外来で診る食道がん・胃がん・大腸がん

総論

がん対策基本法とがん医療

Key Words

がん対策
がん医療
がん
医療政策

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がん対策基本法（図1）[1]

1. 成立の背景と基本理念

がんが国民の疾病による死亡の最大の原因となっている等がんが国民の生命および健康にとって重大な問題となっている．がん対策基本法は，その現状を踏まえて，がん対策の一層の充実を図るため，がん対策に関し，基本理念を定め，国，地方公共団体，医療保険者，国民および医師等の責務を明らかにし，並びにがん対策の推進に関する計画の策定について定めるとともに，がん対策の基本となる事項を定めることにより，がん対策を総合的かつ計画的に推進することを目的としたものである．2006年6月に成立し，2007年4月より施行されている．本法では，①がんの克服を目指し，がんに関する専門的，学際的または総合的な研究を推進するとともに，がんの予防，診断，治療等に係る技術の向上その他の研究等の成果を普及し，活用し，および発展させること，②がん患者がその居住する地域にかかわらず等しく科学的知見に基づく適切ながんに係る医療）を受けることができるようにすること，③がん患者の置かれている状況に応じ，本人の意向を十分尊重してがんの治療方法等が選択されるようがん医療を提供する体制の整備がなされること，の3つを基本理念としている．

2. 関係者の責務

がん対策基本法では，国，地方公共団体等，関係者の責務を謳っている．国は，基本理念にのっとり，がん対策を総合的に策定し，および実施する責務，地方公共団体は，基本理念にのっとり，がん対策に関し，国との連携を図りつつ，自主的かつ主体的に，その地域の特性に応じた施策を策定し，および実施する責務を有するとしている．また，医療保険者は，国および地方公共団体が講ずるがんの予防に関する啓発および知識の普及，がん検診に関する普及啓発等の施策に協力するよう努めなければならないとし，国民は，喫煙，食生活，運動その他の生活習慣が健康に及ぼす影響等がんに関する正しい知識を持ち，がんの予防に必要な注意を払うよう努めるとともに，必要に応じがん検診を受けるよう努めなければならないとしている．さらに，医師その他の医療関係者は，国および地方公共団体が講ずるがん対策に協力し，がんの予防に

寄与するよう努めるとともに，がん患者の置かれている状況を深く認識し，良質かつ適切ながん医療を行うよう努めなければならないとしている．

3．基本的施策

がん対策基本法で，がんの予防および早期発見の推進，がん医療の均てん化の促進等，研究の推進等の3つを基本的施策としてあげている．

がんの予防および早期発見の推進では，喫煙，食生活，運動その他の生活習慣および生活環境が健康に及ぼす影響に関する普及啓発，がんの予防の推進のために必要な施策と，がん検診の方法等の検討，がん検診の事業評価の実施，がん検診に携わる医療従事者に対する研修の機会の確保などその他のがん検診の質の向上等を図るために必要な施策を講ずる．さらに，がん検診の受診率の向上に資するよう，がん検診に関する普及啓発その他の必要な施策を講ずるものとしている．

がん医療の均てん化の促進等では，がん医療に携わる専門的な知識および技能を有する医師その他の医療従事者の育成を図るために必要な施策，がん患者がその居住する地域にかかわらず等しくそのがんの状態に応じた適切ながん医療を受けることができるよう，専門的ながん医療の提供等を行う医療機関の整備を図るために必要な施策，がん患者に対し適切ながん医療が提供されるよう，国立がんセンター，専門的ながん医療を提供する医療機関，その他の医療機関等の間における連携協力体制の整備を図るために必要な施策を講じるとされている．また，がん患者の状況に応じて疼痛等の緩和を目的とする医療が早期から適切に行われるようにすること，居宅においてがん患者に対しがん医療を提供するための連携協力体制を確保すること，医療従事者に対するがん患者の療養生活の質の維持向

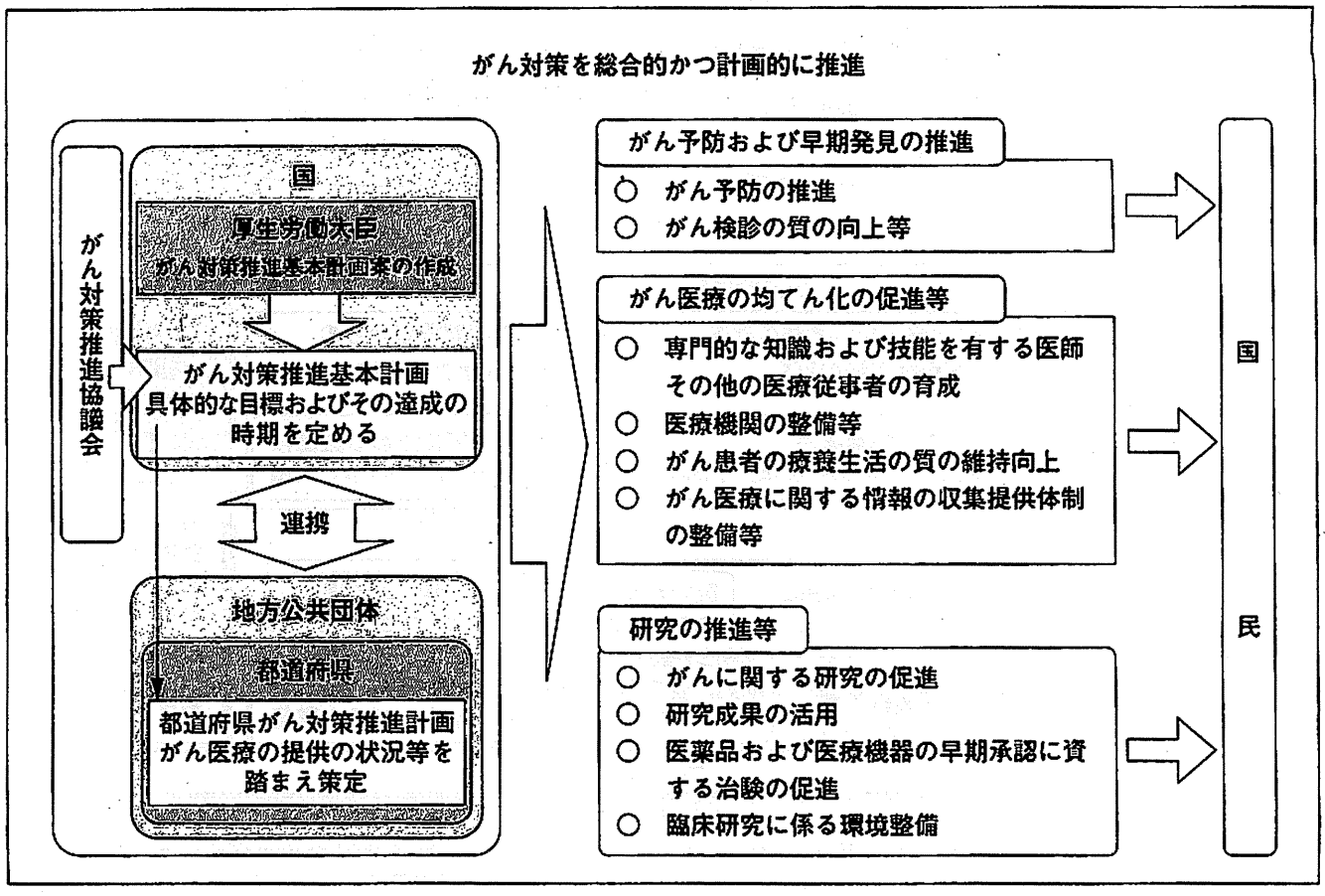

図1 がん対策基本法（2007年4月施行）

上に関する研修の機会を確保すること等がん患者の療養生活の質の維持向上のために必要な施策を講じるとしている．さらに，がん医療に関する情報の収集および提供を行う体制を整備するために必要な施策を講ずるとともに，がん患者およびその家族に対する相談支援等を推進するために必要な施策，がん患者のがんの罹り患，転帰その他の状況を把握し，分析するための取組を支援するために必要な施策を講ずるものとしている．

