あるという判断には，その方法による検診を行って当該疾病による死亡率の有意な減少が認められることを検証しなければならない。結果にいろいろなバイアスが加わっているので，検診発見肺癌群の予後がよいという事実だけでは，その検診方法が妥当であるとは判断できない。症状発見群よりも早くに肺癌を見つけるので，生存期間が延長するように見えるというバイアス（lead-time bias），進行の速い癌よりも緩徐に発育する癌の方が検診で発見されやすく，その後の生存期間も長く見えるというバイアス（length bias），発見された癌は致死的でなく患者の生存に影響しない病変である可能性（overdiagnosis）バイアスなどが問題となる。これらのバイアスの影響を理論的にへらすには，検診群対非検診群の無作為化比較試験によって検診群での肺癌死亡率の有意な減少を証明する必要があるとされている。

Ⅱ．胸部写真による肺癌検診の位置づけ

1970年代後半米国で喫煙歴を有する高危険群に対し胸部写真・喀痰細胞診による大規模無作為化比較試験（Mayo Lung Project など）が複数実施された。どの研究でも検診集団の肺癌死亡率は，非検診群に比較して有意に減少しなかったので，欧米では，公的財源による肺癌集団検診は全く行われていない。2007年の米国における呼吸器疾患診療ガイドラインでも無症状の対象者に胸部写真による肺癌検診を行うことは無意味とされている。日本では，結核検診の胸部写真などを利用した検診が全国的規模で行われ，歴史的に肺癌検診として転用されていた。1987年から老人健康保健法（老健法）にもとづく肺癌検診の体制になった。検診有効性のエビデンスとしては，1990年代に厚生省研究班における複数の症例対照研究で，検診群の肺癌死亡に関するオッズ比は，0.4～0.7と対照群と比べ有意に減少すると報告された。retrospective な研究であるが，本邦の極めて精度の高い肺癌検診グループの成績では，胸部写真および重喫煙者に対する喀痰細胞診による検診が肺癌死亡のリスクを減らしている可能性が検証された。各種がん検診の有効性を体系的文献レビューにより検証した厚生省がん研究助成金「がん検診の有効性評価に関する研究」久道班報告は，肺癌集団検診に関して，従来の方法論の精度では肺癌死亡率の改善には充分でないこと，より精度の高い方法論の導入と有用性を評価しうる研究デザインが必要とされた[2]。1997年から老健法を基盤とした肺癌集団検診の国庫補助は見直しとなり一般財源化されて，肺癌集団検診は各自治体の実施主体性に任された。2002年からは厚労省の健康増進法にもとづく財政補助が肺癌検診にも行われている。しかし全国約1,800市町村のうち40ヵ所（2.2%）では国の指針に従った肺癌検診を実施していない。我が国からの肺癌検診有効性に関する複数の報告も考慮して[3]，米国 Agency of Healthcare Research and Quality（AHRQ）の US Preventive Services Task Force（USPSTF）では，肺癌検診に関する勧告を2004年にグレードDからグレードⅠへ変更した[4]。すなわち，胸部写真および喀痰細胞診による肺癌検診は，「D；無効ないし害が利益を上回る」から「I；現時点ではデータが不十分で勧めることも否定することもできない」という評価に変わった。しかし，2005年の日本の肺癌診療ガイドライン改訂版では，無作為化比較試験の報告が無く，エビデンスが弱いと言うことを理由に，グレードB「勧められる」からグレードC「積極的に勧めるだけの根拠がない」に変わった。無作為化比較試験しか認めない姿勢や欧米データのみに頼る狭隘さは修正すべきである。

現在，癌検診の適正化に関する厚労省研究班の見解（2007年）では，現行の肺癌検診を対策型検診として適切な精度管理下に今後も行うことを勧めている。また，厚労省は癌検診に対して平成21年度に1,300億円の追加予算を計上し，積極的に有効性の証明されている癌検診に関するてこ入れを進めている。

Ⅲ．肺癌集団検診における解決すべき問題（表1）

日本対がん協会などの実績報告からは，住民検診，職域検診などあわせて毎年約300万人の胸部X線検診を行い，人口10万人あたり約70～100人の割合で肺癌を発見している。全国で行われている胸部写真による肺癌検診の標準的な成績と考えられる。ただし公的研究班の結論にもあるように，胸部写真による検診方法では，検診発見肺癌のうちⅠ期の割合は30%以下という状況であり，小型肺癌を効率よく発見する検診方法の開発が必要である。

2006年に国の「がん対策基本法」が成立し，2007年にはこの法律に基づく「がん対策推進計画」が

表 1　肺癌検診を巡る課題と意義そして方策

受診勧奨体制と受診率の向上対策
同一人の経年受診と記録参照の簡便化
精度管理体制
成功体験グループを各地に
要精査機関（追跡調査の協力度）
読影力向上　研修制度・カンファレンス
全国登録データベース
検診方法の研究のための貴重な資料
喫煙　石綿　性差　家族歴ほか
癌検診体制の変革
対策型検診の役割を認識（実施側も市民も）
精度管理の徹底
全国データの集積と解析
妥当な方法論の開発・評価研究の体制整備
リスク群を同定して　効率よい検診モデル
低線量 CT 検診の位置づけ
海外の検診研究の情報
診断環境の激変（Computer-aided diagnosis；CAD）

策定された。その中にはがん検診受診率を50%に引き上げることが詠われている。有効な検診方法であることが証明された癌検診については，全国的に検診受診率を上げることが急務である。日本では乳癌に対するマンモグラフィー検診でも受診率は平均13%とされているが，米国や欧州では，60～80%の受診率となっている。受診率向上のため，欧米では検診対象者データベースを整備して，個人への受診勧奨を効果的に行っている。全国各地域における検診対象者の検診受診率を高める体系的な方策については，相応の財政的な裏付けが必要となる。受診率向上には，メタボ検診のように保険者による検診実績報告の義務化などの方策も考えられるが，癌検診に関する行政機関を見ると，厚労省健康局老人保健課，総務省の市町村癌検診担当部門などにわかれ，縦割り行政の弊害を改善する方策も必要である。

老健法下の集団検診では，設置が義務づけられていた検診団体の活動を監査する精度管理機能（成人病検診精度管理指導協議会）は，少なくとも現状で数都道府県では設置されていない。また要精査とされた受診者の精査受診率も都道府県によってまちまちで，低いところでは10%以下の県もあるとされている。これでは，要精査となった受診者のわずか1割しか精査を受けなかったことになり，やりっ放し検診による質の低下は避けられない。肺癌死亡率の有意な減少を認めた検診は，日本の中で，あくまでも精度の高い検診を行っているところの成果と考えられ，集団検診の質を保証には，日常の精度管理体制が必須である。2007年には，癌検診業務を委託する市町村に対して，厚労省研究班が検診委託事業の仕様書を作成し厚労省から配布されている。この内容を参考に検診業者に検診の質を担保させることも必要である。(http://canscreen.ncc.go.jp/)

Ⅳ．低線量 CT による肺癌検診の可能性[5]

1993年から日本や米国のグループが低線量ヘリカル CT による肺癌検診の試みをはじめた。低線量というのは，電流を20～50mA としたものであり，被爆線量は数 mSV まで低減でき，通常の診断用胸部 CT に比べ一桁は被爆線量が下がることになる。胸部直接写真と比べると約10倍の被曝となっている。現在まで低線量 CT による肺癌検診報告は，パイロット研究の小規模無作為化比較試験以外は対照群をおかない観察研究がほとんどである。受診者の喫煙者割合，男女比，年齢構成など背景因子の異なる集団であるので，発見肺癌率なども報告間での比較は難しい。日本・欧米の複数の報告によると末梢型小型肺腺癌を多数発見すること（胸部写真使用時の数倍），発見肺癌の約7～8割はⅠ期肺癌である。発見肺癌の予後も3～5年生存率で，約80%台の結果が報告されている。対照群をおいていない観察研究なので，結果の解釈には，前述にあるような様々なバイアスを否定できない。米国では，National Lung Screening Trial（NLST）の喫煙者50,000人規模の低線量 CT 対胸部写真3年間計4回のスクリーニングを行う無作為化比較試験が追跡段階に入り，2010年の解析を予定している。また，フランス，イタリア，オランダなどでも低線量 CT 群と，胸部写真ないし非検診の群との無作為化比較試験が進行中である（表2）。

大規模な観察研究としては，日本で，厚生労働省の研究班〔中山富雄班長〕が，大規模コホート研究を実施しており，全国10検診団体で行われている低線量 CT による検診を1回以上受診した人44,000人規模の CT 検診データ，および同じ団体にて胸部写真による検診を受けた84,000人を登録して，法務省の死亡小票閲覧許可を得て転帰の追跡調査が行われている[6]。中間報告の段階では，胸部検診群に比べて，低線量 CT 検診群の男性で4倍，女性で9倍の肺癌が発見されており，over-diagnosis の存在も考えられている。さらに繰り返

表　2　欧州における進行中の無作為化比較試験

Depiscan	仏	40,000名5年間検診 予測発見率0.7% 10年後死亡率50%の減少目標
ITALUNG CT DANTE MILD	伊	3,000名　CT vs 非検診 2,474名　Lung Cancer, 2007. 10,000名
NELSON	蘭	禁煙＋CT vs　非検診 検出力80%で15,428人 10年後死亡率25%の減少目標予定　Int J Cancer, 2006.

