厚生労働科学研究費補助金

がん臨床研究事業

局所限局非小細胞肺がんの集学的治療に関する研究

平成16～18年度　総合研究報告書

主任研究者　加藤　治文

平成19（2007）年4月

目　次

厚生労働科学研究費補助金(がん臨床研究事業)

総合研究報告書

局所限局非小細胞肺がんの集学的治療に関する研究

主任研究者　加藤治文　東京医科大学病院外科学第一講座教授

研究要旨:2002 年 10 月から実施した臨床病期 IB-II 非小細胞肺癌症例に対して Cisplatin+Docetaxel 併用(DC)と Docetaxel (D)単剤という二種類の化学療法のいずれかを行い大規模試験に適当な術前化学療法のレジメンを選択するというランダム化臨床第Ⅱ相試験の評価を行った。術後合併症は併用療法(DC)群に多かったが、Primary endpoint である 1 年無再発生存割合は、DC 群の 77.3%に対し単剤群(D 群)のそれは 59.0%であり、併用群が単剤群を上回っていた。また、治療完遂率、治療奏効割合、完全切除割合のいずれの項目においてもDC群が良好な成績であった。治療関連死はDC群の2例に認められた。これらの結果から、当該病期における次期術前化学療法を含む臨床試験においてはシスプラチン併用療法(DC 療法)を治療レジメンとして選択をすると結論した。次いで、本邦における術後補助化学療法の当該病期における妥当なレジメンを決定する大規模臨床試験(本研究A)のコンセプトシートを作成した。試験のデザインは、術後病理学的に病期 IB-IIIA 期と診断された非小細胞肺癌完全切除例を対象に本邦で有用性が証明されたテガフール・ウラシル配合剤と欧米で評価されたプラチナ化合物を含む 2 剤併用化学療法との無作為化比較試験(第Ⅲ相試験)で、実地臨床試験計画書を作成、計画中であった。しかし、2006 年 6 月の米国臨床腫瘍学会(ASCO)において、シスプラチンを含む 2 剤併用療法による術後化学療法のメタアナリシス:Lung Adjuvant Cisplatin Evaluation(LACE)の結果と対象を臨床病期 IB 期に特化した CALGB9633 の追加報告がなされ、病期によっては化学療法のリスクがベネフィットを上回る可能性が示唆され、術後化学療法によって IA 期ではむしろ死亡リスクが高くなり、ＩＢ 期では生存の延長に寄与することに疑問を残す結果であった。以上の経緯を踏まえグループ内で議論した結果、対象集団をプラチナ製剤の有効性が示された II、III 期と本邦においてのみ有効性が示された IB 期に分けて、新たに大規模臨床試験を計画する方針とした。IB期においてはUFT 投与群を対照として経口抗がん剤であるテガフール・ギメラシル・オテラシルカリウム配合剤(S-1)の有用性を評価する試験を、II-IIIA 期に対しては、プラチナ製剤を含む 2 剤併用療法投与群を対照として経口剤もしくは分子標的薬剤の維持療法としての上乗せ効果を検証する試験をそれぞれ検討中である。当該期間においては本研究の結果を求めることができなかった。

分担研究者;
一瀬幸人(国立病院九州がんセンター腫瘍外科部長)、岡田守人(兵庫県立成人病センター呼吸器外科科長)、國頭英夫(国立がんセンター中央　総合病棟部)、小池輝明(新潟県立がんセンター新潟病院腫瘍外科部長)、近藤丘(東北大学加齢医学研究所呼吸器外科教授)、鈴木健司(国立がんセンター中央病院呼吸器外科医員)、多田弘人(大阪市立総合医療センター呼吸器外科部長)、坪井正博(東京医科大学病院外科学第一講座講師)、太田三徳(大阪府立呼吸器・アレルギー医療センター、呼吸器外科部長)、光冨徹哉(愛知県がんセンター腫瘍外科部長)、吉田純司(国立がんセンター東病院呼吸器外科医長)、山本信之(静岡県立静岡がんセンター呼吸器内科部長)

A.　研究目的:

1)奏効率・毒性の異なる二種類の化学療法レジメンから術前・術後化学療法への適性を検討し、臨床第Ⅲ試験の試験治療を決定する。

2)臨床病期(c-Stage)IB-II 非小細胞肺癌(NSCLC)に対する術後化学療法の安全性および有用性を検証し、本邦における術後化学療法レジメンの妥当性を検討する。

3)臨床病期(c-Stage)IB-II 非小細胞肺癌(NSCLC)に対する術前化学療法の有用性を検討する。

1. 本研究の必要性:

当該疾患の標準的治療は外科的切除もしくは外科切除＋術後補助療法であるが、治療成績は不満足であり、より安全な全身治療の強化による治療成績の向上が期待される。最近、プラチナを用いた術後化学療法の有用性が当該病期において明らかになり、世界的に術後補助化学療法が「標準的治療」の一角を担いつつある。本邦では当該病期の一部(IB)の術後補助療法としてテガフール・ウラシル(UFT)の有効性が明らかになったが、欧米では当該病期に対してプラチナ製剤を含む 2 剤併用療法を標準的レジメンとしている。後者は本邦における安全性は確立しておらず、まずは標準的治療群に組み込まれるべき治療レジメンを決定する大規模比較試験が必要である。一方、術後化学療法の治療完遂率は 50～85%であり、術前では 90%以上のそれが期待できる。プラチナを用いた化学療法の有効性、安全性を考えれば、依然術前化学療法は有望であり、その治療意義を検証する必要がある。

2. 本研究の特色:

1) 欧米では進行病期に汎用される化学療法を用いて同様の症例を対象に術前化学療法と切除単独の比較試験を開始しているが、その化学療法の妥当性については検討されていない。
2) UFT に関する臨床試験は海外になく、欧米では同様の試験デザインで臨床試験が進む予定はない。

B. 研究方法

前研究では、臨床病期 IB-II 非小細胞肺癌症例に対して Cisplatin+Docetaxel (DC)と Docetaxel (D)単剤という二種類の化学療法のいずれかを行い、一年無再発生存割合、治療完遂率、治癒切除率、治療関連合併症をエンドポイントとして大規模試験に適当な術前化学療法を選択する。登録症例数は 80 例。今年度、集積後 1 年の評価を行い、当該病期の術前化学療法における至適治療レジメンを決定する。次いで、本研究では、まず術後の標準的化学療法レジメンを決定する比較試験(研究A)を行った後、先に決定された術前化学療法＋手術群を手術＋術後補助療法群を対照とした比較試験(研究B)で検証する。エンドポイントは生存率もしくは無再発生存割合。研究Aの予定登録は 1 群 300 例、合計 600 例; 2 年間で症例集積を行い、集積終了時点で中間解析を行う。引き続き、研究 B を行う。ここでもエンドポイントは生存率。予定登録は 1 群 150 例、合計 300 例; 2 年間で症例集積を行い、集積終了時点で中間解析を行う。5 年生存率を算定できるまで症例集積治療及び追跡を行って最終解析を行う。

(年度別研究計画):

第1年度:前研究の結果解析。次期臨床研究 A のプロトコール作成

第2年度:研究 A の試験実施計画書の作成

第3年度:研究 A の症例集積、治療、追跡;研究 B 試験デザインの設定

3年計画終了時に研究継続が認められた場合、5年生存率を算定できるまで症例集積治療及び追跡を行って最終解析を行う。

(倫理面への配慮)

参加患者の安全性確保については、毒性中止・無効中止基準等の配慮がなされており、試験参加による不利益は最小化される。

また、ヘルシンキ宣言や米国ベルモントレポート等の国際的倫理原則に従い、これを遵守する。研究の監視:本研究班により、もしくは賛同の得られた他の主任研究者と協力して、臨床試験審査委員会、効果・安全性評価委員会、監査委員会を組織し、研究開始前および研究実施中の第三者的監視を行う。

臨床試験登録の際しては、この治療法が臨床試験であること、標準治療は手術単独であること、また術前治療を行うことに伴うメリット・リスク・不利益などを十分に説明がなされ、患者本人からの文書による同意を必須とする。また、試験の開始にあたり、グループ臨床試験審査委員会、参加各施設倫理委員会(IRB)の承認を得る。

C. 研究結果

2002 年 10 月から実施した臨床病期 IB-II 非小細胞肺癌症例に対して Cisplatin+Docetaxel 併用(DC)と Docetaxel (D)単剤という二種類の化学療法のいずれかを行い大規模試験に適当な術前化学療法のレジメンを選択するというランダム化臨床第 II 相試験の評価を行った。術後合併症は併用療法(DC)群に多かったが、Primary endpoint である 1 年無再発生存割合は、DC 群の 77.3%に対し単剤群(D 群)のそれは 59.0%であり、併用群が単剤群を上回っていた。