研究の推進等では，がんに関する研究の促進，研究成果の活用，医薬品および医療機器の早期承認に資する治験の促進，臨床研究に係る環境整備等をあげ，がんの本態解明，革新的ながんの予防，診断及び治療に関する方法の開発その他のがんの罹患率およびがんによる死亡率の低下に資する事項についての研究が促進され，並びにその成果が活用されるよう必要な施策，がん医療を行う上で特に必要性が高い医薬品および医療機器の早期の薬事法の規定による製造販売の承認に資するようその治験が迅速かつ確実に行われ，並びにがん医療に係る標準的な治療方法の開発に係る臨床研究が円滑に行われる環境の整備のために必要な施策を講ずるものとしている．

がん対策推進基本計画（図2）[2)]

2007年4月，がん対策基本法が施行され，基本法に基づいて，患者・家族の代表を含むがん対策推進協議会が召集され，4月・5月に6回の集中審議を行い，がん対策推進基本計画（案）が作成され，2007年6月15日に閣議決議された．がん対策推進基本計画は，長期的視点に立ちつつ，2007年度～2011年度までの5年間を対象として，がん対策の総合的かつ計画的な推進を図るため，がん対策の基本的方向について定めるとともに，都道府県がん対策推進計画（以下「都道府県計画」とい

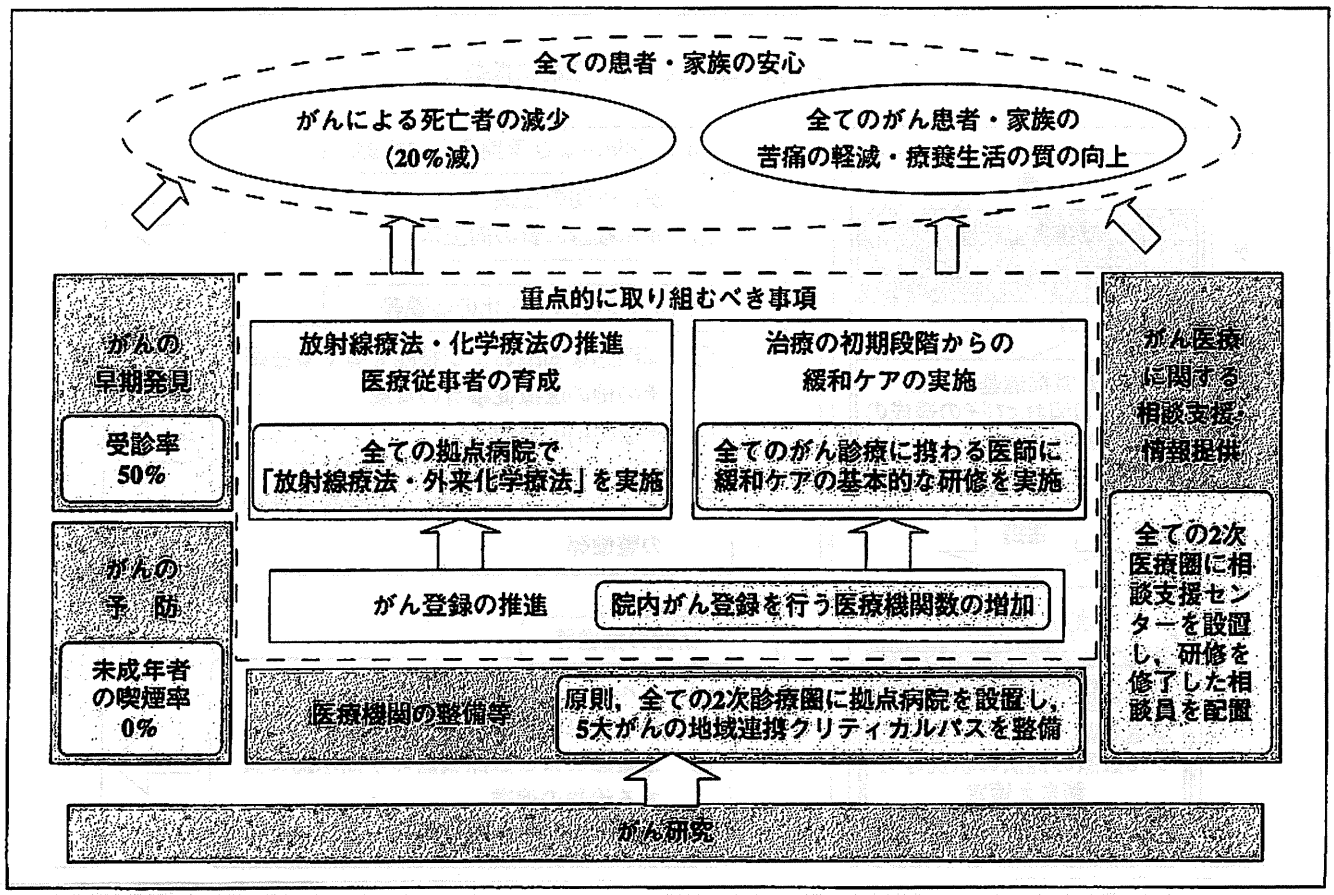

図2 がん対策推進基本計画

う）の基本となるものとされている．

1．重点的に取組むべき課題

基本方針として，がん患者を含めた国民の視点に立ったがん対策の実施，重点的に取り組むべき課題を定めた総合的かつ計画的ながん対策の実施をあげ，重点的に取り組むべき課題として，放射線療法および化学療法の推進並びにこれらを専門的に行う医師等の育成，治療の初期段階からの緩和ケアの実施，がん登録の推進をあげている．全体目標としては，がんによる死亡者の減少とすべてのがん患者およびその家族の苦痛の軽減並びに療養生活の質の維持向上があげられている．

放射線療法および化学療法の推進並びにこれらを専門的に行う医師の育成が重点課題となった背景として，わが国においては，胃がんなど，主として手術に適したがんが多かったこともあり，手術を行う医師が，化学療法も実施するなど，がん治療の中心を担ってきたが，現在は，がんの種類によっては，放射線療法が手術と同様の治療効果を発揮できるようになるとともに，新たな抗がん剤が多く登場し，化学療法の知見が蓄積してきたことから，進行・再発といった様々ながんの病態に応じ，手術，放射線療法および化学療法を効果的に組み合わせた集学的治療が各々を専門的に行う医師により実施されていくことが求められていることがあげられる．

治療の初期段階からの緩和ケアの実施については，がん患者とその家族が可能な限り質の高い療養生活を送れるようにするためには，緩和ケアが，治療の初期段階から行われるとともに，診断，治療，在宅医療など様々な場面において切れ目なく実施される必要があるが，わが国のがん性疼痛の緩和等に用いられる医療用麻薬の消費量が，欧米先進国の数分の一程度にとどまっていることや，がん診療に携わる医師の緩和ケアの重要性に対する認識が不十分であること等の改善が求められていることがあげられる．

2．分野別施策およびその成果や達成度を計るための個別目標

分野別施策として，(1) がん医療，(2) 医療機関の整備等，(3) がん医療に関する相談支援および情報提供，(4) がん登録，(5) がんの予防，(6) がんの早期発見，(7) がん研究，があげられる．(1) がん医療では，①放射線療法および化学療法の推進並びに医療従事者の育成，②緩和ケア，③在宅医療，④診療ガイドラインの作成，⑤その他が小項目としてあげられている．

