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局所限局非小細胞肺がんの集学的治療に関する研究

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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。

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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

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A Randomized Trial of Adjuvant Chemotherapy with Uracil–Tegafur for Adenocarcinoma of the Lung

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ABSTRACT

BACKGROUND

In a previous phase 3 trial of adjuvant chemotherapy after resection of non–small-cell lung cancer, a combination of uracil and tegafur (often referred to as UFT) taken orally was shown to prolong survival. A subgroup analysis disclosed that most patients who benefited had pathological stage I adenocarcinoma.

METHODS

We randomly assigned patients with completely resected pathological stage I adenocarcinoma of the lung to receive either oral uracil–tegafur (250 mg of tegafur per square meter of body-surface area per day) for two years or no treatment. Randomization was performed with stratification according to the pathological tumor category (T1 vs. T2), sex, and age. The primary end point was overall survival.

RESULTS

From January 1994 through March 1997, 999 patients were enrolled. Twenty patients were found to be ineligible and were excluded from the analysis after randomization; 491 patients were assigned to receive uracil–tegafur and 488 were assigned to observation. The median duration of follow-up for surviving patients was 73 months. The difference in overall survival between the two groups was statistically significant in favor of the uracil–tegafur group ($P=0.04$ by a stratified log-rank test). Grade 3 toxic effects occurred in 10 of the 482 patients (2 percent) who actually received uracil–tegafur.

CONCLUSIONS

Adjuvant chemotherapy with uracil–tegafur improves survival among patients with completely resected pathological stage I adenocarcinoma of the lung.

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THE COMBINATION OF URACIL AND tegafur (also referred to as UFT) at a molar ratio of 4:1 is an oral anticancer agent with good absorption in the small intestine.[1] Tegafur is a prodrug that is gradually converted to fluorouracil in the liver by the cytochrome P-450 enzyme. Uracil enhances the serum concentration of fluorouracil by competitive inhibition of dihydropyrimidine dehydrogenase, the enzyme responsible for fluorouracil catabolism.[2] Oral uracil–tegafur generates a higher maximal plasma level of fluorouracil than the protracted intravenous injection of fluorouracil given in a dose that is equimolar to the amount of tegafur in uracil–tegafur.[3]

In patients with advanced non–small-cell lung cancer, the rate of response to treatment with uracil–tegafur ranges from 6 percent to 8 percent,[4,5] and a regimen of daily uracil–tegafur for 2 or 3 weeks plus a bolus injection of cisplatin yields a response rate of 29 to 38 percent and a median survival of 8 to 13 months.[6-8] In two trials of uracil–tegafur plus cisplatin with concurrent radiotherapy in patients with locally advanced non–small-cell lung cancer, the response rates were 80 percent[9] and 94 percent,[10] with a median survival of 16.5 months.[9] The results with uracil–tegafur plus cisplatin are similar to the results of other regimens of cisplatin-based combination chemotherapy.[11,12]

The West Japan Study Group for Lung Cancer Surgery reported that survival was significantly longer in patients assigned to adjuvant treatment with uracil–tegafur than in patients assigned to observation alone after complete resection of stage I, II, or III non–small-cell lung cancer.[13] The five-year survival rate was 64 percent in the uracil–tegafur group and 49 percent in the control group (P=0.02). In a subgroup analysis, there was no significant difference in overall survival between the uracil–tegafur group and the control group among patients with squamous-cell carcinoma (P=0.24). In contrast, patients with adenocarcinoma in the uracil–tegafur group had a significantly better survival than those in the control group (P=0.009).[14] In addition, most patients with adenocarcinoma had stage I disease. These results prompted us to conduct a randomized trial of uracil–tegafur as a postoperative adjuvant treatment for patients with completely resected stage I adenocarcinoma.

METHODS

PATIENTS

Enrollment began in January 1994. Eligible patients had undergone a complete surgical resection of a pathologically documented stage I (T1N0M0 or T2N0M0) adenocarcinoma of the lung (according to the 1986 classification of the American Joint Committee on Cancer).[15] Visceral pleural involvement was classified according to the rules of the Japan Lung Cancer Society,[16] and a tumor that was larger than 3 cm in diameter or a tumor of any size that was exposed on the visceral pleural surface was classified as a pathological T2 tumor. Other inclusion criteria were an age of 45 to 75 years; the absence of preoperative anticancer treatment, previous cancer, and synchronous multiple cancers; an Eastern Cooperative Oncology Group (ECOG) performance status[17] of 0, 1, or 2; a leukocyte count of at least 4000 per cubic millimeter; a platelet count of at least 100,000 per cubic millimeter; a hemoglobin level of at least 100 g per liter; serum aspartate aminotransferase and alanine aminotransferase levels that were no more than twice the upper limit of the normal range; and an absence of severe postoperative complications, such as pneumonia or empyema. Written or oral informed consent was obtained from all patients or their representatives, and the study was approved by the institutional review board of each participating center.

