サブ解析では，5年生存率の上乗せ効果はII期で11.6%，III期では14.7%と報告されている[2]．すなわち，術後補助化学療法の有用性は，病期別にII期およびIII期で認められ，IB期では良好な傾向にあるものの統計学的有意差には至っておらず，IA期においては化学療法により死亡リスクの上昇が示された．最近報告されたNon-small Cell Lung Cancer Collaborative Groupのセカンド・メタアナリシスでも結果は同様であった[3]．

なお，本邦では，IB-IIIA期に対し，補助療法としてカルボプラチン(CBDCA)＋パクリタキセル(PAC)併用療法とCDDP＋ドセタキセル（DTX）併用療法を比較する無作為比較第II相試験（TORG0503）やII-IIIA期に対するテガフール・ギメラシル・オテラシルカリウム（S-1）とCDDP＋S-1を比較する無作為比較第II相試験（WJOG4107），さらにはCDDP＋ゲムシタビン(GEM)，CDDP＋VNRなど単アームのfeasibility studyが行われ，術後補助療法における第三世代抗癌剤を用いたCDDP併用療法の認容性について一定の評価が得られている[4,5]．

進行肺癌の臨床試験からある種の抗がん剤が組織型によってその効果が異なることが示され，最近では上述の病期に加えて組織型を加味した対象に臨床試験が行われている．本邦では，II-IIIA期非扁平上皮非小細胞肺癌に対するペメトレキセド＋シスプラチン併用療法とビノレルビン＋シスプラチン併用療法のランダム化比較第III相試験（JIPANG），高悪性度神経内分泌肺癌に対するイリノテカン＋シスプラチンとエトポシド＋シスプラチン療法のランダム化比較試験（JCOG1205/1206）の多施設臨床第III相試験が実施中である[6]．前者は，先進医療制度を利用した7つの研究グループ(九州肺癌研究機構，瀬戸内肺癌研究会，日本・多国間臨床試験機構，西日本がん研究機構，中日本呼吸器臨床研究機構，東京がん化学療法研究会，胸部腫瘍臨床研究機構）による多グループ共同臨床試験で，この結果次第で保険適応の拡大に繋がる可能性がある．

2. I期に対する経口5-FU系抗癌剤

前述のように，I期におけるシスプラチンを含む2剤併用術後補助化学療法の有用性は否定的である．CALGB（Cancer and Leukemia GroupB）9633において，手術単独とCBDCA＋PACによるIB期を対象とした術後補助化学療法の比較試験が実施された．途中中止された時点での中間報告では手術単独群に比べて術後補助化学療法群における有効性が示されたが，その後観察期間を延長した再解析の結果，両群における有意差はなく，カルボプラチンを含む2剤併用術後補助療法のIB期における有用性は未だに証明されていない．ただし，腫瘍径に関するサブ解析の検討から，4cm以上のIB期完全切除例に対するCBDCA＋PACの有用性が示された[7]．また，JBR10のサブ解析でも同様に，IB期・腫瘍径4cm以上の切除例に対する効果が示されており，プラチナ製剤併用療法による術後補助化学療法については，4cmがその適応のボーダーになる可能性がある．

一方，本邦においては，I期を中心にテガフール・ウラシル配合剤（UFT）による術後補助化学療法の有用性の評価が行われた．西日本肺癌グループでは，I-III期を対象に，CDDP＋VDS＋UFTとUFT単剤，手術単独の3群についての比較試験が行われ，5年生存率でUFT群は64.1%と手術単独群の49.0%と比し，有意に良好であった．Japan Lung Cancer Research Group（JLCRG）によりI期腺癌を対象にUFTを2年間内服する群と無治療群の比較試験が行われ，UFT群ではI期全体の5年生存率で3%の上乗せ効果を示され，特にIB期（T2N0）症例では5年生存率で11%の上乗せ効果が報告された[8]．Hamadaらにより，UFTの有用性を検討した6試験，2,003例のメタアナリシスの結果，全体で4.6%（77.2%→81.8%）の5年生存率の改善を認め，UFTの有効性が確認された[9]．これらの結果から，本邦では，IB期においてUFTを用いた術後補助化学療法が標準的治療として推奨されている．UFTのメタアナリシスサブグループ解析においては，I期のT1a（腫瘍径≦2cm）とT1b（2<腫瘍径≦3cm）に対するUFTの有効性の検討で，I期T1bにおいてはHR：0.62（HR：0.42-0.90）と良好な結果が示された[10]．また，先のIB期を合わせて，2cmを超える症例でHR：0.63（HR：0.43-0.92）と良好な結果が得られた．これらの結果から，本邦では，2cm超のIA期NSCLCに対してもUFTを用いた術後補助化学療法による一定の予後改善が期待され，治療の適応があると考えられる．

上記のエビデンスのもとになった大規模臨床試験の多くはTNM-UICC6（旧分類）に基づいて試験対象が定義されており，現在汎用されているTNM-UICC7の病期とは異なる．しかし，上述の試験においてT2bN0M0の症例数が少数であったこと，T2bN0Mが予後の面からIIA期に分類されたことを受けて，

日本肺癌学会編集の
TNM-UICC7に基づく
するUFTの推奨グレ
当該病期に対して，
ギメラシル・オテラ
較第III相試験（JCO
は，5-FUのプロドラ
ラシル（5-FU分解系
剤），およびオテラシ
素の可逆的阻害剤）を
濃度を高めて抗腫瘍効
の軽減を目的として開
肺癌においては，他癌
dropyrimidine dehyd
向にあったと報告され
においてUFTに配合
DPD阻害作用は強力
れらをふまえて，TS
とされた肺癌に対して
考えられ，I期非小細
として検証する意義は
腫瘍径を除く病理病
子としては脈管侵襲，
index高値）などがあ
リスクが高い症例だか
を制御したいところで
た前向き臨床比較試験
ういった集団において
かになっていない現状
助療法を推奨するだけ
も臨床試験としての使
また，肺腺癌の新W
cinoma in situ（AIS）
noma（野口分類のtype
の組織像を呈する非浸
も5年以内の再発はな
後に微小転移があると
ういった組織像を有す
わらず術後補助療法の

IV. 術後補助化学
るバイオマー

肺がんに対し標準的
て，現状で実用化して

日本肺癌学会編集の「肺癌診療ガイドライン」では，TNM-UICC7に基づくIA期（T1bN0M0），IB期に対するUFTの推奨グレードを「B」としている．

当該病期に対して，本邦ではUFTとテガフール・ギメラシル・オテラシルカリウム配合（TS-1）の比較第III相試験（JCOG0707）が進行中である．TS-1は，5-FUのプロドラッグであるテガフールに，ギメラシル（5-FU分解系の律速酵素の可逆的拮抗阻害剤），およびオテラシルカリウム（5-FUのリン酸化酵素の可逆的阻害剤）を配合することにより，血中5-FU濃度を高めて抗腫瘍効果を増強させ，かつ消化器毒性の軽減を目的として開発された経口抗がん剤である．肺癌においては，他癌に比較して腫瘍組織内のdihydropyrimidine dehydrogenase（DPD）活性が高い傾向にあったと報告されている．ギメラシルは，in vitroにおいてUFTに配合されているウラシルよりもDPD阻害作用は強力であることが分かっている．これらをふまえて，TS-1は，従来5-FUが効きにくいとされた肺癌に対してその有効性をより期待できると考えられ，I期非小細胞肺癌術後化学療法のレジメンとして検証する意義は大きい．

腫瘍径を除く病理病期IA期NSCLCの予後不良因子としては脈管侵襲，CEA高値，核分裂像（mitotic index高値）などがあげられ，予後不良すなわち再発リスクが高い症例だからこそ補助療法により微小転移を制御したいところである．しかし，これらに特化した前向き臨床比較試験は現在までにない．さらに，こういった集団において有効な抗がん剤レジメンが明らかになっていない現状では，実地診療において術後補助療法を推奨するだけの根拠は皆無である．あくまでも臨床試験としての使用に限られるべきである．

また，肺腺癌の新WHO分類にみられるAdenocarcinoma in situ（AIS）およびminimally invasive carcinoma（野口分類のtype A，BそしてCの一部に相当）の組織像を呈する非浸潤肺腺癌においては，少なくとも5年以内の再発はないことが報告されており[11]，術後に微小転移があるとは考えにくい．したがって，こういった組織像を有する症例に対しては，大きさに関わらず術後補助療法の適応はないと思われる．

IV. 術後補助化学療法の効果予測に関するバイオマーカー

肺がんに対し標準的に使用される抗がん剤について，現状で実用化しているバイオマーカーは同定されていない．効果予測あるいは無効予測可能なバイオマーカーが確立されれば，術後補助化学療法において個々の症例においてより安全でより高い再発防止効果を期待できるであろう．たとえば，現在注目されている分子のexcision repair cross-complementing（ERCC）遺伝子については，IALT試験のretrospectiveなサブ解析（IALT Bio Study）から，ERCC1低発現患者では明らかに死亡リスクを軽減されたが，ERCC1高発現の患者では経過観察群よりも術後補助療法群のほうが生存期間はむしろ劣ることが明らかになった[12][13]．一方で，Simon GRらのようにERCC1低発現群の予後不良という逆の報告もあり，現状では必ずしも有用であるとはいえない．こういった抗がん剤の効果予測のバイオマーカーの候補は，他にもBRCA1（対象：CDDPベースの化学療法），RRM1（対象薬：ゲムシタビン），TS（対象薬：ペメトレキセド，TS-1），β-Tubline（対象薬：タキサン系薬剤），Gene signature：（対象：シスプラチン＋ビノレルビン）など多々ある．いずれのマーカーについても，大規模な前向き試験によるvalidationの結果が待たれる[14]．どういった症例が術後補助化学療法の恩恵を受ける集団であるか判別することでより効率的な治療の確立につながると期待される．上述のようなバイオマーカーによる個別化治療を確立することは，術後補助療法においても急務である．

V. おわりに

先述のように，IB期あるいはIA期の一部，II-III期非小細胞肺癌完全切除例に対する術後補助化学療法は標準的治療として位置付けられている．ただし，見方を変えれば，リスクの少ない症例を対象とした臨床試験においてさえも，術後化学療法による5年生存率の上乗せ効果は高々4～10%程度であり，死亡リスク減少効果は15%程度にとどまる．すなわち，術後無治療，すなわち手術単独でも病期相応の予後は期待できる一方で，補助化学療法を行っても全ての再発は抑制できていない．また，特にCDDP併用療法により1%前後の症例で治療関連死亡が観察されているうえ，術後化学療法は経過中に効果の有無を判定することが困難なので，結果的に効果のない症例でも非選択的に治療を受けることになる．このあたりを十分に情報提供して，同意を得たうえで術後補助療法を行う必要がある．特に，実臨床においては臨床試験に登録された症例よりも何らかのリスク因子を単数あるいは複