また、治療完遂率、治療奏効割合、完全切除割合のいずれの項目においても DC 群が良好な成績であった。治療関連死はDC群の2例に認められた。これらの結果から、当該病期における次期術前化学療法を含む臨床試験においてはシスプラチン併用療法(DC 療法)を治療レジメンとして選択をすると結論した。次いで、本邦における術後補助化学療法の当該病期における妥当なレジメンを決定する大規模臨床試験(本研究A)のコンセプトシートを作成した。試験のデザインは、術後病理学的に病期 IB-IIIA 期と診断された非小細胞肺癌完全切除例を対象に本邦で有用性が証明されたテガフール・ウラシル配合剤と欧米で評価されたプラチナ化合物を含む2剤併用化学療法との無作為化比較試験(第Ⅲ相試験)で、実地臨床試験計画書を作成、計画中であった。しかし、2006 年 6 月の米国臨床腫瘍学会(ASCO)において、シスプラチンを含む 2 剤併用療法による術後化学療法のメタアナリシス:Lung Adjuvant Cisplatin Evaluation(LACE)の結果と対象を臨床病期 IB 期に特化した CALGB9633 の追加報告がなされ、病期によっては化学療法のリスクがベネフィットを上回る可能性が示唆され、術後化学療法によってIA 期ではむしろ死亡リスクが高くなり、ⅠB 期では生存の延長に寄与することに疑問を残す結果であった。以上の経緯を踏まえグループ内で議論した結果、対象集団をプラチナ製剤の有効性が示された II、III 期と本邦においてのみ有効性が示された IB 期に分けて、新たに大規模臨床試験を計画する方針とした。IB期においては UFT 投与群を対照として経口抗がん剤であるテガフール・ギメラシル・オテラシルカリウム配合剤(S-1)の有用性を評価する試験を、II-IIIA 期に対しては、プラチナ製剤を含む2剤併用療法投与群を対照として経口剤もしくは分子標的薬剤の維持療法としての上乗せ効果を検証する試験をそれぞれ検討中である。

D. 考察

本邦からⅠ期非小細胞肺癌(腺癌)に対するテガフール・ウラシル配合剤の術後化学療法の大規模臨床試験(N Eng J Med 2004; 350: 1713)とmeta-analysis(J Clin Oncol 2005; 23: 4999)の結果が公表され、本邦においてはテガフール・ウラシル配合剤を用いた術後補助療法が少なくともⅠB 期の標準的治療戦略となりうる可能性が高いことが示された。また本剤が大腸癌や胃癌などの他癌種でも同様に補助療法として有効性が示された。従来進行肺癌での単剤としての有効性は 6~8%と言われていた薬剤が術後補助療法として有効性が示されたことは画期的である。本研究は、昨今のエビデンスに基づき、IB 期とII-III 期を分離してそれぞれ臨床試験を計画し、病期別の標準的補助化学療法の確立を目指す。IB 期ではテガフール・ウラシル配合剤術後投与を標準的治療として、進行肺癌で有効性が示されているテガフール・ギメラシル・オテラシルカリウム配合剤(S-1)の術後補助療法としての有効性を検討するデザインとした。これは術後補助療法として比較的毒性の少ない抗がん剤を長期投与することが良いのか、あるいは相応の毒性のある抗がん剤を進行癌と同様に短期的に投与するのが良いのかという術後補助治療コンセプトあるいは効果のメカニズムに関わる重要な情報を提供する可能性があり、研究の意義は大きい。また、この試験の結果は手術対象病期の非小細胞肺癌の標準的治療を確立するものであり、一般診療に情報還元するとともに、今後の臨床試験のデザインの礎となると予想される。

E. 結論

本研究(研究 A)は、2006 年 3 月末現在試験実施計画書作成中であり、本研究の結論は得られていない。

F. 健康危険情報

健康危険情報として該当する事項はない。

G. 研究発表

1. 論文発表

1) Kato, H., Ichinose, Y., Ohta, M., Hata, E., Tsubota, N., Tada, H., Watanabe, Y., Wada, H., Tsuboi, M., Hamajima, N., Ohta, M. for the Japan Lung Cancer Research Group on Postsurgical Adjuvant Chemotherapy, A Randomized Trial of Adjuvant Chemotherapy with Uracil-Tegafur for Adenocarcinoma of the Lung. New England J. of Medicine 2004, 350(17):1713-1721

2) Kato, H., Nakamura, H., Tsuboi, M., Ikeda, N., Tsuchida, T., Kato, Y., Hirano, T., Treatment of Peripheral Early Stage Lung Cancer. Ann. of Thoracic and Cardiovascular Surgery 2004,

10(1):1-3

3) Nakamura, H., Idiris, A., Kato, Y., Kato, H., An increase in the percentage of HLA-DR-positive peripheral leukocytes predicts a poor prognosis in patients with squamous cell carcinoma of the lung, Oncology Reports 11, 0-00, 2004

4) Tada, H., Tsuchiya, R., Ichinose, Y., Koike, T., Nishizawa, N., Nagai, K., Kato, H., Japan Clinical Oncology Group, A randomized trial comparing adjuvant chemotherapy versus surgery alone for completely resected pN2 non-small cell lung cancer (JCOG9304). Lung Cancer 2004, 43(2):167-173

5) Nakamura, H., Saji, H., Ogata, A., Saijo, T., Okada, S., Kato, H., Lung cancer patients showing pure ground-glass opacity on computed tomography are good candidates for wedge resection. Lung Cancer 2004, 44(1):61-68

6) Ikeda, N., Maeda, J., Yashima, K., Tsuboi, M., Kato, H., Akada, S., Okada, S., A clinicopathological study of resected adenocarcinoma 2 cm or less in diameter. Ann Thorac Surg 2004, 78(3):1011-1016

7) Nakamura, H., Kato, Y., Kato, H., Outcome of surgery for small lung cancer-response to induction chemotherapy predicts survival. Thorac Cardiovasc Surg 2004;9(5):378-82

8) Furukawa K., Miura T., Kato Y., Okada S., Tsutusi H., Shimatani H., Kajiwara N., Taira M., Satoto M., Kato H.: Microwave coagulation Therapy in Canine Peripheral Lung Tissue, J. of Surgical Research 123: 245-250, 2005

9) Kato Y., Hirano T., Yoshida K., Yashima K., Akimoto S., Tsuji K., Ohira T., Tsuboi M., Ikeda N., Ebihara Y., Kato H.: Frequent loss of E-cadherin and/or catenins in intrabroncial lesions during carcinogenesis of the bronchial epithelium, Lung Cancer 48(3): 323-330, 2005

10) Tsuchiya R., Suzuki K., Ichinose Y., Watanabe Y., Yasumitsu T., Ishizuka N., Kato H.: Phase II trial of postoperative adjuvant cisplatin and etoposide in patients with completely resected stage I-IIIa small cell lung cancer: The Japan Clinical Oncology Lung Cancer Study Group Trial (JCOG9101), J of Thoracic and Cardiovascular Surgery 129(5): 977-983, 2005

11) Fujii K., Nakano T., Kanazawa M., Akimoto S., Hirano T., Kato H., Nishimura T.: Clinical-scale high-throughput human plasma proteome analysis: Lung adenocarcinoma, Proteomics 5: 1150-1159, 2005

12) Kato H., Tsuboi M., Kato Y., Ikeda N., Okunaka T., Hamada C.: Postoperative adjuvant therapy for completely resected early-stage non-small cell lung cancer, Int. J Clinical Oncology10: 157-164, 2005

13) I Nakamura H., Fujita K., Nakagawa H., Kishi F., Takeuchi A., Aute I., Kato H.: Expression pattern of the scaffold protein IQGAP1 in lung cancer, Oncology Report13(3): 427-431, 2005

14) Tsuboi M, Kato H, Jiang H, et al: Gefitinib in the adjuvant setting: safety results from a phase III study in patients with completely resected non-small cell lung cancer, Anticancer Drugs. 16(10): 1123-1128, 2005

15) Furukawa K, Kato H, Konaka C, Okunaka T, Usuda J, Ebihara Y : Locally recurrent central-type early stage lung cancer <1.0 cm in diameter after complete remission by photodynamic therapy Chest 128(5): 3269-3275 2005

16) Nakamura H, Aute I, Kawasaki N, Taguchi, Ohira T, Kato H : Quantitative detection of lung cancer cells by fluorescence in situ hybridization: comparison with conventional cytology Chest 128(2): 906-911 2005

17) Saji, H., Song, W.*, Furumoto, K.*, Kato, H., Engleman, E. G.*Systemic antitumor effect of intratumoral injection of dendritic cells in combination with local photodynamic therapy., Clin Cancer Res 12:2568-2574 2006

18) Nitadori, J., Ishii, G., Tsuta, K., Yokose, T., Murata, Y., Kodama, T., Nagai, K., Kato, H., Ochiai, A., Immunohistochemical Differential Diagnosis Between Large Cell Neuroendocrine Carcinoma and Small Cell Carcinoma by Tissue Microarray Analysis With a Large Antibody Panel, Ameican Journal of Clinical Pathology 125(5):682-92 2006

19) Saijo, T., Ishii, G., Nagai, K., Funai, K., Nitadori,

J., Tsuta, K., Nara, M., Hishida, T., Ochiai, A., Differences in clinicopathological and biological features between central-type and peripheral-type squamous cell carcinoma of the lung, Lung Cancer 52(1):37–45 2006