放射線療法および化学療法の推進並びに医療従事者の育成では，がん診療を行っている医療機関が放射線療法および化学療法を実施できるようにするため，まずはその先導役として，すべての拠点病院において，5年以内に，放射線療法および外来化学療法を実施できる体制を整備するとともに，拠点病院のうち，少なくとも都道府県がん診療連携拠点病院および特定機能病院において，5年以内に，放射線療法部門および化学療法部門を設置することが個別目標とされている．また，抗がん剤等の医薬品については，「革新的医薬品・医療機器創出のための5か年戦略」に基づき，5年以内に，新薬の上市までの期間を2．5年短縮することが目標とされている．

緩和ケアでは，10年以内に，すべてのがん診療に携わる医師が研修等により，緩和ケアについての基本的な知識を習得することが目標とされている．また，原則として全国すべての2次医療圏において，5年以内に，緩和ケアの知識および技能を習得しているがん診療に携わる医師数を増加させるとともに，緩和ケアに関する専門的な知識および技能を有する緩和ケアチームを設置している拠点病院等がん診療を行っている医療機関を複数箇所整備することが目標とされている．

診療ガイドラインでは，科学的根拠に基づ

いて作成可能なすべてのがんの種類についての診療ガイドラインを作成するとともに，必要に応じて更新していくことが目標とされている．

医療機関の整備等では，原則として全国すべての2次医療圏において，3年以内に，概ね1か所程度拠点病院を整備するとともに，すべての拠点病院において，5年以内に，5大がん（肺がん，胃がん，肝がん，大腸がん，乳がん）に関する地域連携クリティカルパスを整備することが目標とされている．

がん医療に関する相談支援及び情報提供では，原則として全国すべての2次医療圏において，3年以内に，相談支援センターを概ね1か所程度整備するとともに，すべての相談支援センターにおいて，5年以内に，がん対策情報センターによる研修を修了した相談員を配置することが目標とされている．また，がんに関する情報を掲載したパンフレットの種類を増加させるとともに，当該パンフレットを配布する医療機関等の数を増加させることが目標とされ，加えて，当該パンフレットや，がんの種類による特性等も踏まえた患者必携等に含まれる情報をすべてのがん患者およびその家族が入手できるようにすることが目標とされている．さらに，拠点病院における診療実績，専門的にがん診療を行う医師および臨床試験の実施状況に関する情報等をさらに充実させることも目標されている．

がん登録では，院内がん登録を実施している医療機関数を増加させるとともに，すべての拠点病院における院内がん登録の実施状況を把握し，その状況を改善することが目標とされている．また，すべての拠点病院において，5年以内に，がん登録の実務を担う者が必要な研修を受講すること，がん登録に対する国民の認知度調査を行うとともに，がん登録の在り方についてさらなる検討を行い，その課題および対応策を取りまとめることが目標とされている．

がんの予防では，発がんリスクの低減を図るため，たばこ対策について，すべての国民が喫煙の及ぼす健康影響について十分に認識すること，適切な受動喫煙防止対策を実施すること，未成年者の喫煙率を3年以内に0%とすること，さらに，禁煙支援プログラムのさらなる普及を図りつつ，喫煙をやめたい人に対する禁煙支援を行っていくことが目標とされている．また，健康日本21に掲げられている「野菜の摂取量の増加」，「1日の食事において，果物類を摂取している者の増加」および「脂肪エネルギー比率の減少」等も目標とされている．

がんの早期発見では，がん検診の受診率について，欧米諸国に比べて低いことも踏まえ，効果的・効率的な受診間隔や重点的に受診勧奨すべき対象者を考慮しつつ，5年以内に50%以上（乳がん検診，大腸がん検診等）とすることが目標とされている．また，すべての市町村において，精度管理・事業評価が実施されるとともに，科学的根拠に基づくがん検診が実施されることが目標とされている．

がん研究では，がんによる死亡者の減少，すべてのがん患者およびその家族の苦痛の軽減並びに療養生活の質の維持向上を実現するためのがん対策に資する研究をより一層推進していくことが目標とされている．

3. がん対策を総合的かつ計画的に推進するために必要な事項

がん対策を総合的かつ計画的に推進するために必要な事項として，①関係者等の有機的連携・協力のさらなる強化，②都道府県による都道府県計画の策定，③関係者等の意見の把握，④がん患者を含めた国民等の努力，⑤必要な財政措置の実施および予算の効率化・重点化，⑥目標の達成状況の把握および効果に関する評価，⑦基本計画の見直し，があげられている．この中のがん患者を含めた国民

等の努力として，(a) がん患者およびその家族は，がん医療が医療従事者とのよりよい人間関係を基盤として成り立っていることを踏まえ，相互に信頼関係を構築することができるように努めること，(b) がん患者およびその家族は，医療従事者と協力して治療を進め，治療内容について医療従事者と共有できるようにすること，(c) がん患者および患者団体等は，がん対策において担うべき役割として医療政策決定の場に参加し，行政機関や医療従事者と協力しつつがん医療を変えるとの責任や自覚を持って活動していくこと，があげられている．

おわりに

以上のように，がん対策基本法の成立により，患者の視点に立ったがん対策推進基本計画が策定され，全国に375か所のがん診療連携拠点病院が指定され，さらに，各都道府県でがん対策推進計画が策定され，様々な取組が実施されているところである．このように，基本法によって，がんの医療が変わりつつあると思われ，「基本計画に基づき，国及び地方公共団体，また，がん患者を含めた国民，医療従事者，医療保険者，学会，患者団体を含めた関係団体及びマスメディア等が一体となってがん対策に取り組み，がん患者を含めた国民が，進行・再発といった様々ながんの病態に応じて，安心・納得できるがん医療を受けられるようにするなど，『がん患者を含めた国民が，がんを知り，がんと向き合い，がんに負けることのない社会」の実現を目指して行く』」ことが求められていると考える．

文　献

1) がん対策基本法：
http://www.mhlw.go.jp/shingi/2007/04/dl/s0405-3a.pdf
2) がん対策推進基本計画：
http://www.mhlw.go.jp/shingi/2007/06/s0615-1.html

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www.bjcancer.com

Characteristics and outcomes of patients with advanced non-small-cell lung cancer who declined to participate in randomised clinical chemotherapy trials

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There are inadequate data on the outcomes of patients who declined to participate in randomised clinical trials as compared with those of participants. We retrospectively reviewed the patient characteristics and treatment outcomes of both participants and non-participants in the two randomised trials for chemotherapy-naive advanced non-small-cell lung cancer. Trial 1 compared four platinum-based combination regimens. Trial 2 compared two sequences of carboplatin plus paclitaxel and gefitinib therapies. Nineteen of 119 (16%) and 153 (37%) patients declined to participate in Trials 1 and 2, respectively. Among the background patient characteristics, the only variable associated with trial participation or declining was the patients' attending physicians ($P<0.001$). Important differences were not observed in the clinical outcomes between participants and non-participants, for whom the response rates were 30.6 *vs* 34.2% and the median survival times were 489 *vs* 461 days, respectively. The hazard ratio for overall survival, adjusted for other confounding variables, was 0.965 (95% confidence interval: 0.73–1.28). In conclusion, there was no evidence to suggest any difference in the characteristics and clinical outcomes between participants and non-participants. Trial designs and the doctor–patient relationship may have an impact on the patient accrual to randomised trials.

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Keywords: randomised clinical trial; trial participation; trial effect; lung cancer

Randomised clinical trials (RCTs) are the definitive method for comparing the efficacy of treatments and a crucial step in the development of new cancer treatments. There has always been a big problem that their low accrual rates limit their progress (Lara *et al*, 2001; Corrie *et al*, 2003; Go *et al*, 2006).