数かかえていることが多いので，症例個々に応じた情報提供を心掛けたい．本来術後短期のうちに亡くなることがない症例で副作用死が起こってしまうこと，あるいは回復が遅延することは，確かに一定の確率で起こる可能性があるとはいえ，その患者さんあるいはご家族のみならず医療側にとっても悲しい結果である．副作用等々が受け止められない人は，しばしば鬱など精神障害を伴うケースも少なくない．真摯な姿勢で，インフォームド・コンセントを行う必要がある．本治療は，治療可能な状態で患者さんご本人から治療希望のあった場合にのみ実施すべきものと考える．

文　献

1) Pignon JP, Tribodet H, Scagliotti GV, et al.: Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol, 26: 3552-3559, 2008.
2) Douillard JY, Tribodet H, Aubert D, et al.: Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer: subgroup analysis of the Lung Adjuvant Cisplatin Evaluation. J Thorac Oncol, 5: 220-228, 2010.
3) NSCLC Meta-analyses Collaborative Group, Arriagada R, Auperin A, et al.: Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet, 375: 1267-1277, 2010.
4) Kenmotsu H, Ohde Y, Shukuya T, et al.: Feasibility of postoperative adjuvant chemotherapy of cisplatin plus vinorelbine for completely resected non-small-cell lung cancer: a retrospective study in Japan. Respir Investig, 50: 157-161, 2012.
5) Kenmotsu H, Niho S, Ito T, et al.: A pilot study of adjuvant chemotherapy with irinotecan and cisplatin for completely resected high-grade pulmonary neuroendocrine carcinoma (large cell neuroendocrine carcinoma and small cell lung cancer). Lung Cancer, 2014 Mar 13. pii: S0169-5002 (14) 00128-7.
6) Eba J, Kenmotsu H, Tsuboi M, et al.: A Phase III Trial Comparing Irinotecan and Cisplatin with Etoposide and Cisplatin in Adjuvant Chemotherapy for Completely Resected Pulmonary High-grade Neuroendocrine Carcinoma (JCOG1205/1206). Jpn J Clin Oncol, 44: 379-382, 2014.
7) Strauss GM, Herndon JE 2nd, Maddaus MA, et al.: Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol, 26: 5043-5051, 2008.
8) Kato H, Ichinose Y, Ohta M, et al.: A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. N Engl J Med, 350: 1713-1721, 2004.
9) Hamada C, Tanaka F, Ohta M, et al.: Meta-analysis of postoperative adjuvant chemotherapy with tegafur-uracil in non-small-cell lung cancer. J Clin Oncol, 23: 4999-5006, 2005.
10) Hamada C, Tsuboi M, Ohta M, et al.: Effect of postoperative adjuvant chemotherapy with tegafur-uracil on survival in patients with stage IA non-small cell lung cancer: an exploratory analysis from a meta-analysis of six randomized controlled trials. J Thorac Oncol, 4: 1511-1516, 2009.
11) Asamura H, Hishida T, Suzuki K, et al.: Radiographically determined noninvasive adenocarcinoma of the lung: survival outcomes of Japan Clinical Oncology Group 0201. J Thorac Cardiovasc Surg, 146: 24-33, 2013.
12) Olaussen KA, Dunant A, Fouret P, et al.: DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med, 355: 983-991, 2006.
13) Friboulet L, Olaussen KA, Pignon JP, et al.: ERCC1 isoform expression and DNA repair in non-small-cell lung cancer. N Engl J Med, 368: 1101-1110, 2013.
14) Wislez M, Barlesi F, Besse B, et al.: Customized Adjuvant Phase II Trial in Patients With Non-Small-Cell Lung Cancer: IFCT-0801 TASTE. J Clin Oncol, 2014 Mar 17. [Epub ahead of print].

利益相反

謝礼金：大鵬薬品工業株式会社，日本イーライリリー株式会社，協和発酵キリン株式会社

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Multiple, large, ran
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CURRENT STATUS OF POSTOPERATIVE ADJUVANT CHEMOTHERAPY FOR COMPLETELY RESECTED NON-SMALL LUNG CANCER

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Multiple, large, randomized trials assessing the efficacy of adjuvant chemotherapy for resected non-small cell lung cancer (NSCLC) have been reported in recent years. Three of six trials involving 300 or more patients with early-stage NSCLC demonstrated that adjuvant cisplatin-based chemotherapy can significantly improve 5-year survival in carefully selected patients with resected NSCLC. These benefits were confirmed in a meta-analysis of modern cisplatin-based adjuvant trials. The most consistent benefit was reported in patients with resected stage II and IIIA NSCLC. On the other hand, studies from Japan reported that adjuvant therapy with uracil-tegafur (UFT) afforded an improvement of 4% in the 5-year survival rate and a relative risk reduction of 26% in mortality at 5 years among patients with T1-2N0 (stage I) disease. In particular, the Japan Lung Cancer Research Group demonstrated an improvement in the 5-year survival rate of 11%, favoring chemotherapy with UFT in the subset of patients with T2N0 (stage IB) disease. Two published meta-analyses based on abstracts estimated a relative risk reduction in mortality of 11-13% at 5 years. Thus, the information currently available supports the administration of adjuvant chemotherapy for patients who have undergone complete resection of stages IB-IIIA NSCLC. The recent results of biological research indicate that the expression of some tumor markers including ERCC1 should be evaluated to determine which patients are more likely to benefit from chemotherapy. The next advance will be to identify the subsets of patients who will derive the greatest benefit from adjuvant chemotherapy.

Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data

NSCLC Meta-analysis Collaborative Group*

Summary

Background Individual participant data meta-analyses of postoperative chemotherapy have shown improved survival for patients with non-small-cell lung cancer (NSCLC). We aimed to do a systematic review and individual participant data meta-analysis to establish the effect of preoperative chemotherapy for patients with resectable NSCLC.

Methods We systematically searched for trials that started after January, 1965. Updated individual participant data were centrally collected, checked, and analysed. Results from individual randomised controlled trials (both published and unpublished) were combined using a two-stage fixed-effect model. Our primary outcome, overall survival, was defined as the time from randomisation until death (any cause), with living patients censored on the date of last follow-up. Secondary outcomes were recurrence-free survival, time to locoregional and distant recurrence, cause-specific survival, complete and overall resection rates, and postoperative mortality. Prespecified analyses explored any variation in effect by trial and patient characteristics. All analyses were by intention to treat.

Findings Analyses of 15 randomised controlled trials (2385 patients) showed a significant benefit of preoperative chemotherapy on survival (hazard ratio [HR] 0·87, 95% CI 0·78–0·96, p=0·007), a 13% reduction in the relative risk of death (no evidence of a difference between trials; p=0·18, I^2=25%). This finding represents an absolute survival improvement of 5% at 5 years, from 40% to 45%. There was no clear evidence of a difference in the effect on survival by chemotherapy regimen or scheduling, number of drugs, platinum agent used, or whether postoperative radiotherapy was given. There was no clear evidence that particular types of patient defined by age, sex, performance status, histology, or clinical stage benefited more or less from preoperative chemotherapy. Recurrence-free survival (HR 0·85, 95% CI 0·76–0·94, p=0·002) and time to distant recurrence (0·69, 0·58–0·82, p<0·0001) results were both significantly in favour of preoperative chemotherapy although most patients included were stage IB–IIIA. Results for time to locoregional recurrence (0·88, 0·73–1·07, p=0·20), although in favour of preoperative chemotherapy, were not statistically significant.

Interpretation Findings, which are based on 92% of all patients who were randomised, and mainly stage IB–IIIA, show preoperative chemotherapy significantly improves overall survival, time to distant recurrence, and recurrence-free survival in resectable NSCLC. The findings suggest this is a valid treatment option for most of these patients. Toxic effects could not be assessed.

Funding Medical Research Council UK.

Lancet 2014; 383: 1561–71
Published Online February 25, 2014 http://dx.doi.org/10.1016/S0140-6736(13)62159-5
See Comment page 1528

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Introduction

Worldwide, roughly 1·5 million new cases of lung cancer are diagnosed annually[1] with about 85% being non-small-cell lung cancers (NSCLCs).[2] Surgery is thought the best treatment option, but only about 20–25% of tumours are suitable for potentially curative resection.[3] Two individual participant data meta-analyses[4] showed that postoperative chemotherapy, with or without radiotherapy, improved survival.

Preoperative chemotherapy has the potential to reduce tumour size, increase operability, and eradicate micrometastases. Chemotherapy might also be more effective when the blood supply to the tumour is still intact before surgical resection, and chemotherapy might be better tolerated if patients are not recovering from major surgery. However, preoperative chemotherapy will delay surgery, and if ineffective, tumours can become unresectable.

The findings of several reviews, based on aggregate data from randomised controlled trials,[5–9] have suggested preoperative chemotherapy improves survival. However, these reviews all included different combinations of trials, some of which were confounded by the use of chemotherapy in both arms or radiotherapy in one arm, making the specific effects of preoperative chemotherapy difficult to discern. Furthermore, analyses of other outcomes and how effects vary by patient characteristics were not possible with the aggregate data. Therefore, we did a systematic review and meta-analysis of individual participant data to provide more reliable and up-to-date evidence on the effect of preoperative chemotherapy on

survival and other key outcomes and whether this varies by patient subgroup.

Methods

Design and study selection

Methods were prespecified in a protocol (available on request). Randomised trials comparing chemotherapy with subsequent surgery versus surgery alone were eligible if they started after Jan 1, 1965, and aimed to include chemotherapy-naive NSCLC patients, suitable for surgery, without any previous malignancy. Trials that planned to use postoperative radiotherapy in both arms, or postoperative chemotherapy in the preoperative arm only, were also eligible.

Published and unpublished trials were sought, with no language restrictions, using randomised trial search filters for Medline and Embase[10] with additional terms for NSCLC and chemotherapy. These searches were supplemented by searching trial registers, conference proceedings, review articles, and reference lists of trial publications (appendix). Collaborators were asked if they knew of any additional trials. Searches were regularly updated until May, 2013.

See Online for appendix

Data collection

For all eligible trials and all patients who were randomised, data were sought on the date of randomisation, treatment allocation, type of chemotherapy and number of cycles, age, sex, histology, performance status, date of surgery, extent of resection, clinical and pathological tumour stage, clinical and pathological response, recurrence, survival, cause of death, and date of last follow-up. Standard methods were used to identify missing data and to assess data validity and consistency.[11] Patterns of treatment allocation and the balance of baseline characteristics by treatment group were used to check randomisation integrity and follow-up of surviving patients was checked to ensure it was up to date and balanced by arm and fed into a risk of bias assessment for each trial.[12] Any inconsistencies were resolved and the final dataset verified by the relevant trial contact.