Confirmation of eligibility and randomization were performed by telephone or fax at a central site within 28 days after each patient's operation. All eligible patients were stratified according to age (less than 65 years vs. 65 years or older), sex, and pathological tumor category (T1 vs. T2).[18]

TREATMENT

Patients assigned to the control group were observed, with no treatment after surgery. In the treatment group, uracil–tegafur (250 mg of tegafur per square meter of body-surface area per day) in the form of 100-mg capsules (100 mg of tegafur plus 224 mg of uracil) was given orally before meals twice daily for two years, starting four weeks postoperatively. The dose was rounded up or down to the nearest 100 mg. Most patients received two capsules of uracil–tegafur (200 mg of tegafur and 448 mg of uracil) twice daily. The patients were asked at each follow-up visit whether they had taken the capsules as prescribed.

Toxic effects of uracil–tegafur were graded according to the criteria of the Japan Society of Clinical Oncology, which consist of the World Health Organization criteria with minor modifications.[19] If a grade 2 adverse reaction occurred, the dose of uracil–tegafur was reduced to 200 mg per square meter. Treatment was stopped if there was a grade 3 or higher adverse reaction, a leukocyte count of less than 3000 per cubic millimeter, a platelet count of less than 70,000 per cubic millimeter, a hemoglobin level of less than 9.5 g per deciliter, or an aspartate aminotransferase or alanine aminotransferase level that was more than three times the upper limit of the normal range.

FOLLOW-UP

A follow-up evaluation was performed every three months for the first two years after the operation and every six months thereafter. The evaluation included a physical examination, a complete blood count, blood chemical tests, screening for serum tumor markers, and chest radiography. A computed tomographic (CT) scan of the thorax and brain and either a CT scan or a sonogram of the upper abdomen were obtained every six months for the first two years after the operation and at least twice during the subsequent three years. Whenever possible, a biopsy of any new lesion suspected of being a recurrence or a second primary cancer was performed. A final diagnosis of such lesions was made by the physician in charge.

STATISTICAL ANALYSIS

The primary end point was overall survival; secondary end points were cancer-free survival and safety. All eligible patients were included in the analysis of overall survival and cancer-free survival, and all patients who were given uracil–tegafur were included in the safety assessment.

The sample size was calculated by the method of Schoenfeld and Richter[20] according to the following assumptions: a five-year survival rate of 70 percent in the no-treatment group, a hazard ratio for death of 0.67 in the uracil–tegafur group, a two-year accrual period, a five-year follow-up, a one-sided significance level of 0.05, and a statistical power of 80 percent. Since these calculations resulted in a sample size of 518 patients, the sample size was determined to be 600, with an allowance of about 15 percent for ineligible patients or patients who were lost to follow-up. In May 1995, the sample size was expanded to 984 patients after it became clear that the five-year survival rate for those in the control group was better than expected. The newly adopted five-year survival rate was 83 percent, and the accrual period was extended to three years. A committee for efficacy and safety provided independent monitoring of the study. Haybittle–Peto horizontal boundaries,[21] with a criterion of $P<0.001$, were used in the interim analyses conducted to determine whether the study should be terminated early.

Overall survival was defined as the time from surgery until death from any cause, and cancer-free survival was defined as the time from surgery until the appearance of the first recurrence of cancer, a second cancer, or death from any cause. Survival was estimated by the Kaplan–Meier method, and any differences in survival were evaluated with a stratified log-rank test. Multivariable analyses with the Cox proportional-hazards model were used to estimate the simultaneous effects of prognostic factors on survival.[22] Interactions with prognostic factors were also examined with the Cox proportional-hazards model. The SAS statistical software package (version 6.09, SAS Institute) was used for all calculations. Differences were considered to be statistically significant when the P value was 0.05 or less. All statistical tests were two-sided.