表　3　海外の無作為化比較試験の進行と付随研究の報告

NLST（米）	画像データベース	J Digt Imaging, 20; 2007.
	読影医間の診断能	Radiology, 246; 2008.
	肺気腫に関する性差	Chest, 132; 2007.
Depiscan（仏）	ベースライン成績報告	Lung Cancer, 58; 2007.
ITALUNG（伊）	ベースライン成績報告	Lung Cancer, e; 2008.
	肺気腫	Eur J Radiol, e; 2008.
NELSON（蘭）	結節の鑑別診断	Radioloy, e; 2008.
	デザイン被験者数	Int J Cancer, 120; 2007.
	受診者の試験に関する心理	Cancer, 113; 2008.
	受診者の肺癌リスクの認識	Lung Cancer, e; 2008.

し低線量CT検診を受けたグループでは，男性では進行がんの発見率低下が顕著でなく，女性ではstage shiftを伺わせる傾向が見られている。本研究は比較試験ではないが，この集団の年齢調整肺癌死亡率の減少が見られるか否かの解析が行われている。米国のコーネル大学Henshchkeを中心としたInternational-Early Lung Cancer Action Program（I-ELCAP）では，日本なども含めて世界各国の参加検診グループ・参加医療機関からCT検診の画像と臨床とのデータを26,000人分インターネットを介したウェッブ登録により集積した[7]。2005年4月には奈良で，日本肺癌学会集団検診委員会との共催による第13回国際会議が開かれた（Eguchi JTO 2006）。これらの検討を通して，Henschkeらは，年齢や喫煙歴別に，個人の肺癌リスクモデルの構築，個人救命率のシミュレーションを作成して，個人検診の際の受診者向けの判断資料とした。また，検診発見肺癌の自然史，画像と予後との相関などの研究を報告している。

V．今後の検診体制とその意義に関する考察

低線量CTによる肺癌検診は，経費，被曝線量などの課題があるが，一方では，多検出器CTなどCT機器の急速な進歩，Computer-aided diagnosis（CAD）ソフトウェアなど診断環境の発展などによって，急速にそのシステムが進歩しつつあり，旧来のCT機器による読影診断のみの無作為化比較試験の結果がどこまでの意義を保つかは疑問視する意見もある。子宮癌検診，胃癌検診などの歴史を見ると，治療方法に関する大規模な無作為化比較試験のようなエビデンス基準は，癌検診の場合に必ずしも当てはまらないことがありうる。日本では，2009年に，NPO肺がんCT検診認定機構が日本CT検診学会（http://www.jscts.org/jp/）などを中心に設立された。関連諸学会と連携して，検診担当医師・放射線技師による低線量CT検診認定医およびCT検診スクリーナー制度を発足させた。スクリーナー技師および読影医の技能を向上維持させるための講習会やe-learning programが具体化している。

欧米の肺癌検診無作為化比較試験では，低線量CTと自動診断支援ツール（CAD）の応用開発，受診者の心理分析，肺気腫などの非癌疾患など副次的な研究も進んでおり，生体の重要臓器に関する診断能を高め，癌や生活習慣病の検診に応用する可能性が提示されつつある。多検出器CTや情報機器の急激な進歩は，これらの自動診断支援ツールの開発に拍車をかけるものとなっている（表3）。

表 4　非喫煙者肺癌の遺伝子的特性

	非喫煙者肺癌	喫煙者肺癌
#16p gain	59%	＜5%
KRAS 変異	0～7%	30～43%
EGFR 変異	45%	7%
P53 変異 G-T/G-A 比	0.23	1.5
メチル化指数	low	high
P16, *APC* メチル化	less common	common
hMSH2 蛋白発現欠失	40%	10%

Subramanian & Govindan, Lancet Oncol, 2008.

肺癌治療の分野では，東洋人・非喫煙者などに高率に見られる EGF 受容体遺伝子変異と喫煙肺癌に見られる p53，k-ras などの遺伝子変異など分子生物学的な肺癌の多様性が少しずつ個別化治療に応用されつつある（表4）。分子マーカーを用いた新たな高危険群の同定が可能となると，リスクに応じた検診間隔や方法論が適切に細分化されると考えられる。背景因子の分析まで可能な Population-based screening の大規模なデータと，生物学的な検討結果が結びつくと，肺癌の原因解明の突破口となる可能性がある。さらに画像だけでなく，血漿 DNA による肺癌リスクの検討なども研究対象となっている。今後の肺癌検診は，すべての対象者を一律の間隔で検診するのではなく，リスク群ごとに，有効性の証明された方法で効率的に検診することを目標として，肺癌検診モデルを構築すべきである。また併行して受診率，精検受診率の向上，精査機関の基準設定，検診精度の監査など実効のあがる地域的肺癌検診体制を確立することが必要である。

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Recommendations for Uniform Definitions of Surgical Techniques for Malignant Pleural Mesothelioma

A Consensus Report of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group

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Introduction: Extrapleural pneumonectomy has been well defined; however, surgeons vary regarding the surgical extent and goals of "pleurectomy/decortication" (P/D). We explored mesothelioma surgeons' concepts of P/D with the aim of unifying surgical nomenclature.

Methods: A web-based survey was administered to surgeons who operated on malignant pleural mesothelioma (MPM) for diagnosis, staging, palliation, or cytoreduction. One hundred thirty surgeons from 59 medical centers were included. Surgeons who did not perform surgery for MPM within the last year were excluded.

Results: There were 62 (48%) respondents from 39 medical centers in 14 countries. The mean number of patients with MPM seen annually at each medical center was 46, and the mean annual number of cytoreductive procedures performed per surgeon was 8. Most (88%) agreed that the goal of cytoreductive surgery should be macroscopic complete resection of tumor. P/D was defined as resection of parietal and visceral pleura with the aim of achieving macroscopic complete resection by 72% of respondents. If the diaphragm or pericardium required resection, 64% preferred the term "radical P/D," whereas "P/D" (40%) or "total pleurectomy" (39%) was preferred if these structures were not removed. Most surgeons believed that extrapleural pneumonectomy (90%) or "radical P/D" (68%) could provide adequate cytoreduction, whereas only 23% thought that P/D could.

Conclusions: There was significant variation regarding surgical nomenclature for procedures for MPM. The International Staging Committee of the International Association for the Study of Lung Cancer and the International Mesothelioma Interest Group recommend that P/D should aim to remove all macroscopic tumor involving the parietal and visceral pleura and should be termed "extended" P/D when the diaphragm or pericardium is resected.

Key Words: Mesothelioma, Pleural neoplasm, nomenclature, Surgery.

(*J Thorac Oncol.* 2011;6: 1304–1312)

Surgery for malignant pleural mesothelioma (MPM) may include relatively minor procedures for diagnosis and staging, more involved debulking operations for palliation, and extensive cytoreductive procedures where the goal is to lengthen survival by reducing the intrathoracic tumor burden to microscopic levels. The latter is usually accomplished either by extrapleural pneumonectomy (EPP) or by a procedure that is presently classified as "pleurectomy/decortication" (P/D), generally as part of a multimodality treatment regimen. Although the surgical technique of EPP has been standardized, there is a variation among surgeons with respect to what is involved in P/D.[1–5] For some mesothelioma surgeons, P/D refers to a surgical procedure that aims to remove all macroscopic tumor from the affected hemithorax.[6] This typically includes resection of the entire parietal and

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Disclosure: The authors declare no conflicts of interest.

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visceral pleura, with resection of portions of the pericardium and diaphragm if involved by tumor. Others refer to this extensive procedure as a "radical" P/D, reserving the term P/D for resection of only the parietal and visceral pleura.[7,8] Still others use the term P/D to describe a palliative procedure where the intention is debulking of tumor to ameliorate pain and pleural effusion and improve respiratory mechanics.[9] Occasionally, operative reports will describe P/D when little more than a thoracotomy and generous pleural biopsy has been performed.

In collaboration with the International Mesothelioma Interest Group (IMIG), the International Association for the Study of Lung Cancer (IASLC) recently formed a subcommittee of the International Staging Committee to improve the current staging system for MPM. The mesothelioma subcommittee "Mesothelioma Domain" of the International Staging Committee recently completed an analysis of a large retrospective database and is now developing an international, multidisciplinary, and multi-institutional cohort study that will collect information on extent of disease, personal and demographic characteristics, comorbid illness, treatment, and survival of newly diagnosed patients with MPM. Because there is considerable variation regarding the surgical management of mesothelioma, and in particular P/D, the mesothelioma subcommittee thought that it was important to arrive at definitions of surgical procedures for MPM that would be unambiguous and broadly acceptable to most thoracic surgeons. To arrive at a consensus regarding surgical definitions, a survey was conducted among surgeons who perform surgery for MPM.

METHODS

A web-based questionnaire was created by members of the IASLC mesothelioma subcommittee using a commercially available, online survey designer (www.surveymonkey.com). Unlike a recent survey of surgical opinion in mesothelioma, which included thoracic surgeons regardless of their level of experience with the disease, we polled only surgeons who had a clinical or research interest in MPM and who were presumed able to offer expert opinion.[10,11] Surgeons were identified by having published on MPM during the past 5 years, by affiliation with a medical center known to specialize in MPM, by affiliation with the IMIG, or by peer reference. One hundred thirty surgeons from 59 centers worldwide were identified and asked to complete the electronic survey. The survey was designed to examine prevailing views about nomenclature for various surgical resections commonly performed for pleural mesothelioma and concepts regarding cytoreduction (Figures. 1–4). In addition to multiple-choice options, most questions also offered respondents an opportunity to add text-based comments. We explored opinions regarding use of the terms "partial pleurectomy," "pleurectomy/decortication," "total pleurectomy," and "radical pleurectomy/decortication." Because EPP has been standardized from a procedural standpoint, we did not further explore terminology for this operation. The survey collected data over a 3-week period from October 11 through October 29, 2010. Two reminders were sent electronically to participants during this period. Responses from thoracic surgeons who did not perform any type of surgery for MPM (including either surgery for diagnosis, staging, palliation, and/or cytoreduction) were censored from further analysis. Responses were analyzed according to the raw data, and results were reviewed with the members of the IASLC Mesothelioma Domain and the Advisory Board, and consensus achieved before the manuscript was prepared. It was then submitted to all members of the IASLC Staging Committee and to board members of the IMIG for approval before the manuscript and recommendations were finalized.