Definition of outcomes

Our primary outcome, overall survival, was defined as the time from randomisation until death (any cause), with living patients censored on the date of last follow-up. Secondary outcomes were recurrence-free survival, time to locoregional and distant recurrence, cause-specific survival, complete and overall resection rates, and postoperative mortality. There were concerns that for patients receiving their surgery immediately in the surgery-alone arm, any recurrences could be identified sooner than in the preoperative chemotherapy arm. This might erroneously suggest a benefit of chemotherapy. Thus, analyses of recurrence outcomes were calculated from a landmark time of 6 months from the date of randomisation to allow for all patients to have completed their allocated treatment.[13] Events arising within 6 months of randomisation were regarded as events at this landmark time. Recurrence-free survival was defined as time from the landmark date until locoregional recurrence, distant recurrence, or death, whichever happened first. Patients alive without recurrence were censored on the date of last follow-up. To avoid bias from under-reporting of subsequent events, time to locoregional (distant) recurrence was defined as time from the landmark date to first locoregional (distant) recurrence, and patients experiencing previous distant (local) recurrences were censored on the date of distant (local) recurrence. Patients experiencing a locoregional and distant recurrence on the same date were counted in both analyses. For trials that only recorded the first recurrence, patients having a local (distant) recurrence were censored in the analysis of distant (local) recurrence; all other patients without recurrence were censored on the date of death or last follow-up.

We used data on cause of death to assess the effects of chemotherapy on lung and non-lung cancer survival. However, although eight trials supplied these data, only two provided sufficiently detailed information to discriminate between treatment-related and other non-cancer causes, making it impossible to define these outcomes accurately.

The overall resection rate was defined as the proportion of patients having either a complete or incomplete resection. The complete resection rate was defined as the proportion of patients having a complete resection. Postoperative mortality was defined as the proportion of patients dying within 30 days of surgery, and early mortality was defined as death within 6 months of date of randomisation, to allow for completion of all treatment in each arm.

Statistical analysis

Unless otherwise stated, all analyses were prespecified in the protocol, and done on an intention-to-treat basis. For time-to-event outcomes, we used the log-rank expected number of events and variance to calculate hazard ratio (HR) estimates of effect for each individual trial, which were then combined across trials using a stratified-by-trial, two-stage, fixed-effect model.[14] The random-effects model[15] was used to assess the robustness of the results. χ^2 heterogeneity tests were used to assess differences in the effect of treatment or treatment by covariate interactions across trials. Results for time-to-event outcomes are also presented as non-stratified Kaplan-Meier curves.[16] The median follow-up was computed for all patients using the reverse Kaplan-Meier method.[17] For dichotomous outcomes, such as resection rate, the numbers of events and patients were used to calculate Peto odds ratio (OR) estimates of effect[14] for trials, which were then pooled across trials, using a fixed-effect model.

To explore any effect of trial-level characteristics on the effect of chemotherapy, pooled HRs were calculated for

each prespecified trial group. χ^2 tests for interaction and the F ratio were used to assess differences in treatment effect across trial groups. To investigate the effect of patient characteristics on the effect of chemotherapy, the relevant treatment by patient covariate interaction term was included in a Cox regression for each trial. The resulting within-trial interactions (HRs) were then pooled across trials using the stratified-by-trial, fixed-effect model.[18] These analyses are focused on the primary outcome of survival.

	Accrual years	Number of patients	Clinical stage	Preoperative chemotherapy used (dose per cycle)	Postoperative chemotherapy cycles planned	Postoperative radiotherapy planned	Reached target accrual	Stopping reason	Median follow-up (years)
France 1990[20]	1985–87	26	I–III	Cyclophosphamide (600 mg/m²), vindesine (3 mg/m²), cisplatin (100 mg/m²); 2 cycles every 4 weeks	2	No	No	High progression rate with preoperative chemotherapy	3·2
MD Anderson 1994[21]	1987–93	60	IIIA	Cyclophosphamide (500 mg/m²; d1), etoposide (100 mg/m²; d1–3), cisplatin (100 mg/m²; d1); 3 cycles every 4 weeks	3 to responders	Yes, if surgery incomplete or unresectable	No	Benefit of preoperative chemotherapy	6·7
Spain 1994[22]	1989–91	59	IIIA	Mitomycin (6 mg/m²), ifosfamide (3 g/m²), cisplatin (50 mg/m²); 3 cycles every 3 weeks	0	Yes	No	Benefit of preoperative chemotherapy	6·3
MIP-91[23]	1991–97	355	I–IIIA	Mitomycin (6 mg/m², d1), Ifosfamide (1·5 g/m², d1–3), cisplatin (30 mg/m², d1–3); 2 cycles every 3 weeks	2 to responders	Yes, if surgery incomplete or pT3 or pN2	Yes	NA	12·9
SWOG S9015[24]	1992–94	21	I–IIIA	Etoposide (80 mg/m²; d1–3), carboplatin (350 mg/m²; d1); 2 cycles every 3 weeks	3 to responders	No	No	Poor accrual	6·3
JCOG 9209[24]	1993–98	62	IIIA	Vindesine (3 mg/m²; d1,8), cisplatin (80 mg/m²; d1); 3 cycles every 4 weeks	0	Yes, if surgery incomplete	No	Poor accrual	5·7
Netherlands 2000[25]	1994–99	79	IB–II	Paclitaxel (175 mg/m²; d1), carboplatin (AUC=7; d1); or teniposide (120 mg/m²; d1–3), cisplatin (80 mg/m²; d1); at least 2 cycles every 3 weeks	0	No	No	Poor accrual	2·2
Finland 2003[26]	1995–99	62	III	Docetaxel (100 mg/m²; d1); 3 cycles every 3 weeks	0	No	No	Poor accrual	3·1
MRC BLT[27]	1995–2001	10	I–III	Vindesine (3 mg/m²; d1,8), cisplatin (80 mg/m²; d1); or vinorelbine (30 mg/m²; d1,8), cisplatin (80 mg/m²; d1); or mitomycin (6 mg/m²; d1), ifosfamide (3 g/m²; d1), cisplatin (50 mg/m²; d1); or mitomycin (6 mg/m²; d1), vinblastine (6 mg/m²; d1), cisplatin (50 mg/m²; d1); number of cycles/interval unknown	0	Yes	No	Poor accrual	3·9
MRC ILP22[28]	1997–2005	519	I–III	Mitomycin (8 mg/m²; first 2 cycles only), vinblastine (6 mg/m²; max 10 mg), cisplatin (50 mg/m²); or mitomycin (8 mg/m²; first 2 cycles only), ifosfamide (3 g/m²), cisplatin (50 mg/m²); or vinorelbine (30 mg/m²; d1,8; max 60 mg), cisplatin (80 mg/m²; d1); or paclitaxel (175 mg/m²), carboplatin (AUC=5); or gemcitabine (1250 mg/m²; d1,8), cisplatin (80 mg/m²; d1); or docetaxel (75 mg/m²), carboplatin (AUC=6); 3 cycles every 3 weeks	0	Yes, if surgery incomplete or progression	Yes	NA	7·6
SWOG S9900[29]	1999–2004	354	IB–IIIA	Paclitaxel (225 mg/m²), carboplatin (AUC=6); 3 cycles every 3 weeks	0	No	No	Positive results of adjuvant chemotherapy trials	5·5
China 2002[30]	1999–2004	55	IIIA	Docetaxel (75 mg/m²; d1), carboplatin (AUC=5; d1); 2 cycles every 3 weeks	0	Yes, if surgery incomplete	No	Positive results of adjuvant chemotherapy trials/ poor accrual	7·8
China 2005[31]	1999–2004	40	IIIA	Gemcitabine (1200–1250 mg/m²; d1,8), cisplatin (30 mg/m²; d1–3); or gemcitabine (1200–1250 mg/m²; d1,8), carboplatin (AUC=5; d1); 2 cycles every 3 weeks	2 to responders	No	No	Poor accrual	3·3
ChEST[32]	2000–04	270	IB–IIIA	Gemcitabine (1250 mg/m²; d1,8), cisplatin (75 mg/m²; d1); 3 cycles every 3 weeks	0	No	No	Positive results of adjuvant chemotherapy trials	3·10
NATCH[33]	2000–07	413	IA–IIIA	Paclitaxel (200 mg/m²), carboplatin (AUC=6); 3 cycles every 3 weeks	0	Yes, if pathological pN2	Yes	NA	4·8

NA=not applicable. AUC=area under the curve.

Table 1: Trial characteristics

	Surgery	Chemotherapy plus surgery
Age, years		
<60	450 (38%)	486 (42%)
60–64	239 (20%)	202 (17%)
65–69	259 (22%)	251 (22%)
≥70	244 (20%)	224 (19%)
Unknown	2 (<1%)	2 (<1%)
Sex		
Male	970 (81%)	918 (79%)
Female	221 (19%)	244 (21%)
Unknown	3 (<1%)	3 (<1%)
Histology		
Adenocarcinoma	353 (29%)	327 (28%)
Squamous	616 (52%)	573 (49%)
Large cell	49 (4%)	78 (7%)
Other	162 (14%)	176 (15%)
Unknown	14 (1%)	11 (1%)
Clinical stage		
IA	63 (5%)	71 (6%)
IB	545 (46%)	501 (43%)
IIA	21 (2%)	29 (3%)
IIB	309 (26%)	278 (24%)
IIIA	246 (21%)	270 (24%)
IIIB	4 (<1%)	9 (<1%)
IV	0 (<1%)	3 (<1%)
Unknown	6 (<1%)	4 (<1%)
Performance status		
0	471 (43%)	463 (43%)
1	514 (46%)	494 (45%)
2+	123 (11%)	125 (12%)
Unknown	4 (<1%)	4 (<1%)

Data are n (%). Data for all characteristics, except performance status, were available for 14 of the 15 trials (99% of all patients). For performance status, data were available for 11 of the 15 trials (92% of all patients).

Table 2: Characteristics of included patients

Absolute differences in outcome at 5 years were calculated from the HR and the control group baseline event rate.[19] All p values are two-sided.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 19 eligible randomised controlled trials; 17 published[20–36] and two unpublished [37,38] (appendix). Data could not be supplied for three trials,[34–36] and one trial only recruited two patients.[37] Although data were obtained for all 24 patients excluded from the investigators' original analyses, and reinstated in this meta-analysis, data for two other patients could not be obtained. Therefore, this meta-analysis is based on data from 15 trials[20–33,38] (2385 patients), representing 92% of patients who were randomised, from all known eligible trials. Any risk of bias associated with the randomisation procedure and completeness of outcome data in these 15 trials was judged to be low and the effects of early stopping were minimised by the collection of updated follow-up and investigated in the analyses.