The protocol committee of the Japan Lung Cancer Research Group designed the study. Taiho Pharmaceutical Company collected and analyzed the data, and the authors interpreted the data and wrote the report. The authors had access to the primary data.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From January 1994 through March 1997, 999 patients were enrolled and randomly assigned to receive uracil–tegafur (498 patients) or no treatment (501 patients). Seven patients in the uracil–tegafur group and 13 patients in the control group were ineligible for the following reasons: pathological N1 or M1 disease in 7 patients, histologic findings other than adenocarcinoma in 6, no laboratory data at registration in 2, and miscellaneous reasons in 5. Therefore, there were 491 eligible patients in the uracil–tegafur group and 488 in the control group. Table 1 lists the base-line clinical characteristics of the two groups, which did not differ significantly. All but one patient in each group underwent lobectomy.

Table 1. Base-Line Characteristics of the Patients.

Characteristic	Uracil–Tegafur Group (N=491)	Control Group (N=488)
Age		
Mean (yr)	62	62
Range (yr)	45–75	45–75
<65 yr (no.)	274	275
≥65 yr (no.)	217	213
Female sex (no.)	253	249
ECOG performance status (no.)*		
0	376	369
1	105	113
2	10	6
Pathological tumor stage (no.)		
T1	362	354
T2	129	134
Invasion of pleura (no.)†		
0	340	346
1	120	114
2	29	28
Unknown	2	0
Tumor size (no.)		
≤2 cm	208	204
>2 to ≤3 cm	174	170
>3 cm	109	114
Location of the tumor (no.)		
Right upper lobe	182	189
Right middle lobe	41	34
Right lower lobe	102	87
Right lobes	2	2
Left upper lobe	107	114
Left lower lobe	54	60
Left lobes	3	2
Type of surgery (no.)		
Lobectomy	490	487
Pneumonectomy	1	1

* ECOG denotes Eastern Cooperative Oncology Group. Higher performance-status numbers indicate greater impairment.

† 0 indicates a tumor with no pleural involvement or a tumor that reaches the visceral pleura but does not extend beyond the elastic layer, 1 a tumor that extends beyond the elastic layer of the visceral pleura but is not exposed on the pleural surface, and 2 a tumor that is exposed on the pleural surface but does not involve the parietal pleura.

ADVERSE REACTIONS AND COMPLIANCE

Of the 498 patients originally assigned to the uracil–tegafur group, 482 actually received uracil–tegafur. Few severe adverse reactions were associated with uracil–tegafur. A grade 3 adverse reaction developed in 10 of 482 patients (2 percent), and no grade 4 adverse reactions occurred (Table 2).

Compliance with instructions to take uracil–tegafur was calculated on the basis of the number of patients who actually took uracil–tegafur and the number of patients who were assigned to it, excluding those with a recurrence or second cancer and those who died. The rate of compliance was 80 percent (95 percent confidence interval, 77 to 84 percent) at 6 months, 74 percent (95 percent confidence interval, 70 to 78 percent) at 12 months, 69 percent (95 percent confidence interval, 65 to 73 percent) at 18 months, and 61 percent (95 percent confidence interval, 57 to 66 percent) at 24 months. The main reasons for discontinuation of uracil–tegafur were an adverse reaction (in 123 patients), the patient's decision (52 patients), and the doctor's judgment (34 patients).

OVERALL SURVIVAL

The median follow-up among surviving patients was 72 months in the uracil–tegafur group and 73 months in the control group. Data were censored for 426 patients in the uracil–tegafur group and 399 in the control group. At the last follow-up visit, 65 patients in the uracil–tegafur group and 89 in the control group had died, and the overall survival rates in the two groups differed significantly on the basis of the stratified log-rank test (Fig. 1A). The five-year overall survival rate was 88 percent (95 percent confidence interval, 85 to 91 percent) in the uracil–tegafur group and 85 percent (95 percent confidence interval, 82 to 89 percent) in the control group. When the survival analysis was performed with the inclusion of all 999 randomized patients, the result did not change (P=0.047).

The predetermined covariates were age (<65 years vs. ≥65 years), sex, ECOG performance status (0 vs. 1 or 2), pathological T status (T1 vs. T2), and the assigned treatment. The covariates were selected according to multivariate analysis with the use of a stepwise procedure. All P values were less than 0.05. The selected covariates were as follows: age (hazard ratio for patients ≥65 years, 2.02; 95 percent confidence interval, 1.46 to 2.80; P<0.001), sex (hazard ratio for women, 0.66; 95 percent confidence interval, 0.48 to 0.91; P=0.01), T category (hazard ratio for T2, 1.95; 95 percent confidence interval, 1.41 to 2.69; P<0.001), and treatment group (hazard ratio for the uracil–tegafur group, 0.72; 95 percent confidence interval, 0.53 to 1.00; P=0.05).

