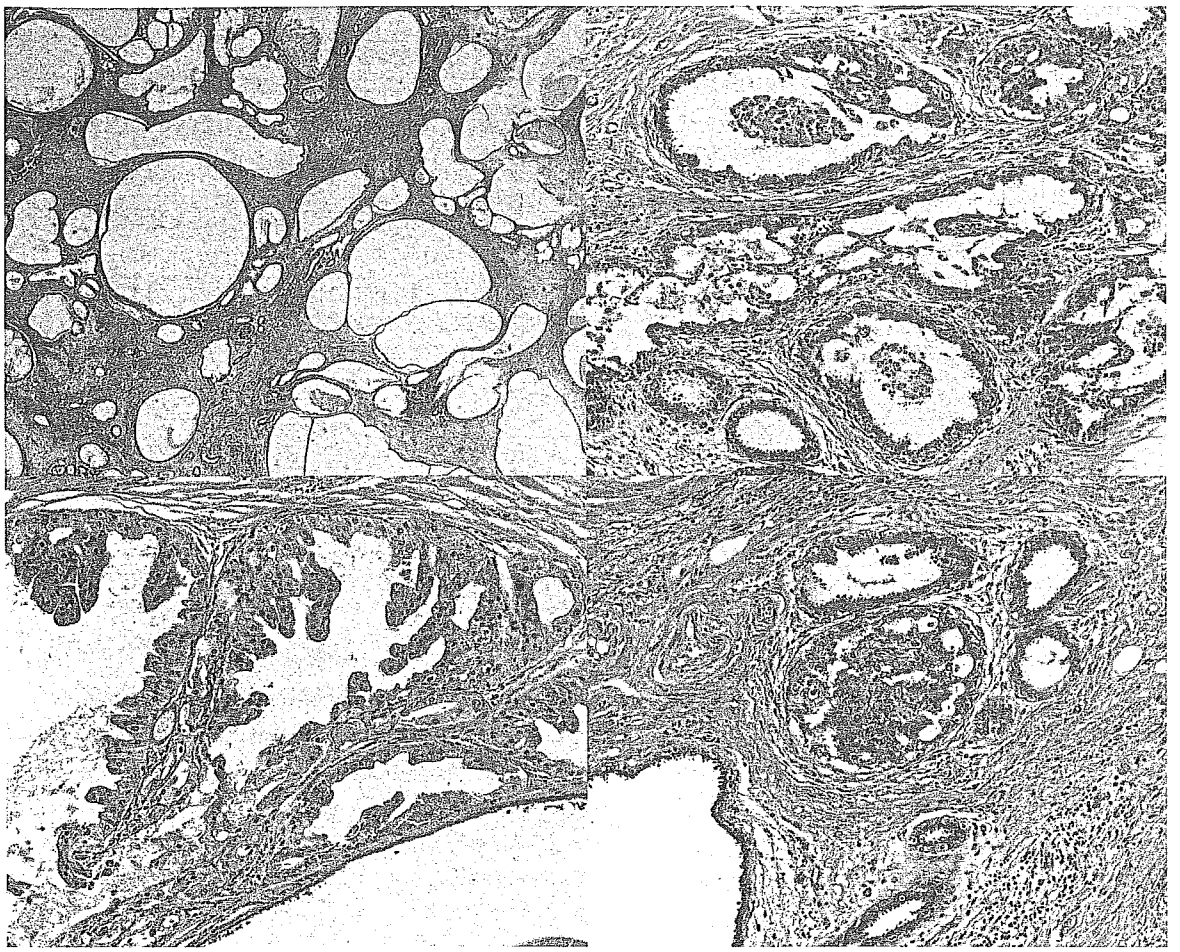


Fig. 8 (a) Histological section showing the typical "Swiss cheese" appearance×10. (b) Ordinary hyperplasia×40, (c) Apocrine metaplasia×100. (d) Papilloma of peripheral type Hematoxylin and eosin×100.

と，T1強調造影画像で濃染する分葉状腫瘤を示し，dynamic studyは後期相でプラトーとなる漸増型であった．またT2強調画像で腫瘤影の内部に多発する小嚢胞像がJPに最も特徴的であるとも述べている．我々の第2例はdynamic studyで早期濃染型を示し，悪性をより疑わせるものであったが，内部には嚢胞を思わせる低信号域を認めており，JPを示唆する所見であると思われた．

細胞診は線維嚢胞性変化を疑う細胞像でJPに特異的な像は見られないが，USの特異な所見など臨床情報を考慮に入れることによって，JPを疑うことができると考える[12]．

JPの発癌に対するリスクに関しては諸説述べられているが，Rosen[5]によると，乳癌の続発は観察期間の中央値（median）14年でJPの患者41例中4例であった（10％）．この4例すべてに乳癌の家族歴があり，病変は再発を繰り返し，両側性であった．一方で再発しない，片側性のJPの患者にはこの観察期間に乳癌は発生しておらず，これらの患者には近い将来の乳癌発生リスクを強調すべきでない．乳癌の家族歴を有し，両側性で，再発を繰り返すJPが重大な発癌のリスクファク

ターであると報告している．

治療に関しては，良性である本疾患では局所切除で充分と考えられ，過大な侵襲は避けなければならない．よって術前にJPを疑うことができるか否かが肝要である．またその後の定期検査こそが重要であり，特に乳癌の家族歴を有する者，両側性，再発性では厳重に経過を観察する必要があると考える．

結語

若年女性のエコー像でスイスチーズをイメージさせる限局した多発嚢胞像を呈し，細胞診で良性増殖性病変が疑われる症例では，JPを鑑別に上げられることが望まれる．

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マンモグラフィ読影講習会の教育効果と精度管理


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要旨：日本女性の乳がん死亡減少につながる乳がん検診を行うためには、質がよく、かつ受診率の高いマンモグラフィ検診が必須である。読影講習会は、医師の読影力の向上とともに、有効な乳がん検診に携わるという認識を持つことを目的としている。

読影実験・教育実験を経て講習会を開始

マンモグラフィ読影講習会（以下講習会）の立ち上げの基礎作りとして、読影実験や教育実験が順次行われた。

(1)読影実験

マンモグラフィの読影精度に関する研究（1995年11月）

150症例300乳房・38名の読影者（医師、放射線技師）の協力を得て読影実験（試験形式）を行った結果、マンモグラムの「読影精度は経験症例数に比例する」との結果を得た。

この結果を受けて講習会の基礎作りとして次に教育実験を行った。

(2)教育実験Ⅰ

マンモグラフィの読影診断精度と教育効果に関する研究（1996年6月）

読影実験協力者の半数に対し半日の講習を行い、その後読影実験を施行した。その結果、講習を受けた群と受けなかった群には読影力向上に差はなく、「簡単な講習は読影精度の向上には寄与しない」との結果を得た。

(3)教育実験Ⅱ

マンモグラフィ検診における診断と読影に関する研究（1998年3月）

40名の医師を被験者とし、2日間の講習会を行った。講習会のプログラムは乳がんの臨床、マンモグラフィの基礎、乳がんの病理と画像、乳房画像診断用語の解説の講義とグループ講習（8テーマ）および講習前と後で読影試験を行い読影力の差から講習会の教育効果を検討した。

受講後は、受講者全体および読影経験別のいずれも読影力の向上が認められた。講習会の教育効果を得るためには「講義、読影グループ講習（マンツーマンに近い少人数）の講習と読影試験が必要」との結果を得た。

2日間というこのプログラムに従った講習会が、以後の講習会の原型となった（図1）。すべての講習会で読影試験が行われ、評価基準（図2）に従ってA評価およびB評価者には、精中委の認定医として認定証が発行されている。このプログラムは、2000年（平成12年）3月の厚生省（当時）通達、老健第65号に基本プログラムとして記載されるに至った。

(4)読影講習会の現況

講習会は、98年12月から始まり、1講習会の受講者数は、49名（1グループ約7名の7グループ講習）を基本として行われてきた。98年から99年度は講習会開催10回、以後00年度9回、01年度20回、02年度19回、03年度31回、04年度42回と増加してきた。特に今年度に入って増加の勢いを増し、05年9月10日で

1．受講者の読影力の向上←実験により証明済み
2．テーマ別課題の解決
3．教材の整備
4．受講者・講師の感想→アンケート調査
5．講師の養成・トレーニング（指導者研修会）
6．リフレッシュコースの開設