Ten trials[22,24–30,32,33] gave chemotherapy only preoperatively and five trials[20,21,23,31,38] used chemotherapy preoperatively and then postoperatively, usually to responders. All trials used platinum-based chemotherapy, except one,[26] which used docetaxel alone (table 1). Seven trials[20–24,27,32] used cisplatin, four[29,30,33,38] carboplatin, and three[25,28,31] either cisplatin or carboplatin. Eight trials[21–24,27,28,30,33] used postoperative radiotherapy in both arms.

Data on age, sex, histology, and stage were provided for all but one trial,[20] and performance status for 11 trials (table 2).[21,23,25–30,32,33,38] Based on the available data, patients were mostly men (80%) with a median age of 62 years (IQR 55–68) and good performance status (88%). They had mainly clinical stage IB–IIIA tumours (93%) that were predominantly squamous cell carcinomas (50%) or adenocarcinomas (29%). The median follow-up of all patients was 6 years (IQR 4·2–8·2; table 1).

Survival results were based on 15 randomised controlled trials (2385 patients, 1427 deaths) and show a clear benefit of preoperative chemotherapy (HR 0·87, 95% CI 0·78–0·96; p=0·007; figures 1, 2). This represents a 13% reduction in the relative risk of death, translating to a 5% absolute improvement in survival at 5 years (from 40% to 45%). Despite design differences between trials, for example, a variety of chemotherapy regimens, exclusive use of preoperative chemotherapy, use of postoperative radiotherapy in both arms, and inclusion of all stages of patients or only a specific stage of patient, there was no clear evidence of statistical heterogeneity (p=0·18).

There is no clear evidence that the effect of chemotherapy on survival differed according to whether chemotherapy was given preoperatively or both preoperatively and postoperatively (interaction p=0·23), the number of preoperative chemotherapy cycles (interaction p=0·68), the type of chemotherapy regimen (interaction p=0·94), the number of chemotherapy agents per regimen (interaction p=0·84), or both the type of chemotherapy regimen and number of agents (interaction p=0·79; table 3). Analyses of the type of regimen, the number of agents per regimen, and both the type of regimen and number of agents were repeated only in those trials that gave platinum-based regimens, and gave similar results (interactions p=0·91, p=0·60, and p=0·62 respectively; table 3). We did not identify evidence of a difference in effect of chemotherapy on survival by whether regimens were cisplatin or carboplatin-based (interaction p=0·48) or whether postoperative radiotherapy was used (interaction p=0·87; table 3).

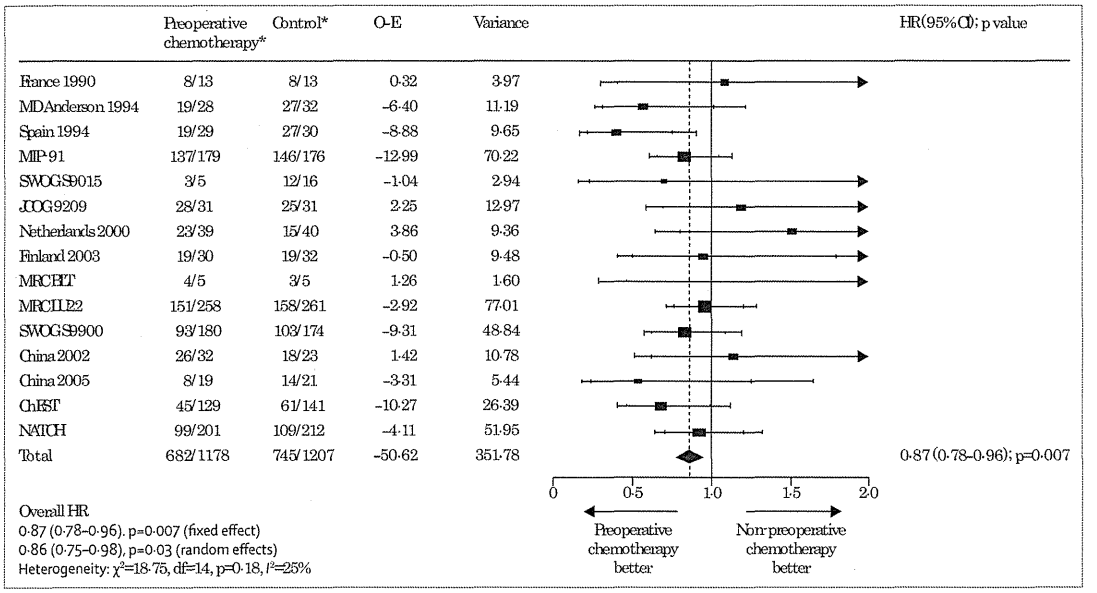


Figure 1: Effect of preoperative chemotherapy on survival
Each square denotes the HR for that trial comparison with the horizontal lines showing the 95% and 99% CIs. The size of the square is directly proportional to the amount of information contributed by the trial. The black diamond gives the pooled HR from the fixed effect model; the centre of this diamond denotes the HR and the extremities the 95% CI. O-E=observed minus expected. HR=hazard ratio. MIP=mitomycin, ifosphamide, cisplatin. SWOG=South West Oncology Group. JCOG=Japanese Cancer Oncology Group. MRC=Medical Research Council. BLT=Big Lung Trial. ChEST=Chemotherapy for Early Stages Trial. NATCH=Neoadjuvant/Adjuvant Trial of Chemotherapy. df=degrees of freedom. *Number of events/number entered.

Although the interaction test is not significant there is some suggestion of a larger relative effect in trials where postoperative chemotherapy is given to responders (HR 0·78, 95% CI 0·64–0·95, p=0·02) than in those giving preoperative chemotherapy alone. Exploratory analyses examining whether such an approach modifies the effect of chemotherapy on time to local recurrence showed a similar pattern (preoperative chemotherapy HR 0·94, 95% CI 0·75–1·18, p=0·60; preoperative plus postoperative chemotherapy HR 0·73, 95% CI 0·50–1·07, p=0·11), but again no clear evidence of an interaction (p=0·26). However, for time to distant recurrence, there is evidence of a difference in effect by chemotherapy scheduling (p=0·05), with a substantially greater relative benefit in trials giving postoperative chemotherapy (HR 0·53, 95% CI 0·39–0·73, p<0·001) than in those using just preoperative chemotherapy (HR 0·78, 95% CI 0·63–0·96, p=0·02).

12 trials did not reach their target accrual. Two[21,22] closed early after recording a benefit of chemotherapy, one[20] due to high progression rates in the chemotherapy arm, six due to poor accrual[24–27,31,38] and three due to positive results in postoperative chemotherapy trials.[29,30,32] Based on all trials, although we found some evidence of a difference in effect by the reason for early stopping of trials, small trials with extreme positive and negative estimates seem to strongly affect this result (table 3). An exploratory analysis, excluding smaller trials (100 patients or fewer), was based on 80% of the data (77% of all deaths),[23,28,29,32,33] and showed no clear difference in effect between trials stopping early and those reaching their target accrual (interaction p=0·24).

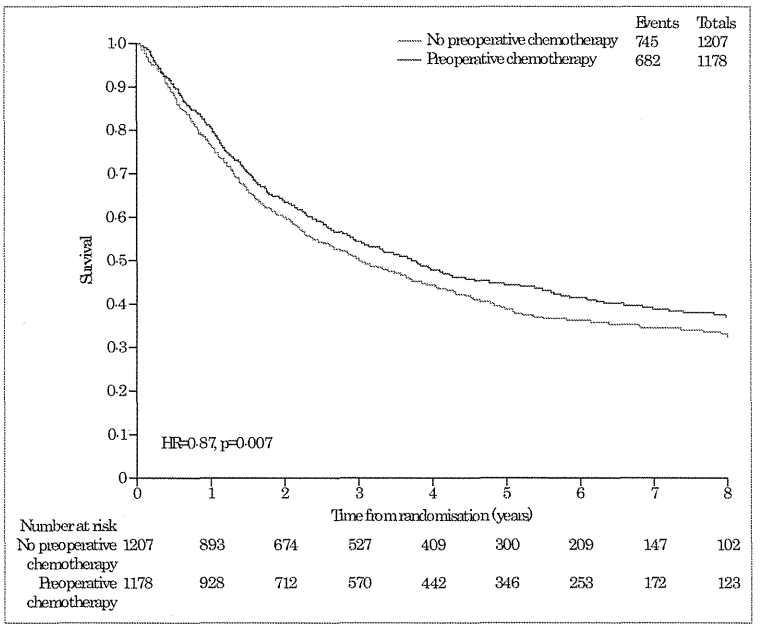


Figure 2: Kaplan-Meier curves (non-stratified) of the effect of preoperative chemotherapy on time to survival

	Number of trials	Number of deaths/ patients	Hazard ratio (95%CI), p value	Hetero-geneity p value	Fratio p value	Interaction p value
Survival by planned chemotherapy schedule (n=15 trials)					0·32	0·23
Preoperative chemotherapy only	10	1045/1883	0·90 (0·80–1·02), 0·09	0·10		
Preoperative and postoperative chemotherapy (to responders)	5	382/502	0·78 (0·64–0·95), 0·02	0·62		
Survival by number of preoperative chemotherapy cycles (n=14 trials)					0·74	0·68
2 cycles	6	418/576	0·89 (0·74–1·08), 0·25	0·39		
3 cycles	8	1002/1799	0·85 (0·75–0·96), 0·01	0·10		
Survival by chemotherapy regimen (n=14 trials)					0·96 (all trials), 0·94 (platinum-only trials)	0·95 (all trials), 0·91 (platinum-only trials)
Platinum plus second generation chemotherapy	7	543/694	0·86 (0·72–1·02), 0·08	0·03		
Platinum plus third generation chemotherapy	6	801/1540	0·85 (0·74–0·97), 0·02	0·57		
Non-platinum chemotherapy	1	38/62	0·95 (0·50–1·79), 0·87	NA		
Survival by the number of chemotherapy agents (n=15 trials)					0·90 (all trials), 0·70 (platinum-only trials)	0·84 (all trials), 0·60 (platinum-only trials)
Non platinum single agent regimen	1	38/62	0·95 (0·50–1·79), 0·87	NA		
Doublet regimen	9	907/1702	0·88 (0·78–1·01), 0·06	0·42		
Triplet regimen	5	475/611	Fixed effect 0·83 (0·69–1·00), 0·05; random effects 0·79 (0·53–1·18), 0·25	0·01		
Survival by chemotherapy regimen and number of chemotherapy agents (n=14 trials)					0·89 (all trials), 0·95 (platinum-only trials)	0·79 (all trials), 0·62 (platinum-only trials)
Non-platinum single agent regimen	1	38/62	0·95 (0·50–1·79), 0·87	NA		
Platinum second generation, doublet	2	68/83	1·08 (0·66–1·76), 0·76	0·42		
Platinum second generation, triplet	5	475/611	Fixed effect 0·83 (0·69–1·00), 0·05; random effects 0·79 (0·53–1·18), 0·25	0·01		
Platinum third generation, doublet	6	801/1540	0·85 (0·74–0·97), 0·02	0·57		
Survival by cisplatin or carboplatin regimen (n=12 trials)					0·54	0·48
Cisplatin-based	7	830/1289	0·83 (0·72–0·95), 0·01	0·08		
Carboplatin-based	5	492/905	0·90 (0·75–1·07), 0·23	0·88		
Survival by planned postoperative radiotherapy (n=15 trials)					0·64	0·57
No postoperative radiotherapy given	8	431/852	0·83 (0·68–1·00), 0·05	0·40		
Postoperative radiotherapy given	7	996/1533	0·88 (0·78–1·00), 0·05	0·09		
Survival by whether trial stopped early (all trials: n=15 trials)					0·10	0·05
Reached target accrual	3	800/1287	0·90 (0·79–1·04), 0·16	0·66		
Stopped for benefit of chemotherapy	2	92/119	0·48 (0·31–0·74), <0·001	0·43		
Stopped for high progression on chemotherapy arm	1	16/26	1·08 (0·41–2·90), 0·87	NA		
Stopped for poor accrual/positive adjuvant trials	9	519/953	0·88 (0·74–1·05), 0·17	0·31		