20) Hirano ,T., Kato ,H. Present status of clinical proteomic analysis for the early detection and determination of therapeutic strategy in lung cancer, Ann Thorac Cardiovasc Surg 12: 4-9, 2006

21) Rusch, VW., Tsuchiya, R., Tsuboi, M., Pass, HI., Grunenwald, D., Goldstraw, P., Surgery for bronchioloalveolar carcinoma and "very early" adenocarcinoma: an evolving standard of care?, J Thorac Oncol. 1: S27-S31, 2006

22) Ohira, T., Suga, Y., Nagatsuka, Y., Usuda, J., Tsuboi, M., Hirano, T., Ikeda, N., Kato, H. Early-stage lung cancer: diagnosis and treatment. Int J Clin Oncol. Feb;11(1):9-12. 2006

23) Tsuboi, M., Kato, H., Ichinose, Y., Ohta, M., Hata, E., Tsubota, N., Wada, H., Hamada, C., Hamajima, N., Ohta, M., On behalf of the Japan Lung Cancer Research Group (JLCRG) on Postsurgical Adjuvant Chemotherapy, The influence of tumor size, histological differentiation and smoking history in patients with completely resected stage I adenocarcinoma of the lung; Subset analyses of the Japan Lung Cancer Research Group (JLCRG) trial, J Clin Oncol. 24: 413S, 2006

24) 加藤 治文, (監訳:加藤 治文, 池田 徳彦, 坪井 正博, 編: Fossella, F.V., Komaki, R., Putnam, J.B. Jr.) MD アンダーソン癌センターに学ぶ癌治療 肺癌, シュプリンガ・ジャパン株式会社, 2006

2. 学会発表

1) Kato, H., New strategies for early detection of lung cancer, invited lecture, XV International Congress of Cytology, Santiago Chile (2004.4.15)

2) Kato, H., Treatment alternatives for early lung cancer, XIII world Congress for Bronchology and XIII world Congress for Bronchoesophagology, Barcelona (2004.6.21)

3) Kato, H., Adjuvant chemotherapy with UFT for resected NSCLC, IASLC Workshop, Yokohama (2004.10.26)

4) Kato, H., The postoperative adjuvant trials with UFT for p-stage 1 non-small cell lung cancer, ASCO-JSCO Joint Symposium, Kyoto (2004.10.29)

5) I-ELCAP Workshop, Intervention research, The 10th International Conference on Screening for Lung Cancer, New York (2004.4.24)

6) Tsuboi, M., Kato, H., Japanese Clinical Trial; ongoing&closed, 17th annual meeting of General Thoracic Surgical Club, Arizona, USA (2004.3.11)

7) Tsuboi, M., Kato, H., Japanese UFT Trials on Post-operative Adjuvant Therapy in Early Stage NSCLC, The 1st WJTOG International Symposium on Lung Cancer Clinical Trial, Nara, Japan (2004.4.30)

8) Tsuboi, M., Kato, H., Clinical issues from Japanese experiences with Gefinitib (Iressa), 2nd IASLC/ASCO/ESMO International Meeting: Molecular Targeted Therapies in Lung Cancer, Algarve, Portugal (2004.9.2)

9) Tsuboi, M., Kato, H., Japanese experiences :the postoperative adjuvant trials with UFT for p-stage I non-small cell lung, 9th Central European Lung Cancer Conference, Gdansk, Poland (2004.9.25)

10) Tsuboi, M., Kato, H., Adjuvant chemotherapy with UFT for BAC, Introduction of JCOG 0201 protocol, 1st ASCO/IASLC consensus meeting for BAC in NY, USA (2004.11.5)

11) Kato, H., History of PDT, 16th World Congress of the International Society for Laser Surgery and Medicine, September 10th, 2005, Tokyo

12) Kato, H., Tsuboi, M., The new technologies for the diagnosis and therapy of lung cancer, 14th Panhellenic Congress on Thoracic Diseases・December 3rd, 2005, Thessaloniki, Greece

13) Kato, H., Tsuboi, M., Recent advances in endoscopic techniques; AF, OCT and EBUS, CALC International Lung cancer Forum of 2005 (6th)・November 11th, 2005, Shanghai, Chaina

14) Kato, H., Tusboi, M., Asamura, H., Japanese Clinical Trials; ongoing & closed, 18th annual

meeting of General Thoracic Surgical Club, March 11th, 2005., Florida, USA

15) Kato, H., Tusboi, M., EGFR mutations and EGFR-TK inhibitors in lung cancer, Lilly Asian Advisary Board meeting, June 25th, 2005., Shanghai, Chaina

16) Kato, H., Tsuboi, M., Adjuvant chemotherapy for completely resected Non-small Cell Lung Cancer, Lilly Asian Advisary Board meeting, June 25th, 2005., Shanghai, Chaina

17) Kato, H., Tsuboi, M., Postoperative adjuvant chemotherapy for early-staged NSCLC, Lung cancer conference in Seoul National University, February 21st, 2005, Seoul, Korea

18) Kato, H., Tsuboi, M., Mediastinal lymph node dissection; surgical techniques and survival impact, Korean Thoracic Surgical meeting, February 22nd, 2005, Seoul, Korea

19) Kato, H., The role of molecular markers, The 15th International conference on Screening for Lung Cancer (2006.10.20) New York, USA

20) Tsuboi, M., Kato, H., Adjuvant chemotherapy for stage I NSCLC in Japan, IASLC Workshop on Stereotactic Radiation Therapy and Surgery for Stage I Non-Small Cell Lung Cancer (2006.2.18) Hawaii, USA

21) Tsuboi, M., Asamura, H., Kato, H., Japanese clinical trials; ongoing & closed studies, 19th annual meeting of General Thoracic Surgical Club (2006.3.9) Arizona, USA

22) Tsuboi, M., Kato, H., Adjuvant chemotherapy in early stage NSCLC, 2nd international lung cancer symposium (2006.7.8) Nara

23) Tsuboi, M., Kato, H., A case for change: Data from the Japanese Joint Committee of Lung Cancer Registry of 6,644 resected cancers, CHEST 2006 (2006. 10.26) Salt Lake City, USA

24) Tsuboi, M., Kato, H., Japanese experiences with EGFR-TKIs, 3rd IASLC/ASCO/ESMO International Conference onTargeted Therapies in Lung Cancer (2006.11.9) Sicily, Italy

25) Tsuboi, M., Kato, H., The adjuvant chemotherapy in early stage non-small cell lung cancer; Taxol adjuvant therapy in 2006, KASLC autumn meeting 2006 (2006.11. 18) Seoul, Korea

26) Tsuboi, M., Kato, H., Ichinose, Y., Ohta, M., Hata, E., Tsubota, N., Wada, H., Hamada, C., Hamajima, N., Ohta, M., On behalf of the Japan Lung Cancer Research Group (JLCRG) on Postsurgical Adjuvant Chemotherapy, The influence of tumor size, histological differentiation and smoking history in patients with completely resected stage I adenocarcinoma of the lung; Subset analyses of the Japan Lung Cancer Research Group (JLCRG) trial, 42nd Annaul meeting, American Society of Clinical Oncology (ASCO) (2006.6.2-6) Atlanta, USA

27) Ohira, T., Usuda, J., Suga, Y., Miyajima, K., Nakajima, N., Oikawa, T., Kataba, H., Kojika, M., Saji, H., Tsuboi, M., Hirano, T., Kato, H., Molecular characterizations in clinical non-small-cell lung cancer (NSCLC) samples obtained during surgery, 97th American Association for Cancer Research (2006.4.4) Washington DC

28) Miyajima, K., Ohira, T., Usuda, J., Saji, H., Tsuboi, M., Hirano, T., Kato, H., Suzuki, M., Toyooka, S., A .F. Gazdar*, The relationship between RASSF1A aberrant methylation and survival in small sized lung adenocarcinoma, 42nd American Society of Clinical Oncology (2006.6.2-6) Atlanta, Georgia,U.S.A.

29) Miyajima, K., Ohira, T., Suga, Y., Takahashi, M., Usuda, J., Nagatsuka, Y., Kajiwara, N., Uchida, O., Tsuboi, M., Hirano, T., Kato, H., A. F Gazdar*, The Relationship Between RASSF1A Aberrant Methylation And Survival In Small Sized Lung Adenocarcinoma., 86th American Association for Thoracic Surgery (20064.29-5.3) Philadelphia,PA, U.S.A.