RESULTS

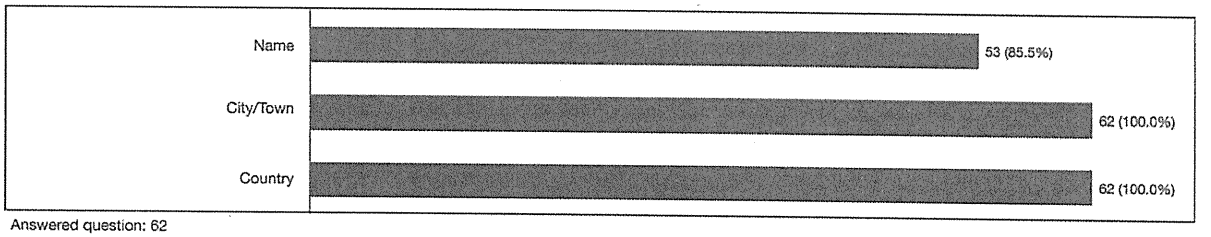
Respondents

The survey was sent through email to 130 thoracic surgeons, of which 62 (47.7%) responded. Respondents were affiliated with 39 different medical centers in 14 countries. Most were from centers in Europe (47%) or North America (42%) with only six (10%) responders from Asia and one from Australia (Table 1). Three participants did not perform any type of surgery for MPM and were censored from further analysis (Figure 1). One respondent provided incomplete data leaving a total of 58 respondents who provided analyzable data. The mean number of patients with MPM seen annually at participating centers was 40 (median, 32; range, 3–150), and the mean number of mesothelioma surgical cases annually performed by respondents ($n = 58$) was 20 (median, 16; range, 2–80). Ninety-eight percent of surgeons performed surgery for diagnosis, 82% for surgical staging, 85% performed cytoreductive surgery, and 71% performed surgery for palliation. Only 34 of 58 surgeons (59%) performed surgery for all four indications. Three (5%) surgeons performed palliative surgery but not cytoreductive surgery. Of surgeons who practiced cytoreductive surgery ($n = 49$), the mean number of cases performed within the 12-month period preceding the survey was 10.4 (range, 1–30).

Surgical Definitions

Most respondents (95%) felt that there was a need to refine surgical nomenclature to account for the procedural differences between P/D for palliation and P/D performed for macroscopic complete resection (MCR) or maximal cytoreduction (Figure 2). Thirty-nine of 58 (67%) respondents defined "partial pleurectomy" as a partial debulking of tumor for palliative purposes. Of these, 21 (36%) considered it to include resection of both parietal and visceral tumor, whereas the others considered it to include removal of only parietal tumor. Ten (17%) surgeons considered "partial pleurectomy" to be a subtotal removal of parietal and visceral tumor for palliation with the expectation of leaving gross residual disease behind, and another four (7%) defined the procedure as the removal of all gross parietal and visceral tumor with the intention of achieving an R0 or R1 resection without removal of the diaphragm or pericardium. Only three (5%) respondents felt that it should be defined as resection of parietal pleura for diagnostic purposes only. Forty-two of 58 (72%) respondents considered the term "P/D" to imply resection of all gross parietal and visceral tumor with the objective of achieving resection of all macroscopic disease. Of these, 18 (31%) considered the procedure to also include resection of the diaphragm and/or pericardium even if in-

Question 1. Please enter your name (optional), city and country:



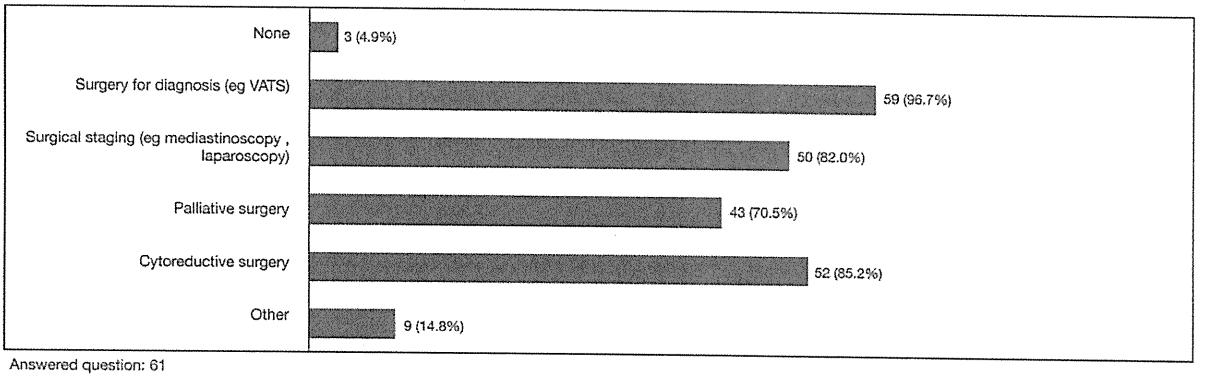
Answered question: 62
Skipped question: 0

Question 2. How many patients with malignant pleural mesothelioma were registered at your institution in the last 12 months?

Answer Options	Response Average	Response Total	Response Count
Number	40.4	2,381	60

Answered question: 62
Skipped question: 0

Question 3. I currently perform the following types of surgery for mesothelioma (answer all that apply):



Answered question: 61
Skipped question: 1

Question 4. How many patients with malignant pleural mesothelioma did you perform surgery on in the last 12 months (for diagnosis, staging, palliation or cytoreduction?

Answer Options	Response Average	Response Total	Response Count
Number	20.0	1,158	58

Answered question: 58
Skipped question: 4

Question 5. How many patients with malignant pleural mesothelioma did you perform cytoreductive surgery on in the last 12 months?

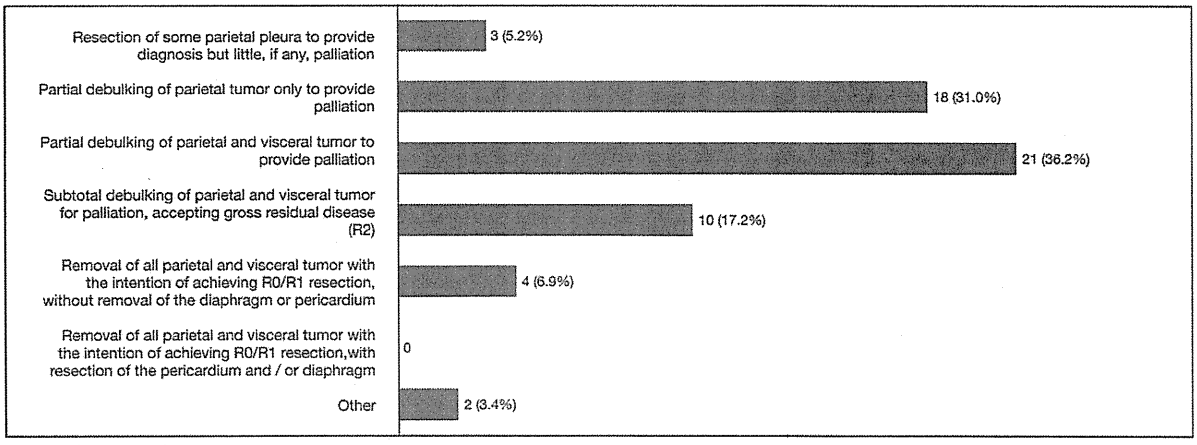
Answer Options	Response Average	Response Total	Response Count
Number	8.8	512	58

Answered question: 58
Skipped question: 0

FIGURE 1. Questions 1 to 5. Demographic and practice information of the respondents.

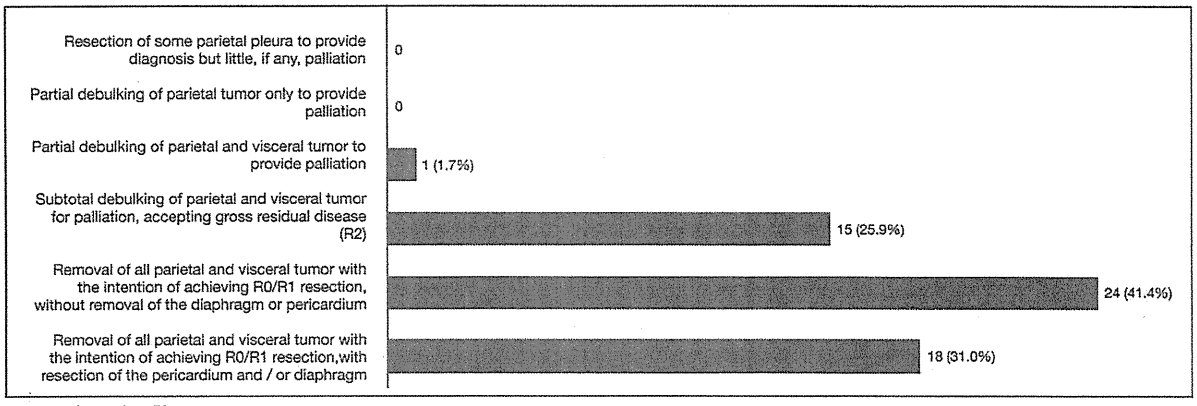
volved by tumor. Nevertheless, 15 (26%) surgeons considered "P/D" to be a subtotal removal of parietal and visceral tumor for palliation with the expectation of leaving gross residual disease behind (R2), and one (2%) respondent defined the procedure as a partial debulking of parietal and visceral tumor for palliation.