Table 2. Adverse Reactions to Uracil–Tegafur.

Adverse Reaction	Grade of Toxicity*			
	1	2	3	4
	% *of patients*			
Leukopenia	2	1	0	0
Thrombocytopenia	<1	0	0	0
Anemia	1	<1	0	0
Increase in bilirubin	1	<1	0	0
Increase in aspartate aminotransferase	6	2	<1	0
Increase in alanine aminotransferase	6	2	0	0
Increase in alkaline phosphatase	2	<1	0	0
Anorexia	9	8	1	0
Nausea or vomiting	10	3	1	0
Diarrhea	2	1	<1	0
Alopecia	<1	0	0	0

* Toxicity was graded according to criteria of the Japan Society of Clinical Oncology. Grades range from 1 to 4, with a higher grade indicating a more severe reaction.

We also evaluated interactions between the four prognostic factors (sex, age, pathological tumor category, and size of the tumor) (Fig. 2) and the treatment. We included tumor size in the analysis because the tumor category is determined mainly by the maximal diameter of the primary tumor. As Figure 2 shows, there were significant interactions between the tumor category and size of the tumor and the treatment.

The survival rate among patients with T2 disease in the uracil–tegafur group was significantly higher than that in the control group, whereas among patients with T1 disease, there was no significant difference in survival between the uracil–tegafur and control groups. The five-year survival rate among patients with T2 disease was 85 percent (95 percent confidence interval, 79 to 91 percent) in the uracil–tegafur group and 74 percent (95 percent confidence interval, 66 to 81 percent) in the control group (Fig. 1B). The difference in overall survival between the two groups was statistically significant (P=0.005 by the log-rank test). The five-year survival rate among patients with T1 disease was 89 percent in the uracil–tegafur group and 90 percent in the control group (Fig. 1C). In the subgroups of patients with a tumor that was less than 2 cm in diameter, 2 to 3 cm, and greater than 3 cm, the five-year survival rate was 89 percent, 89 percent, and 85 per-