30) Tsuboi, M., Kato, H., JCOG LCSSG ongoing & planning trials, Korean Lung Cancer Surgical Study meeting (2006.8.24) Seoul, Korea

31) 加藤 治文, 肺癌の診断と治療, 第47回日本臨床細胞学会総会学術集会 (2006.6.9) 横浜

32) 加藤 治文, 肺癌治療の現状と外科治療, 第7回肺がん撲滅デー市民公開講座「専門医が勧める肺がん治療」(2006.11.25) 東京

33) 加藤 治文, 局所限局非小細胞肺がんの集学的治療に関する研究, がん臨床研究・研究成果

発表会（厚生労働省科学研究費研究成果等普及啓発事業）（2006.1.16）東京

H. 知的財産権の出願・登録状況（予定を含む。）

1. 特許取得：特記すべき事項なし。
2. 実用新案登録：特記すべき事項なし。
3. その他：特記すべき事項なし。

別紙5

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kato, H., Nakamura, H., Tsuboi, M., Ikeda, N., Tsuchida, T., Kato, Y., Hirano, T.	Treatment of Peripheral Early Stage Lung Cancer	Ann. of Thoracic and Cardiovascular Surgery	10(1)	1-3	2004
Ikeda, N., Maeda, J., Yashima, K., Tsuboi, M., Kato, H., Akada, S., Okada, S.	A clinicopathological study of resected adenocarcinoma 2 cm or less in diameter	Ann Thorac Surg	78(3)	1011-1016	2004
Nakamura, H., Kato, Y., Kato, H.	Outcome of surgery for small lung cancer-response to induction chemotherapy predicts survival	Thorac Cardiovasc Surg	52	206-210	2004
Nakamura H, Aute I, Kawasaki N, Taguchi, Ohira T, Kato H.	Quantitative detection of lung cancer cells by fluorescence in situ hybridization: comparison with conventional cytology.	Chest	128(2)	906-911	2005
Furukawa K., Miura T., Kato Y., Okada S., Tsutusi H., Shimatani H., Kajiwara N., Taira M., Satoto M., Kato H.	Microwave coagulation Therapy in Canine Peripheral Lung Tissue.	Journal of Surgical Research	123	245-250	2005
Kato Y., Hirano T., Yoshida K., Yashima K., Akimoto S., Tsuji K., Ohira T., Tsuboi M., Ikeda N., Ebihara Y., Kato H.	Frequent loss of E-cadherin and/or catenins in intrabroncial lesions during carcinogenesis of the bronchial epithelium.	Lung Cancer	48(3)	323-330	2005
Tsuchiya R., Suzuki K., Ichinose Y., Watanabe Y., Yasumitsu T., Ishizuka N., Kato H.	Phase II trial of postoperative adjuvant cisplatin and etoposide in patients with completely resected stage I-IIIa small cell lung cancer: The Japan Clinical Oncology Lung Cancer Study Group Trial (JCOG9101)	Journal of Thoracic and Cardiovascular Surgery	129(5)	977-983	2005
Fujii K., Nakano T., Kanazawa M., Akimoto S., Hirano T., Kato H., Nishimura T.	Clinical-scale high-throughput human plasma proteome analysis: Lung adenocarcinoma.	Proteomics	5	1150-1159	2005
Kato H., Tsuboi M., Kato Y., Ikeda N., Okunaka T., Hamada C.	Postoperative adjuvant therapy for completely resected early-stage non-small cell lung cancer.	Int J Clinical Oncology	10	157-164	2005
Nakamura H., Fujita K., Nakagawa H., Kishi F., Takeuchi A., Aute I., Kato H.	Expression pattern of the scaffold protein IQGAP1 in lung cancer.	Oncology Reports	13(3)	427-431	2005
Tsuboi M, Kato H, Nagai K, Tsuchiya R, Wada H, Tada H, Ichinose Y, Fukuoka M, Jiang H.	Gefitinib in the adjuvant setting: safety results from a phase III study in patients with completely resected non-small cell lung cancer.	Ant-icancer Drugs	16(10)	1123-1128	2005

Furukawa K, Kato H, Konaka C, Okunaka T, Usuda J, Ebihara Y.	Locally recurrent central-type early stage lung cancer <1.0 cm in diameter after complete remission by photodynamic therapy.	Chest	128(5)	3269-3275	2005
Saji, H. Song, W.*, Furumoto, K.*, Kato, H., Engleman, E. G.*	Systemic antitumor effect of intratumoral injection of dendritic cells in combination with local photodynamic therapy.	Clin Cancer Res	12	2568-2574	2006
Nitadori, J. Ishii, G., Tsuta, K., Yokose, T., Murata, Y., Kodama, T., Nagai, K., Kato, H., Ochiai, A.	Immunohistochemical Differential Diagnosis Between Large Cell Neuroendocrine Carcinoma and Small Cell Carcinoma by Tissue Microarray Analysis With a Large Antibody Panel	Ameican Journal of Clinical Pathology	125(5)	682-692	2006
Saijo, T. Ishii, G., Nagai, K., Funai, K., Nitadori, J., Tsuta, K., Nara, M., Hishida, T., Ochiai, A.	Differences in clinicopathological and biological features between central-type and peripheral-type squamous cell carcinoma of the lung	Lung Cancer	52(1)	37-45	2006
Hirano ,T. Kato ,H.	Present status of clinical proteomic analysis for the early detection and determination of therapeutic strategy in lung cancer	AnnThorac Cardiovasc Surg	12	4-9	2006
Rusch, VW. Tsuchiya, R., Tsuboi, M., Pass, HI., Grunenwald, D., Goldstraw, P.	Surgery for bronchioloalveolar carcinoma and "very early" adenocarcinoma: an evolving standard of care?	J Thorac Oncol	1	S27-S31	2006
Ohira, T. Suga, Y., Nagatsuka, Y., Usuda, J., Tsuboi, M., Hirano, T., Ikeda, N., Kato, H.	Early-stage lung cancer: diagnosis and treatment.	Int J Clin Oncol	Feb;11(1)	9-12.	2006
Tsuboi, M. Kato, H., Ichinose, Y., Ohta, M., Hata, E., Tsubota, N., Wada, H., Hamada, C., Hamajima, N., Ohta, M., On behalf of the Japan Lung Cancer Research Group (JLCRG) on Postsurgical Adjuvant Chemotherapy	The influence of tumor size, histological differentiation and smoking history in patients with completely resected stage I adenocarcinoma of the lung; Subset analyses of the Japan Lung Cancer Research Group (JLCRG) trial	J Clin Oncol	24	413S	2006

Editorial

Treatment of Peripheral Early Stage Lung Cancer

Harubumi Kato, Haruhiko Nakamura, Masahiro Tsuboi, Norihiko Ikeda, Takaaki Tsuchida, Yasufumi Kato, and Takashi Hirano

Introduction

Not only is the incidence of lung cancer increasing around the world, this disease has become the leading cause of cancer death. Since lung cancer kills 85% to 90% of its victims, it is recognized as one of the most difficult to cure diseases. Although the therapeutic results are quite unsatisfactory as a whole, earlier stages of lung cancer, stages IA and IB show better therapeutic results (Table 1).[1] To improve the therapeutic results of lung cancer, efforts for early detection and treatment are essential. In our institution, the 5-year survival rate has gradually improved over the past five decades. These results could be due to improvement of therapeutic procedures including surgery, chemotherapy, radiotherapy, laser therapy and immunotherapy. Furthermore, the improvement of survival may be partially due to lung cancer mass screening made by the Health Insurance Act of 1987.

Lung cancer mass screening by chest computed tomography (CT) was begun in Japan 10 years ago and now is becoming subsequently used in the United States and Europe. Since large numbers of peripheral tiny lung shadows were detected in many of the CT screening pilot trials,[2,3] it is important to establish an internationally accepted definition of peripheral type early stage lung cancer.

In this editorial the authors describe the present status and prospects for the treatment of early stage lung cancer.

The Criteria of Early Stage Lung Cancer

Since there are no authorized international criteria of early stage lung cancer, establishment of criteria is urgently required. According to the location of the tumor, early stage lung cancers are classified into two categories; central type and peripheral type.

In Japan, the criteria of early stage lung cancer were first proposed about 30 years ago, in 1975. Peripheral type early stage lung cancer was defined as a tumor located in an airway more peripheral than subsegmental bronchi, and the longest dimension of the tumor should be 2 cm or less and with no recognized lymph node and distant metastases. In central type early stage lung cancer, the tumor should be located in a segmental bronchus or more proximal airway, and the depth of tumor invasion should be limited to within the bronchial wall with no lymph node or distant metastases. These criteria of central type early stage lung cancer were first defined pathologically in a resected lung by Ikeda in a study supported by the Ministry of Health and Welfare in Japan. Now we have criteria of endoscopically diagnosed central type early stage lung cancer defined by the Japan Lung Cancer Society.[4]

Therapeutic Guidelines of Early Stage Lung Cancer

In Japan, the therapeutic guidelines of lung cancer established on Evidence-based Medicine were made with the support of the Ministry of Health, Labor and Welfare in 2002. In these guidelines, surgical resection and PDT are recommended for treatment of central type early stage lung cancer.[5]

The Possibility of Limited Resection by Video-assisted Thoracoscopic Surgery (VATS)

The standard therapeutic procedure for peripheral type early stage lung cancer is believed to be lobectomy with mediastinal lymph node dissection. However the question was raised whether lobectomy is really needed for tiny tumors, particularly those less than 1 cm in greatest

From Department of Surgery, Tokyo Medical University, Tokyo, Japan

Address reprint requests to Harubumi Kato: Department of Surgery, Tokyo Medical University, 6-7-1 Nishi-shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan.