A number of studies have examined the motivations of patients for accepting or declining entry to RCTs (Jenkins and Fallowfield, 2000; Madsen *et al*, 2000, 2002; Ellis *et al*, 2001; Wright *et al*, 2004; Ho *et al*, 2006; Albrecht *et al*, 2008). The results of questionnaire surveys administered to patients regarding clinical trials revealed that two of the most common reasons for entering the trial were the hope for personal benefit and the opportunity to contribute to the research knowledge thereby benefiting others in the future (Jenkins and Fallowfield, 2000; Madsen *et al*, 2000, 2002; Ellis *et al*, 2001; Wright *et al*, 2004; Albrecht *et al*, 2008). On the other hand, the common reasons for declining participation were worries about the process of randomisation, overestimation of the benefits of standard therapy and fear of the trial's experimental nature (Jenkins and Fallowfield, 2000; Ellis *et al*, 2001; Ho *et al*, 2006).

However, inadequate data are available on the actual outcomes of non-participants compared with those participating in RCTs (Schmoor *et al*, 1996; Braunholtz *et al*, 2001; Burgers *et al*, 2002; Peppercorn *et al*, 2004; West *et al*, 2005). Although several reports and their review (Braunholtz *et al*, 2001) have suggested the existence of a 'trial effect', in which participants enjoy favourable outcomes, others, especially those which attempted to exclude the confounding factors, have refuted this finding (Schmoor *et al*, 1996; Burgers *et al*, 2002; Peppercorn *et al*, 2004; West *et al*, 2005).

On the other hand, if participation in prospective trials is associated with certain clinical characteristics of the patients, generalisability of the conclusion from the data to the clinical practise, even in patients who meet the restrictive eligibility criteria, should be in question.

The purpose of this study was to analyse the characteristics and outcomes of the patients who met the eligibility criteria but declined to participate in RCTs, as compared with those who did participate, and to search for clues to improve patient accrual to clinical trials.

MATERIALS AND METHODS

Between October 2000 and October 2005, each of the 272 patients, who fulfilled the entry criteria of our top priority studies during the period, was informed of all aspects of RCTs on non-small-cell lung cancer (NSCLC) and was invited to participate in one of the two trials to be conducted at the National Cancer Center Hospital, Tokyo, Japan. We make it a rule for each patient with advanced

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lung cancer to be hospitalised for the first-line chemotherapy. All patients are then checked for the eligibility criteria of clinical trials available at the time and recorded in our database, whether or not they are treated on trials.

Signed informed consent was obtained from the patients for future statistical analysis of their clinical courses and outcomes, even when they were treated outside clinical trials.

Trial 1 was conducted to compare the four platinum-based combination regimens (cisplatin–irinotecan, carboplatin–paclitaxel, cisplatin–gemcitabine and cisplatin–vinorelbine) in patients with untreated advanced NSCLC between October 2000 and June 2002 (Ohe *et al*, 2007). When patients declined to participate, cisplatin-based combination regimens, such as cisplatin–irinotecan, the reference arm of the trial, were recommended. The patients ultimately selected the treatment following discussions with their families and the physicians.

Trial 2 was conducted between June 2003 and October 2005 to compare the following two treatment arms; (A) four courses of carboplatin and paclitaxel (CP) followed by gefitinib, and (B) gefitinib until disease progression followed by CP, in patients with advanced NSCLC (Nokihara *et al*, 2008). When patients declined to participate, platinum-based combination regimens, such as CP, were recommended. The patients ultimately selected the treatment following discussions with their families and the physicians; treatment options included gefitinib as first-line chemotherapy, when the patients and their families wished to start with it.

Patients in each trial had to meet the following criteria: histologically and/or cytologically documented NSCLC; clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy); no earlier systematic chemotherapy; at least one measurable lesion; age 20–74 years old; Eastern Cooperative Oncology Group Performance Status (PS) of 0 or 1; adequate haematological, hepatic and renal functions; and partial pressure of arterial oxygen of 60 torr or more. Each patient was required to submit a written informed consent before entry.

Four physicians (A, B, C and D) participated in Trial 1 and five physicians (A, B, C, D and E) in Trial 2. All were male. Physicians A, B, C and D had 16, 14, 11 and 9 years of experience, respectively, at the time of activation of Trial 1 (October 2000), and Physician E had 9 years of experience at the start of Trial 2 (June 2003). One of the five attending staff physicians and one to two residents or trainees attended each consultation. Which doctor actually offered the RCTs depended on each case and was not recorded, but the attending staff physician finally confirmed the decision by the patient.

Paper and/or electronic medical records from the initial visit to our centre to the end of the follow-up were retrospectively reviewed. Demographic data (age, gender, smoking history), medical information (tumour histology, clinical stage, performance status, therapy characteristics), and clinical outcomes (response rate, follow-up time, overall survival time, 1- and 2-year survival rates) were abstracted and analysed. The response was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) (Therasse *et al*, 2000) by the attending physicians. It is our policy to assess clinical responses with RECIST, even in routine practise. Follow-up time at our institution was defined as the period from the initiation of the first day of the initial therapy or decision of no therapy, to the last day at our institution (including death during follow-up). Survival data of the patients who left our institution could be collected by enquiry into official agency for family registry in Japan.

χ^2-tests and logistic regression analysis was used to assess associations between patient characteristics and the rate of declining to participate. Overall survival (OS) curves were produced using the Kaplan–Meier method and compared with the log rank test. All participants (those who agreed to be enroled into the RCT) and non-participants (those who declined to participate in the RCT) were included in the OS analysis. A Cox proportional hazards model was used to adjust for other potential confounding factors (age, gender, smoking history, clinical stage and PS) in comparing the OS of participants and non-participants. *P*-values <0.05 were considered statistically significant. The data collected were analysed using an SPSS II statistical package.

Japanese ethics guidelines for clinical and epidemiological studies, which took effect in August 2007, do not mandate institutional review board (IRB) approval for a single-institutional, retrospective data analysis from the medical charts, when the predesignated person of the institution so judges. This study was thus exempted from ethical review of IRB in due process, on the judgment of the responsible official, deputy director of National Cancer Center Hospital.

RESULTS

There were no significant differences in the outcomes between the arms of each trial. In Trial 1, no statistically significant differences in the response rate, progression-free survival and OS were observed between the four regimens. In Trial 2, there were no statistically significant differences in the median survival time (MST) (18.8 and 17.2 months) and the survival rate at 1 year between the two arms. Seventy-five patients declined to participate in those trials, and 1 of the 197 who initially accepted entry withdrew consent, refusing to continue the trial immediately after randomisation.

Table 1 shows the patient characteristics and rate of declining. 100 patients accepted and 19 patients (16%) declined entry to Trial 1, and 96 patients accepted and 57 patients (37%) declined entry to clinical Trial 2 (including the one patient already mentioned who withdrew consent after randomisation) ($P<0.001$). No significant influence on the rate of declining of patient gender, age,

Table 1 Patient characteristics and rate of declining

	Clinical trial 1			Clinical trial 2			Total		
	P	NP	ROD (%)	P	NP	ROD (%)	P	NP	ROD (%)
No.	100	19	16	96	57	37	196	76	28
Gender									
Male	64	12	16	55	34	38	119	46	28
Female	36	7	16	41	23	36	77	30	28
Age									
<60	46	9	16	37	29	44	83	38	31
⩾60	54	10	16	59	28	32	113	38	25
Smoking history									
+	69	9	12	55	33	38	124	43	26
–	31	10	24	41	24	37	72	33	31
Clinical stage									
III	24	6	20	21	19	48	45	25	36
IV	76	13	15	75	38	34	151	51	25
PS									
0	27	4	13	47	19	29	74	23	24
1	73	15	17	49	38	44	122	53	30
Physicians									
A	32	5	14	23	25	52	55	30	35
B	28	0	0	25	1	4	53	1	2
C	18	2	10	34	4	11	52	6	10
D	22	12	35	7	18	72	29	30	51
E	—	—	—	7	9	56	7	9	56

Abbreviations: NP = non-participants, P = participants; PS = performance status; ROD = rate of declining.