図3　マンモグラフィ講習会（読影）の改善した主な項目（アンケート調査から）

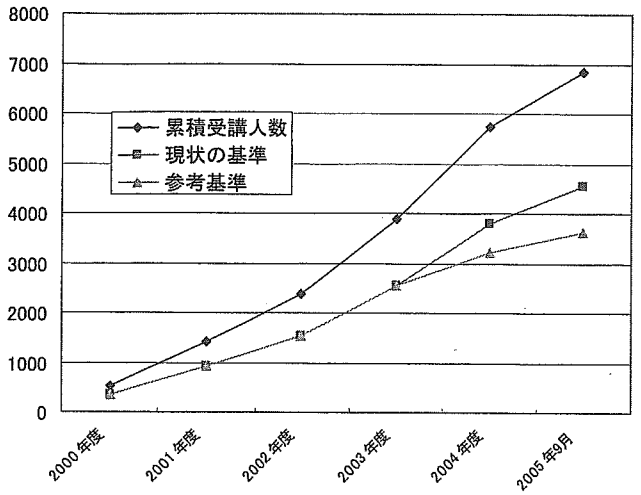

図4　講習会受講者数と認定取得者数

表1　マンモグラフィ検診精度管理中央委員会講習会読影講習受講者
（2005年9月10日現在）

専門科	A	B	C	D	合計
外科	580	2739	622	192	4133
放射線科	244	1049	150	51	1494
産婦人科	20	446	262	141	869
その他	23	211	81	46	361
合計	867	4445	1115	430	6857

表2　講習会アンケート調査集計結果（2000年3月～05年度）

	講習会数	累積受講人数	現状の基準	参考基準
2000年度(＊)		510	357	357
2001年度	20	1412	920	920
2002年度	19	2372	1538	1538
2003年度	31	3887	2563	2563
2004年度	42	5749	3783	3217
2005年9月	23	6851	4550	3618
2006年3月末(＊＊)	59	8670	5720	

（＊）：2000年3月～2001年3月
（＊＊）：2005年9月以降予測値

いては、教育・研修委員会でも試算している。それによると、地域により偏りがあるものの、計算上は現時点でもほぼ数が足りてきており、今後すでに予定されている講習会、さらにはグレイドアップ試験での認定増加を見込むと、量的にはすでに足りてきていると考えられている。

(2)読影医の質はこれで良いのか

教育・研修委員会では、これからは読影医の質を向上させる必要があると考えている。事実、04年4月から05年2月まで、図2の下欄に示した評価基準（参考基準として示す）で読影試験を実施した。

マンモグラフィ検診が救命につながる評価として、評価Bを感度85%、特異度85%以上と認定した。その結果、読影試験の認定取得率は約半分に低下した。その原因は、アンケート調査から見る範囲では、講習会受講者が、それまでの受講者のように乳がんの診断や治療などに関わってこなかった医師が、読影のために急遽受講、受験した背景があることが示唆された。

画像診断の中でも、撮像においても特異な画像であるマンモグラムの読影が、画像読影に慣れた放射線科医は別として、2日間の講習を受講しただけでは直ちに救命につながる読影力を取得することは困難と思われる。講習会までにマンモグラム読影の勉強を十分に積んだ医師の場合には、2日間の講習でも十分に認定を取得できることも、アンケート調査などでうかがわれる。講習会の事前読影勉強会開催などにも教育・研修委員会として援助し、講習会の教育効果が上がるように配慮している。

さらに、問題は、一度取得した認定の更新がないことであろう。これまでのアナログマンモグラフィに対し、デジタルマンモグラフィが増加してきたことに対応するため、読影部分を含めてガイドラインの改訂を行うなど、画像も読影も急速に進化している。少なくともマンモグラフィ検診に携わる読影医として、自己の読影力がどの程度のレベルにあるのか、5年に一度は最低グレイドアップ試験をフィルムリーディングの機会として活用してもらいたいと思う。

参考基準でも今後の認定取得増加数を考慮すると、十分な読影医数が確保できるはずである（図4）。種々の理由により、教育・研修委員会が提示した参考基準と更新制は現基準に戻すこととなったが、このような読影レベルで本当に安全なのかを、受診する側と検診に関わる側とで考えていただきたい。

日本女性を乳がん死から救うために、安全で質の良いマンモグラフィ検診を、本当に安心して検診し、安心して受診してもらえるようにと願っている。

※　※

古妻嘉一（こつま・よしかず）●42年大阪府生まれ。68年神戸大医卒。同年より阪大医学部附属病院にて研修、71年同大医学部第2外科入局。74年より附属病院医員、77年より文部教官助手（医学部）、79年退職。81年大阪府泉佐野市にて古妻クリニック開設（有床診療所）、03年閉院。同年新大阪に乳がん検診・研修を主とした古妻クリニックを移転開設して現在に至る。第14回日本乳癌検診学会総会会長。

基本要件：最低２日間の講習と読影試験

1　講義　・検診の背景と読影講習会の教育効果
　　・乳癌の一般的知識
　　・マンモグラフィの基礎
　　・診断用語とカテゴリー分類

2　グループ講習　少人数（５～８名）／テーマ別（６～８テーマ）

3　読影試験　100例の左右マンモグラム読影

図１　マンモグラフィ読影講習会基本プログラム

マンモグラム読影試験の評価基準（１）

A	C感度・特異度ともに８５％以上	検診マンモグラム読影と指導の実力あり
B－１	感度・特異度ともに８０％以上	検診マンモグラム読影の実力あり
B－２	感度８０％以上で、感度＋特異度＝１７０％	
C	感度・特異度ともに７０％以上	指導医とともにマンモグラム読影が可能
D	上記に達しない	読影を始める前に基礎の学習が必要

感　度：精査が必要な乳房に対して、カテゴリー３以上と評価できた率
特異度：精査の必要のない乳房に対して、カテゴリー２以下と評価できた率
C感度：精査が必要な乳房に対して、正しいカテゴリー（C）分類が行えた率
＊視触診医も評価C以上が望ましい

（マンモグラム読影試験の参考評価基準）（２）

評価A	：感度９０％以上、・特異度９２％以上	検診マンモグラムの第２読影者（読影責任者）
（A－S	：加えてカテゴリー感度８５％以上）	（検診マンモグラムの第２読影者（読影責任者）および講習会講師）
評価B	：感度８５％以上、特異度８５％以上	検診マンモグラムの第１読影者
評価C	：感度７５％以上、特異度８０％以上	評価B以上の読影者とともに読影
評価D	：上記に達しないもの	

（5年毎の更新を行う）

図２　マンモグラム読影試験の評価基準

21回、年度末までには合計59回の講習会開催が予定されている。受講者数も延べ６８５７名に達している。

また、認定読影医数は５３１２名（受講者の約66％）で、この認定医の氏名および所属名は精中委ホームページにて都道府県別に公開されている（集計は精中委教育・研修委員会による、05年９月10日現在、表１）。

今後の開催数から05年度末には受講者総数は約８６７０名、認定医数約５７２０名になると予測される。

精中委教育・研修委員会では、講習会以外にグレイドアップ試験（年４回）、講師経験者を対象とした指導者研修会（年１回）を開催するとともに、日本乳癌検診学会や日本乳癌学会を含めた学会等で、フィルムリーディングも共催し読影力の向上を目指している。

教育効果を上げるために精度管理が必要

講習会により読影力の向上が見られることは、講習会が始まる事前の教育実験で証明されている。しかし、講習会をより教育効果を上げるものにするためには、講習会自体の精度管理が必要である。

講習会の精度管理を目的として、00年３月の大阪１講習会（99年度老人保健事業推進費等補助金による「マンモグラフィによる乳がん検診の推進と精度向上に関する研究：主任研究者・大内憲明）から、受講者に対してアンケート調査を実施し、以後、すべての講習会にて調査を行ってきた。調査は講習会受講者全員を対象とし、できるだけ各講習会内にて回収できるようにした。

アンケート集計結果は表２に示した（回答の未回収もあり、教育・研修委員会の集計とは数値が異なる）。講習会の精度判定は、受講者の読影症例数から講習会のランク分けを行い、初心者講習会（α－講習会）、中級（β－講習会）、上級（γ－講習会）と分け、各ランクの講習会毎に設定された読影試験評価A＋Bの割合をクリアできている講習会を精度が保たれた講習会と判定した。

講習会開催回数が増加し始めた00年後半には、講習会の精度が低下し出したため、講師のアンケート調査などを開始し、また、グレイドアップ試験での受験者に対するアンケート調査を行い、これらの集計結果から講習会や試験の改善を行った。全体講義やグループ講習の時間配分、グループ講習の内容の充実、読影試験問題の改正などを行ってきた（図３）。

その結果、講習会における読影試験の認定取得率は、講習会によりやや偏りがあるものの、平均約70％を維持しているようである。

試験結果が認定取得に至らなかった受講者には、６カ月間の読影勉強期間を設け、グレイドアップ試験を受験し、受講者すべてが読影認定を取得できるように配慮している。

今後は量的充足とともに質的充足を

講習会の目的は、マンモグラフィ検診での読影医の充足である。それには量的充足と質的充足の両方が必須である。

(1)読影医は不足しているのか？

表１、２で示したように、講習会受講済みの医師は９０００名に、このうち認定取得者は６０００名に達しようとしている。さらに06年度も講習会が同じようなペースで各地にて企画されている。

マンモグラフィ検診に必要な読影医数につ

Limited resection trial for pulmonary ground-glass opacity nodules: Fifty-case experience

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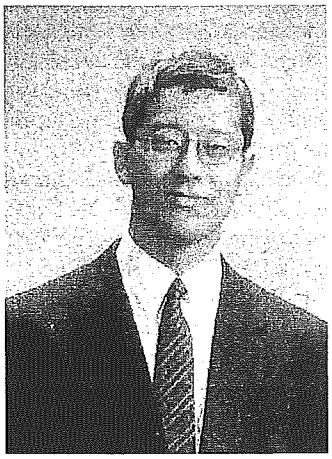

Dr Yoshida

Objective: This study was undertaken to determine the recurrence rate after limited resection of small lung carcinoma and to evaluate intraoperative frozen-section examination accuracy for Noguchi classification.