Table 1. Survival rates according to pathologic stages (n=7,047)

p-stage	n	1 year	2 year	3 year	4 year	5 year
IA	2,142	96.5	92.8	87.9	82.7	79.2
IB	1,488	90.2	80.3	72.4	65.6	60.1
IIA	261	90.7	78.6	68.4	62.9	58.6
IIB	785	81.3	64.5	52.7	47.6	42.2
IIIA	1,337	74.7	53.8	40.3	32.6	28.4
IIIB	759	64.6	40.2	28.4	22.5	20
IV	275	60.3	39.4	29.9	22.5	19.3

n: numbers of patients with lung cancer

dimension. There are several reports on limited resection of small lung cancer.[6,7] Some of these results showed satisfactory 5-year survival rates. Clinical trials to clarify the possibility of limited resection are needed for particularly small lung cancers showing ground glass opacity (GGO), or ground glass attenuation (GGA) . Most of these lesions showed no lymph node metastases, and a 100% 5-year survival was obtained in such cases who underwent resection. A multi-center clinical trial sponsored by the Japan Clinical Oncology Group (JCOG) just started to examine the suitability of limited resection for peripheral small lung cancer. Wedge resection of small lung cancer by VATS without lymph node dissection is one type of the minimally invasive surgery. If some types of lung cancer could be shown to be resected by VATS without any increase of local recurrence, this method could become a future standard treatment for peripheral small lung cancer.

The Rate of Lymph Node Metastasis of Peripheral Small Nodular Cancer

In the past five years, 783 patients with lung cancer underwent surgery in our institution. Among them there were 150 patients with peripheral nodules less than 2 cm in diameter, including 135 adenocarcinomas. Lobectomy was performed in 93 cases and limited resection was performed in 42 cases. The pathological prognostic factors were investigated for the future selection of surgical procedures in the peripheral small nodules. Of cases less than 1 cm, 97.5% of cases showed no lymph node involvement, however even in such tiny tumors 2.5% of them already showed N2 disease. In the cases between 1 and 1.5 cm, 91.9% of cases showed no metastasis, however 8.1% showed either N1 or N2 involvements. In the cases between 1.5 and 2 cm, lymph node involvement was recognized in 12%. Therefore it seems that the tumor size does not have a large correlation with lymph node involvement.

According to Noguchi's classification,[8] bronchioloalveolar cell carcinoma showing findings of GGO on CT images did not have any nodal metastases.[9] The CT images of our cases were classified into four categories according to the percentages of areas of GGO findings in relation to the entire tumor; 100% GGO, between 50% and 100%, less than 50% and 0% GGO findings. According to these criteria, 16 cases consisted of GGO in 100% of the tumor area and 21 cases consisted of between 50% and 100% GGO. These two groups showed no lymph node metastases. Furthermore, in cases with GGO findings consisting of less than 50% or 0% of the lesion, cases with a tumor size of less than 1 cm showed no lymph node metastasis. However, two cases with a tumor size more than 1 cm had nodal metastases. In the cases with 0% GGO, the presence of lymph node metastases was not related to the sizes of the tumor. The overall 5-year survival rate in adenocarcinoma 2 cm or less in tumor size was 93.3%.

The survival curves according to the postoperative stage showed a 98.1% 5-year survival rate in stage IA, 54.7% in stage IIIA and no 5-year survivals in stages IIA and IV. Since the number is small in stages IIA and IV, it is necessary to increase the number for accurate evaluation. In the survival curves according to the tumor size, tumors less than 1 cm showed a 100% 5-year survival rate. In tumors between 1 and 1.5 cm the survival rate was 86.5%, and in cases between 1.5 and 2 cm, the 5-year survival rate was 92.4%. On the survival curves according to area of GGO finding, the cases consisting of more than 50% GGO showed 100% 5-year survival rate and the cases consisting of less than 50% GGO had 91.1% 5-year survival rate. From these data it seems that the proportion of GGO in the tumor may be related to prognosis. The survival rate was 100% in cases of limited operation and 91.5% in lobectomy cases. The better result of limited resection than lobectomy might be due to selection bias.

Future Surgical Procedures for Peripheral Early Stage Lung Cancer

Tumors with 100% GGO findings on CT images could indicate the suitability of surgical limited resection by VATS. Lesions consisting of between 50% and 100% of GGO in area may also be indication for limited resection in cases less than 2 cm in diameter, and also perhaps in cases consisting of between 10% and 50% GGO finding with a tumor size less than 1 cm in diameter.

The evaluation of limited resection for the small peripheral nodules were reported previously by several researchers,[6,7,9] however different opinions concerning these modalities have been reported.[10,11] There are still controversies concerning limited resection of peripheral small lung cancers. A randomized clinical trial by the Lung Cancer Study Group (LCSG) demonstrated disadvantages of limited resection for T1N0 tumors in relation to lobectomy.[11] Therefore clinical evidence of the usefulness of limited resection for peripheral early stage lung cancers should be proven. The features of peripheral lung cancers suitable for limited resection without lymph node dissection should be clarified. That will make it possible to determine the optimal CT findings for limited resection.

In our experience, even if the primary lesion was less than 1 cm in size, nodal involvement was confirmed histologically in some cases. Prognostic factors may not solely depend on tumor size but also on the percentage of the area of GGO. It is necessary to clarify the findings of CT images of non-invasive cancer by a clinical multicenter study.

Acknowledgment

The authors are indebted to Prof. J. Patrick Barron of the International Medical Communication Center of Tokyo Medical University for his review of this manuscript.

References

1. Shirakusa T, Kobayashi K. Lung cancer in Japan. Analysis of lung cancer registry for resected cases in 1994. Japanese joint committee of lung cancer registry. *Jpn J Chest Surg* 2002; **16**: 757–68.
2. Kaneko M, Eguchi K, Ohmatsu H, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. *Radiology* 1996; **201**: 798–802.
3. Sone S, Takashima S, Li F, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet* 1998; **351**: 1242–5.
4. The Japan Lung Cancer Society. Classification of Lung Cancer. Tokyo: Kanahara, 2000; pp 34–5.
5. Furuse K, Fukuoka M, Kato H, et al. A prospective phase II study on photodynamic therapy with photofrin II for centrally located early-stage lung cancer. The Japan Lung Cancer Photodynamic Therapy Study Group. *J Clin Oncol* 1993; **11**: 1852–7.
6. Jensik R, Faber L, Kittle C. Segmental resection for bronchogenic carcinoma. *Ann Thorac Surg* 1979; **28**: 475–83.
7. Kodama K, Doi O, Higashiyama M, Yokouchi H. Intentional limited resection for selected patients with T1 N0 M0 non-small-cell lung cancer: a single-institution study. *J Thorac Cardiovasc Surg* 1997; **114**: 347–53.
8. Noguchi M, Morikawa A, Kawasaki M, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer* 1995; **75**: 2844–52.
9. Watanabe S, Watanabe T, Arai K, Kasai T, Haratake J, Urayama H. Results of wedge resection for focal bronchioloalveolar carcinoma showing pure ground-glass attenuation on computed tomography. *Ann Thorac Surg* 2002; **73**: 1071–5.
10. Miller D, Rowland C, Deschamps C, Allen M, Trastek V, Pairolero P. Surgical treatment of non-small cell lung cancer 1 cm or less in diameter. *Ann Thorac Surg* 2002; **73**: 1545–50.
11. Ginsberg R, Rubinstein L. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg* 1995; **60**: 615–22.

A Clinicopathological Study of Resected Adenocarcinoma 2 cm or Less in Diameter

Norihiko Ikeda, MD, PhD, Junichi Maeda, MD, Koichi Yashima, MD, Masahiro Tsuboi, MD, Harubumi Kato, MD, PhD, Soichi Akada, MD, PhD, and Shinya Okada, MD, PhD

Departments of Thoracic Surgery, Radiology, and Pathology, Tokyo Medical University, Tokyo, Japan

Background. The biological behavior of small adenocarcinoma is different in each patient and these are especially enormous differences when evaluating solid tumors and nonsolid tumors.

Methods. A total of 159 adenocarcinomas 2 cm or less in diameter were studied. Several clinicopathological factors were retrospectively analyzed.

Results. The diameter of the primary tumors was less than 1 cm in 47 patients, 1–1.5 cm in 49 patients, and 1.5–2 cm in 63 patients, respectively. Almost all patients (147) were pathologic N0 and there were 12 node-positive patients (7.5%). Lymph-node involvement was observed in 1 patient with a tumor diameter measuring less than 1 cm and in 11 patients with a tumor diameter measuring 1–2 cm. According to Noguchi' s classification, 33 patients belonged to class A or B, 71 patients belonged to class C, and 55 patients belonged to class D, E, or F. The ratio of ground-glass opacity (GGO) area in the main tumor in high resolution computed tomography was classified into two groups with a threshold of 50%. There were 44 patients with a GGO ratio of equal to or greater than 50%, none of which indicated lymph-node metastasis or tumor recurrence during follow-up (5-year survival = 100%). On the contrary among 115 patients with a GGO ratio less than 50%, lymph-node involvement was indicated in 12 patients (10.4%) and the 5-year survival rate was 83.9%.

Conclusions. The biological malignancy of small adenocarcinomas might be accurately evaluated by the proportion of GGO area as well as the Noguchi classification.