Table 2 Prediction of participation or declining to trials

	Univariate analysis[a]		Multivariate analysis[b]	
	Odds ratio (95% CI)	***P*-value**	**Odds ratio (95% CI)**	***P*-value**
Gender (male *vs* female)	1.008 (0.586–1.733)	0.977	0.646 (0.300–1.391)	0.264
Age (<60 *vs* ⩾60)	0.735 (0.432–1.250)	0.254	0.701 (0.376–1.310)	0.266
Smoking history (+ *vs* −)	1.394 (0.815–2.386)	0.225	2.538 (1.162–5.541)	0.019
Clinical stage (III *vs* IV)	0.608 (0.339–1.089)	0.093	0.681 (0.346–1.340)	0.266
PS (0 *vs* 1)	1.398 (0.792–2.467)	0.247	0.785 (0.396–1.554)	0.487
Physicians (A–E)		<0.001		<0.001

Abbreviations: NP = non-participant; P = participant; PS = performance status; ROD = rate of declining. [a]By Pearson's χ^2-test. [b]By logistic regression analysis.

Table 3 Number of courses of the first-line chemotherapy

	Clinical trial 1		Clinical trial 2		
	Participants	**Non-participants**	**Participants**	**Non-participants**	***P*-value**
	100	16	96	57	
First-line cycles					
1	10 (10%)	4 (25%)	6 (12%)	4 (9%)	0.418[a]
2	18 (18%)	4 (25%)	8 (16%)	12 (27%)	
3	37 (37%)	7 (44%)	5 (10%)	9 (20%)	
⩾4	35 (35%)	1 (6%)	30 (61%)	20 (44%)	
Gefitinib median duration (day)			73	99	0.118[b]
Range			13–752	34–1065	
IQR			29–204	38.5–512	

Abbreviation: IQR = interquartile range. [a]By Pearson's χ^2-test. [b]By log rank test.

smoking history, tumour histology, clinical stage or PS was observed (Table 2). There were, however, large differences in the rates of decline among the attending physicians who informed the patients about the trials and asked them to participate ($P<0.001$).

The treatment regimens for those who declined participation in the clinical trials were as follows. The majority of those who declined participation in Trial 1 selected one of the four platinum-based combination regimens presented in the trial: cisplatin–irinotecan 4, cisplatin–vinorelbine 3, cisplatin–gemcitabine 1, carboplatin–paclitaxel 4. Three patients in Trial 1 desired to have no more active treatments and opted for supportive care only, but later received active treatment at their referred hospitals. The detail of their therapy is unknown.

The majority of those who declined participation in Trial 2 selected carboplatin-based combination chemotherapy: carboplatin–paclitaxel 34 and carboplatin–gemcitabine 11, there by reflecting the shift to carboplatin for advanced NSCLC in Japan at the time of Trial 2, on the basis of the reports on the activity of the carboplatin-based regimens (Kelly *et al*, 2001; Schiller *et al*, 2002; Ohe *et al*, 2007). Twelve patients (21%) selected gefitinib as first-line chemotherapy.

Survival was analysed for all of the 196 participants and 76 of the non-participants. Post-therapy was analysed for all of the 196 participants and 73 of the non-participants, who were treated at our centre. There was one possible treatment-related death due to perforation of the colon during gefitinib treatment in Trial 2. No other toxic deaths were observed among either participants or non-participants. More participants of both the clinical trials were given four cycles or more of the first-line chemotherapy, probably reflecting protocol regulations (Table 3).

Table 4 summarises the treatment after the initial therapy. There were no significant differences between participants and non-participants in the number of chemotherapy regimens. Six (8%) of those who declined participation in the trial later participated in early-phase clinical trials of experimental therapies.

Table 4 Treatment after the first-line chemotherapy

	Participants 196 (%)	**Non-participants 73 (%)**	***P*-value[a]**
Chemotherapy regimen			
0[b]	26	40	0.108
1	38	26	
2	22	25	
3	9	8	
>4	5	1	
Radiotherapy	49	34	0.031
Pleural or pericardial drainage	10	5	0.227
Operation on metastatic brain tumors	1	3	0.122
Early-phase trials	13	8	0.300

[a]By Pearson's χ^2-test. [b]Patients received first-line chemotherapy only.

We have observed no clinically relevant differences in the clinical outcomes between participants and non-participants (Table 5). Clinical response to the initial therapy was analysed for all of the 196 participants and 73 of the non-participants, excluding three patients who were not treated at our institute. The response rate was 30.6% in participants and 34.2% in non-participants ($P=0.325$). The median follow-up time at our centre was 388 days for participants and 406 days for non-participants, which was not statistically different.

The OS was not different between participants and non-participants (Table 5 and Figure 1), with a hazard ratio of participants *vs* non-participants of 0.998 (95% confidence interval: 0.76–1.32). No significant difference in OS was observed either in Trial 1 (Figure 2) or in Trial 2 (Figure 3).

Table 5 Clinical outcomes

	Clinical trial 1		Clinical trial 2		Total		
	Participants	**Non-participants**	**Participants**	**Non-participants**	**Participants**	**Non-participants**	***P*-value**
Response rate (%)[a]	29 (29/100)	12.5 (2/16)	32.3 (31/96)	40 (23/57)	30.6 (60/196)	34.2 (25/73)	0.569[b]
Median follow-up time (day)	329	339	493	444	388	406	0.846[c]
Range	45–2704	1–2176	36–2036	22–1688	36–2704	1–2176	
IQR	177–665	59–582	213–861	175–658	197–742	146–604	
Median survival time (day)	416	408	573	519	489	461	0.987[c]
Range	34–2704	53–2380	40–2036	35–1688	34–2704	35–2380	
IQR	264–815	140–698	251–938	276–1012	259–863	229–774	
1-year survival (%)	56.0	63.2	65.6	64.9	60.7	64.5	0.567[b]
2-year survival (%)	29.4	21.1	38.5	29.8	33.9	27.6	0.379[b]

Abbreviation: IQR = interquartile range. [a]Excluding three patients who did not receive active treatment at our center. [b]By Pearson's χ^2-test. [c]By log rank test.

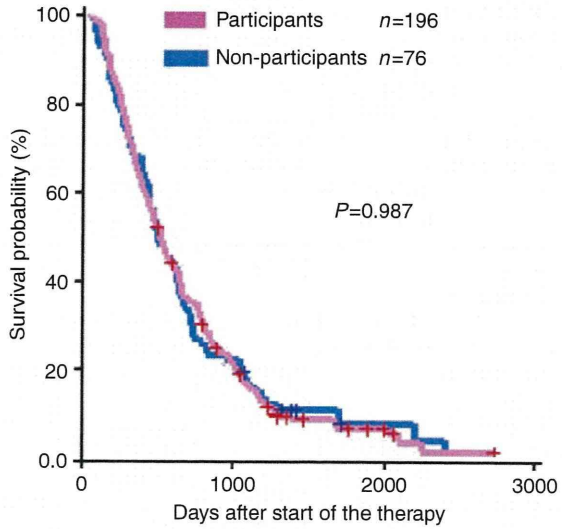

Figure 1 Overall survival of those who declined to participate in randomised trials (blue line, $n = 76$) as compared with the participants (pink line, $n = 196$). No significant difference can be observed.