Methods: Enrollment requirements were as follows: pulmonary nodule 2 cm or smaller, diagnosed or suspected clinical T1 N0 M0 carcinoma in the lung periphery, and ground-glass opacity findings and lack of evident pleural indentations or vascular convergence on high-resolution computed tomographic scan. A wedge or segmental resection specimen, removed with custom stapler cartridges, was immediately reinflated and examined by frozen-section with hematoxylin-eosin and Victoria blue–van Gieson stains. If the tumor was confirmed as Noguchi type A or B with resection margins greater than 1 cm, the patient was closed and followed up on an outpatient basis. End points were 5-year disease-free survival and intraoperative classification accuracy.

Results: From August 1998 through October 2002, a total of 50 patients were enrolled (20 men and 30 women, ages 30-77 years). Tumor sizes ranged from 2 to 21 mm (11 mm average). There were 2 Noguchi type A tumors, 23 Noguchi type B tumors, 15 Noguchi type C tumors, 5 atypical adenomatous hyperplasias, 4 fibroses, and 1 granuloma. Frozen-section accuracy was approximately 98% (39/40). One intraoperative type B diagnosis was revised to type C after postoperative pathologic study. No morbidity, mortality, or recurrence has been seen with a median follow-up of 50 months.

Conclusion: Noguchi type A and B tumors may well be in situ carcinomas, and frozen-section examination was highly accurate. Neither local recurrence nor distant metastases have been found to date. Limited resection initial results appear promising.

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The Lung Cancer Study Group has performed the only prospective, randomized trial of limited resection versus lobectomy to date. They concluded that lobectomy was the appropriate surgical treatment for T1 N0 M0 non–small cell lung carcinomas, because limited resection resulted in greater local recurrence.[1] The Lung Cancer Study Group trial did not include many small cancers, and ground-glass opacity (GGO)[2] nodules were not recognized at the time of the study. Since then, several researchers have reported, although in retrospective study designs, that limited resection could be an acceptable alternative for patients with T1 N0 M0 disease.[3,4] We decided to do more investigations and evaluations. In 1998, we reviewed peripheral lung cancers smaller than 1 cm in diameter and found that almost half of them displayed an invasive nature. We concluded that tumor size alone cannot be a positive indicator for limited resection.[5]

Shimosato and colleagues[6] retrospectively evaluated cancer fibrotic focus or scarring and patient prognosis. They found that increasing fibrotic focus or scarring

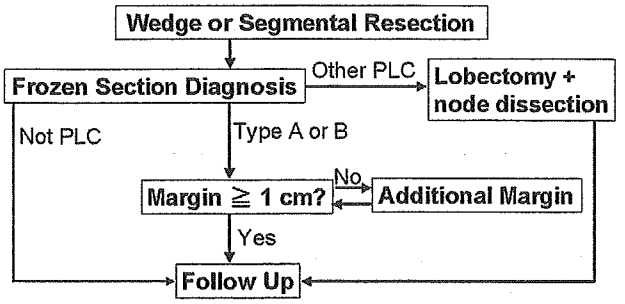

Figure 1. Treatment sequence. *PLC,* Primary lung cancer

GTS

was positively related to pleural invasion, lymph node metastasis, and blood vessel invasion. Patient prognosis was poorer with increased focus or scarring. They believed that scarring and resulting pleural indentations occurred with tumor development.

Noguchi and associates[7] developed a six-category classification for lung adenocarcinomas less than 2 cm in diameter. They concluded, on the basis of histologic characteristics and outcomes, that localized bronchioloalveolar carcinoma (type A) and localized bronchioloalveolar carcinoma with foci of collapse (type B) were pathologically and biologically in situ noninvasive peripheral carcinomas, whereas localized bronchioloalveolar carcinoma with foci of fibroblastic proliferation (type C) was an advanced invasive stage of types A and B. This differentiation required careful histologic examination.

We speculated that if Noguchi type A and B tumors truly are in situ, noninvasive carcinomas, limited resection might be the procedure of choice. With this goal in mind, we developed some unique tools and methods for intraoperative diagnosis of these tumor types. With these methods, we found that we were able to reliably differentiate Noguchi types A and B from type C during the surgical procedure. As a result, in 1998 at our institution we started a prospective limited resection clinical trial to confirm the reliability of the tumor type differentiation methods and to determine the survival of those with limited resection based on the tumor differentiation results for probable in situ adenocarcinoma in the lung periphery. We describe the study design, unique tools and methods, and preliminary results after completion of the planned 50 patient enrollment.

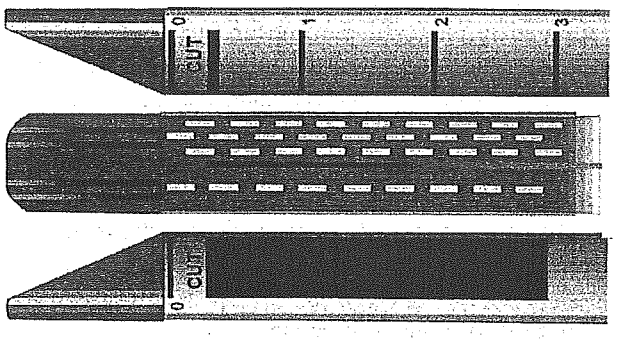

Figure 2. Customized stapler (ENDO-GIA 30 3.5/3-1; Tyco Healthcare Japan, Tokyo, Japan).

Patients and Methods

Our objectives were to evaluate intraoperative frozen-section examination in the identification of Noguchi type A or B tumors, to perform limited resection for Noguchi A and B and other benign or noninvasive nodules, and to determine the extent of local recurrence or distant metastases in all patients at 5-year follow-up. Enrollment required patients with a tumor less than 2 cm in diameter diagnosed or suspected as a clinical T1 N0 M0 carcinoma in the lung periphery on the basis of a computed tomographic (CT) scan. They had to have a high-resolution CT scan with findings suggestive of a Noguchi type A or B tumor: GGO and lack of evident pleural indentations or vascular convergence.[8] Written informed consent was obtained from each participant. Patients with a malignancy history within the past 5 years and those not candidates for lobectomy and systematic lymph node dissection were excluded.

Figure 1 shows the treatment flow chart. We performed wedge or segmental resection, depending on the tumor location. When a tumor was deep in the middle of a segment, segmentectomy was chosen. Also, when a tumor could not be localized during surgery, we performed a segmentectomy to avoid missing the tumor. Our pathologist (T.Y.) examined the frozen-section specimen immediately. If the tumor was confirmed as Noguchi type A or B with a resection margin greater than 1 cm, the patient was closed up and followed up on an outpatient basis. If the margin was not sufficient, additional margin was resected. If the tumor was a primary malignancy, but not type A or B, lobectomy and systematic lymph node dissection were performed. Patients are followed up on an outpatient basis at least every 6 months by physical check-up, plain chest radiograph, and laboratory tests. Patients who underwent limited resection for Noguchi type A or B disease have chest CTs every year.

It is fairly difficult to perform Noguchi classification from a simple frozen section. To facilitate the examination, we used several innovative tools and techniques in our trial. We believe these contributed significantly to the trial results. Figure 2 shows the stapler cartridge (ENDO-GIA 30 3.5/3-1; Tyco Healthcare Japan, Tokyo, Japan), custom modified as requested by our chief thoracic surgeon (K.N.). Rather than three lines of staples on both sides, it has a single staple line on the black, resected specimen side. This makes it easier to cut a narrow pathologic examination specimen margin strip for negative cut-end confirmation.