Question 6. In your opinion which of the following procedures would describe a 'partial pleurectomy' the best?



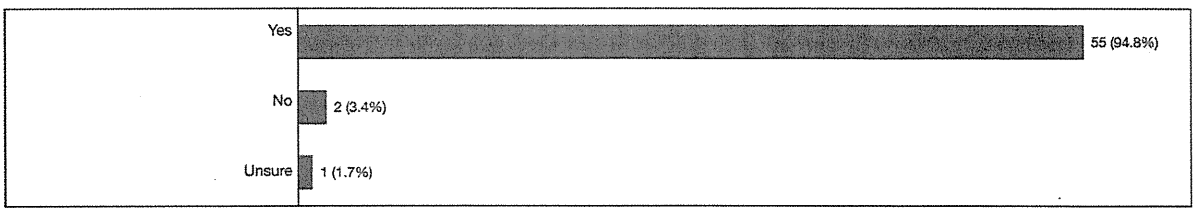
Answered question: 58
Skipped question: 0

Question 7. In your opinion which of the following procedures would describe a 'pleurectomy / decortication' the best?



Answered question: 58
Skipped question: 0

Question 8. Do you think there is a need to develop terminology that would differentiate between the extent of resection associated with pleurectomy/decortication for palliation versus complete macroscopic resection (cytoreduction)?

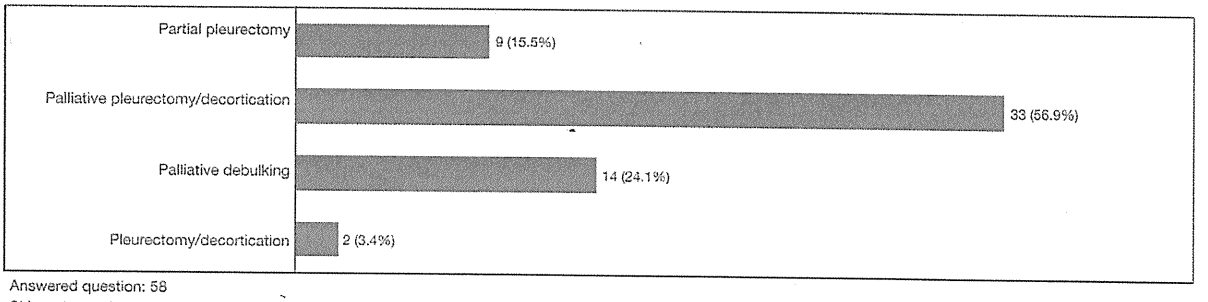


Answered question: 58
Skipped question: 0

FIGURE 2. Questions 6 to 8. Opinions regarding definition of partial pleurectomy and pleurectomy/decortication.

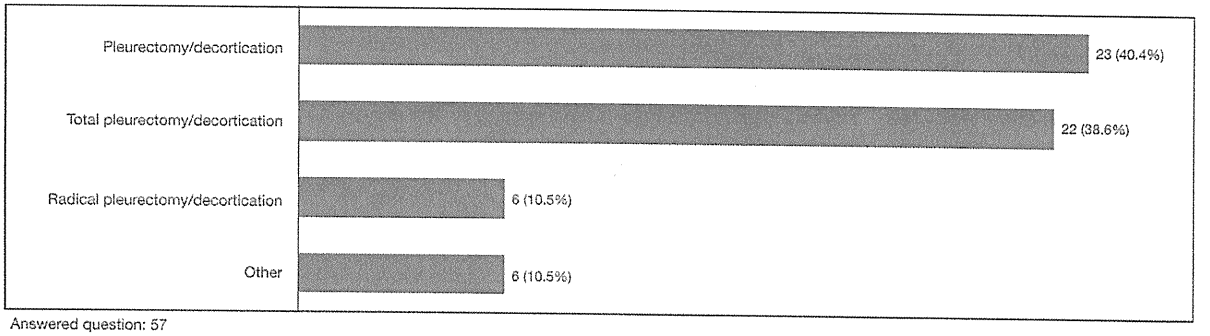
To further explore opinions regarding the extent of "P/D," two scenarios were provided where the intent was to resect parietal and visceral tumor so that no residual macroscopic tumor remained (Figure 3). In one scenario, the diaphragm and pericardium were resected, and in the other scenario they were not. With regard to the first (diaphragm and/or pericardial resection), the majority (64%) referred to the procedure as "radical P/D." Eleven (19%) surgeons preferred the term "total pleurectomy" and only three (5%) used "P/D." One surgeon considered this a "partial resection." To describe the second scenario (no diaphragm or pericardial resection), 23 (40%) chose the term "P/D," whereas 22 (39%) preferred "total pleurectomy." Only six (10.5%) surgeons called this procedure a

Question 9. In a patient who undergoes parietal and visceral pleural resection for palliative purposes only, without the intention of achieving complete macroscopic resection, which of the following terms do you think is most appropriate?



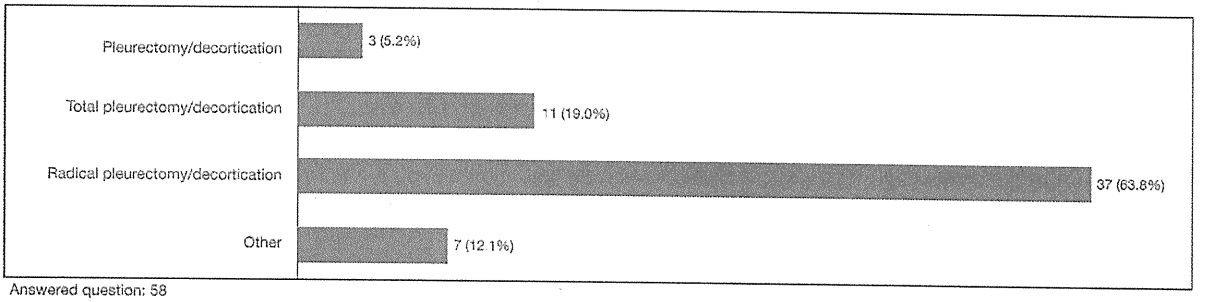
Answered question: 58
Skipped question: 0

Question 10. In a patient who undergoes parietal and visceral pleural resection (but not resection of the pericardium or diaphragm) with the intention of achieving macroscopic complete resection which of the following terms do you think is most appropriate?



Answered question: 57
Skipped question: 1

Question 11. In a patient who undergoes parietal and visceral pleural resection with the intention of achieving a macroscopic complete resection and the diaphragm and/or the pericardium is resected, which of the terms do you feel is most appropriate to use?



Answered question: 58
Skipped question: 0

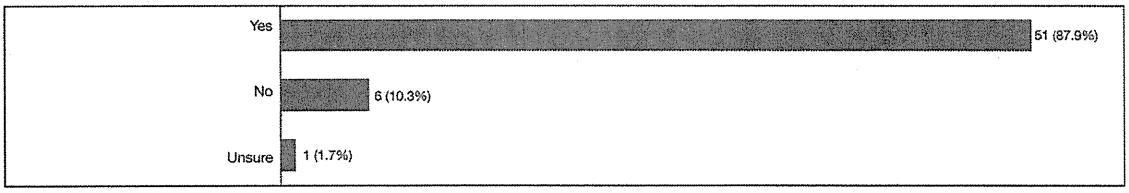
FIGURE 3. Questions 9 to 11. Opinions regarding the surgical extent of pleurectomy/decortication.

"radical P/D." Two (3.4%) respondents used the term "palliative debulking" and another two (3.4%) used "partial pleurectomy." One (1.7%) respondent preferred the term "subtotal P/D."

Cytoreduction

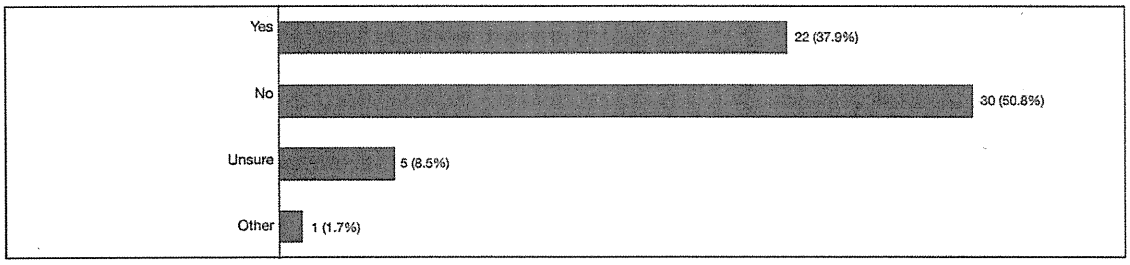
Fifty-one (88%) respondents agreed with the premise that the goal of cytoreductive surgery in MPM should be the removal of all visible or palpable tumor (R0 or R1) or a "macroscopic complete resection" (MCR) (Figure 4). When asked which cytoreductive procedure was capable of providing MCR, 51 (90%) chose EPP and 39 (68%) "radical P/D," but only 13 (23%) thought that "P/D" could. One of the factors that influence performance of P/D versus EPP is whether tumor involves the fissures. Twenty-two (38%) respondents agreed that P/D could usually provide a MCR if tumor involved the fissure, however, 30 (51%) did not. In addition, the majority of respondents (86%) did not believe that video-assisted thoracoscopic surgery was capable of providing as complete a cytoreduction as an open procedure. Nevertheless, three (5%) respondents did, and another agreed that it could in patients with stage I disease. The remaining four respondents were uncertain.