NA=not applicable.

Table 3: Effect of preoperative chemotherapy by prespecified trial group

We did not identify clear evidence that the effect of preoperative chemotherapy on survival differed by age, age group, performance status, or histology (figure 3). Although, overall, there is no evidence of a difference in effect by sex, there is heterogeneity in the interaction (figure 3). Some trials suggest the effect might be greater in women and others in men, but it is not clear why. Also, there was a significant interaction between the effect of preoperative chemotherapy and stage in the ChEST trial,[32] but not in the other trials, or across all trials (interaction p=0·83; appendix). An exploratory analysis, splitting clinical stage I disease into IA and IB, also identified an interaction between the treatment effect and clinical stage in the ChEST trial, but not across trials (p=0·64, heterogeneity p=0·22). Thus, the overall HR of 0·87 was applied to the control group survival for each stage, giving an absolute survival improvement at 5 years of 5% for all stages, taking it from 50% to 55% in stage I, from 30% to 35% in stage II, and from 20% to 25% in stage III. However, most patients in stage I are IB (89%), in stage II are IIB (92%), and in stage III are IIIA (98%), therefore we can be most confident of results for these patients.

Mortality within 30 days of surgery could be calculated for nine trials,[23,25,26,28–32,38] (1611 patients, 52 deaths) that

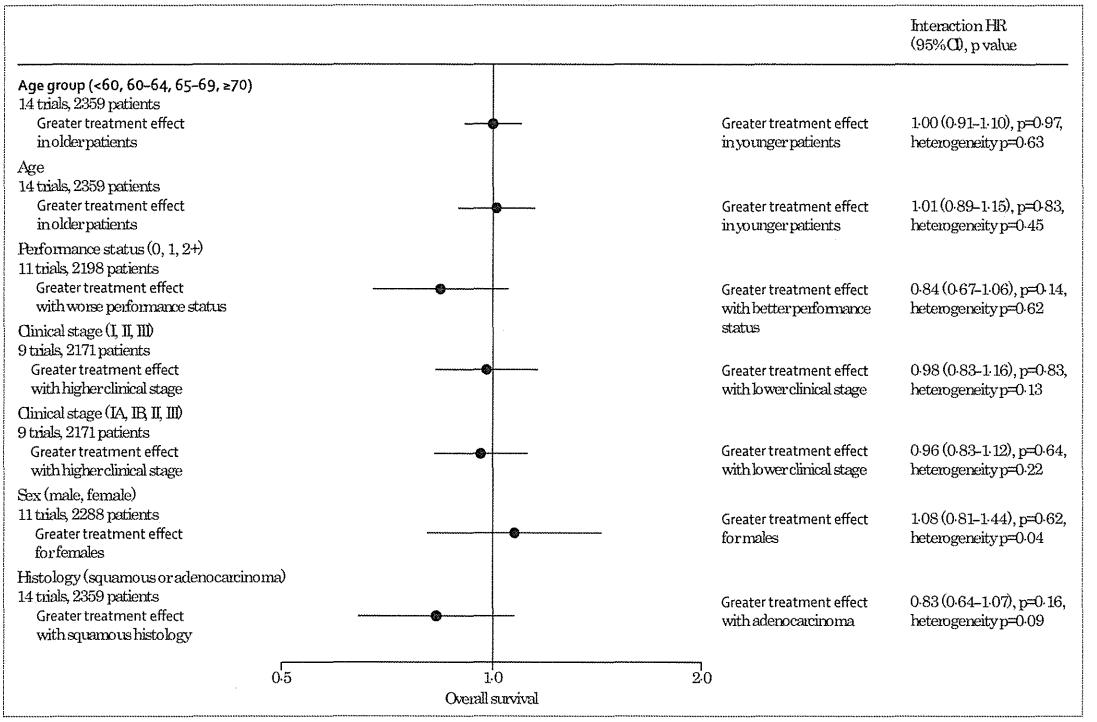


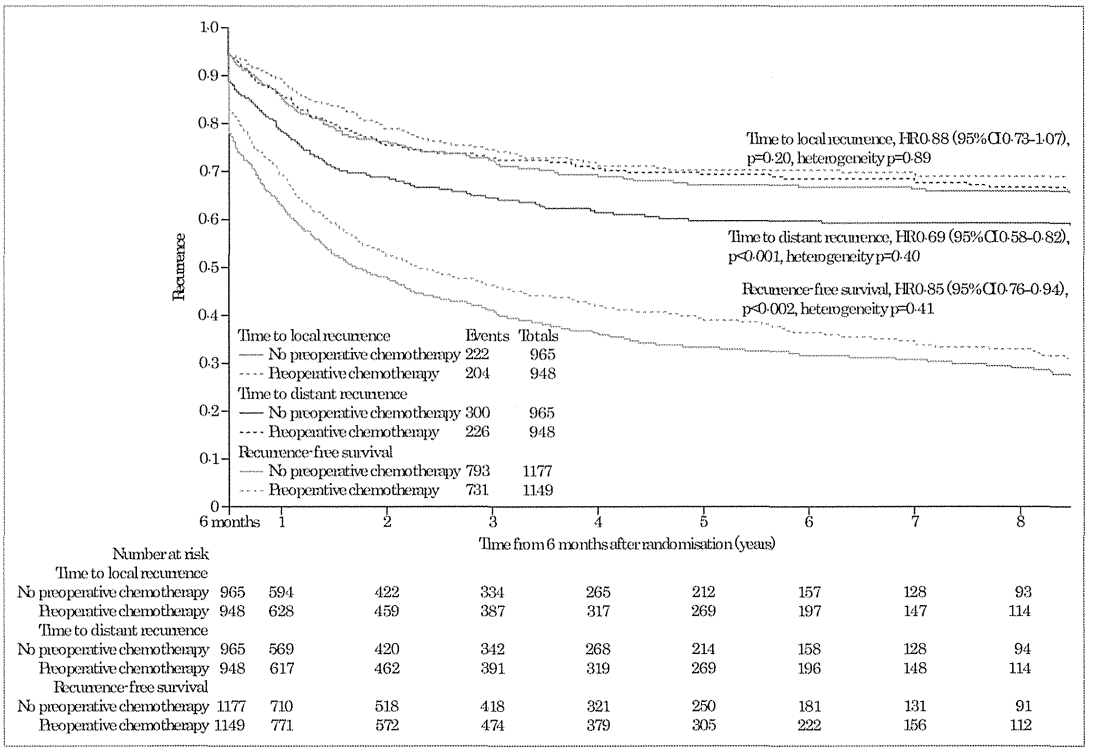
Figure 3: **Forest plot of the interactions between the effect of preoperative chemotherapy on survival and covariates**
The circles represent (fixed effect) meta-analyses of the HRs representing the interactions between the effect of chemotherapy and patient characteristics; the horizontal line shows the 95% CI. HR=hazard ratio.

supplied date of surgery. Four of these[26,30,31,38] had no deaths within 30 days of surgery in either arm and an OR was not estimable. Overall, we did not identify a difference between treatment arms (OR 1·48, 95% CI 0·85–2·58, p=0·17; heterogeneity p=0·45, appendix). Based on all 15 trials (2381 patients, 254 deaths), we also did not identify a deleterious effect of preoperative chemotherapy on mortality within 6 months of randomisation (OR 0·88, 95%CI 0·67–1·14, p=0·33; heterogeneity p=0·60).

11 trials[21,23–26,28–32,38] (1778 patients) provided data on extent of resection. For the overall resection rate, ORs could not be estimated for four trials[21,23,29,31] because they had 100% resection rates in both arms. The remaining seven trials[24–26,28,30,32,38] represented less than half of the total data and, with possible variation in the classification of extent of incomplete resection, this analysis was deemed unreliable. Based on all 11 trials, there was no evidence of an effect of preoperative chemotherapy on complete resection (OR 0·88, 95% CI 0·68–1·14, p=0·33; appendix), but the effect did vary between trials (heterogeneity p=0·006). This variation might relate to differences in the types of patients or surgery, because the baseline complete resection rate for control patients ranged from 67% to 95%, with the exception of one trial[21] where it was substantially lower (31%).

Recurrence-free survival data were available for 14 trials[20,21,23–33,38] (2326 patients, 1524 events). The findings provide clear evidence of a benefit of preoperative chemotherapy (HR 0·85, 95% CI 0·76–0·94, p=0·002, heterogeneity p=0·41, figure 4), translating to an absolute improvement in recurrence-free survival of 6% at 5 years, taking it from 30% to 36%.

Data on both time to locoregional recurrence and distant recurrence were available for 13 trials[20,21,23–32,38] and 1913 patients (426 events and 526 events respectively). In these patients, 630 (33%) were alive and free from disease. For the remaining 1283 patients, the first events recorded were locoregional recurrence for 305 (24%), distant recurrence for 397 (31%), both locoregional and distant recurrence for 115 (9%), and death without recurrence for 466 (36%; appendix). There is clear evidence of a benefit of preoperative chemotherapy on time to distant recurrence (HR 0·69, 95% CI 0·58–0·82; p<0·001; heterogeneity p=0·40; figure 4), but the effect on time to locoregional recurrence was less clear (HR 0·88, 95% CI 0·73–1·07; p=0·20; heterogeneity p=0·89; figure 4). These findings translate into an absolute improvement in time to distant recurrence of 10% at 5 years (from 60% to 70%). There is a potential improvement on time to locoregional recurrence of 3% at 5 years.