(Ann Thorac Surg 2004;78:1011–6)

Lung cancer is the greatest cause of cancer-related death in the world because most lung cancers are detected at a late stage and curative treatment is not an option. Nevertheless a cure rate of greater than 70% was obtained in completely resected patients of stage I cancer [1]. Prevention and early detection are thus essential with regard to the reduction of lung cancer mortality. Adenocarcinoma is the most common type of lung cancer arising from the peripheral lung parenchyma. Chest x-ray surveys have been considered useful for early detection. However if the lesions are located in a "dead angle" on the chest roentgenogram film, such as behind the aorta or heart, abnormalities may be overlooked. Bronchioloalveolar carcinoma (BAC) seldom reveals abnormalities on chest roentgenogram because it grows without destroying alveolar structure [2]. Helical computed tomography (CT) screening has greatly increased the sensitivity of cancer detection compared with that of conventional chest roentgenogram screening [3–7]. A prospective randomized trial comparing the lung cancer mortality rate of a CT screening group with that of a conventional chest roentgenogram screening group has been conducted by the National Cancer Institute [8]. In this respect, the biggest issue facing thoracic surgeons is the treatment strategy for small cancers detected by CT screening, including the possibility of limited resection. BAC is known to exhibit a relatively nonaggressive nature, therefore a favorable outcome can be expected after curative operation [2, 9–12]. However patients with solid images on chest CT tend to have invasive adenocarcinomas and their survival is definitely worse than that of BAC [9–11]. Pathologic classification of the tumor is essential regarding the evaluation of the aggressiveness of each patient [2] but postoperative pathologic findings cannot exhibit a strong impact on the choice of treatment.

There are several reports indicating that the ratio of the size of ground-glass opacity (GGO) and that of consolidation on high resolution CT (HRCT) is strongly related to the stage and prognosis of the cancer [10, 13–15]. Lung cancers with a large GGO component tend to be BAC or minimally invasive adenocarcinomas that exhibit favorable prognoses [10, 13–15]. If a definition of peripheral early cancer could be established, it would be useful with regard to selecting optimal treatment for individual patients. For this purpose we retrospectively analyzed clinicopathological features of adenocarcinomas with a diameter of 2 cm or less resected in our hospital between 1997–2002.

Patients and Methods

Patients

A total of 983 lung cancer operations were performed from January 1997 to December 2002 at the Department

Accepted for publication March 15, 2004.

Address reprint requests to Dr Ikeda, 6-7-1, Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan; e-mail: ikeda@wd5.so-net.ne.jp.

Published by Elsevier Inc

0003-4975/04/$30.00
doi:10.1016/j.athoracsur.2004.03.048

Ann Thorac Surg
2004;78:1011–6

Table 1. Patient Characteristics

Character	
Age	
Average	63
Minimum	40
Maximum	84
Sex	
Male	67
Female	92
Smoking habit	
Non-smoker	89
Smoker	70
Operative procedure	
Lobectomy	112
Segmantectomy	20
Wedge resection	27

of Thoracic Surgery, Tokyo Medical University Hospital (Tokyo, Japan). Among these, there were 168 patients with peripheral adenocarcinomas less than 2 cm in diameter as well as a total of 159 patients who had undergone high-resolution computed tomography (HRCT) and in whom complete records were available for study (Table 1). There were 67 men and 92 women ranging in age from 40–84. There were 89 nonsmokers and 70 smokers. The primary lesions were detected by chest x-ray in 115 patients: detection was determined by mass survey or private general check-up in 81 patients, follow-up for other diseases in 18 patients, and respiratory symptoms in 16 patients. The other 44 patient's lesions were detected by chest CT performed by mass survey program or private general check-up.

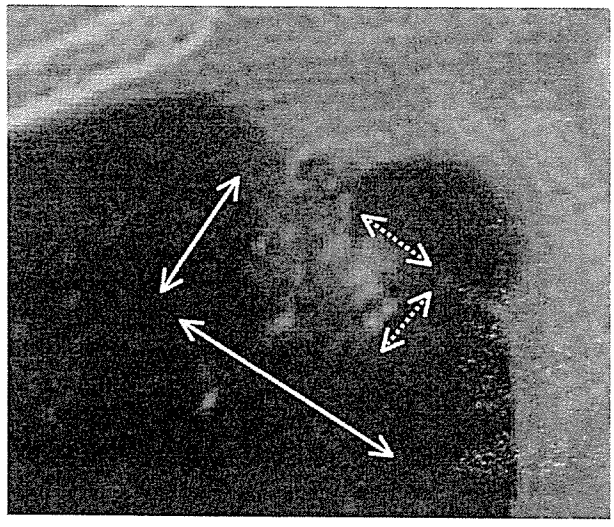

Fig 1. Thin section computed tomographic scan of lung cancer depicting solid attenuation and ground-glass opacity (GGO). The largest area of tumor (solid line) *and solid attenuation* (dotted line) *were decided based on this film. The proportion of GGO area to the entire tumor was defined; GGO ratio = (maximum GGO − maximum consolidation)/maximum GGO. Max GGO* (solid arrow); *Max consolidation* (dotted arrow).

All patients underwent a physical examination and blood examination, respiratory function test, electrocardiogram, and chest radiography. Also, all patients received helical CT of the chest preoperatively with 10-mm thick continuous sections. HRCT images with 1–2 mm slices of the primary tumors were then performed to obtain the precise findings of GGO and consolidation of the tumors. Histologic typing was diagnosed based upon the classification of the World Health Organization (WHO) and we also classified all of the patients into six subtypes using the Noguchi classification. The staging of patients was determined by the thoracic wall, node involvement, and metastases (TNM) classification of the International Union Against Cancer (UICC).

Lobectomy combined with systemic mediastinal lymph-node dissection was performed in 112 patients and limited surgery was performed in 47 patients. Of these 47 patients, 37 received intentionally limited operation because of the nonaggressive appearance on HRCT and the remaining 10 patients because of impaired condition. Segmentectomy with mediastinal sampling was performed in 27 patients and wedge resection without nodal dissection was performed in 20 patients. All patients that underwent wedge resection indicated pure GGO or enormously GGO-dominant findings on HRCT as well as being clinically node negative.

CT Findings

In this study the ratio of the size of solid attenuation to that of GGO was extensively analyzed. GGO was defined as a hazy increase in lung attenuation without obscuration of the underlying vascular marking. At least two experienced chest surgeons and radiologists reviewed the hard-copy films of HRCT and determined the maximal area of GGO and tumor. Discrepancies between reviewers were resolved by consensus. The ratio area of GGO to the area of primary tumor was calculated as illustrated in Figure 1. Patients were divided into two groups: those with a GGO ratio greater than 50% and those with a GGO ratio less than 50%.

Pathology

Resected lungs were fixed in formalin and stained by hematoxylin and eosin staining in a routine manner and also stained with elastica van Gieson. Experienced pathologists diagnosed the subtypes of primary tumors according to the Noguchi classification as well as the nodal status. The Noguchi classification is presented in Table 2. Types A and B are considered to be noninvasive cancers and types D, E, and F are considered to be invasive cancer.

Statistics

We examined the relation of the proportion of GGO area to maximal tumor size, stage, Noguchi classification, and other prognostic factors. The χ^2 test using StatView 5.0 (SAS Institute Inc., Cary, NC) was performed and the differences were considered to be statistically significant

Table 2. Tumor Size and Nodal Status

Tumor Size	N0	N1	N2
1.0 cm or less (n = 47)	46	0	1
1.0–1.5 cm (n = 49)	46	1	2
1.5–2.0 cm (n = 63)	55	2	6

when the p value was less than 0.05. All patients were periodically examined and the average length of follow-up was 40 months. The 5-year survival curve was obtained using the Kaplan–Meier method.

Results

A total of 159 patients were studied. The size was classified into three categories: 1 cm or less, 1–1.5 cm, and 1.5–2 cm. There were 47, 49, and 63 patients, respectively. There were 147 pathologic N0 patients and lymph-node metastasis was recognized in 12 patients (7.5%); N1 in 3 patients and N2 in 9 patients. Table 3 lists the rate of lymph-node involvement according to tumor size. Lymph-node involvement was not indicated in 98% of patients who had a tumor size of 1 cm or less, however even in patients with tiny tumors, 2% indicated N2 disease. In patients who had a tumor size of 1 and 1.5 cm, 94% indicated no metastasis but 6% were either N1 or N2. In patients who had a tumor size of 1.5 and 2 cm, lymph-node involvement was recognized in 13%.

In this study the proportion of the size of GGO to that of the tumor was extensively analyzed. We divided patients into two categories according to how much of the lesion consisted of GGO findings. According to these criteria, 44 tumors consisted of greater than 50% of GGO and 115 tumors consisted of less than 50% of GGO. Patients with a GGO ratio of greater than 50% indicated no lymph-node metastases. On the contrary all node-positive patients indicated a GGO ratio of less than 50% (Table 3). The relationship between the proportion of GGO area on HRCT and the Noguchi classification is indicated in Table 4.