Question 12. The goal of cytoreductive surgery for malignant pleural mesothelioma should be the removal of all visual and palpable tumor, in other words, a macroscopic complete resection (R0/R1):



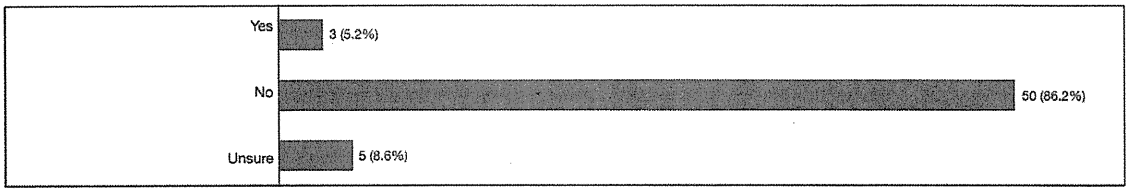
Answered question: 58
Skipped question: 0

Question 13. In a patient with tumor involving the fissure(s) pleurectomy / decortication can usually achieve macroscopic complete resection:



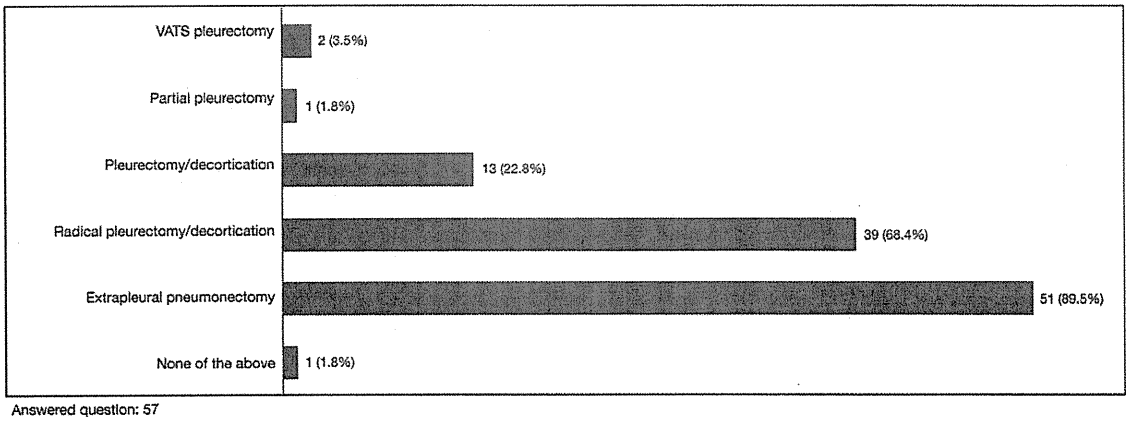
Answered question: 58
Skipped question: 0

Question 14. VATS pleurectomy / decortication can usually achieve as as good a tumor cytoreduction as open pleurectomy / decortication:



Answered question: 58
Skipped question: 0

Question 15. Which of the following procedures do you consider capable of providing adequate cytoreduction (R0/R1)?



Answered question: 57
Skipped question: 1

FIGURE 4. Questions 12 to 15. Opinions regarding surgical goals and technical ability to achieve macroscopic complete resection.

TABLE 1. Geographic Distribution of Physicians Who Responded to the Online Survey

Country	No. of Responses	Percentage
United States	23	37.1
United Kingdom	10	16.1
Japan	6	9.7
Italy	5	8.1
Spain	3	4.8
Canada	3	4.8
Turkey	2	3.2
Switzerland	2	3.2
Germany	2	3.2
Belgium	2	3.2
Greece	1	1.6
Australia	1	1.6
Netherlands	1	1.6
France	1	1.6

DISCUSSION

The first description of P/D is attributed to Fowler[12] who reported the successful treatment of a man with chronic empyema and bronchopleural fistula in 1893. Nevertheless, it was not until 20 years later when four patients successfully underwent P/D at the Mayo Clinic that the procedure began to gain popularity and gradually superceded thoracoplasty as the preferred method for the initial treatment for chronic empyema and trapped lung.[13] It is worth noting that "decortication" involved freeing of the fibrinous rind away from the visceral pleura and not resection of the visceral pleura itself. In the 1950s and 1960s, parietal pleurectomy was used for the treatment of spontaneous pneumothorax,[14,15] and in 1963, Jensik et al.[16] at the University of Chicago reported the use of parietal pleurectomy for treatment of malignant pleural effusions, showing a 96% freedom from recurrence in 50 patients. As meticulously described by Beattie,[17] parietal pleurectomy began with creation of an extrapleural plane before insertion of a rib spreader, with continued dissection "up over the apex of the thoracic cavity, and down to and around the lung hilum." Once the upper half of the parietal pleura had been freed, it was excised, and the lower half then dissected down to the costophrenic sulcus. It was noted that it was usually impossible to remove the diaphragmatic pleura which was left attached to the intact diaphragm.

The first report of pleural resection for MPM was by Martini et al.[18] in 1975 who described outcomes of parietal pleurectomy in 83 patients with malignant pleural effusions, of which 14 had mesothelioma. At 1 year, 79% of patients were noted to have been alive, with little or no clinical limitation in pulmonary reserve, and the median survival of those with MPM was 16 months. A year later, this series was expanded to include 33 patients with MPM who had a median survival of 21 months. It should be noted that in these early descriptions of pleurectomy for mesothelioma "all pleura covering the rib cage and mediastinum (was) removed," but attempts were not made to remove the visceral pleura or resection of the diaphragm or pericardium.[19] The operation became referred to as "subtotal parietal pleurectomy" as neither the visceral, diaphragmatic nor pericardial pleurae were removed.[20]

Coincidentally, EPP (also termed pleuropneumonectomy) for MPM began to be performed, its proponents arguing that pleurectomy could not possibly achieve the same degree of tumor clearance as EPP, largely because with pleurectomy tumor frequently remained on the diaphragm, pericardium, and the visceral surfaces and fissures of the lung.[21,22] Perhaps in response to this challenge, pleurectomy evolved in some surgeons' hands into a more extensive procedure than had been described previously. In 1989, Rusch and Livingston[23,24] described "radical decortication" in conjunction with intrapleural chemotherapy and, in the article that followed, P/D was defined as parietal pleurectomy with either partial or complete visceral pleurectomy according to the extent of tumor involvement. The diaphragm and/or pericardium were frequently resected and reconstructed but with preservation of the underlying peritoneum. Variations on this theme have been reported by others, the common thread being resection of tumor involved parietal and visceral pleurae.[25] In one of the larger and more recent series, Richards et al.[4] from the Brigham and Women's Hospital described P/D as resection of the parietal and visceral pleurae along with involved areas of the pericardium and diaphragm. As described by others, the intended goal was to obtain a MCR, arbitrarily defined as tumor residual less than 1.0 cm.[3,5,26] The clear intent of these cytoreductive procedures is to resect all gross tumor while preserving underlying lung parenchyma. This has not gained unanimous acceptance however. For example, Butchart[9] has referred to P/D as "debulking" surgery which did not include resection of the diaphragm. The term P/D is still frequently applied to procedures that remove some parietal and visceral pleural tumor and yet which are strictly palliative in intent leaving behind considerable amounts of gross tumor. Perhaps, this is why in an effort to differentiate the more intensive cytoreductive procedure from less extensive ones several authors have recently applied the qualifier "radical" when referring to a maximally cytoreductive P/D.[7,8] Thus, 35 years after the initial description, there remains some ambiguity regarding the definition of P/D for MPM.

The overall response rate to our survey was less than 50% but is on a par with response rates of other recent web-based surgical surveys. The thoracic surgeons who completed the survey were experienced in MPM surgery—performing what would be considered a high volume of operations for this rare disease. Respondents were primarily from North America and Europe, so it can be argued that the findings may be biased toward Western practice, but this primarily reflects the incidence of MPM and the geographic location of centers involved in surgical and multimodality treatment for MPM. The survey confirmed significant variation among thoracic surgeons regarding the definition of P/D. When pleural resection was performed for palliative purposes, most respondents did not refer to the procedure as "P/D" but rather used terms such as partial pleurectomy, palliative debulking, or palliative P/D. Thus, based on the

findings of the survey, P/D seems to imply a level of completeness or thoroughness of tumor resection that did not apply to debulking or palliative procedures. Nevertheless, when the diaphragm or pericardium had to be resected to achieve MCR, most surgeons (64%) favored the term "radical" P/D.

Finally, we explored the opinion regarding completeness of resection achievable with surgery for mesothelioma. The majority of surgeons polled believed that MCR should be the goal of cytoreductive surgery, regardless of whether that involves EPP or a lung-preserving operation. This is certainly in line with the current surgical philosophy of high-volume centers.[3,5,26] Furthermore, most agreed that either "radical P/D" or EPP could provide MCR in appropriately selected patients, but most responders did not consider that P/D (without diaphragm or pericardial resection) could do so. Nevertheless, this clearly depends on the extent of the disease.

RECOMMENDATION

On the basis of the survey data, which represented the opinions of experienced MPM surgeons from multiple centers in different geographical regions, the IASLC Mesothelioma Domain and the IMIG have recommended the following terminology to be used in the forthcoming Mesothelioma Staging Project:

a. EPP: en bloc resection of the parietal and visceral pleura with the ipsilateral lung, pericardium, and diaphragm. In cases where the pericardium and/or diaphragm are not involved by tumor, these structures may be left intact.
b. Extended P/D: parietal and visceral pleurectomy to remove all gross tumor with resection of the diaphragm and/or pericardium. The IASLC Mesothelioma Domain suggests use of the term "extended" rather than "radical" in this instance as the latter implies a completeness of resection with added therapeutic benefit. There is currently insufficient evidence that resection of the pericardium and diaphragm provides either.
c. P/D: parietal and visceral pleurectomy to remove all gross tumor without diaphragm or pericardial resection.
d. Partial pleurectomy: partial removal of parietal and/or visceral pleura for diagnostic or palliative purposes but leaving gross tumor behind.