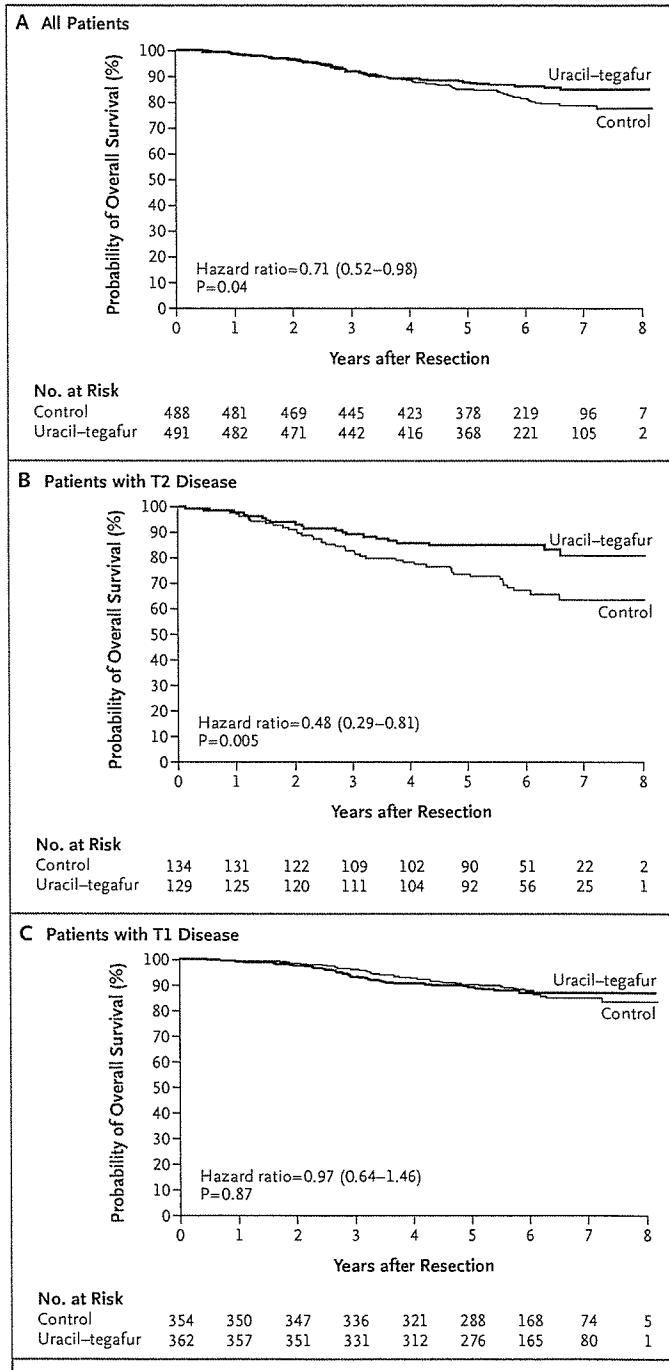

Figure 1. Overall Survival among All 979 Eligible Patients (Panel A), 263 Patients with T2 Disease (Panel B), and 716 Patients with T1 Disease (Panel C) Who Were Randomly Assigned to the Uracil–Tegafur Group and the Control Group.

The hazard ratios indicate the risk of death in the uracil–tegafur group as compared with the control group; 95 percent confidence intervals are shown in parentheses. P values were calculated with the use of the stratified log-rank test.

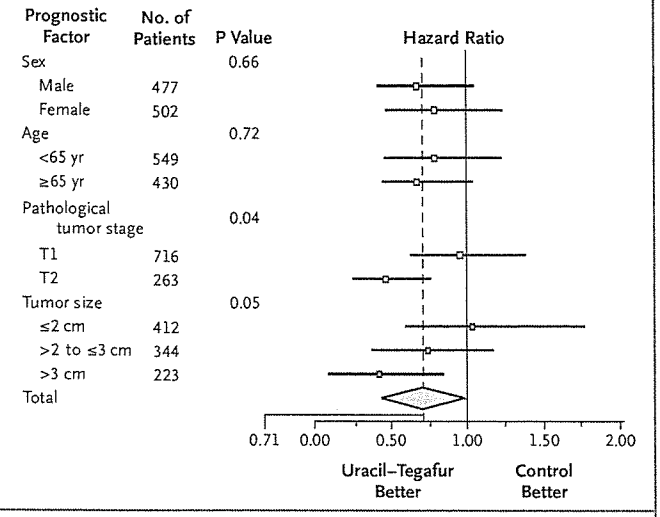

Figure 2. Hazard Ratios for Death in Patients in the Uracil–Tegafur Group as Compared with the Control Group, According to Four Prognostic Factors.

Each square represents the estimated treatment effect, the horizontal lines represent the 95 percent confidence intervals, and the diamond corresponds to the 95 percent confidence intervals for the entire group of patients. The P value for the tumor size is for the comparison of patients who had tumors that were 2 cm or less in diameter with patients who had tumors that were more than 3 cm.

cent, respectively, in the uracil–tegafur group and 91 percent, 86 percent, and 74 percent, respectively, in the control group.

PATTERN OF FAILURE AND CANCER-FREE SURVIVAL

A recurrence or a second primary cancer as the first treatment failure after surgery was documented in 23 percent of the uracil–tegafur group and 26 percent of the control group (Table 3). Among the 716 patients with T1 disease, recurrence or a second primary cancer was observed in 69 of 362 patients (19 percent) in the uracil–tegafur group and 76 of 354 patients (21 percent) in the control group; among the 263 patients with T2 disease, 42 of 129 patients (33 percent) in the uracil–tegafur group and 53 of 134 patients (40 percent) in the control group had recurrence or a second primary cancer as the first treatment failure. On the basis of a Kaplan–Meier analysis, the difference in cancer-free survival between the two groups was not statistically significant (P=0.25 by the stratified log-rank test). The survival of patients after the diagnosis of a recurrence or a second primary cancer did not differ significantly between the groups (P=0.14 by the log-rank test): the one-year and two-year survival rates after diagnosis were 65 percent and 50 percent, respectively, in the uracil–tegafur group and 65 percent and 42 percent, respectively, in the control group.

DISCUSSION

The Japanese Association for Chest Surgery and Japan Lung Cancer Society recently reported the long-term survival rate of 7408 patients with lung cancer who had undergone a surgical resection in 1994, the year that our trial started.[23] The main histologic types were adenocarcinoma (in 56 percent of the patients) and squamous-cell carcinoma (in 33 percent). Among patients with pathological stages T1N0M0 and T2N0M0, the five-year survival rates were 79 percent and 60 percent, respectively. In our study of adenocarcinoma, the five-year survival rate in the control group was 90 percent among patients with T1N0M0 disease and 74 percent among those with T2N0M0 disease. Although the figures in the two studies cannot be directly compared, owing to different histologic patterns and times when the data were collected, the excellent five-year survival rate for the control patients in our study[24,25] indicates that our collaborative group has made improvements in the quality of the surgical treatment and the accuracy of surgical staging.