Twenty-five out of 44 patients (76%) of types A and B indicated a GGO component of greater than 50% on HRCT. Seventeen out of 71 patients (24%) of type C indicated greater than 50% GGO and the remaining 54 patients (76%) indicated less than 50% GGO. Fifty three out of 55 patients (96%) of types D, E, and F tumors indicated less than 50% GGO. A favorable correlation between CT findings and the Noguchi classification was recognized.

Table 3. GGO Area and T,N Status

GGO%	T ≦ 1	1 < T ≦ 5	1.5 < T ≦ 2	
50 ↑	18	16	10	44
50 ↓	29 (1)[a]	33 (3)[a]	53 (8)[a]	115 (12)[a]

[a] The number in parentheses corresponds to the number of node-positive cases.

GGO = ground-glass opacity.

Table 4. GGO Area and Noguchi Classification

GGO%	A, B	C	D, E, F	
50 ↑	25	17	2	44
50 ↓	8	54	53	115

GGO = ground-glass opacity.

The relationship between representative clinicopathological factors and the proportion of GGO area is indicated in Table 5. According to the χ^2 test, the ratio of GGO area to that of the tumor is related to the tumor size ($p = 0.0135$) and pathologic stage ($p = 0.04$). In particular a significant relationship was obtained regarding the pathologic features including Noguchi classification ($p = 0.0001$), vascular invasion, and lymphatic invasion .

Patients were followed-up in the outpatient clinic and periodically received blood examinations, chest roentgenogram, and chest CT. The median follow-up period for all patients was 40 months. The overall 5-year survival rate of patients studied was 88.0% (Fig 2), but it was 96.7% in patients with tumors less than 1 cm in diameter, 81.6% in patients with tumors between 1 and 1.5 cm, and 84.4% in patients with tumors between 1.5 and 2 cm (Fig 3).

The 5-year survival rate according to how much of the lesion consisted of GGO findings was also analyzed. In patients with tumors greater than 50% GGO, a 100% 5-year survival rate was obtained, but in patients with tumors less than 50% GGO an 83.9% 5-year survival rate was obtained (Fig 4)

The survival rate according to the Noguchi classification is illustrated in Figure 5. A 100% 5-year survival rate was obtained in types A and B, 97.4% in type C, and 67.1% in types D, E, and F, respectively, which was statistically lower than the results of types A, B, and C.

Comment

Because of the increasing widespread application of helical CT, the detected number of small lung peripheral nodules has enormously increased [3–7]. In addition the size of peripheral type adenocarcinomas has been smaller on average when they were detected. This has raised several issues: discerning how to discriminate

Table 5. Relationship Between Prognostic Factors and GGO Ratio on HRCT

Prognostic Factor	χ^2	p Value
Gender	0.162	0.687
Tumor size	8.616	0.0135
p stage		
I or II–IV	4.168	0.0412
Noguchi classification		
A, B, C or DEF	14.442	0.0001
Vascular invasion	6.76	0.0093
Lymphatic invasion	5.326	0.0206

GGO = ground-glass opacity; HRCT = high resolution computed tomography.

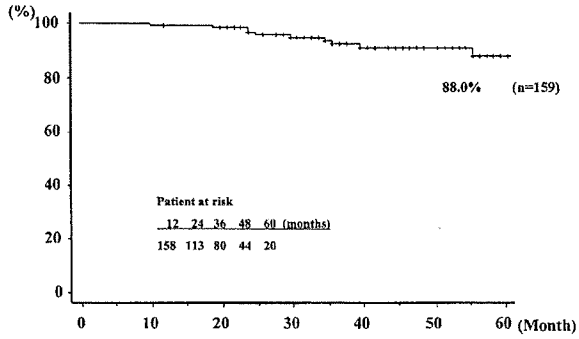

Fig 2. Five-year survival rate of adenocarcinoma less than or equal to 2 cm was 88.0%.

malignant from benign nodules, the usefulness of CT screening in diminishing lung cancer mortality, the optimal intervention in patients who have small nodules, and so on [16, 17]. The management of small cancers is a particular concern of thoracic surgeons, because some of these small cancers might be managed appropriately by limited resection. As previously reported adenocarcinoma tends to metastasize to the regional lymph nodes even if small in size. Nearly 20% of adenocarcinomas less than 2 cm in diameter were reported to be node positive and 5% of adenocarcinomas less than 1 cm were also considered as N1 or N2 disease [18–20]. The Lung Cancer Study Group failed to demonstrate positive results with regard to limited resection for clinical T1 lung cancers. The limited surgery group indicated a local recurrence rate of 5–6 times higher than the lobectomy group [21]. Thus lobectomy and locoregional lymph-node dissection have been recommended as standard lung cancer procedures. However if peripheral early cancer is properly defined, such patients could be managed by lesser resection, which would be useful with regard to decreasing the operative mortality and morbidity as well as enhancing the performance status of the patients.

In our study 12 out of 159 patients (7.5%) exhibited lymph-node metastasis and even tumors measuring 1 cm or less indicated lymph-node metastasis in 2% of patients. The 5-year survival rate did not indicate a statistically significant difference between the three groups

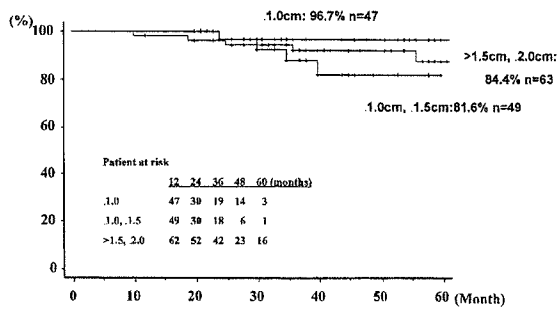

Fig 3. Five-year survival rate according to tumor size. Less than or equal to 1 cm = 96.7%, 1.0–1.5 cm = 81.6%, 1.5–2.0 cm = 84.4%.

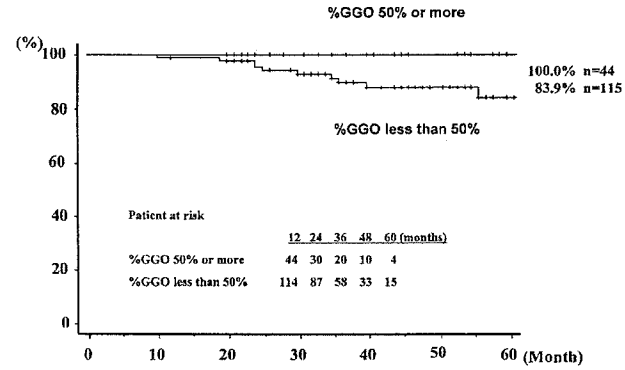

Fig 4. Five-year survival rate according to the proportion of ground-glass opacity (GGO) area. A GGO dominant patient indicated a 100% 5-year survival, whereas patients exhibiting a GGO area less than 50% indicated an 83.9% 5-year survival.

according to tumor size in this study. There are reports that 5%–8% of such tiny adenocarcinomas indicated lymph-node metastasis [18, 22]. Kondo reported 57 adenocarcinomas measuring 1 cm or less, none of which indicated lymph-node metastasis, and 49 revealed BAC without destructive growth that were categorized as nonaggressive tumors [23]. This demonstrates that the indications of limited surgery cannot be determined by size alone. In our study, 47 patients received limited resection. Out of these, mediastinal lymph node or sampling were performed in 20 patients and the rest of 27 patients received wedge resection without nodal dissection. Of these 27 patients stage migration may occur because nodal status was not evaluated pathologically. However these patients indicated pure GGO or overwhelmingly dominant GGO findings on chest CT as well as being clinically node negative. Such patients have been reported to be free from lymph-node metastasis [10, 12–15, 20] and recurrence was not observed in any of these patients by chest CT examination during follow-up.

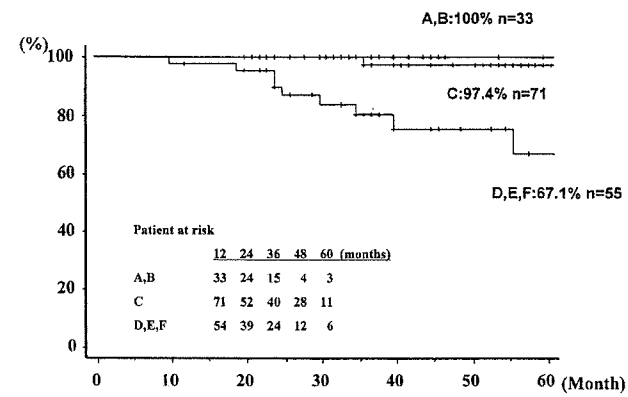

Fig 5. Five-year survival rate according to the Noguchi classification. Noguchi A, B indicated a 100% 5-year survival, type C indicated a 97.4% 5-year survival, and types D, E, and F, indicated a 67.1% 5-year survival, respectively.