With no obvious specimen bronchus or bronchiole for phosphate-buffered saline solution injection, specimen inflation to facilitate alveolar structure observation is difficult. To inflate the resected specimen's alveolar structure, our pathologist used a technique known, but not normally used in neoplastic lung disease diagnosis.[9] With the specimen in a closed, phosphate-buffered saline solution–filled syringe, the piston was pulled back quickly and repeatedly, reinflating the alveolar structure by replacing alveolar air with phosphate-buffered saline solution (Figure 3). After

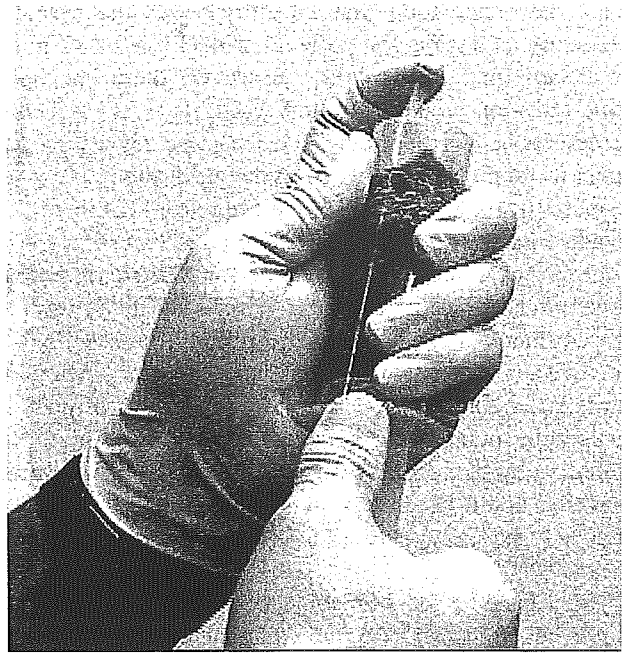

Figure 3. Specimen vacuum reinflation.

slicing the specimen into 2-mm thick slices and a second reinflation, the pathologist stereoscopically examined the slices, looking for the most severe structure destruction indications. The maximum stromal destruction slices or the largest area slice were cut by cryostat, stained with hematoxylin-eosin, and examined microscopically.

In addition to routine hematoxylin-eosin staining, our pathologist (T.Y.) thought Victoria blue–van Gieson (VvG) staining would improve Noguchi classification accuracy, because it reveals whether the alveolar wall elastic fibers are intact,[10] providing a powerful aid in improving intraoperative classification accuracy. If the elastic fibers were destroyed by tumor cells, as shown in Figure 4, *A*, the tumor was diagnosed as Noguchi type C, whereas if they were intact, as in Figure 4, *B*, the classification was type A or B. This diagnostic judgment was based on our group's previous report (Yokose and associates[11]) that patients without stromal destruction, as shown by VvG staining, survived 5 years without recurrence.

Noguchi and associates[7] reported no cancer recurrences at 5 years after lobectomy and lymph node dissection in the type A and B population.[7] Statistically, it is impossible to compare the limited resection outcome for these tumors with the event-free standard surgery outcome. We reported an 85% 5-year survival rate among patients with tumors 2 cm or smaller and T1 N0 M0 pathologic class who underwent lobectomy and systematic lymph node dissection at our institution.[12] Allowing 4 local recurrences in 50 patients, a 90% confidence interval of 86% to 98% results, and the lower limit would be better than our earlier study. We therefore decided to recruit 50 patients, with a trial-quitting rule of 5 local recurrence cases.

The first end point was accurate frozen-section examination results for carcinoma invasiveness. The second, and more important, end point was 5-year disease-free survival. This study protocol was reviewed by the National Cancer Center Hospital East institutional review board and was approved in July 1998.

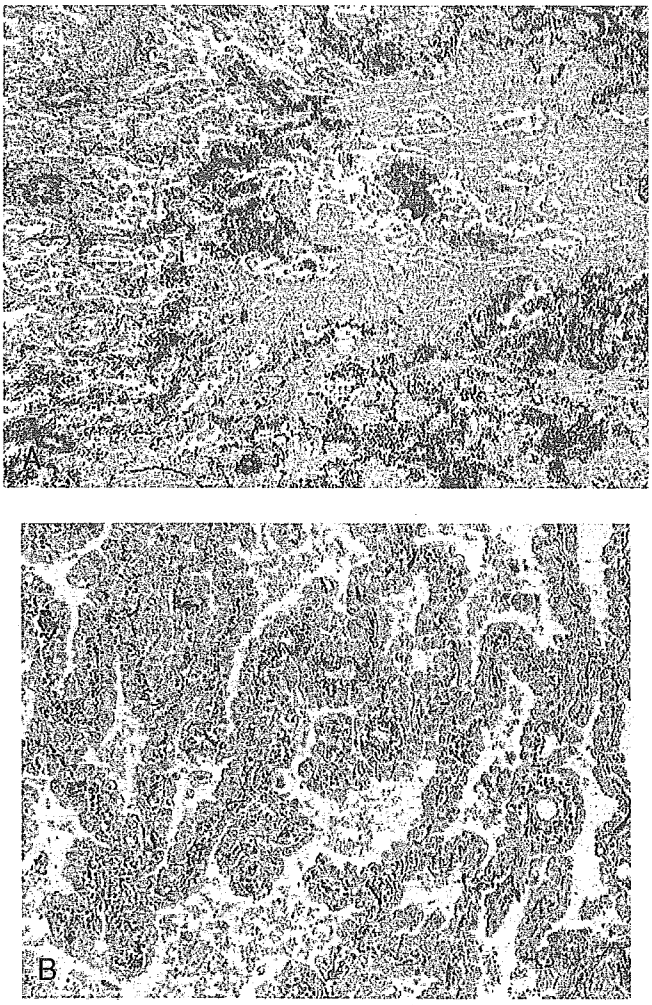

Figure 4. VvG staining showing elastic fiber destruction in type C tumor (A) and intact elastic fibers in type A tumor (B). (Magnification 100×.)

Results

This prospective study (August 1998–October 2002) enrolled 50 patients comprising only 5.3% of all patients with resected lung cancer at our institution during this period. There were 20 men and 30 women, with ages ranging from 30 to 77 years (average 61 years). Tumor sizes ranged from 2 to 21 mm (average 11 mm). Thirty patients had wedge resection, 6 segmentectomy, and 14 lobectomy with lymph node dissection. Nineteen of the 30 wedge procedures were performed thoracoscopically by three-port access, and the other 11 needed a small thoracotomy.

Three-port procedures were performed when the tumor was subpleural or when the tumor was shallow or hard

TABLE 1. Histologic subtype and tumor size distribution in resected specimens

Subtype	No. of cases	Range (mm)	Median (mm)	Resection type (W/S/L)
Type A	2	9-10	—	1/1/0
Type B	23	6-21	12	21/2/0
Type C	15	10-19	14	1/0/14
Atypical adenomatous hyperplasia	5	5-14	8	2/3/0
Fibrosis	4	6-15	10	4/0/0
Granuloma	1	6	—	1/0/0

W/S/L, Wedge resection/segmentectomy/lobectomy plus lymph node dissection, in numbers of patients.

enough to directly palpate with one or two fingers through the ports. Initially, because of the nature of GGOs, we were not sure that we would be able to palpate and localize these lesions. However, we found the GGO-containing lung parenchyma to have a different texture than the surrounding normal parenchyma. When it was impossible to determine the tumor location or periphery through the thoracoscopy ports, the procedure was converted to a small thoracotomy. Segmentectomy and lobectomy were done through a muscle-sparing thoracotomy, typically about 12 cm in length.

During the trial, Noguchi classification assessment took about an hour because of the extensive image recording required for study purposes. There were 2 Noguchi type A tumors, 23 Noguchi type B tumors, 15 Noguchi type C tumors, 5 atypical adenomatous hyperplasias (AAH), 4 fibroses and 1 granuloma. Their size distribution is summarized in Table 1. In addition to the intraoperative slides, further postoperative slides were prepared and studied. The postoperative slides did not differ significantly from the intraoperative slides. One initial frozen-section type B diagnosis was revised to type C after postoperative pathologic study. We discussed this with the patient in detail, and he chose not to have any further treatment. He is still alive without any signs of recurrence after more than 5 years.

No morbidity or mortality has been seen. During the follow-up period, with a range of 19 to 68 months (median 50 months), as this is being written (May 2004), there have been no recurrences. Enrollment concluded without a forced quit.

Discussion

The Lung Cancer Study Group conducted a prospective randomized trial to evaluate the role of limited resection versus lobectomy for T1 N0 M0 non–small cell lung carcinomas. They reported significantly increased local recurrence and marginally but not significantly higher cancer death rates in the limited resection group relative to the lobectomy group. On the basis of their observations, they concluded that lobectomy was the surgical treatment of choice for patients with T1 N0 M0 non–small cell lung carcinomas.[1] However, there has been some question whether limited resection is always contraindicated. We reported a retrospective review of peripheral lung cancers of all types less than 1 cm in diameter in 1998.[5] Of the 16 small tumors, 7 displayed an invasive nature. We therefore concluded that tumor size alone is not a sufficient indicator for limited resection. This observation is consistent with a recent report on subcentimeter lung cancers from the Mayo Clinic.[13] However, in patients with impaired respiratory function, limited resection has been tried and has often yielded acceptable outcomes.[14] Several researchers have reported, although in retrospective studies, that limited resection could be an acceptable alternative in patients with T1 N0 M0 disease and insufficient pulmonary reserve.[3,4]

Noguchi and associates[7] conjectured that type A and type B tumors are in situ carcinomas, whereas type C is an advanced stage of types A and B. If Noguchi type A and B peripheral tumors are truly in situ, noninvasive carcinomas, limited resection would be the management of choice for these tumors. As a result, in August 1998 we started this prospective clinical trial with intraoperative frozen-section examination to establish the Noguchi classification and limited resection for probable in situ adenocarcinoma with GGO characteristics in the lung periphery.