APPENDIX A: IASLC INTERNATIONAL STAGING COMMITTEE

Peter Goldstraw, Past Chair, Royal Brompton Hospital and Imperial College, London, United Kingdom; Ramón Rami-Porta, Chair, Hospital Universitari Mutua Terrassa, Terrassa, Spain; Hisao Asamura, Chair Elect, National Cancer Center, Tokyo, Japan; David Ball, Peter MacCallum Cancer Institute, Melbourne, Australia; David Beer, University of Michigan, Ann Arbor, Michigan; Elisabeth Brambilla, Centre Hospitalier Universitaire Albert Michallon, Grenoble, France; Vanessa Bolejack, Cancer Research and Biostatistics, Seattle, Washington; Paul Bunn, Ex Office, University of Colorado Cancer Center, Aurora, Colorado; Kari Chansky, Cancer Research and Biostatistics, Seattle, Washington; John Crowley, Cancer Research and Biostatistics, Seattle, Washington; Frank Detterbeck, Yale University, New Haven, Connecticut; Wilfried Eberhardt, University of Essen, Essen, Germany; John Edwards, Northern General Hospital, Sheffield, United Kingdom; Françoise Galateau-Sallé, Centre Hospitalier Universitaire, Caen, France; David Gandara, Ex Office, University of California Davis Cancer Center, Sacramento, California; Dorothy Giroux, Cancer Research and Biostatistics, Seattle, Washington; Fergus Gleeson, Churchil Hospital, Oxford, United Kingdom; Patti Groome, Queen's Cancer Research Institute, Kingston, Ontario, Canada; James Huang, Memorial Sloan-Kettering Cancer Center, New York City, New York; James Jett, Ex Office, National Jewish Health, Denver, Colorado; Catherine Kennedy, University of Sydney, Sydney, Australia; Jhingook Kim, Samsung Medical Center, Seoul, Korea; Haruhiko Kondo, Shizuoka Cancer Center, Shizuoka, Japan; Mark Krasnik, Gentofte Hospital, Copenhagen, Denmark; Diana Lowry, Cancer Research and Biostatistics, Seattle, Washington; Jan van Meerbeeck, University Hospital, Ghent, Belgium; Takashi Nakano, Hyogo College of Medicine, Hyogo, Japan; Andrew Nicholson, Royal Brompton Hospital, London, United Kingdom; Anna Nowak, University of Western Australia, Subiaco, Australia; Harvey Pass, Board Liaison, New York University, New York, New York; Michael Peake, Glenfield Hospital, Leicester, United Kingdom; Pieter Postmus, Free University Medical Center, Amsterdam, The Netherlands; Thomas Rice, Cleveland Clinic, Cleveland, Ohio; Kenneth Rosenzweig, Mount Sinai Hospital, New York, New York; Valerie Rusch, Memorial Sloan-Kettering Cancer Center, New York, New York; Nagahiro Saijo, National Cancer Center Hospital East, Chiba, Japan; Paul van Schil, Antwerp University Hospital, Edegem (Antwerp), Belgium; Jean-Paul Sculier, Institut Jules Bordet, Brussels, Belgium; Leslie Sobin, Armed Forces Institute of Pathology, Washington, DC; Charles Thomas, Oregon Health & Science University, Portland, Oregon; Charles F. Thomas Jr, Mayo Clinic, Rochester, Minnesota; William Travis, Memorial Sloan-Kettering Cancer Center, New York, New York; Ming Tsao, The Princess Margaret Hospital, Toronto, Ontario, Canada; Masahiro Tsuboi, Board Liaison, Kanagawa Cancer Center, Yokohama, Japan; Andrew Turrisi, Sinai Grace Hospital, Detroit, Michigan; Eric Vallières, Swedish Cancer Institute, Seattle, Washington; Johan Vansteenkiste, University Hospitals, Leuven, Belgium; Hirokazu Watanabe, National Cancer Center Hospital, Tokyo, Japan; and Yi-long Wu, Guangdong Provincial Peoples Hospital, Guangzhou, People's Republic of China.

APPENDIX B: INTERNATIONAL MESOTHELIOMA INTEREST GROUP (IMIG) BOARD MEMBERS

Steve Albelda, University of Pennsylvania, Philadelphia, Pennsylvania; Sam Armato, The University of Chicago Medical Center, Chicago, Illinois; Paul Baas, The Netherlands Cancer Institute, Amsterdam, The Netherlands; Courtney Broaddus, University of California San Francisco, San Francisco, California; Dean Fennell, Queen's University Belfast, Belfast, Northern Ireland, United Kingdom; Rabab Gaa-

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APPENDIX C: ADVISORY BOARD OF THE IASLC MESOTHELIOMA DOMAIN

Paul Baas, The Netherlands Cancer Institute, Amsterdam, The Netherlands; Jeremy Erasmus, M. D. Anderson Cancer Center, Houston, Texas; Seiki Hasegawa, Hyogo College of Medicine, Hyogo, Japan; Kouki Inai, Hiroshima University Postgraduate School, Hiroshima, Japan; Kemp Kernstine, City of Hope, Duarte, California; Hedy Kindler, The University of Chicago Medical Center, Chicago, Illinois; Lee Krug, Memorial Sloan-Kettering Cancer Center, New York, New York; Kristiaan Nackaerts, University Hospitals, Leuven, Belgium; and David Rice, M. D. Anderson Cancer Center, Houston, Texas.

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Cytological Characteristics of Pulmonary Pleomorphic and Giant Cell Carcinomas

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Key Words
Cytology · Giant cell carcinoma · Lung neoplasms · Pleomorphic carcinoma · Sarcomatoid carcinoma

Abstract
Objective: To establish cytological features of pulmonary pleomorphic carcinoma (PC) or giant cell carcinoma (GC), we evaluated the cytological characteristics of these tumors using a multidisciplinary approach. ***Study Design:*** Samples from 13 surgically resected and histologically confirmed PC or GC patients were collected from our institutes. Eight cases without prior chemotherapy before surgery were selected, and cytological features were analyzed. ***Results:*** The background contained numerous lymphocytes and neutrophils. The tumor cells were arranged in flat loose clusters, but some were in fascicles. The shape of the tumor cell was spindle or pleomorphic, and the sizes of the tumor cells varied by more than 5-fold. The tumor cells had an abundant, thick and well-demarcated cytoplasm. The location of the nucleus was centrifugal, and the nucleus was oval or irregularly shaped. Multinucleated giant cells were frequently observed. The size of the nucleus was more than 5 times that of normal lymphocytes, and its size also varied by more than 5-fold. The nuclear membrane was thin, and nuclear chromatin was coarsely granular, while the nucleolus was single and round. ***Conclusion:*** PC or GC has characteristic cytological features, however, spindle cells tended to be hardly observed in cytological specimens in some cases.

Pleomorphic carcinoma (PC) is defined as a poorly differentiated non-small cell lung carcinoma (NSCLC), namely squamous cell carcinoma, adenocarcinoma or large cell carcinoma containing spindle cells and/or giant cells, or a carcinoma containing only spindle cells and giant cells [1]. The spindle or giant cell component should comprise at least 10% of the tumor. Giant cell carcinoma (GC) is NSCLC composed of highly pleomorphic mono- and/or multinucleated tumor giant cells. This tumor is composed entirely of giant cells and does not have specific patterns of adenocarcinoma, squamous cell or large-cell carcinoma. The tumor cells are discohesive and tend to dissociate from each other [1].

The prognosis for PC patients is worse than that for patients with other NSCLC in surgically operated cases [2–4]. However, there have been some contradictory reports that PC has similar clinical behavior and prognosis as other NSCLC [5–7]. Histologic diagnosis is usually

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Table 1. Clinical summary of cases with pleomorphic carcinoma or giant cell carcinoma

Case	Age/ sex	Location	Smoking pack-years	Size mm	Stage	Adjuvant therapy	Follow up		Compo-nent
							months	prognosis	
1	69/F	LU/P	49	17		none	14	alive	S/G/A/L
2	76/M	LU/P	122	55	IIIA	chemo. + rad.	7	alive	S/G/A/L
4	62/M	RU/P	126	80	IV	none	3.5	dead	S/A
7	68/M	LL/P	18	16	IA	none	32	recurrence	S/G/A
8	68/M	LL/P	50	32	IIB	none	21	recurrence	S/A
9	82/M	RM/P	60	60	IIB	none	60	alive	S/G
10	39/F	LL/C	8	50	IIIA	rad. + chemo.	40	alive	S/G/A
12	78/M	RU/P	55	25	IV	UFT	23	alive	G

LU = Left upper lobe; RU = right upper lobe; LL = left lower lobe; RM = right middle lobe; P = peripheral; C = central; S = spindle cells; G = giant cells; A = adenocarcinoma; L = large cell carcinoma; Chemo. = chemotherapy; Rad. = radiotherapy; UFT = 5-fluoro-uracil derivative.

made with surgically removed tumors; however, diagnosis has to be made based on small biopsies or cytological specimens for patients with an advanced-stage tumor. Because of the difficulty in making a definite diagnosis of PC or GC, it is not clear whether the prognosis of patients with those tumors in the advanced stage is worse than that for patients with other NSCLCs. Although cytological findings of PC or GC have been documented in a few reports [8–13], there have been no multi-institutional studies carried out by pulmonary cytopathologists. The aim of this study was to elucidate the cytological characteristics of PC or GC with specimens obtained from the touch imprints of surgically removed tumors or pre-operative transbronchial cytology specimens in patients whose tumor was surgically removed and confirmed histologically to be PC or GC, and to extend application of those findings to specimens obtained from brushing or curettage of advanced-stage tumors.