Therefore we classified these patients as N0 in this study. Noguchi classified small adenocarcinomas into six categories (types A–F) and this classification indicated a favorable correlation with the biologically aggressive nature of the tumor [2]. Types A and B are localized BAC with or without foci indicating a collapse of alveolar structures that are recognized to be noninvasive. Types D, E, and F are poorly differentiated, tubular, papillary type, respectively, and are invasive. Pathologic analysis revealed that all type A and B patients were N0, however 25%–56% of type D, E, and F patients indicated lymph-node metastasis [2]. Many thoracic surgeons postulated that certain types of adenocarcinomas might be candidates for limited resection and have sought for criteria of "peripheral early cancer." The Noguchi classification is useful with regard to evaluating the aggressive nature in individual patients, but this criteria is based on postoperative pathologic findings and could not have a strong impact on the choice of treatment. Therefore we require criteria that are available preoperatively to define early minimally invasive cancers.

Increased amounts of collagenization or hyalinization microscopically detected in the central fibrotic focus in adenocarcinoma have been reported to influence the prognosis and the smaller the central fibrosis, the more favorable the prognosis [24, 25]. Suzuki reported that central fibrosis in a tumor corresponds to consolidation on HRCT. Thus the ratio of the area of GGO and that of consolidation seems to be strongly related to nodal status and stage [25].

In our study there were 12 N1 or N2 out of 159 patients, in all of whom the proportion of the area of GGO to the entire tumor was less than 50%. All patients with a ratio of GGO greater than 50% survived without recurrence during the follow-up period, although patients with GGO less than 50% indicated an 83.9% 5-year survival rate. The proportion of the GGO area correlates well with the Noguchi classification [26]. There were 33 Noguchi type A and B patients, 25 of which indicated a GGO area of greater than 50% and 8, of which indicated a GGO area of less than 50%. As for type D, E, and F patients, 53 out of 55 indicated a low GGO% and only 2 patients belonged to the high GGO ratio group. A statistically significant correlation was obtained between GGO% and Noguchi classification but types A and B could be completely diagnosed by HRCT findings as they should be the suitable indication of limited surgery. The 5-year survival rate of the high GGO group was 100% and the 5-year survival rate of the low GGO group was 83.9%. Similar results were obtained by Matsuguma who compared the preoperative HRCT findings with pathologic results in 96 patients who underwent surgical resection because of stage Ia cancers [14]. They determined that patients in whom the proportion of GGO to the whole tumor on CT was equal to or greater than 50% exhibited no nodal metastasis or postoperative recurrence. Small cancers with a high GGO ratio might be candidates for limited resection and a large multicenter study is necessary to confirm this postulate.

Limited resection has mostly been performed on patients with poor pulmonary reserve. Intentional limited surgery has not been common, particularly because lobectomy has been considered to be the standard treatment, which was confirmed by a randomized trial of the Lung Cancer Study Group [21]. However some successful results regarding limited surgery for T1 N0 tumors were published by Yamato who proposed limited resection for BAC by employing intraoperative pathological examination to confirm the absence of nodal metastasis [27]. They planned to convert limited resection to lobectomy if some invasive signs were recognized by frozen section. Tsubota performed extended segmentectomy for 55 patients with peripheral cancers measuring less than 2 cm in diameter and only 1 patient locally recurred in whom N2 disease was not indicated during operation [28]. Nakata performed thoracoscopic wedge resection for 33 pure GGO patients with tumors measuring less than 1 cm and no recurrence or metastasis was indicated during the follow-up period [12]. However well-differentiated adenocarcinomas or GGO-dominant tumors are considered to be indolent and slow-growing, therefore a long-term observation period is necessary to evaluate whether limited surgery could be an alternative to lobectomy.

In this study the ratio of GGO and consolidation on chest CT allows for the evaluation of the aggressive nature of small adenocarcinomas. However further investigation is required in this area, especially to characterize GGO on HRCT. Also genomic or proteomic studies are necessary to provide the clues to discriminate tumors with an indolent nature from those with an aggressive nature. Comprehensive research including pathology and molecular analysis will alter the conventional method of management regarding tiny cancers, which will be of great importance in daily practice.

The authors are indebted to Professor James Patrick Barron and Assistant Professor Raoul Breugelmans of the International Medical Communications Center at Tokyo Medical University (Tokyo, Japan) for their review of this manuscript.

References

1. Naruke T, Goya T, Tsuchiya R, et al. Prognosis and survival in resected lung carcinoma based on the new international staging system. J Thorac Cardiovasc Surg 1988;96:440–7.
2. Noguchi M, Morikawa A, Kawasaki M, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. Cancer 1995;75:2844–52.
3. Henschke C, McCauley D, Yakelevitz D, et al. Early Lung Action Project. Overall design and findings from baseline screening. Lancet 1999;354:99–105.
4. Sobue T, Moriyama N, Kaneko M, et al. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. J Clin Oncol 2002;20:911–20.
5. Sone S, Takashima S, Li F, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. Lancet 1998;351:1242–5.
6. Kaneko M, Eguchi K, Ohmatsu H, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. Radiology 1996;201:798–802.
7. Nawa T, Nakagawa T, Kusano S, et al. Lung cancer screening using low-dose spiral CT- results of baseline and one-year follow-up studies. Chest 2002;122:15–20.

8. Marcus PM. Lung cancer screening: an update. J Clin Oncol 2001;19(Suppl 18):83S–6.
9. Suzuki K, Asamura H, Kondo H, et al. Clinical predictors of minimally invasive peripheral adenocarcinoma of the lung: possible indications for limited surgical resection. Lung Cancer 2000;29:142.
10. Suzuki K, Asamura H, Kusumoto M, et al. "Early" peripheral lung cancer: Prognostic significance of ground glass opacity on thin-section computed tomographic scan. Ann Thorac Surg 2002;74:1635–9.
11. Higashiyama M, Kodama K, Yokouchi H, et al. Prognostic value of bronchiolo-alveolar carcinoma component of small lung adenocarcinoma. Ann Thorac Surg 1999;68:2069–73.
12. Nakata M, Sawada S, Saeki H, et al. Prospective study of thoracoscopic limited resection for ground-glass opacity selected by computed tomography. Ann Thorac Surg 2003; 75:1601–6.
13. Aoki T, Tomoda Y, Watanabe H, et al. Peripheral lung adenocarcinoma correlation of thin-section CT findings with histologic prognostic factors and survival. Radiology 2001; 220:803–9.
14. Matsuguma H, Yokoi K, Anraku M, et al. Proportion of ground grass opacity on high-resolution computed tomography in clinical T1N0M0 adenocarcinoma of the lung: A predictor of lymph node metastasis. J Thorac Cardiovasc Surg 2002;124:278–84.
15. Takashima S, Li F, Maruyama Y, et al. Discrimination of subtypes of small adenocarcinoma in the lung with thin-section CT. Lung Cancer 2002;36:175–82.
16. Warner E, Mulshine J. Surgical considerations with lung cancer screening. J Surg Oncol 2003;84:1–6.
17. Rusch V. High-resolution computed tomography in clinical T1N0M0 adenocarcinoma of the lung. J Thorac Cardiovasc Surg 2002;124:221–2.
18. Asamura H, Nakayama H, Kondo H, et al. Lymph node involvement, recurrence, and prognosis in resected small, peripheral, non-small-cell lung carcinomas: are these carcinomas candidates for video-assisted lobectomy? J Thorac Cardiovasc Surg 1996;111:1125–34.
19. Konaka C, Ikeda N, Hiyoshi T, et al. Peripheral non-small cell lung cancers 2.0 cm or less in diameter: proposed criteria for limited pulmonary resection based upon clinicopathological presentation. Lung Cancer 1998;21:185–91.
20. Suzuki K, Nagai K, Yoshida J, et al. Predictors of lymph node and intrapulmonary metastasis in clinical stage IA non-small cell lung carcinoma. Ann Thorac Surg 2001;72:352–6.
21. Lung Cancer Study Group. Randomized Trial of lobectomy versus limited resection for T1N0 non-small cell lung cancer. Ann Thorac Surg 1995;60:615–23.
22. Yoshida J, Nagai K, Yokose T, et al. Primary peripheral lung carcinoma smaller than 1 cm in diameter. Chest 1998;114: 710–2.
23. Kondo D, Yamada K, Kitayama Y, et al. Peripheral lung adenocarcinomas. 10 mm or less in diameter. Ann Thorac Surg 2003;76:350–5.
24. Shimosato Y, Suzuki A, Hashimoto T, et al. Prognostic implications of fibrotic focus (scar) in small peripheral lung cancers. Am J Surg Pathol 1980;4:365–73.
25. Suzuki K, Yokose T, Yoshida J, et al. Prognostic significance of size of central fibrosis in peripheral adenocarcinoma of the lung. Ann Thorac Surg 2000;69:893–7.
26. Ikeda N, Tsuboi M, Hiyoshi T, et al. A clinicopathological study of resected adenocarcinoma less than 2 cm in size. Lung Cancer 2003;41:S51.
27. Yamato Y, Tsuchida M, Watanabe T, et al. Early results of a prospective study of limited resection for bronchioloalveolar adenocarcinoma of the lung. Ann Thorac Surg 2001;71:971–4.
28. Tsubota N, Ayabe K, Doi O, et al. Ongoing prospective study of segmentectomy for small lung tumors. Ann Thorac Surg 1998;66:1787–90.