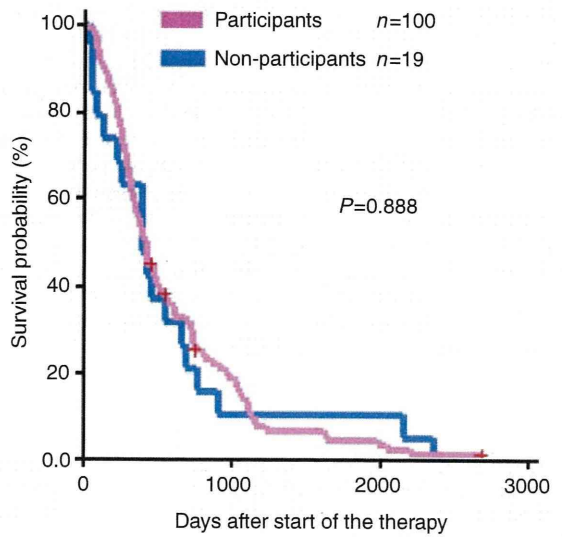

Figure 2 Overall survival of those who declined to participate in Trial 1 (blue line, $n = 19$) as compared with the participants (pink line, $n = 100$). No significant difference can be observed.

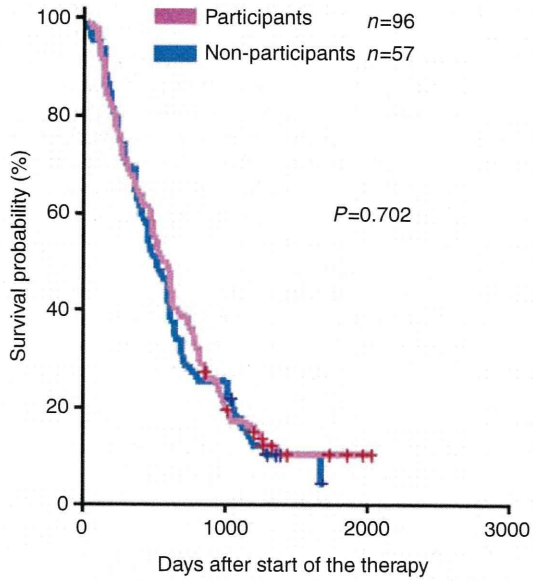

Figure 3 Overall survival of those who declined to participate in Trial 2 (blue line, $n = 57$) as compared with the participants (pink line, $n = 96$). No significant difference can be observed.

With the Cox proportional hazards model adjusted for gender, age, smoking history, clinical stage and PS, the hazard ratio of participants *vs* non-participants was 0.965 (95% confidence interval: 0.73–1.28, $P = 0.805$). Among the patient characteristics, PS was the only significant factor associated with OS in multivariate analysis ($P = 0.006$, by Cox proportional model).

DISCUSSION

It has been argued that trial participants have better outcomes than those who are not enroled in clinical trials. Several investigations have reported a favourable overall trend with trial entry (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004; West *et al*, 2005). This 'trial effect' could derive from several factors, such as protocol effect (the way treatments are delivered), care effect (extra care related to data gathering), Hawthorne effect (changes in doctor or patient behaviour on the basis of the knowledge that they are under observation) or placebo effect (psychologically mediated benefits) (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004).

In majority of the reports comparing outcomes between participants and non-participants of clinical trials, however, the

non-participant 'controls' were chosen from differently pooled database, which could include baseline imbalances between groups and hindsight bias (Davis *et al*, 1985; Braunholtz *et al*, 2001; Peppercorn *et al*, 2004). In this study, we compared the characteristics and outcomes of those who met the eligibility criteria but declined to participate in randomised trials, and instead chose to receive standard therapy. We thus aimed at excluding confounding factors as much as possible.

On the other hand, physician triage is pointed out to be one of the barriers to cancer clinical trial accrual (Lara *et al*, 2001; Corrie *et al*, 2003; Go *et al*, 2006; Ho *et al*, 2006). We excluded the barrier by making it a rule to offer clinical trials to every patient with advanced NSCLC who satisfied the eligibility criteria.

The response rate, MST, 1-year and 2-year survival rates were all similar in both groups. We have to admit that response evaluation might not be as strict in off-protocol therapy. However, the hazard ratio for the OS was very close to 1. Although the confidence interval of 0.73 to 1.28 could not rule out the existence of clinically important difference in the treatment effect, it could not by any means be taken as a clinically relevant prognostic factor. We thus believe this confidence interval of the adjusted hazard ratio, 0.73–1.28, was narrow enough to justify the conclusion that the clinical outcomes of trial participants and non-participants were not different in our study. The differences in the number of cycles of chemotherapy given to participants and non-participants may suggest the so-called protocol effect (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004), in which explicit careful description of treatment regimens could lead to improvement of outcomes. On the other hand, there clearly existed no 'care effect' representing the differences in incidental aspects of treatment or care between participants and non-participants, which the protocol may require, such as extra follow-up or extra nursing care (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004). In our cases, the same treatment teams took charge of and followed both groups of patients in the same manner, and found no differences in the post-treatment characteristics or follow-up periods. Thus, our first finding was that the clinical trials themselves seemed to have no influence on the outcomes or pattern of care of the patients.

The second finding was that we could not find any demographic characteristics to influence the patients' willingness to participate in clinical trials. Taken together with the first finding, both the characteristics and outcomes of the non-participants were very similar to the participants. This would imply that the participants ably represented the whole patient population of the disease status who met the eligibility criteria, and that conclusions from the clinical trials could be generalised.

Our study, however, could only show the similarity in the prognosis of the participants and non-participants, and, unlike an earlier report (Link *et al*, 1986), not that of the treatment effect itself. This could not be evaluated because there were no significant differences in the clinical effect between the arms in both Trial 1 and Trial 2. If newer, much more effective experimental treatment were presented in the trials, the outcome could be better in trial participants, which was the case in the adjuvant chemotherapy trial for osteosarcoma (Link *et al*, 1986). In that report, eligible patients who declined randomisation, but were given adjuvant chemotherapy, also had better outcomes. Therefore, a very effective treatment could lead to a better outcome both on and off trial. Ideally, strict comparison of the effects of the study participation itself would require randomised design of the trial participation (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004), which is almost impossible to conduct.

Thirdly, the declining rate seemed to be influenced by the trial design. Trial 1 was the comparison of four similar platinum-doublet regimens. On the other hand, Trial 2 was the comparison of two arms with sequentially different types of chemotherapy. In general, people might have the impression that injection therapy would be more effective, and less convenient, than oral administration. It is easy to understand that more patients felt difficulty in accepting the randomisation of different types of therapy, such as Trial 2 (Schmoor *et al*, 1996; Jenkins and Fallowfield, 2000).

The declining rate also seemed to be greatly affected by the attending physician. The attending physician with longer experience as a thoracic oncologist tended to have lower rate of declination. Even though we do not have records on who actually informed the participants regarding the trial, residents or trainees under Physician A seemed to have had more chance to lead the consultation, which might have affected the rate of declination. Trust in the doctor is one of the most important reasons for agreeing to enter an RCT, whereas it has also been cited as the main reason for declining to participate (Jenkins and Fallowfield, 2000; Ellis *et al*, 2001; Stryker *et al*, 2006). Patients prefer the doctor to make the treatment decisions rather than to be randomised. A recent report emphasises the influence of physicians' clinical communication on patients' decision-making on participation in clinical trials (Albrecht *et al*, 2008). Improving communication and more interventions by clinical research coordinators and other medical staff members in all eligible patients may improve the accrual rate (Fallowfield *et al*, 1998; Wright *et al*, 2004; Stryker *et al*, 2006).

Finally, it was interesting to find that 8% of those who declined the RCTs participated in early-phase trials during follow-up. It is possible that the lack of effective therapies had changed their recognition of clinical trials. However, it might support the psychological states of patients as reported in earlier studies (Jenkins and Fallowfield, 2000; Ellis *et al*, 2001; Wright *et al*, 2004); patients expect experimental therapies to give them improved effectiveness but with fear of uncertainty. They are reported to have negative opinions regarding the principle of randomisation. Better understanding of the patients' decision-making process and the factors influencing their psychological states may lead to improvement in RCT accrual.