Number at risk									
Time to local recurrence									
No preoperative chemotherapy	965	594	422	334	265	212	157	128	93
Preoperative chemotherapy	948	628	459	387	317	269	197	147	114
Time to distant recurrence									
No preoperative chemotherapy	965	569	420	342	268	214	158	128	94
Preoperative chemotherapy	948	617	462	391	319	269	196	148	114
Recurrence-free survival									
No preoperative chemotherapy	1177	710	518	418	321	250	181	131	91
Preoperative chemotherapy	1149	771	572	474	379	305	222	156	112

Figure 4: Kaplan-Meier curves (non-stratified) of the effect of preoperative chemotherapy on time to distant and locoregional recurrence and recurrence-free survival

Analyses of recurrence outcomes were calculated from a landmark time of 6 months from the date of randomisation; for this reason time on the x-axis starts at 6 months.

Discussion

Based on data from 15 randomised trials (92% of all patients who were randomised), we have shown a 5% absolute benefit of preoperative chemotherapy on 5 year survival in patients with resectable NSCLC. There was no clear evidence of a difference in this effect by treatment type, scheduling, trial design differences, or by patient characteristics, although the results are most reliable for stage IB–IIIA. There seemed to be no excess of early mortality in the preoperative chemotherapy arm as a result of deferred surgery.

Although this meta-analysis included most patients known to have been randomised, four eligible trials (198 patients) could not be included. We could estimate an HR[39] for survival for one trial of 90 patients,[36] but not the remaining three trials. Two of these[34,35] (106 patients) did not report the appropriate information, and one (two patients) was unpublished.[37] When the single estimated HR was combined with the overall result for the meta-analysis, the effect on survival remained the same (HR 0·87, p=0·006), but being based on 96% of patients who were randomised, it provides more convincing evidence of a benefit of preoperative chemotherapy. This systematic review and meta-analysis will be updated if further eligible trials are identified.

One reason for using preoperative chemotherapy is that it might make tumours more operable, potentially improving the likelihood of a complete resection. Conversely, delays to surgery could make it harder to achieve a complete resection. However, we did not identify clear evidence of a positive or negative effect of chemotherapy on the complete resection rate or a benefit on locoregional recurrence. However, we did note a 10% absolute benefit of preoperative chemotherapy on distant recurrence at 5 years, suggesting that it might have greater potential to eradicate micrometastases than postoperative chemotherapy, where the absolute benefit was 5% at 5 years.[4]

Comparing the effect of preoperative and postoperative chemotherapy directly, using data from this meta-analysis and two previous ones of postoperative chemotherapy in NSCLC proved problematic. Although it was possible to make the datasets comparable in terms of the regimens used, we could not make them comparable in terms of their patient characteristics, particularly stage. Only pathological stage was available for the postoperative chemotherapy meta-analysis, and agreement between clinical and pathological staging in the control group patients of the current meta-analysis was only around 60%. However, survival in the control group of the present

meta-analysis is somewhere between that noted for patients receiving surgery alone and those receiving surgery plus radiotherapy as definitive treatment,[4] suggesting that the present population spans the two. Although this difference makes a formal indirect comparison of the effects of preoperative and postoperative chemotherapy difficult, the benefit noted is on a similar scale. Others have attempted formal comparison based on aggregate data[8] and concluded the effect of chemotherapy on overall or recurrence-free survival is similar, irrespective of chemotherapy timing. However, they did not include key large trials, published more recently, and have included a trial confounded by the use of radiotherapy in only one arm.[40]

We included one three-arm trial (NATCH[33]) with both preoperative and postoperative chemotherapy arms, but because it was underpowered, the authors did not report their direct comparison. Nevertheless, they provided us with analyses showing similar effects of preoperative and postoperative chemotherapy on survival (HR 0·93, 95% CI 0·71–1·23, p=0·61) and recurrence-free survival (HR 0·88, 95% CI 0·68–1·13, p=0·31; Rosell R, unpublished). Similarly, a recent trial[41] (198 patients), of preoperative versus postoperative chemotherapy reported no difference in disease-free survival (HR 0·88, 95% CI 0·58–1·33, p=0·54), although power could also be an issue in this trial.

The findings of NATCH[33] showed a difference in treatment compliance between the preoperative (90%) and the postoperative (60%) chemotherapy arms. Of the trials included in our report, the ten[20,22–26,28,29,32,33] that reported the number of patients receiving all scheduled preoperative chemotherapy (2–3 cycles), identified a similarly high compliance rate with preoperative chemotherapy (mean compliance rate 85%, range 71–100%). By contrast, for the 14 trials in the postoperative chemotherapy systematic review[4] that reported patients receiving scheduled chemotherapy (2–6 cycles), the mean compliance rate was somewhat lower (62%, range 41–98%). This implies that patients might receive more of their planned chemotherapy if it is given before surgery.

The results so far seem to suggest similar effects with either preoperative or postoperative chemotherapy, giving a choice of treatment options. Clinicians might consider that preoperative chemotherapy is preferable for poorer prognosis patients with larger, more advanced stage tumours, less able to tolerate chemotherapy after surgery, or in regions where surgery waiting lists are longer. Postoperative chemotherapy might be preferred by surgeons and by patients wishing to have potentially curative treatment immediately, or for those with earlier stage disease. It also allows for more reliable pathological staging to establish if subsequent chemotherapy is appropriate.

Because this meta-analysis shows that preoperative chemotherapy has a greater effect on metastases, and a previous one[4] shows that postoperative chemotherapy has a greater effect on local control, it is tempting to speculate that combined preoperative and postoperative chemotherapy would confer a greater benefit on local and distant control and survival. This is not entirely borne out by the present survival results by chemotherapy scheduling and generally only those patients responding to preoperative chemotherapy were also given postoperative chemotherapy such that most would have received preoperative chemotherapy alone. However, exploratory analyses do suggest a synergistic effect of combining preoperative and postoperative chemotherapy on time to metastases. However, it should be noted that more cycles of chemotherapy were planned in the trials of combined preoperative and postoperative chemotherapy (2–3 plus 2–3 cycles postoperatively) compared with those of just preoperative chemotherapy (2–3). Moreover, a recently reported trial that compared the use of preoperative chemotherapy plus postoperative chemotherapy[42] to responders with postoperative chemotherapy in 528 similar patients identified no evidence that preoperative plus postoperative chemotherapy was better (HR 1·01, 95% CI 0·79–1·30, p=0·92). Nevertheless, further head-to-head comparisons of these approaches might be warranted.

The potential benefit of preoperative chemotherapy would need to be balanced against possible toxic effects. However, although we were unable to assess toxic effects at the patient level in this study, trial reports for 13 of the included trials described mild or acceptable toxic effects and that chemotherapy was generally well tolerated. Further questions regarding which drugs to use, the duration of chemotherapy, and if the effect might be modified by predictive genetic biomarkers will need to be answered by new or ongoing trials. Nevertheless, these results provide the most complete evidence so far of the effects of preoperative chemotherapy, showing a significant improvement in overall survival, time-to-distant recurrence, and recurrence-free survival.

Contributors

AA, SB, TLC, CLP, JPP, LHMR, and JFT, with the help of the members of the Advisory Group, contributed to the conception of the study. SB and LHMR collected and checked the data with the help of the trial investigators who validated the reanalysis of their trials. SB and LHMR did the statistical analysis. The report was drafted by SB, LHMR, and JFT and submitted for comments to the members of the Project Management Group and the Advisory Group. The investigators contributed to the interpretation of the results during the investigators' meeting and various revisions of the report.

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Declaration of interests
HJMG has served as a consultant for Eli Lilly, Pfizer, and Roche. VW has received honoraria from Roche, Lilly, GlaxoSmithKline, AstraZeneca, Chugai, Boehringer Ingelheim, and Amgen; travel grants from AstraZeneca, Lilly, and Roche; and a research grant from Roche. The other authors declare that they have no competing interests.

Acknowledgments
The NSCLC Collaborative Group thanks all patients who took part in the trials and contributed to this research. The meta-analysis would not have been possible without their participation or without the collaborating institutions that provided their trial data. The MRC Project Management Group was funded by the UK Medical Research Council and the IGR Project Management Group was supported by Institut Gustave-Roussy, Programme Hospitalier de Recherche Clinique (AOM 05 209), Ligue Nationale Contre le Cancer, and Sanofi-Aventis (unrestricted grants). We thank Valter Torri for his assistance with data retrieval and David Fisher and Jack Bowden for their help on particular analyses.

References
1 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69–90.
2 American Cancer Society. Cancer facts and figures 2007 Atlanta: American Cancer Society, 2007
3 Datta D, Lahiri B. Preoperative evaluation of patients undergoing lung resection surgery. Chest 2003; 123: 2096–103.
4 NSCLC Meta-analyses Collaborative Group. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010; 375: 1267–77
5 Berghmans T, Paesmans M, Meert AP, et al. Survival improvement in resectable non-small cell lung cancer with (neo)adjuvant chemotherapy: results of a meta-analysis of the literature. Lung Cancer 2005; 49: 13–23.
6 Nakamura H, Kawasaki N, Taguchi M, Kabasawa K. Role of preoperative chemotherapy for non-small-cell lung cancer: a meta-analysis. Lung Cancer 2006; 54: 325–29.
7 Burdett S, Stewart LA, Rydzewska L. A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. J Thorac Oncol 2006; 1: 611–21.
8 Lim E, Harris G, Patel A, Adachi I, Edmonds L, Song F. Preoperative versus postoperative chemotherapy in patients with resectable non-small cell lung cancer: systematic review and indirect comparison meta-analysis of randomized trials. J Thorac Oncol 2009; 4: 1380–88.
9 Song WA, Zhou NK, Wang W, et al. Survival benefit of neoadjuvant chemotherapy in non-small cell lung cancer: an updated meta-analysis of 13 randomized control trials. J Thorac Oncol 2010; 5: 510–16.
10 Lefebvre C, Manheimer E, Glanville J, and the Cochrane Information Retrieval Methods Group. Searching for studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Chichester: John Wiley & Sons Ltd; 2008: 95–150.
11 Stewart LA, Clarke MJ. Practical methodology of meta-analyses (overviews) using updated individual patient data. Cochrane Working Group. Stat Med 1995; 14: 2057–79.
12 Moher D, Liberati A, Tetzlaff J, Altman DG, and the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097 DOI: 10.1371/journal.pmed.97
13 Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 2009; 27: 5062–67
14 Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985; 27: 335–71.
15 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177–88.
16 Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. J Am Stat Assoc 1958; 53: 457–81.
17 Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996; 17: 343–46.
18 Fisher DJ, Copas AJ, Tierney JF, Parmar MKB. A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners. J Clin Epidemiol 2011; 64: 949–67
19 Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual patient data: is there a difference? Lancet 1993; 341: 418–22.
20 Dautzenberg B, Benichou J, Allard P, et al. Failure of the perioperative PCV neoadjuvant polychemotherapy in resectable bronchogenic non-small cell carcinoma. Results from a randomized phase II trial. Cancer 1990; 65: 2435–41.
21 Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. J Natl Cancer Inst 1994; 86: 673–80.
22 Rosell R, Gómez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. N Engl J Med 1994; 330: 153–58.
23 Depierre A, Milleron B, Moro-Sibilot D, et al, and the French Thoracic Cooperative Group. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. J Clin Oncol 2002; 20: 247–53.
24 Nagai K, Tsuchiya R, Mori T, et al, and the Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group. A randomized trial comparing induction chemotherapy followed by surgery with surgery alone for patients with stage IIIA N2 non-small cell lung cancer (JCOG 9209). J Thorac Cardiovasc Surg 2003; 125: 254–60.