As noted, Shimosato and associates[6] evaluated cancer fibrotic focus or scarring and patient prognosis. Increased lymph node metastasis and pleural and blood vessel invasion were present with greater scarring and fibrotic focus. Aoki and colleagues[15] noted the pleural indentation and vascular convergence increased with tumor development in Noguchi type B and C tumors. This information was incorporated into our patient selection criteria.

A concern in our trial was the accuracy of frozen-section examination. The correct classification as atypical adenomatous hyperplasias or Noguchi type A,[16] or as Noguchi type B or type C tumors,[7] has been reported as being difficult, even more so with frozen sections. We think that the equipment developed for this trial and the methods and techniques applied contributed significantly to our outcomes. Finding the GGO "spongelike" structure could be felt in the lung made locating the lesion and ensuring sufficient resection margin much easier. The customized stapling cartridge and negative-pressure specimen inflation were useful in frozen-section preparation. They made it much easier to work with the specimen. Stereoscopic microscopy enabled the pathologist to locate regions of interest for detailed examination. For Noguchi subtype determination, VvG staining proved to be a powerful aid in separating Noguchi type A and B

from type C. These tools, methods, and techniques, together with the expertise of our pathologist, resulted in high frozen-section examination accuracy: only 1 type B lesion in 50 cases was recategorized as type C postoperatively. This patient underwent only a wedge resection and, after being fully informed of the underdiagnosis, potential outcomes, and additional treatment options, decided not to undergo any further treatment. He is still alive after more than 5 years without recurrence.

The other patients with 14 Noguchi type C tumor, whose diagnoses were confirmed by postoperative pathologic study, underwent lobectomy and systematic lymph node dissection after the frozen-section diagnosis. Detailed pathologic study after the operation revealed no nodal involvement, pulmonary metastases, lymphatic permeation, or vascular invasion in the specimens. It is likely that these patients will survive. Kondo and colleagues[17] studied air-containing lesions 2 cm or smaller, including GGO or subsolid tumors. These lesions were of interest if their opacity area decreased by more than 50% on the mediastinum-setting CT from the lung-setting CT. They reported that this patient cohort survived 5 years without recurrences after either standard or limited resection, and most of them had no node metastases or vessel involvement. So although Noguchi type C tumors are invasive, they may well represent an early invasive stage. On the basis of our finding of no nodal involvement, lymphatic permeation, or vascular invasion, and Kondo and colleagues' similar results and survival rates,[17] we conjecture that Noguchi type C tumors in our trial might well also have been curatively treated by limited resection. However, we did not address this issue in our trial.

During the trial, Noguchi classification assessment took about an hour. This was mostly because we extensively recorded sample images for study purposes. Our pathologist believes that in routine practice, without extensive image recording, the determination can be accomplished in 15 to 20 minutes.

There was no definite difference in size distribution among subtypes. However, all Noguchi type C tumors were 1 cm or larger, whereas other subtypes included subcentimeter tumors. This strengthens the suggestion that limited resection is indicated when a GGO tumor is smaller than 1 cm. Although this contradicts our previous review[5] and a recent report on subcentimeter lung cancers by the Mayo Clinic,[13] that is probably because those series included non-GGO lesions.

In conclusion, Noguchi classification type A and B tumors appear to be in situ, noninvasive carcinomas, and limited resection achieves the goals of local control and survival. With about 5.5 years total on this study, it may be still too early for strong conclusions. Considering the probable slow-growing nature of GGO lesions,[18] 5 years of follow-up is not long enough to conclude that the disease is cured. We will probably have to continue our follow-up for an additional 5 years. However, initial results are encouraging. With the customized stapling cartridges, negative-pressure specimen preparation and inflation, stereoscopic microscopy, VvG staining, and a skilled pathologist, frozen-section classification of Noguchi subtype has been highly accurate. Our results suggest that lung tumors 2 cm or less in diameter with high-resolution CT scan findings of GGO and without evident pleural indentations or vascular convergence may be safely managed with only limited resection.

We thank the International Early Lung Cancer Action Program for presentation opportunities and encouraging us to report our results. We are indebted to Professor Joe B. Putnam, Jr, Chair of the Department of Thoracic Surgery of Vanderbilt University Medical Center, Nashville, Tenn, for his manuscript review. The principal author thanks his friend Mr Brian Curry, communication consultant, for his continuous help in focusing on clarity, conciseness, and comprehension.

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REVIEW ARTICLE

Evolving Concepts in the Pathology and Computed Tomography Imaging of Lung Adenocarcinoma and Bronchioloalveolar Carcinoma

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ABSTRACT

Purpose

To review recent advances in pathology and computed tomography (CT) of lung adenocarcinoma and bronchioloalveolar carcinoma (BAC).

Methods

A pathology/CT review panel of pathologists and radiologists met during a November 2004 International Association for the Study of Lung Cancer/American Society of Clinical Oncology consensus workshop in New York. The purpose was to determine if existing data was sufficient to propose modification of criteria for adenocarcinoma and BAC as newly published in the 2004 WHO Classification of Lung Tumors, and to address the pathologic/radiologic concept of diffuse/multicentric BAC.

Results

Solitary small, peripheral BACs have an excellent prognosis. Most lung adenocarcinomas with a BAC pattern are not pure BAC, but rather adenocarcinoma, mixed subtype with invasive patterns. This applies to tumors presenting with a diffuse/multinodular as well as solitary nodule pattern. The percent of BAC versus invasive components in lung adenocarcinomas appears to be prognostically important. However, a consensus definition of "minimally invasive" BAC with a favorable prognosis could not be achieved. While recognition of a BAC component is possible, the diagnosis of BAC with exclusion of invasive adenocarcinoma cannot be made by small biopsy or cytology specimens.

Conclusion

There is a need to work toward a mutual understanding and consensus between pathologists, clinicians, and researchers with the use of the term BAC versus adenocarcinoma. Future studies should make some attempt to quantitate these components and/or other features such as size of scar, size of invasive component, or pattern of invasion. Hopefully, this work will allow definition of a category of adenocarcinoma, mixed subtype with predominant BAC/minimal invasion and a favorable prognosis.

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INTRODUCTION

We are in the midst of a historic evolution in the study of lung adenocarcinoma, with advances occurring at every level, including pathology, clinical investigation, radiology, molecular biology, and therapy.[1-4] This article reviews the history of the histologic subclassification of lung adenocarcinoma by the WHO and recent developments in our understanding of the computed tomographic (CT) features and pathology of

lung adenocarcinoma. This review also includes the recommendations of a Pathology/Radiology Panel of lung cancer experts developed during a workshop on bronchioloalveolar carcinoma, held November 4 to 6, 2004 in New York City sponsored by the International Association for the Study of Lung Cancer (IASLC) and the American Society of Clinical Oncology. Preparation for this workshop included a meeting of the Pathology Panel held August 20 to 23, 2004 in Washington DC. With the advent of CT screening for lung cancer,[5-10] there has been enormous interest in the CT features and pathology of peripheral lung adenocarcinomas and much has been learned from the correlation of CT images with histology in these tumors. The development of molecular targeted therapies, particularly for epidermal growth factor, has also generated a great deal of interest in correlating the pathology and CT findings of these tumors with molecular and clinical findings.[2-4,11-13]

HISTORY OF LUNG ADENOCARCINOMA HISTOLOGIC SUBCLASSIFICATION BY THE WHO

The evolution in our understanding of the pathology of lung adenocarcinoma is reflected in the substantial changes in histologic subclassification by the WHO from the 1967 to 1981 to the 1999 and 2004 classifications. In the 1967 WHO classification, there were two major subtypes of lung adenocarcinoma (Table 1): Bronchogenic adenocarcinoma and bronchioloalveolar carcinoma (BAC).[14] Bronchogenic adenocarcinoma was then divided into acinar and papillary subtypes. In the 1981 WHO classification, four subtypes of lung adenocarcinoma were recognized including acinar, papillary, BAC and solid carcinoma with mucus formation (Table 1).[15]

However, in the 1999 WHO classification, several major changes were made that were preserved with the 2004 WHO classification (Table 1).[16,17] With the recognition that most lung adenocarcinomas are histologically heterogeneous and consist of more than one subtype, the category of adenocarcinoma with mixed subtypes was added to the four subtypes from the 1981 WHO classification acknowledging that mixed subtype would be the most common histologic type of lung adenocarcinoma.[17] BAC was also modified, formally recognizing three types: nonmucinous (Fig 1), mucinous (Fig 2), and mixed mucinous and nonmucinous. The nonmucinous BACs consist of varying mixtures of type II pneumocytes and Clara cells; however, there is no known clinical significance to determination of these cell types and this is not required to make the diagnosis of BAC.[16,17] The most significant change in the 1999 WHO classification was the requirement that all BACs demonstrate pure lepidic growth without invasion of stroma, blood vessels, or pleura.[16,17] In the previous WHO classifications there was no emphasis on the importance of the amount of BAC component and as a result widely varying histologic criteria were used in publications about this tumor. According to these stricter criteria, most lung adenocarcinomas with a BAC component are now classified as adenocarcinoma, mixed subtype, and the invasive patterns present (acinar, papillary or solid) should be mentioned (Fig 3). The other major change in the 1999 WHO classification was the addition of a group of uncommon variants.