Our study has several limitations. One is that it was conducted at a single academic institution; the situation might well have been different in others or when the research was performed on a multi-institution basis. The second is that we analysed data from only two trials and could not definitely conclude that a trial design would affect the patient accrual. Third, we have no data on the reasons for patient participation. That information would be definitely useful for analysing factors for consent or declining to participate, and would help to improve the accrual rate. Further research is required.

In conclusion, there was no evidence of any difference in the response rates and survival times between participants and non-participants. The declining rate of clinical trials was influenced by the referring physicians and trial designs. Further analysis of the decision-making process of those offered trials is warranted, for it may improve patient accrual to RCTs.

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Original article

Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer

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Background: Locally advanced gastric cancer with extensive lymph node metastasis is usually considered unresectable and so treated by chemotherapy. This trial explored the safety and efficacy of preoperative chemotherapy followed by extended surgery in the management of locally advanced gastric adenocarcinoma.

Methods: Patients with gastric cancer with extensive lymph node metastasis received two or three 28-day cycles of induction chemotherapy with irinotecan (70 mg/m^2 on days 1 and 15) and cisplatin (80 mg/m^2 on day 1), and then underwent gastrectomy with curative intent with D2 plus para-aortic lymphadenectomy. Primary endpoints were 3-year overall survival and incidence of treatment-related death.

Results: The study was terminated because of three treatment-related deaths when 55 patients had been enrolled (mortality rate above 5 per cent). Two deaths were due to myelosuppression and one to postoperative complications. Clinical response and R0 resection rates were 55 and 65 per cent respectively. The pathological response rate was 15 per cent. Median overall survival was 14·6 months and the 3-year survival rate 27 per cent.

Conclusion: This multimodal treatment of locally advanced gastric cancer provides reasonable 3-year survival compared with historical data, but at a considerable cost in terms of morbidity and mortality.

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Introduction

Macroscopically complete tumour removal is a prerequisite to cure gastric cancer[1,2]. Japanese surgeons have explored the benefits and disadvantages of para-aortic nodal dissection for locally advanced tumours with nodal metastases[3–6]. The Japanese Gastric Cancer Association (JGCA) defines para-aortic lymph nodes as being regional lymph node stations (JGCA-N3)[7]. Tumours with bulky nodal metastases surrounding the coeliac artery and its branches (JGCA-bulky N2) are usually considered unresectable. The prognosis of patients with JGCA-N3 or JGCA-bulky N2 is extremely poor even when the entire tumour and lymph nodes can be resected with curative intent. Further, complete resection of these tumours often requires combined organ resection, such as distal pancreatectomy, resulting in major surgical complications[8]. Even after this surgery with curative intent, most tumours recur, suggesting that distant micrometastases were already present.

In contrast to the Japanese staging system, the tumour node metastasis (TNM) staging of the International Union Against Cancer (UICC) defines para-aortic metastases as

The Editors are satisfied that all authors have contributed significantly to this publication

distant metastases[9]. In Western countries, tumours with JGCA-N3 or JGCA-bulky N2 are therefore regarded as unresectable disease that warrants palliative chemotherapy. These patients rarely survive for more than 3 years when they receive chemotherapy alone or when surgery is followed by postoperative chemotherapy. To improve this dismal prognosis, a different strategy should be developed.

Preoperative chemotherapy has some theoretical benefits in these patients in comparison with postoperative chemotherapy. First, extended surgery can be performed easily and safely because the chemotherapy usually leads to shrinkage of lymph nodes, increasing the likelihood of R0 resection. Second, more intensive chemotherapy is possible with high compliance. Third, distant micrometastases can be treated early, before local therapy has begun. Recently, the effectiveness of a regimen of preoperative and postoperative epirubicin, cisplatin and infused fluorouracil for less advanced disease was suggested[10]. Combined chemotherapy using irinotecan hydrochloride plus cisplatin is also an attractive regimen for preoperative chemotherapy. In a phase II trial using this regimen in patients with metastatic gastric cancer, a response rate of 48 per cent and acceptable toxicity were reported[11].

The present study was conducted to evaluate the efficacy and safety of preoperative chemotherapy with irinotecan plus cisplatin followed by gastrectomy with D2 plus para-aortic nodal dissection for locally advanced gastric cancer with extensive lymph node metastases.

Methods

The study was conducted as a prospective multi-institutional phase II trial between 2000 and 2003 involving the 21 institutions of the Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group (JCOG). Patients with locally advanced gastric cancer presenting at their institution were considered for participation in the study. The absence of peritoneal dissemination was confirmed by laparoscopy before entry into the study.

Eligibility criteria

Eligibility criteria included: histologically proven gastric adenocarcinoma; para-aortic nodal metastases and/or bulky N2 cancers confirmed by contrast-enhanced computed tomography (CT) (definitions in *Fig. 1*); no metastases outside the para-aortic region, as confirmed by contrast-enhanced CT; no peritoneal or pleural effusion; no

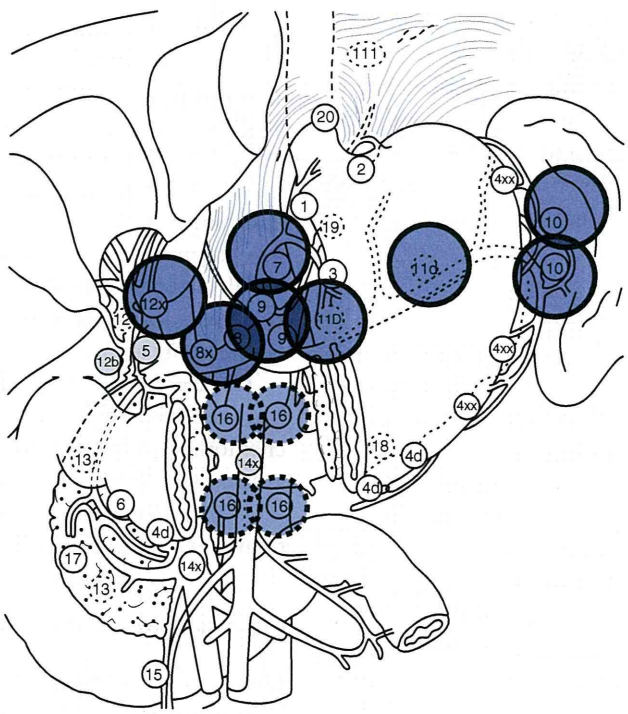

Fig. 1 Definitions of bulky N2 and para-aortic nodal metastases. Bulky N2 (in solid circles): at least one node of 3 cm or more in diameter, or at least three consecutive nodes each of diameter 1·5 cm or more, along the coeliac, splenic, common or proper hepatic arteries. Para-aortic nodes (in dashed circles): at least one node of 1 cm or more in diameter around the abdominal aorta

clinically apparent brain or bone metastases; no peritoneal metastases and negative cytology at laparoscopy; non-scirrhous type macroscopically; 20–70 years of age; Eastern Cooperative Oncology Group performance status 0 or 1; no previous chemotherapy or radiotherapy. In addition, patients had to have no signs of organ failure, as assessed by a white blood cell (WBC) count minimum of 4000/mm^3 and maximum of 12 000/mm^3, platelet count of 100 000/mm^3 or above, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than three times the upper limit of normal, total bilirubin 1·5 mg/dl or less, creatinine 1·2 mg/dl or less and creatinine clearance 60 ml/min or above, and haemoglobin 9·0 g/dl or more. There had to be no ischaemic change or ventricular arrhythmia on exercise electrocardiography, a forced expiratory volume in 1 s of 50 per cent or more, arterial partial pressure of oxygen (PaO_2) of 70 mmHg or above, and indocyanine green test in 15 min of 10 per cent or less in cases of liver dysfunction, negative serology for viral hepatitis and no past history of hepatitis. All patients gave written informed consent.