25 Splinter TA, van Putten JW, Meuzalaar J, Smit EF, Kho GS, Groen HJ. Randomized multicenter phase II study of chemotherapy followed by surgery versus surgery alone in stage I and II non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 2000; 19: 495 (abstr 1937).

26 Mattson KV, Abratt RP, ten Velde G, Krofta K. Docetaxel as neoadjuvant therapy for radically treatable stage III non-small-cell lung cancer: a multinational randomised phase III study. Ann Oncol 2003; 14: 116–22.

27 Waller D, Peake MD, Stephens RJ, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. Eur J Cardiothorac Surg 2004; 26: 173–82.

28 Gilligan D, Nicolson M, Smith I, et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/ NVALT 2/ EORTC 08012 multicentre randomised trial and update of systematic review. Lancet 2007; 369: 1929–37.

29 Pisters KM, Vallières E, Crowley JJ, et al. Surgery with or without preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer: Southwest Oncology Group Trial S9900, an intergroup, randomized, phase III trial. J Clin Oncol 2010; 28: 1843–49.

30 Wu Y-L, Gu L-J, Weng Y-M, Feng W-N, Cheng C. Neo-adjuvant chemotherapy with docetaxel plus carboplatin for non-small cell lung cancer. Ann Oncol 2002; 13 (suppl 5): 140 (abstr 510P).

31 Yang X, Wu Y, Gu L, et al. A randomized trial comparing neoadjuvant gemcitabine plus carboplatin or cisplatin followed by surgery with surgery alone in Clinical Stage IIIA non-small-cell lung cancer (NSCLC). Lung Cancer 2005; 49: S288 (abstr P-645).

32 Scagliotti GV, Pastorino U, Vansteenkiste JF, et al. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer. J Clin Oncol 2012; 30: 172–78.

33 Felip E, Rosell R, Maestre JA, et al, and the Spanish Lung Cancer Group. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol 2010; 28: 3138–45.

34 de Boer RH, Smith IE, Pastorino U, et al. Pre-operative chemotherapy in early stage resectable non-small-cell lung cancer: a randomized feasibility study justifying a multicentre phase III trial. Br J Cancer 1999; 79: 1514–18.

35 Yi X, Zhang R, Ding J, Gao W, Ma Q, Zhong C. A clinicopathologic study on neoadjuvant chemotherapy in the treatment of non-small-cell lung cancer. Zhongguo Fei Ai Za Zhi 2003; 6: 124–28 (in Chinese).

36 Sorensen JB, Riska H, Ravn J, et al. Scandinavian phase III trial of neoadjuvant chemotherapy in NSCLC stages IB-IIIA/T3. Proc Am Soc Clin Oncol 2005; 23: 7146.

37 Chaudhri N. Randomized phase III trial of surgery alone or surgery plus preoperative gemcitabine-cisplatin in clinical early stages of non-small cell lung cancer. http://clinicaltrials.gov/show/NCT00540280 (accessed Nov 6, 2013).

38 Bunn P. Phase III randomized comparison of pre- and postoperative chemotherapy with VP-16/ CBDCA vs surgery alone in patients with operable nonsmall cell carcinoma of the lung. http://www.cancer.gov/clinicaltrials/search/view?cdrid=77308&version=HealthProfessional (accessed Nov 6, 2013).

39 Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998; 17: 2815–34.

40 Pass HI, Pogrebniak HW, Steinberg SM, Mulshine J, Minna J. Randomized trial of neoadjuvant therapy for lung cancer: interim analysis. Ann Thorac Surg 1992; 53: 992–98.

41 Yang X-N, Cheng G, Ben X-S, et al. Survival study of neoadjuvant versus adjuvant chemotherapy with docetaxel combined carboplatin in resectable stage IB to IIIA non-small cell lung cancer. ASCO Annual Meeting 2013:7537

42 Westeel V, Quoix E, Puyraveau M, et al, and the Intergroupe Francophone de Cancérologie Thoracique. A randomised trial comparing preoperative to perioperative chemotherapy in early-stage non-small-cell lung cancer (IFCT 0002 trial). Eur J Cancer 2013; 49: 2654–64.

Lung abscess combined with chronic osteomyelitis of the mandible successfully treated with video-assisted thoracoscopic surgery

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Abstract

With the progress of antibiotic therapy, the mortality of lung abscess has been improved, and surgical intervention has declined. However, surgery is still required in selected cases that are intractable to antibiotic treatment. Video-assisted thoracoscopic surgery (VATS) is beneficial for treatment and/or diagnosis of pulmonary disease as it provides a less invasive surgical technique and reduces prolongation of post-operative recovery. However, the indication of VATS lobectomy for lung abscess is controversial as a result of particular complications, i.e. wet lung, intrapleural adhesion and ease of bleeding. We herein report a rare combination of lung abscess and osteomyelitis of mandible resulting from the same pathogen successfully treated with VATS lobectomy. We propose VATS lobectomy for lung abscess. This procedure might be the best treatment candidate for selected cases of lung abscess.

Please cite this paper as: Arai H, Inui K, Watanabe K, Watanuki K, Okudela K, Tsuboi M, Masuda M. Lung abscess combined with chronic osteomyelitis of the mandible successfully treated with video-assisted thoracoscopic surgery. *Clin Respir J* 2015; 9: 253–256.

Ethics
Informed consent was obtained from the patient.

Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Key words
lung abscess – osteomyelitis – surgery – VATS

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Received: 13 October 2013
Revision requested: 16 January 2014
Accepted: 25 January 2014

DOI:10.1111/crj.12115

Authorship and contributorship
We confirm that all authors have made a substantial contribution to the information or material submitted for publication, and that all have read and approved the final version for submission to *The Clinical Respiratory Journal*.

Introduction

Lung abscess remains one of the causes of death with a significant mortality rate. The basic treatment for lung abscess is antibiotic therapy. With the progress of antibiotics, the contribution of surgery for lung abscess has decreased. However, some cases still require surgical intervention including lobectomy.

Video-assisted thoracoscopic surgery (VATS) has provided many benefits to patients with pulmonary disease, especially with benign, early staged primary lung cancer or poor physical status. But indication of VATS lobectomy for lung abscess therefore remains controversial. We herein report a rare combination of lung abscess and osteomyelitis of mandible resulting from the same pathogen successfully treated with VATS lobectomy.

Case report

A 66-year-old Japanese man visited the Division of Oral and Maxillofacial Surgery of our hospital with

a complaint of severe pain, pus, local heat and swelling in the lower left tooth region, beginning 2 weeks earlier. He was diagnosed with chronic osteomyelitis of the mandible due to α-*Streptococcus*. The patient underwent catheterization of superficial temporal artery for intra-arterial infusion of antibiotics and decorticotomy of mandible (Fig. 1). He received antibiotic therapy (doripenem hydrate) via catheter for 10 days, ampicillin hydrate by intravenous injection for 12 days and cefcapene pivoxil hydrochloride hydrate by oral administration. As a result, his symptoms improved.

Preoperative chest X-ray showed an abnormal shadow in the right middle lung field, and chest computed tomography (CT) revealed an irregular shaped mass in the right pulmonary upper lobe (RUL). He was then referred to our department (Respiratory Disease Center) after the operation. He had no past medical history, and his smoking history was 20 cigarettes per day for 45 years. The mass was located in segments S2a–S3a, measuring about 30 mm maximum diameter (Fig. 2). Bronchoscopic examination of lung biopsy was performed twice with 6 months between biopsies. Both histopathological diagnoses were 'chronic inflammation with no malignancy', and cultures of bronchial lavage revealed α-*Streptococcus*. The diagnosis was determined to be lung abscess due to the same pathogenic bacteria of chronic osteomyelitis of the mandible. Despite prolonged antibiotic therapy, the mass did not change in size in 6 months based on CT examination.

He underwent RUL lobectomy by VATS [40 mm mini thoracotomy + 2 ports (13.5 mm)] for refractory lung abscess due to α-*Streptococcus*. Because the mass

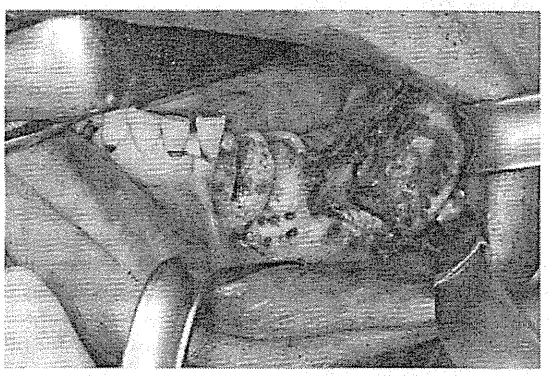

Figure 1. Decorticotomy of the left sequestral mandibular bone. The bone marrow was sclerosed, and there was minimal bleeding at the surgical site.