Another major change in the 1999 WHO classification was the addition of atypical adenomatous hyperplasia (AAH) as a preinvasive lesion for lung adenocarcinoma.[16] This was preserved in the 2004 WHO classification.[17] AAH is an atypical bronchioloalveolar proliferation that resembles, but falls short of, criteria for BAC. It consists of a localized proliferation of mild to moderately atypical pneumocytes that usually measure less than 5 mm (Fig 4).[16,17]

In the 2004 WHO classification, the only major change was to move adenocarcinoma, mixed subtype to the top of the list of subtypes, due to its frequency.[17] Importantly, the criteria for BAC were unchanged. A minor change was made to the category of well-differentiated fetal adenocarcinoma, by dropping the "well-differentiated"

Table 1. History of Lung Adenocarcinoma Subclassification According to the WHO

1967[14]	1981[15]	1999[16]	2004[15,17]
Bronchogenic	Acinar adenocarcinoma	Acinar	Adenocarcinoma, mixed subtype
Acinar	Papillary adenocarcinoma	Papillary	Acinar adenocarcinoma
Papillary	Bronchiolo-alveolar carcinoma	Bronchioloalveolar carcinoma	Papillary adenocarcinoma
Bronchioloalveolar	Solid carcinoma with mucus formation	Nonmucinous	Bronchioloalveolar carcinoma
		Mucinous	Nonmucinous
		Mixed mucinous and nonmucinous	Mucinous
		Solid adenocarcinoma with mucin	Mixed nonmucinous and mucinous or indeterminate
		Adenocarcinoma with mixed subtypes	Solid adenocarcinoma with mucin production
		Variants	
		Well-differentiated fetal adenocarcinoma	Fetal adenocarcinoma
		Mucinous (colloid) adenocarcinoma	Mucinous (colloid) adenocarcinoma
		Mucinous cystadenocarcinoma	Mucinous cystadenocarcinoma
		Signet-ring adenocarcinoma	Signet-ring adenocarcinoma
		Clear-cell adenocarcinoma	Clear-cell adenocarcinoma

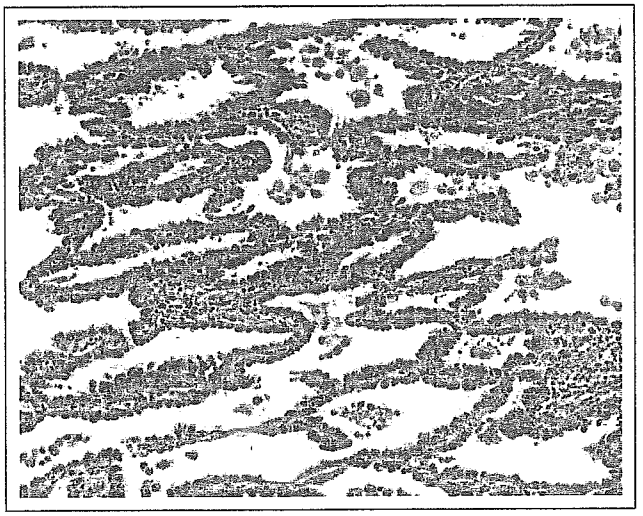

Fig 1. Bronchioloalveolar carcinoma, nonmucinous type. The alveolar walls are lined by a cellular proliferation of atypical pneumocytes that have a hobnail morphology. No invasion is seen.

because it was recognized that there are high-grade fetal adenocarcinomas.

GROSS AND RADIOLOGIC PATTERNS OF BRONCHIOLOALVEOLAR CARCINOMA AND INVASIVE ADENOCARCINOMA

BAC and mixed subtype adenocarcinomas with a BAC component have been recognized to have several gross pathologic and radiologic manifestations in the lung (Table 2). These include: (1) a solitary peripheral nodule (Figs 5-7), (2) multiple nodules (Fig 8), and (3) lobar consolidation (Fig 9).[17-26] When there is a prominent BAC component, the nodules may be ill-defined by gross pathologic exam and mostly ground glass by CT exam (Fig 5).

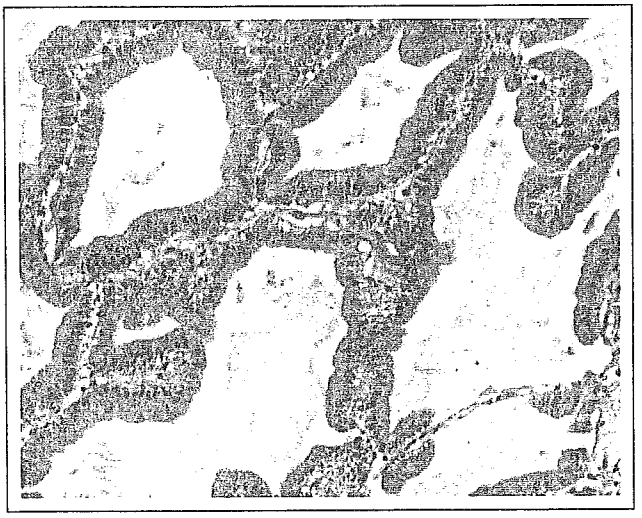

Fig 2. Bronchioloalveolar carcinoma, mucinous type. The alveolar walls are lined by a cellular proliferation of columnar cells with abundant apical mucin and small basally oriented nuclei. No invasion is seen.

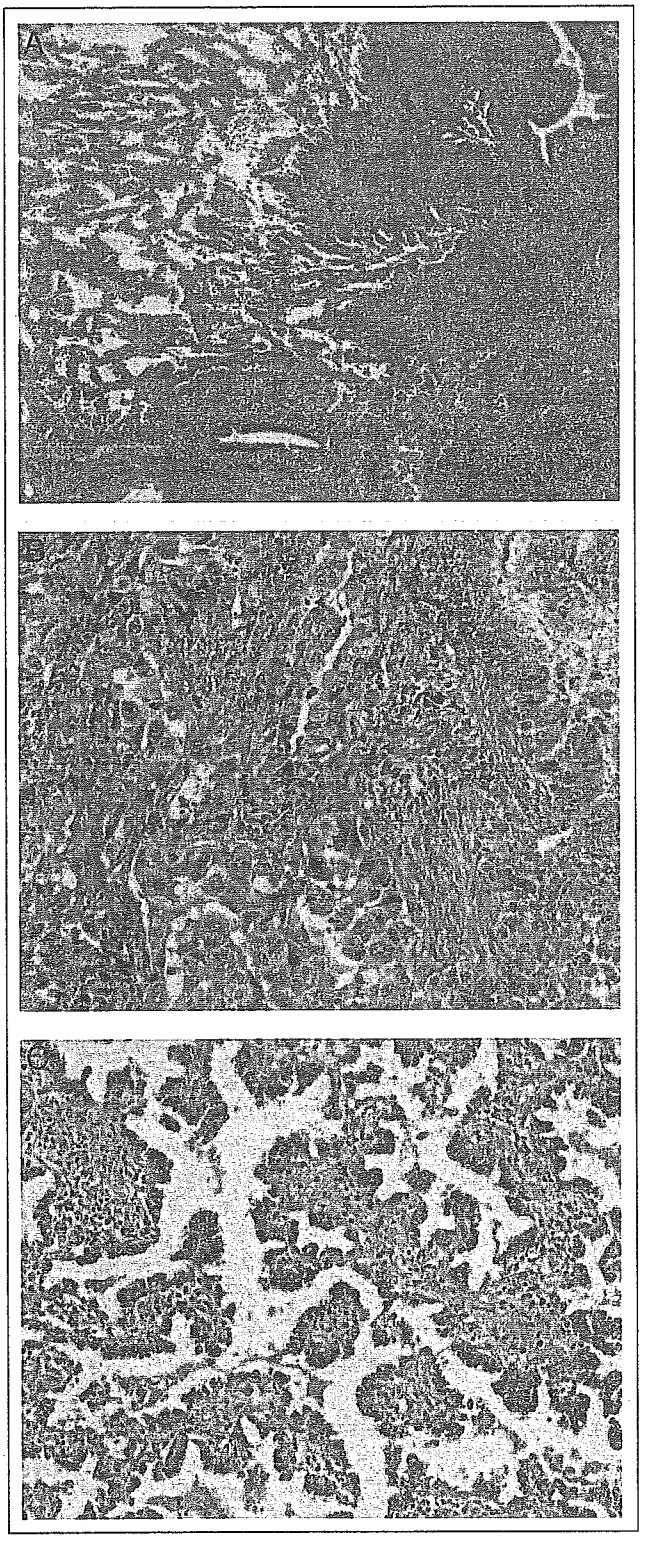

Fig 3. Adenocarcinoma, mixed subtype. (A) A bronchioloalveolar pattern is seen to the left and an invasive component on the right (hematoxylin and eosin X 4). (B) The invasive component consists of acinar glands infiltrating a fibrous stroma (hematoxylin and eosin X 40). (C) Papillary adenocarcinoma is present elsewhere in this tumor. This consists of malignant cuboidal epithelial cells growing along fibrovascular cores in a papillary configuration (hematoxylin and eosin X 10).