Materials and Methods

We collected 16 resected tumors that were identified as PC or GC from our own institutes or from consultation cases. Pathological findings were reviewed by 3 pulmonary pathologists (K.H., T.K., and Y.M.), after which 13 of the tumors were diagnosed as PC or GC. Members of the Committee on Pulmonary Cytology of the Japan Lung Cancer Society evaluated the findings of their own original cytological and pathological specimens using a microscope and made digital images of representative microscopic findings for the 13 selected tumors. The digital images were copied to a CD and distributed to each member of the committee. Autopsy cases and patients who received chemotherapy before surgery were eliminated from this study, and 8 cases were selected for analyses of cytological features. All of the authors are experienced pulmonary cytopathologists with Board Certification from the Japanese Society of Clinical Cytology, and all are members of the Committee on Pulmonary Cytology of the Japan Lung Cancer Society.

Each member of the Committee on Pulmonary Cytology evaluated the cytological findings of the samples independently. We defined sarcomatoid component of PC as malignant giant and/or spindle cells. We defined epithelial component of PC as malignant tumor cells with glandular or squamous differentiation. Component of large-cell carcinoma is also included in epithelial component of PC. We defined large-cell carcinoma component as tumor cells which have a tendency to form loosely structured clusters composed of cells of unequal sizes without glandular or squamous differentiation. We evaluated cytological features of sarcomatoid component in each of the cases using the following parameters of the tumor cells by light microscopy: component of tumor cells, background, number, sizes of clusters, nuclear overlapping, arrangement, shape, size, variability in size, pleomorphism, surface, adhesion, color of the cytoplasm, nature of the cytoplasm, nuclear to cytoplasmic ratio, localization of the nucleus (centrifugal or peripheral), shape of the nucleus, size of the nucleus, pleomorphism of the nucleus, nuclear membrane, amount of chromatin, chromatin texture, distribution of chromatin, size and shape of the nucleolus, and number of nucleoli in the nucleus.

The age of the patients ranged from 39 to 82 years old (mean 67.8 years). Six were men and 2 were women. The tumor existed at the periphery of the lung in 7 cases and at the central part of the lung in 1 case. All of the patients were smokers. They smoked from 8 to 126 pack-years (average 61 pack-years). The size of the tumor was from 16 to 80 mm in diameter (average 42 mm). Lobectomy with lymph node dissection was performed in 7 cases, and partial resection of the lung without lymph node dissection was done in 1 case because of poor pulmonary function (case 1). The tumor stages were IA in 1 case, IIB in 2 cases, IIIA in 2 cases, and IV in 2 cases. The TNM classification of case 1 is T1NXMX (table 1).

Results

The cytological specimens were obtained with touch imprint in 4 cases, and with transbronchial brushing in 3 cases; 2 of these were also evaluated with a touch imprint sample, and 1 with transbronchial curettage. The histological diagnosis was PC in 7 cases and GC in 1. The NSCLC component of tumor cells in PC was adenocarcinoma in 6 cases, while in 1 case the tumor was composed of only spindle cells and giant cells.

Clinical Findings and Clinical Courses

The white blood cell counts were elevated to 9,400/μl in 1 case but were within normal range in the other 7 cases. Tumor markers were elevated in 5 cases. CEA was high in 4 cases (cases 1, 7, 8, and 9), and the CA19-9 level was also high in 1 (case 8). The CYFRA level was high in 1 case (case 4). One patient had metastasis to the brain (case 4), and another had metastasis to the right adrenal gland at the time of surgical removal of the lung tumor (case 12). Removal of the metastatic adrenal gland was performed after resection of the lung tumor. Chemoradiotherapy was performed in 2 patients after surgery. Recurrence was observed in 2 cases: 1 had a recurrent tumor in the lung (case 7) and another in the brain (case 8). Radiotherapy to the recurrent tumor in the lung was performed. The observation period from the time of the surgery was 3.5–60 months (average 29.7 months); 1 patient is dead, 2 are alive with recurrence, and 5 are alive without recurrence (table 1).

Cytological Findings

There was no difference in cytological findings depending on how the cytological specimens were obtained. However, the amount of tumor cells was small in transbronchial curettage samples, and large in transbronchial brushing samples and in touch imprint of the surgically resected tumor.

The background contained numerous lymphocytes and neutrophils with or without necrotic debris (fig. 1). There were a large number of tumor cells on the slides in some cases, but not in others. The size of the clusters seen on the slides was small, and the number of tumor cells forming the clusters was less than 20 in half of the cases. The shape of the tumor cell was spindle, or pleomorphic, and variable (fig. 2, 3). The tumor cells were large and the pleomorphism was marked. The tumor cell sizes varied by more than 5-fold in half of the cases. The pleomorphic cells varied in diameter from 40 to 80 μm, and occasionally reached up to 120 μm. The tumor cells had an abundant, thick and well-demarcated green cytoplasm that

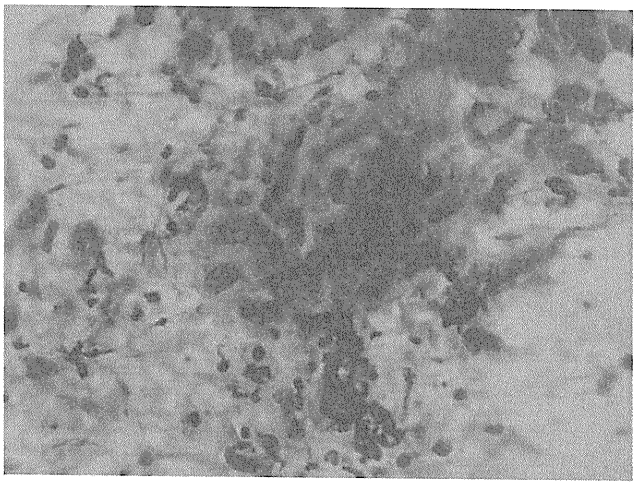

Fig. 1. Touch imprint cytology of the resected tumor from case 10. Pleomorphic spindle cells were observed in a necrotic background. Papanicolaou stain, ×40.

was green and vacuolated in some of the cells. The nuclear to cytoplasmic ratio was high. The location of the nucleus was centrifugal, and the nucleus was oval or irregularly shaped. Multinucleated giant cells were observed frequently. The nucleus was more than 5 times the size of normal lymphocytes in half of the cases and its size varied by more than 5-fold in half of the cases, ranging from 15 to 30 μm. The nuclear membrane was thin, and the nuclear chromatin was coarsely granular with an increased amount of chromatin, compared to non-tumor cells. The distribution of chromatin was uneven in most cases. The nucleolus was single, medium-sized, and round. The tumor cells were arranged in flat loose clusters (fig. 2, 3), but some were in fascicles (fig. 4). Cohesive clusters of atypical epithelial cells were also observed (fig. 5).

The components of tumor cells in pathological and cytological specimens are listed in table 2. The spindle cell component was observed in cytological specimens from 4 cases, and in pathological specimens from 7 cases. The giant cell component was observed in cytological specimens from all cases with a giant cell component in the pathological specimens. The adenocarcinoma component was observed in cytological specimens from 4 cases, and in pathological specimens from 6 cases. The large-cell carcinoma component was observed in cytological specimens obtained from all cases with a large cell carcinoma component. Summary of cytological features of sarcomatoid component of pleomorphic carcinoma and giant cell carcinoma is listed in table 3.

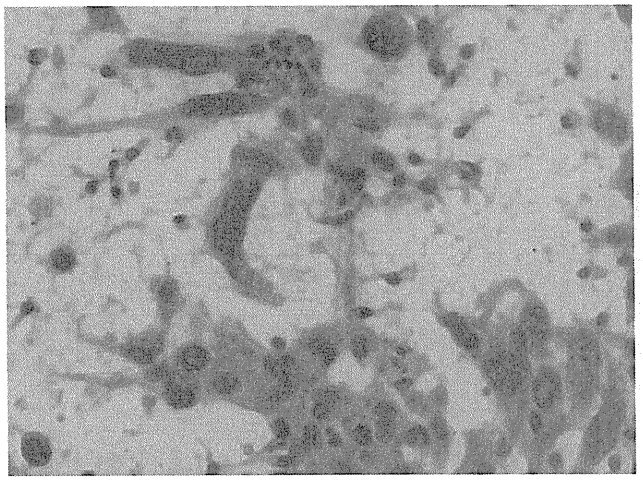

Fig. 2. Transbronchial brushing cytology of case 9. Pleomorphic spindle cells were arranged in loose clusters. Papanicolaou stain, ×40.

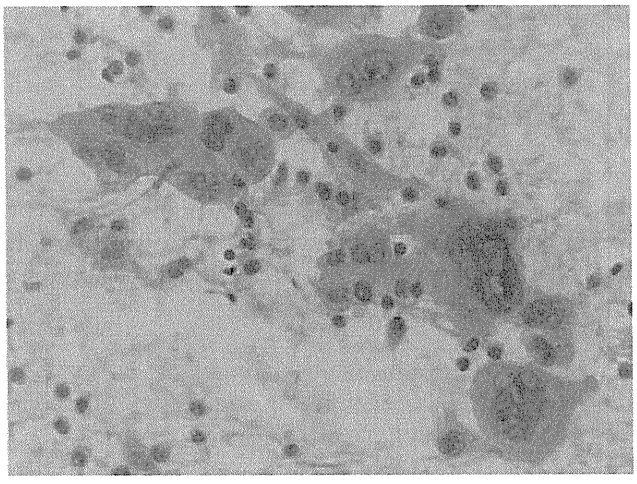

Fig. 3. Multinucleated cells were arranged in loose clusters in a background of lymphocytes (case 1). Papanicolaou stain, ×40.