Our study shows that adjuvant chemotherapy with uracil–tegafur has a beneficial effect on the survival of patients with resected stage I adenocarcinoma of the lung. This benefit, however, was not observed in patients with T1N0 disease. In the past few years, the number of patients in whom small adenocarcinomas have been discovered has increased owing to the increased use of computed tomography. In our study, 412 of 979 patients (42 percent) had an adenocarcinoma that was less than 2 cm in diameter. Adenocarcinomas of this size often include bronchoalveolar carcinoma, which is unlikely to recur after resection.[26] Therefore, a small adenocarcinoma usually has a very good prognosis[26,27]: in our study, the five-year survival rate of patients with tumors that were 2 cm or less in diameter was 91 percent. For this reason, we believe that patients with small tumors should be excluded from adjuvant trials unless a subgroup with a poor prognosis is identified.

In contrast, treatment with uracil–tegafur tended to improve the survival rate among patients with a tumor that was 2 to 3 cm in diameter and provided

a definitive survival benefit for patients with a tumor that was more than 3 cm in diameter. These findings indicate that the effect of uracil–tegafur may be related to certain biologic factors. In a retrospective study, Tanaka et al.[28] found that the prognosis was good for patients with non–small-cell lung cancer characterized by a high apoptotic index and no aberrant expression of p53 who received postoperative uracil–tegafur.

Patient compliance is usually a problem in trials of adjuvant chemotherapy. In trials of cisplatin-based chemotherapy, which was scheduled to be administered in three or four cycles postoperatively, only 50 to 70 percent of the planned treatment was given.[29-32] In our trial, we planned to give uracil–tegafur daily for two years. However, only 61 percent of patients assigned to the treatment completed the two-year course. The main reasons for discontinuing uracil–tegafur were adverse reactions (which were infrequent and usually mild) and the patient's decision, which suggests that compliance in trials of adjuvant chemotherapy may not be related to the severity of adverse events.

The main difference between trials of cisplatin-based adjuvant chemotherapy and trials of adjuvant chemotherapy with uracil–tegafur is the duration of the treatment. The cisplatin-based regimens entail three or four cycles (9 to 16 weeks) of chemotherapy,[29-32] whereas uracil–tegafur is taken daily for 1 or 2 years.[13,33-36] Fluorouracil is not a dose-dependent drug but a time-dependent agent. Therefore, a daily regimen of uracil–tegafur is an effective way of maintaining the blood level of fluorouracil. In addition, uracil–tegafur and its metabolites have an inhibitory effect on tumor angiogenesis in mice.[37] If this effect occurs in humans, then the daily, long-term administration of uracil–tegafur may be beneficial.

So far, six randomized trials,[13,33-36] including the present one, have been conducted that compare surgery alone with adjuvant chemotherapy with uracil–tegafur. Among them, three trials have shown a survival benefit from treatment with uracil–tegafur.[13,34] A meta-analysis of those six trials showed that adjuvant chemotherapy with uracil–tegafur improved the overall survival (hazard ratio for death, 0.77; 95 percent confidence interval, 0.63 to 0.94; P=0.01).[38] It is unclear whether patients with stage II or stage III disease benefit from treatment with uracil–tegafur and whether treatment for one year is equivalent to treatment for two years. However, our study indicates that patients with completely resected stage I disease, especially T2N0 adenocarcinoma, will benefit from adjuvant chemotherapy with uracil–tegafur.

Table 3. Pattern of Treatment Failure.

Pattern	Uracil–Tegafur Group (N=491)	Control Group (N=488)
	no. of patients (%)	
Intrathoracic only		
Local recurrence	17	8
Pulmonary metastases	36	38
Local recurrence plus pulmonary metastases	3	12
Second cancer	11	11
Extrathoracic only		
Recurrence	23	33
Second cancer	14	18
Intrathoracic plus extrathoracic recurrence	7	9
Total	111 (22.6)	129 (26.4)

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APPENDIX

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Editorial

Treatment of Peripheral Early Stage Lung Cancer

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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

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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.