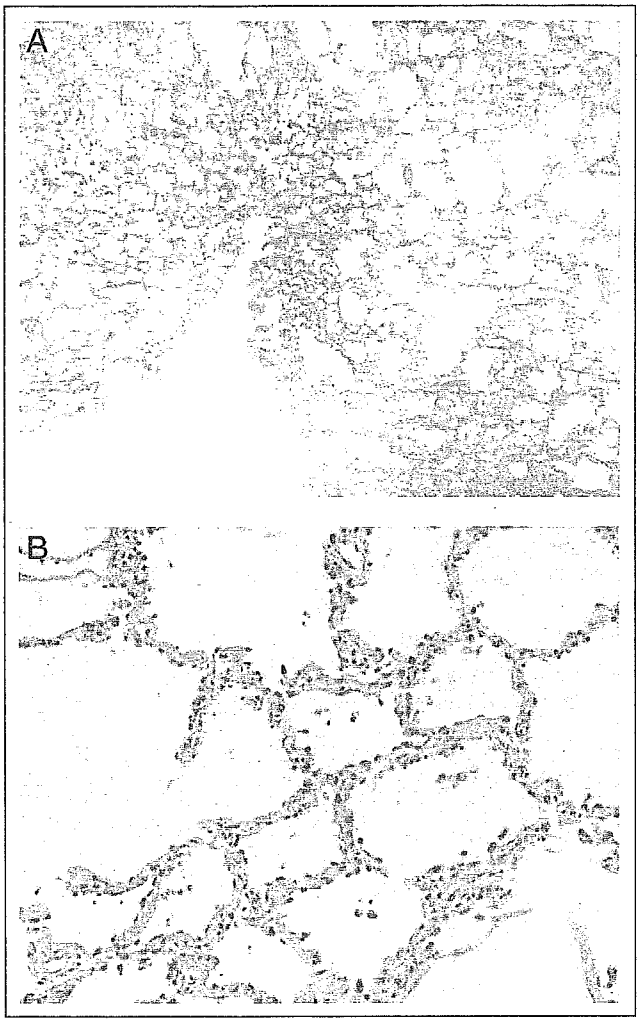

Fig 4. (A) Atypical adenomatous hyperplasia: Two localized nodular areas of atypical adenomatous hyperplasia shows hypercellular alveolar walls (hematoxylin and eosin X 2). (B) The alveolar walls are lined by atypical pneumocytes. There are gaps between the pneumocytes and there is mild thickening of alveolar walls (hematoxylin and eosin X 20).

Adenocarcinomas with an invasive component are more likely to be sharply circumscribed on gross pathologic exam and have a solid appearance by CT (Fig 6). A combination of these gross and CT characteristics may be seen in mixed subtype adenocarcinomas with both BAC and invasive components (Fig 7). When multiple nodules occur, they can be unilateral (Fig 8) or bilateral. They also may consist of a large dominant mass with satellite nodules within the same lobe or multiple nodules in more than one lobe.[17,24,25] The lobar consolidation pattern shows a diffuse parenchymal infiltration that grossly and radiologically is difficult to distinguish from lobar pneumonia (Fig 9).[17,25-27]

Table 2. Bronchioloalveolar Carcinoma: Gross Patterns of Lung Involvement

Solitary nodule
Multiple nodules (unilateral or bilateral)
Dominant nodule with satellites
Multicentric nodules involving one or more lobes
Lobar consolidation

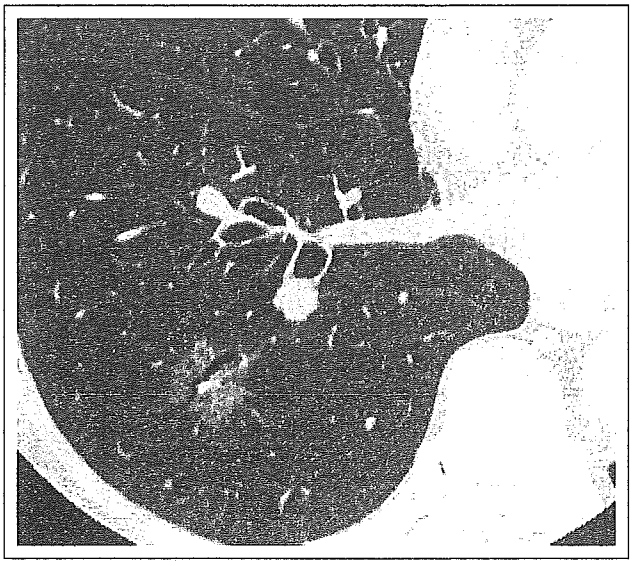

Fig 5. Ground glass density or nonsolid nodule. Chest computed tomography image focused on the right lower lobe shows a 1.5-cm ground-glass density or nonsolid nodule.

Due to significant differences in pathologic, radiologic, and clinical implication among these patterns of presentation by lung adenocarcinoma, the following discussion will be divided into two major categories: (1) solitary, small, peripheral lung adenocarcinomas; and (2) multiple nodules or diffuse consolidation patterns.

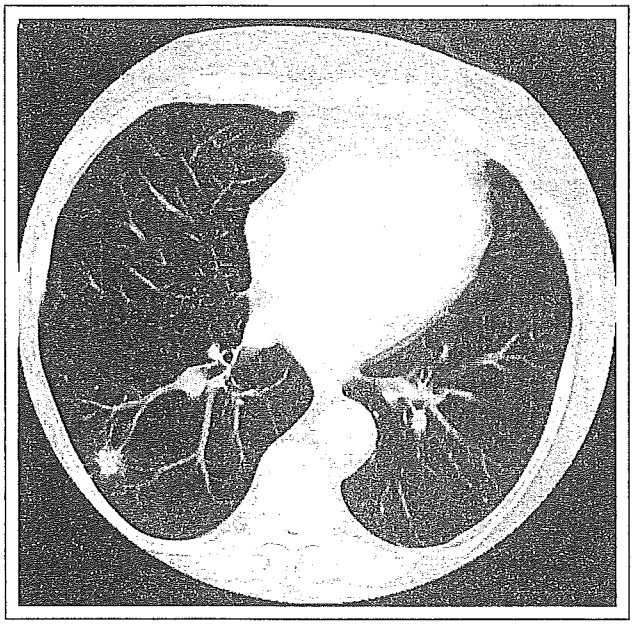

Fig 6. Solid nodule. Chest computed tomography image at the level of right inferior pulmonary vein shows a 1-cm solid nodule with feeding vessels.

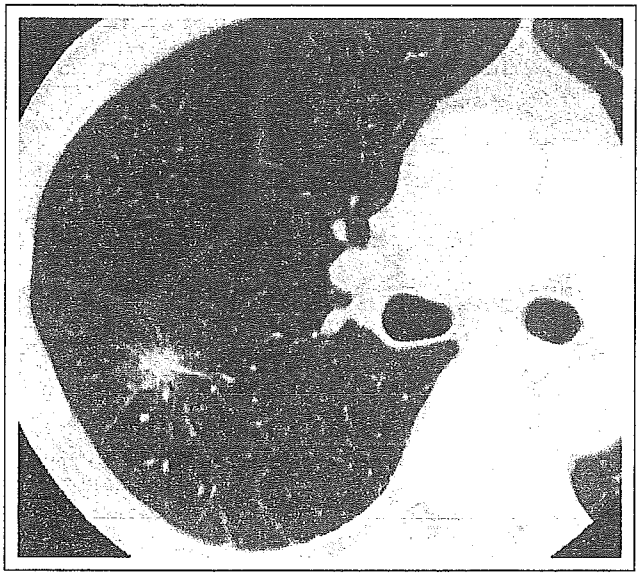

Fig 7. Part-solid nodule. Chest computed tomography image shows a 2-cm spiculated mixed-density nodule with solid central part and nonsolid peripheral portion. The adjacent major fissure is pulled toward the nodule.