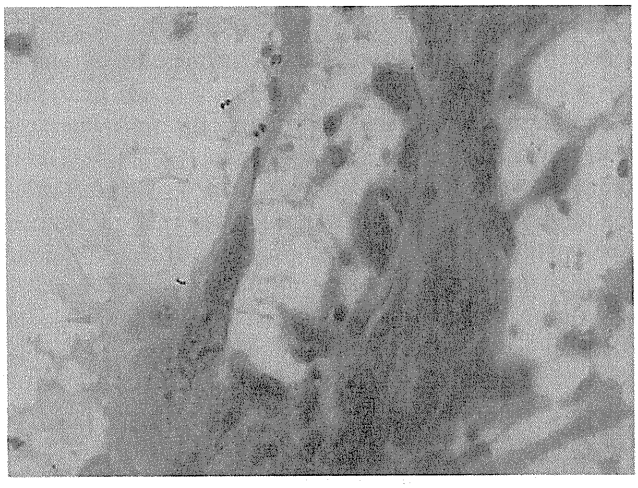

Fig. 4. Transbronchial brushing cytology of case 9. Pleomorphic spindle cells were arranged in fascicles. Papanicolaou stain, ×40.

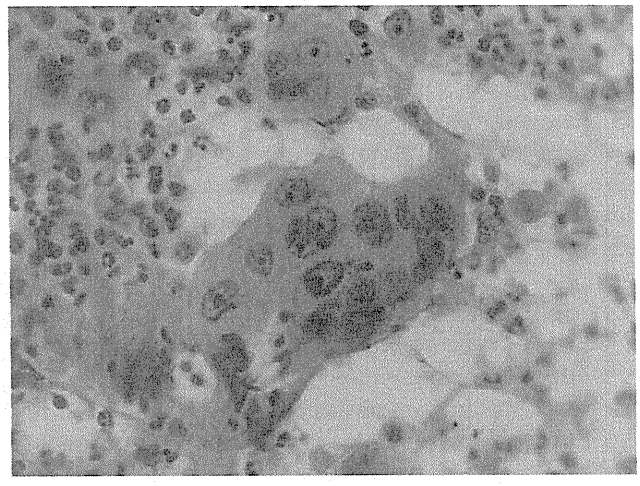

Fig. 5. Cohesive clusters of atypical epithelial cells were observed in a background of neutrophils (case 2). Papanicolaou stain, ×40.

Discussion

Hummel et al. reported that cytological findings of PC include a conspicuous population of pleomorphic spindle cells arranged singly, in loose clusters, and in fascicles, and as microtissue fragments in a necrotic background [8]. Myxoid stromal fragments are also present. In addition, cohesive clusters of typical epithelial cells have been noted. There have been reports that pre-operative transbronchial brushing cytology of the PC revealed adenocarcinoma or atypical cells [10, 11]. Cytological study of the tumor in cases 1, 2, and 4 in our study revealed adenocarcinoma and giant cells, but not spindle cells, although spindle cells were components of the tumor. The results of our study and others suggest that spindle cells have poor adhesiveness to each other, and that they detach eas-

Table 2. Components of tumor cells observed in pathological and cytological specimens

Case	Methods	Component of tumor cells in pathological specimens				Component of tumor cells in cytological specimens			
		spindle cells	giant cells	AD	LA	spindle cells	giant cells	AD	LA
1	TI	present	present	present	present	X	present	present	present
2	TI	present	present	present	present	X	present	present	present
4	Cr	present		present		X		present	
7	TI	present	present	present		present	present	X	
8	TI	present		present		present		present	
9	Br	present	present			present	present		
10	Br	present	present	present		present	present	X	
12	Br		present				present		

AD = Adenocarcinoma; Br = brushing; Cr = curettage; LA = large-cell carcinoma; TI = touch imprint; X = absent.

Table 3. Summary of cytological features of sarcomatoid component of pleomorphic carcinoma and giant cell carcinoma

Background	necrosis	present	2/8 (25%)
	type of cells	lymphocytes, neutrophils	7/8 (88%)
Amount of tumor cells		large	5/8 (63%)
Clusters	size	small	4/8 (50%)
	nuclear overlapping	not obvious	8/8 (100%)
	arrangement	2-dimensional	6/8 (75%)
Cells	shape	spindle, pleomorphic, variable	8/8 (100%)
	size	large	7/8 (88%)
	variability in size	5 times or more	4/8 (50%)
	pleomorphism	marked	7/8 (88%)
	margin	demarcated	5/8 (63%)
	cell adhesion	poor	7/8 (88%)
Cytoplasm	color	green/blue	8/8 (100%)
	nature	translucent or vacuole, thick	8/8 (100%)
Nucleocytoplasmic ratio		increased	7/8 (88%)
Nucleus	location	centrifugal	5/8 (63%)
	shape	irregular, oval	8/8 (100%)
	size	5 times of lymphocyte or more	4/8 (50%)
	variability in size	5 times or more	4/8 (50%)
	nuclear membrane	thin, slightly thick	8/8 (100%)
	hyperchromatism	present	8/8 (100%)
	chromatin texture	coarsely granular	7/8 (88%)
	distribution of chromatin	uneven	5/8 (63%)
Nucleolus	shape	round	7/8 (88%)
	size	medium	4/8 (50%)
	number	single	7/8 (88%)

ily from the glass slide during the staining process. On the other hand, the adenocarcinoma component was not observed in cytological specimens from cases 7 and 10. Pathological specimens from case 7 revealed that the adenocarcinoma component was a solid adenocarcinoma with mucin that had bizarre nuclei. Giant cells and spindle cells were marked in this case, and mucin in the cytoplasm was difficult to discern in cytological specimens. Pathological specimens in case 10 revealed that the adenocarcioma component comprised a small percentage of the tumor. This may be the reason why the adenocarcinoma component did not appear in cytological specimens from case 10.

There have been only a few cytological studies of GC [12, 13]. GC cytology specimens have exhibited numerous mono- or multinucleate giant cells with significant pleomorphism in size and shape. The cytoplasm of the giant cells is abundant, eosinophilic, microvesicular, and well demarcated. Most of the tumor cells have round, oval or irregularly shaped macronuclei with coarse, granular chromatin and large, prominent nucleoli. Their cytoplasm is occasionally infiltrated with neutrophils. The tumor cells usually occurred singly, and the background contains tumor diathesis with numerous polymorphonuclear leukocytes [12, 13].

Giant cells are one component of PC or GC [1]. However, there is no clear definition of how large these giant cells are. Fishback et al. reported that the single large pleomorphic nucleus of GC measured greater than the diameter of four small resting lymphocytes [14]. Guillan and Zelman reported that the giant cells varied in size from 50 to 120 μm in diameter [15], and Hellstrom and Fisher reported that the giant cells measured from 80 to 100 μm [16]. This vague definition of giant cells causes confusion among pathologists. In our study, the mononucleated giant tumor cells had large nuclei, the size of which was greater than the diameter of 5 resting lymphocytes in half of the cases. There was variability in the size of the nuclei, and the size of the largest nucleus was 5 times greater than that of the smallest nucleus of the tumor cells in half of the cases.

It has been reported that the prognosis for PC patients is worse than that for patients with other NSCLC in surgically resected cases [2–4]. In contrast, Nakajima et al. reported similar clinical behaviors and prognosis between PC and other NSCLC [7]. Pelosi et al. reported that stage I PC behaves more aggressively than ordinary NSCLC; however, the differences were not statistically significant for both overall and disease-free survival curves [6]. Yamamoto et al. reported that the overall 5-year survival rate of surgically resected PC was 80.0% and the disease-free survival rate was 63.3%, which were both far better than rates reported elsewhere [5].

PCs have been reported to be highly metastatic. In our study, some patients had a recurrence even though the tumor was stage I or II; the patient with a stage IA tumor had a recurrence in the lung 31 months after surgery (case 7), and 1 patient with a stage IIB tumor had a brain metastasis 21 months after the surgery (case 8). In contrast, some patients had a favorable prognosis. One patient with a stage IIB tumor is alive 5 years after surgery without any adjuvant therapy (case 9). One patient with a stage IIIA tumor underwent thoracic radiotherapy and chemotherapy (CDDP + GEM) and is alive without recurrence 40 months after the surgery (case 10). One patient (case 12) had an enlarged right adrenal gland the size of which was 15 mm, and its size had become 53 mm six months later. It was surgically removed and confirmed to be metastasis from a pulmonary PC. The patient is alive 23 months after the surgery of the lung tumor.

The contradictory prognoses of PC in different studies may be due to the different criteria of PC used among pathologists. Because ours is a multidisciplinary study, we selected cases that underwent pathological review by pathologists specialized for lung cancers. We did not include patients treated with chemotherapy or radiotherapy before the surgery, because these therapies may modify the tumor cells and enlarge them even further. The present study, by analyzing carefully selected PC or GC cases, suggests that some patients with PC or GC can expect long survival after resection of the tumor with adjuvant therapy. We could not address the pathological or molecular differences between long-survivors and short-survivors suffering from PC or GC. Further studies are needed to clarify the mechanisms of different biological behaviors among this type of lung carcinoma.

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