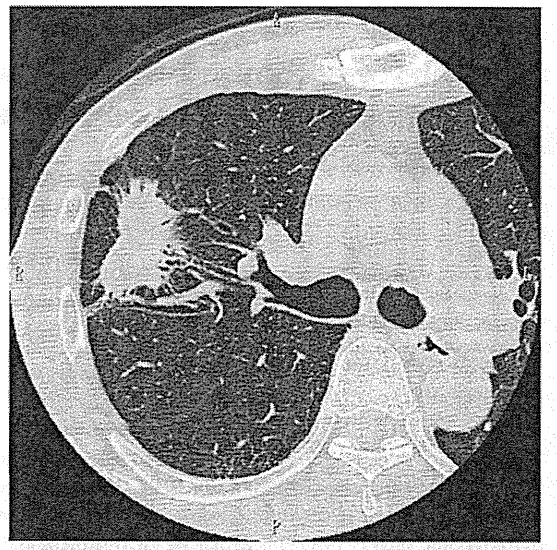

Figure 2. Chest computed tomography (CT) showing the shadow of an irregular shaped mass in the S2-S3 region of the right pulmonary upper lobe.

was too large and located in two segments from S2 to S3, wedge resection and segmentectomy were inappropriate for complete extraction of the tumor. At the discolored white region of visceral pleura of the upper lobe, a hard mass was recognized by palpation using the endo-forceps. There were only a few membranous adhesions between RUL and the anterior chest wall. As no adhesion at the subpleural lesion of the hilum existed, dissection and transection of pulmonary vessels using an endovascular stapler could be performed safely. The operative time was 163 min, with a blood loss of 120 mL. Tube drainage lasted for 3 days. He was discharged from the hospital on the 11th postoperative day without wound pain or dyspnea on effort. Grossly the tumor was located in the S2a–S3a region with necrosis, measuring $30 \times 22 \times 15$ mm (Fig. 3). Histologically, the abscess was recognized in the center of the mass surrounded by obstructive pneumonia and infiltration of inflammatory cells. There were no granuloma and malignant cells. The lung abscess may have developed because of occult aspiration of α-*Streptococcus*, which caused chronic osteomyelitis of the mandible.

Discussion

Chronic osteomyelitis of the mandible is extremely rare. Currently, inflammatory disorder can occur after

The Clinical Respiratory Journal (2015) • ISSN 1752-6981

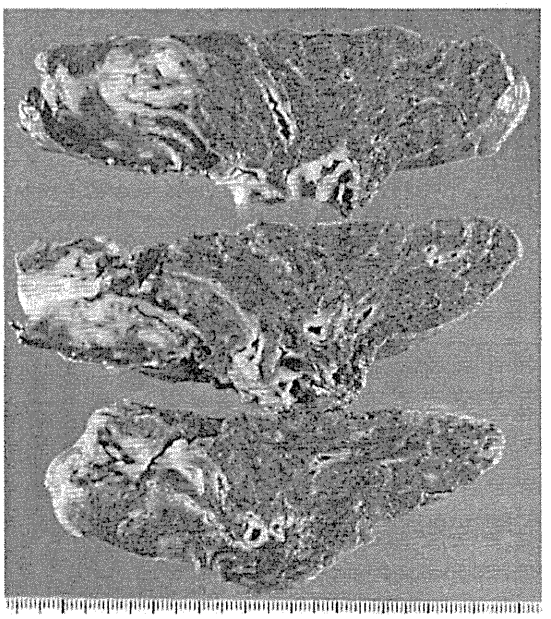

Figure 3. Macroscopic findings in the resected lung. A white-colored mass with necrosis on sectioning was located in the S2a–S3a region. Histologically, non-specific suppurative inflammatory changes were found.

a chronic odontogenic infection, especially in developed countries (1, 2), often by normal oral flora (3, 4). Sufficient debridement of necrotic tissue, decorticotomy and sequestrectomy followed by appropriate, prolonged antibiotic therapy are important as treatment (1, 3, 5).

Lung abscess is defined as necrosis of the pulmonary parenchyma and microbial infection. Aspiration of normal oral flora is a major factor in its etiology (6–8). In addition to aspiration, gingivo-dental disease and diabetes mellitus are also important for the mechanism of pathogenesis (7, 8). Periodontal disease has an incidence of about 15% among extrapulmonary-associated conditions (8), but the accurate incidence of a combination of chronic osteomyelitis of the mandible and lung abscess is unknown. In our case, the patient had no other pre-existing pulmonary disease in the background of the lung and no immunological abnormality that could have led to refractory lung abscess.

The basic treatment of lung abscess is appropriate and sufficient antibiotic therapy (7). With the progression of antibiotics, mortality of lung abscess has declined to 15%–20% compared with the preantibiotic era (30%–40%) (8). Surgery is not always required for treatment and its incidence is declining. Now, about 10%–20% of lung abscess cases require an operation for treatment (7, 9). In Japan, there were 67 960 cases of general thoracic surgery during 2010. The number of operations for 'inflammatory pulmonary disease' was 3140 (4.6%) cases; the number of lobectomy for lung abscess was unknown (The Japanese Association for Thoracic Surgery 2012) (10).

Surgical indications include (i) very large (>6 cm) and toxic lung abscess that is not responding to medical management for 8 weeks; (ii) persisting symptoms and signs; (iii) chronicity with a duration of 6–8 weeks without clear progress; and (iv) complications of lung abscess such as significant recurrent hemoptysis, bronchopleural fistula, empyema and suspicion of carcinoma (7, 9, 11). Lobectomy and pneumonectomy are common surgical procedures. Segmentectomy and wedge resection are not recommended because of the risk of spreading pathogens to the pleural cavity (7). Generally, surgery for lung abscess can be technically difficult and risky, as a result of intrapleural cavity or perihilar adhesion, ease of bleeding and bronchial artery development. Almost all patients with lung abscess are elderly and have a poor physical status, wet lung and many complications. Moreover, post-operative management is troublesome because complications. One investigator mentioned that the post-operative mortality was 11% in 1980 (11).

VATS lobectomy for lung abscess is controversial, but is much less invasive and a useful technique for diagnosis and treatment of some pulmonary diseases. In Japan, 70.5% of cases of thoracic surgery (47 945/67 960) underwent with VATS during 2012. The benefit to patients especially that with restricted physical conditions is significant as it leads to minimal physical damage.

In this case, there was no dense adhesion in the pleural cavity and perihilar region. These intraoperative findings may be related to the location of the lesion apart from the visceral pleura and the hilum, and to the previous prolonged antibiotic therapy. We propose that abscesses located apart from the hilum and pre-operative sufficient antibiotic therapies are indications of VATS lobectomy. The most essential technical point of surgery is careful blunt dissection of the perivascular sheath in one layer to prevent massive bleeding. On the other hand, complications related to isolation of great pulmonary vessels are indications for thoracotomy not VATS, given the risk of hemorrhage.

In conclusion, VATS lobectomy might be useful treatment for refractory lung abscess in select cases.

References

1. Yeoh SC, MacMahon S, Schifter M. Chronic suppurative osteomyelitis of the mandible: case report. Aust Dent J. 2005;50: 200–3.
2. Bernier S, Clermont S, Maranda G, Turcotte JY. Osteomyelitis of the jaws. J Can Dent Assoc. 1995;61: 441–2, 445–8.
3. Kim S-G, Jang H-S. Treatment of chronic osteomyelitis in Korea. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001;92: 394–8.
4. Hudson JW. Osteomyelitis of the Jaws: a 50-year perspective. J Oral Maxillofac Surg. 1993;51: 1294–301.
5. van Merkesteyn JPR, Groot RH, van den Akker HP, Bakker DJ, Borgmeijer-Hoelen AMMJ. Treatment of chronic suppurative osteomyelitis of the mandible. Int J Oral Maxillofac Surg. 1997;26: 450–4.
6. Yu H. Management of pleural effusion, empyema, and lung abscess. Semin Intervent Radiol. 2011;28: 75–86.
7. Hagan JL, Hardy JD. Lung abscess revisited. A survey of 184 cases. Ann Surg. 1983;197: 755–62.
8. Hirshberg B, Sklair-Levi M, Nir-Paz R, Ben-Sira L, Kivoruk V, Kramer MR. Factors predicting mortality of patients with lung abscess. Chest. 1999;115: 746–50.
9. Miller JI. Bacterial infections of the lungs and bronchial compressive disorders. In: Shields TW, Locicero JIII, Ponn RB, Rusch VW, editors. *General Thoracic Surgery*, 6th edn. Philadelphia, PA, Lippincott Williams & Wilkins, 2005: 1219–24.
10. Kuwano H, Amano J, Yokomise H. Thoracic and cardiovascular surgery in Japan during 2010: annual report by The Japanese Association for Thoracic Surgery. Gen Thorac Cardiovasc Surg. 2012;60: 680–708.
11. Delarue NC, Pearson FG, Nelenio JM, Cooper JD. Lung abscess: surgical implication. Can J Surg. 1980;23: 297–302.

JJCO Japanese Journal of Clinical Oncology

Clinical Trial Notes

Jpn J Clin Oncol 2014;44(4)379–382
doi:10.1093/jjco/hyt233
Advance Access Publication 27 January 2014

A Phase III Trial Comparing Irinotecan and Cisplatin with Etoposide and Cisplatin in Adjuvant Chemotherapy for Completely Resected Pulmonary High-grade Neuroendocrine Carcinoma (JCOG1205/1206)

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Received October 12, 2013; accepted December 16, 2013

A randomized Phase III trial commenced in Japan in March 2013. Post-operative adjuvant chemotherapy with etoposide plus cisplatin is the current standard treatment for resected pulmonary high-grade neuroendocrine carcinoma including small cell lung cancer and large cell neuroendocrine carcinoma. The purpose of this study is to confirm the superiority of irinotecan plus cisplatin in terms of overall survival over etoposide plus cisplatin as post-operative adjuvant chemotherapy for pathological Stage I–IIIA completely resected pulmonary high-grade neuroendocrine carcinoma patients. A total of 220 patients will be accrued from 54 Japanese institutions within 6 years. The primary endpoint is overall survival and the secondary endpoints are relapse-free survival, proportion of treatment completion, adverse events, serious adverse events and second malignancy. This trial has been registered at the UMIN Clinical Trials Registry as UMIN000010298 [http://www.umin.ac.jp/ctr/index.htm].

Key words: lung neoplasms – high-grade neuroendocrine carcinoma – adjuvant chemotherapy – Phase III

INTRODUCTION

Lung cancer has been the leading cause of cancer-related deaths in Japan since 1988. High-grade neuroendocrine carcinoma (HGNEC) including small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC) accounts for ~15% of all lung cancers (1,2).

LCNEC was first proposed by Travis et al. (3), who added LCNEC as the fourth category of pulmonary neuroendocrine tumors, which had originally been classified into three categories, typical carcinoid, atypical carcinoid and SCLC. Although it has been classified into a non-small cell lung cancer (NSCLC) by the WHO classification, LCNEC has neuroendocrine features and an aggressive clinical course that are common with SCLC and both are recognized as HGNEC. LCNEC is typically diagnosed post-operatively using surgical specimens and rarely diagnosed pre-operatively with biopsy specimens because of the difficulties associated with its diagnosis from a small amount of specimens. Furthermore, a differential diagnosis between LCNEC