Solitary, Small, Peripheral Lung Adenocarcinomas

Pathologic aspects. Over the past 10 years, a series of important articles about solitary, small (2 or 3 cm or less) peripheral nodular lung adenocarcinomas has revolutionized our concept of the pathology of these tumors. This began in 1995 with the work of Noguchi et al,[28] which pointed out that small peripheral lung adenocarcinomas with a pure BAC pattern and no invasion had 100% 5-year survival, and patients with mixed BAC and invasive components had a survival of 75% in contrast to those with a purely invasive growth pattern who had a survival of 52%.[28] These findings greatly influenced the 1999 WHO/IASLC Classification Panel, who proposed a new, stricter definition of BAC that required it to show pure lepidic growth without invasion of stroma, pleura, or

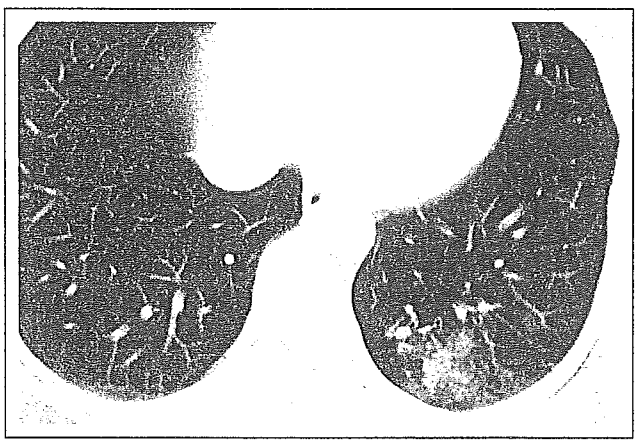

Fig 8. Multicentric bronchioloalveolar carcinoma. Chest computed tomography image shows multiple nodules in the left lower lobe.

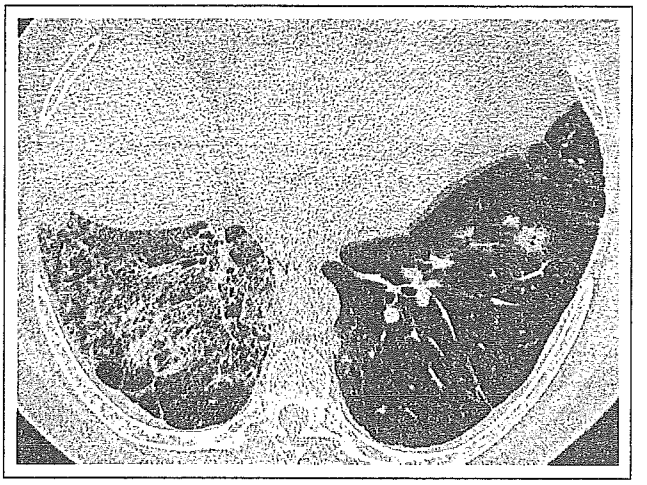

Fig 9. Bilateral multifocal bronchioloalveolar carcinoma with consolidative pattern. Computed tomography image shows large consolidation in the right lower lobe and nodules in the left lower lobe.

blood vessels.[16] The same proposal was also adopted by the 2004 WHO classification.[17] One implication of these criteria is the importance of complete histologic sampling of tumors 3 cm or less in diameter if they have a BAC component, so that focal areas of invasion can be identified.

Subsequently, multiple other reports have examined solitary, small, peripheral lung adenocarcinomas using different approaches to identify histologic prognostic factors.[8,29-31] Each study identified different histologic features to define a subgroup of mixed subtype adenocarcinomas that have a predominant BAC component and a favorable prognosis. These prognostically important histologic features included size of scar (5 mm or greater; greater than 5 mm to 15 mm; and greater than 15 mm),[8,10] percentage of lepidic growth,[10] percentage of papillary growth,[10] vascular invasion,[10] size of invasive area (5 mm or less versus > 5 mm),[30] and pattern of stromal invasion ([1] within area of BAC growth; [2] localized on periphery of scar; [3] into center of scar).[29]

Suzuki et al[8] demonstrated prognostic importance of the size of scar: 5-year survival of 100% if the scar was 5 mm or smaller; 72% if the scar was more than 5 mm and 15 mm or less in size; and 40% if the scar size was larger than 15 mm. Yokose et al[10] found no deaths in 66 patients whose tumors had more than 75% lepidic growth, a central focus of fibrosis 5 mm or less in diameter, and no elastic fiber framework destruction by tumor cells. Multivariate analysis showed that vascular invasion and > 25% papillary growth were unfavorable prognostic factors.[10] The paper by Terasaki et al[30] had no survival data, but reported a more abnormal immunophenotype for the mixed subtype adenocarcinomas that had a BAC component (group 2) compared with tumors consisting of pure BAC (group 1), and they divided the group 2 cases

into those with invasive areas ≥ 5 mm or compared with invasive areas < 5 mm.

Sakurai et al[29] approached the problem by dividing the pattern of stromal invasion into three categories: grade 0, pure BAC with no invasion; grade 1, invasion in the area of BAC growth; grade 2, stromal invasion on the periphery of a fibrotic focus; and grade 3, stromal invasion into the center of a fibrotic focus. These authors found that tumors with grade 1 and 2 invasion had an excellent prognosis similar to pure BACs (grade 0). They proposed that tumors with grade 1 or grade 2 invasion could be regarded as "minimally invasive" or "early" adenocarcinomas.[29] Since the term "grade" is already used for assessing the degree of histologic differentiation, it would be better to refer to these as "patterns" of invasion rather than "grades."

At the November 2004 BAC meeting in New York, a pathology panel was organized, consisting of the IASLC Pathology Panel supplemented by additional experts from several institutions who had a dedicated interest in BAC. This pathology panel evaluated each of these papers and concluded that it was premature at the present time to generate a definition of minimally invasive adenocarcinoma with a predominant BAC component and the current data are insufficient to make a change in the 2004 WHO classification of BAC and adenocarcinoma. Nevertheless, these studies strongly suggest that such a category can be defined and future studies will need to determine the optimal pathologic criteria.

Radiologic aspects. Due to the strong correlation between CT and pathologic features, as well as the numerous radiologic studies on solitary, peripheral, small lung adenocarcinomas, a CT review panel of expert radiologists was assembled to supplement the pathology panel at the New York BAC meeting. While a variety of different terms have been used for the radiologic appearance of adenocarcinoma nodules, the following terms were recognized by the CT Review Panel: (1) ground glass opacity (GGO) or nonsolid; (2) mixed density or mixed-ground glass opacity; and (3) solid. There are many CT studies that have made detailed correlations with pathology, survival, and/or surgical approach. A few of these studies are summarized in the following paragraphs to illustrate some important radiology-pathology correlations. Not all GGOs represent BAC or adenocarcinomas, but criteria for separating benign from malignant solitary pulmonary nodules is addressed in detail elsewhere.[23,32-40]

Prognostic factors by CT have been shown in several studies. Takashima et al[41] found that lesion size of < 15 mm, GGO areas greater than 57%, and BAC histology correlated with a favorable prognosis by univariate analysis; the percentage of GGO areas was the only independent prognostic factor by multivariate analysis. They demonstrated that air bronchograms and histologic grade were of prognostic importance in multivariate analysis of 52 patients with mixed subtype lung adenocarcinomas with a BAC component.[18] Aoki et al[42] found that small peripheral lung adenocarcinomas with more than 50% GGO by thin-section CT had significantly less lymph node metastases or vascular invasion than those with less than 10% GGO. Survival was significantly better for patients with tumors having greater than 50% GGO compared to those with less than 50% GGO.[42] Coarse spiculation and thickening of bronchovascular bundles around the tumors was associated with lymph node metastases or vascular invasion.[42]

Yang et al[43] found that 94% of pure BAC without alveolar wall collapse demonstrated pure GGO by CT, while 71% of BAC with some alveolar wall collapse appeared as heterogeneous, low-attenuation nodules. They also found that 50% of mixed subtype adenocarcinomas with a BAC component were homogeneous nodules with a soft-tissue density and 29% appeared as nodules with ground-glass attenuation in the periphery and a high-density central zone. Among tumors with a BAC component, the size and CT values of mixed subtype adenocarcinomas were larger than those of pure BACs ($P < .05$). Conversely, the percentage of ground-glass attenuation and retained air space in mixed subtype adenocarcinomas was smaller than those in pure BACs ($P < .01$). All tumors that were completely invasive with no BAC component were homogeneous nodules with soft-tissue density.[43]

One of the clinical implications of identifying a pure GGO pattern in a small peripheral lung adenocarcinoma is the potential for limited wedge resection rather than standard lobectomy. This approach has been suggested in the study by Nakamura et al[44] where no intrathoracic recurrence or distant metastases could be found in 27 patients with tumors that showed a pure GGO pattern. Asamura et al[45] also studied 48 lung carcinomas measuring ≤ 1 cm that had three high-resolution CT patterns: nonsolid GGO type (n = 19); part-solid GGO type (n = 9); and solid type (n = 20). They found no recurrences and BAC histologic type for all 28 GGO (nonsolid and part-solid) lesions, a finding they felt supported use of limited resection for GGO lesions.[45] However, not all pure GGO lesions are pure BACs histologically; they can have a component of invasive adenocarcinoma. Nakata et al[46] found mixed subtype adenocarcinomas with invasive adenocarcinoma as well as BAC in 7% of tumors measuring ≤ 1 cm with a pure GGO pattern by CT and in 38.5% of tumors with a similar CT appearance that were between 1 and 2 cm in size. Watanabe et al[47] reported 17 patients with localized BAC showing pure ground glass attenuation who had a pure BAC pattern on pathology and demonstrated no deaths or relapses with a median of 32 months follow-up.

Serial CT studies with follow-up have demonstrated progression of lung adenocarcinomas with GGO components.