Exclusion criteria included: active gastrointestinal bleeding, infection, watery diarrhoea, synchronous or metachronous (within 10 years) malignancy other than carcinoma *in situ*, pregnancy or lactation, treatment with a major tranquillizer, lung fibrosis or interstitial pneumonitis, and bowel obstruction. Patients with allergic reactions to iodine were excluded because contrast-enhanced CT could not be performed. All patients were registered centrally at the JCOG Data Centre, where data management, central monitoring and statistical analysis were conducted. For quality assurance, a site visit audit was performed by the JCOG Audit Committee.

Preoperative chemotherapy

Irinotecan 70 mg/m^2 was administered on days 1 and 15 and cisplatin 80 mg/m^2 was given on day 1 as one course, repeated every 4 weeks[11]. If the patient had a WBC of 4000/mm^3 or less, platelet count of 10 000/mm^3 or lower, diarrhoea of grade 1 or above (increase of four or more stools per day over pretreatment), an episode of infection or abnormal serum creatinine concentration, administration of irinotecan and/or cisplatin was postponed until recovery. If recovery did not occur within 2 weeks, chemotherapy was stopped. On day 15 of each course, if the patient had an adverse event the second administration of irinotecan was postponed, and was not given if the adverse event was still observed on day 22. If the patient had haematological adverse events of grade 4 (haemoglobin level less than 6·5 g/dl, leucocyte count below 1000/mm^3, neutrophil count less than 500/mm^3, or platelet count below 25 000/mm^3), diarrhoea of grade 3 or higher (increase of more than seven stools per day or incontinence, or need for parenteral support for dehydration), or if the second administration of irinotecan was not given in the last course, the next dose of irinotecan was reduced to 60 mg/m^2. If the patient had a serum creatinine level of 1·2–1·5 mg/dl, the next dose of cisplatin was reduced to 60 mg/m^2. If serum creatinine was 1·5 mg/dl or above, initiation of the next course was delayed.

Some 7–13 days after the second administration of irinotecan in each course, resectability was evaluated based on CT findings by the Response Evaluation Criteria in Solid Tumours (RECIST)[12]. If curative resection was considered possible after the second course, the patient had surgery immediately. If curative resection was considered difficult, a further course of chemotherapy was added before surgery.

Surgery

Resection criteria included: R0 resection deemed possible by gastrectomy with D2 plus para-aortic nodal dissection, and no evidence of organ failure as assessed by a WBC count greater than 3000/mm^3 and less than 12 000/mm^3, platelet count above 100 000/mm^3, AST and ALT levels less than three times the upper limit of normal, total bilirubin less than 1·5 mg/dl, creatinine below 1·5 mg/dl and creatinine clearance above 50 ml/min, and PaO_2 greater than 70 mmHg. Eligible patients were operated on 3–6 weeks after chemotherapy.

After laparotomy, resectability was again evaluated and, if intraperitoneal wash cytology was negative, R0 resection was attempted by gastrectomy with D2 plus para-aortic nodal dissection, as described previously[13]. If necessary, D2 plus para-aortic nodal dissection was combined with splenectomy and/or distal pancreatectomy.

The treatment protocol was completed when a patient had received two or three courses of preoperative chemotherapy and had undergone R0 resection by gastrectomy with D2 plus para-aortic nodal dissection (*Fig. 2*). After completion of the protocol, no further treatment was given until tumour recurrence.

Quality control of surgery

During the recruitment period, participating surgeons and data centre representatives met three times per year to monitor the study. At each meeting, videos of various surgical procedures, including nodal dissection, were presented by several participating institutions,

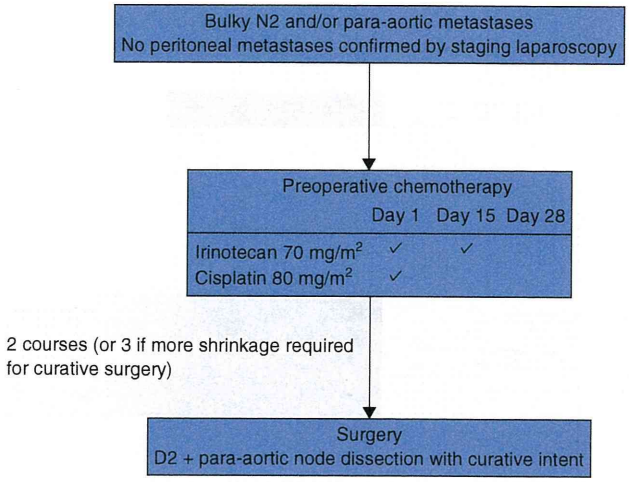

Fig. 2 Study outline

and technical details were discussed for critique. To assess compliance with lymphadenectomy, the number of dissected nodes was recorded.

Objectives and evaluation

Primary endpoints were overall survival and incidence of treatment-related death. Secondary endpoints were number of R0 resections, response to chemotherapy, chemotherapy-related toxicity and surgical complications. Clinical response was evaluated by RECIST[12], based on CT with a central review. Surgical specimens were evaluated pathologically and graded according to the proportion of tumour affected by degeneration or necrosis[14]: grade 0, no part of tumour affected; grade 1a, less than one-third affected; grade 1b, between one-third and two-thirds affected; grade 2, between two-thirds and entire tumour affected; and grade 3, no residual tumour. A pathological response was defined as one-third or more of the tumour affected (grade 1b, 2 or 3). Adverse events during chemotherapy were evaluated by the National Cancer Institute – Common Toxicity Criteria version 2.0[15].

Statistical analysis

For sample size calculation, treatment was considered effective if the lower limit of the 95 per cent confidence interval (c.i.) for 3-year survival exceeded 15 per cent. In terms of feasibility and efficiency, sample size was determined as 60 with a 3-year entry and 3-year follow-up period. In this setting, the exact binomial lower confidence limit for a 3-year overall survival rate of 30 per cent (18 of 60) was 18·9 per cent and that for 25 per cent (15 of 60) was 14·8 per cent. This was considered sufficiently precise to make inferences based on 3-year survival. Hence, the sample size was calculated as 60.

The survival curve was estimated using the Kaplan–Meier method; 95 per cent c.i. were calculated with the Greenwood formula[16]. Treatment was considered safe if point estimates of treatment-related death did not exceed 5 per cent. The stopping rule for safety was prespecified so that the study would be terminated when treatment-related death had been observed in three patients (treatment-related death exceeding 5 per cent). Statistical analysis was performed with SAS® version 8.2 (SAS Institute, Cary, North Carolina, USA). This phase II trial was approved by the JCOG Protocol Review Committee and institutional review board of each institution involved.

Results

Between August 2000 and May 2003, 55 patients were entered into the study and underwent preoperative chemotherapy. All patients were followed for more than 3 years after registration. When 55 patients had been registered, three were judged as treatment-related deaths by the JCOG data and safety monitoring committee, and the study was terminated according to the stopping rules. Thus, the treatment-related death rate was 5 (95 per cent c.i. 1 to 15) per cent. *Table 1* shows patient demographics and tumour characteristics. A flow diagram from chemotherapy to surgery is shown in *Fig. 3*. The clinical response rate for all eligible patients was 55 (95 per cent c.i. 41 to 68) per cent (30 of 55 patients) (*Fig. 3*).

Table 1 Demographics and tumour characteristics in 55 eligible patients

Median (range) age (years)	63 (46–70)
Sex ratio (M : F)	42 : 13
ECOG performance status	
0	47
1	8
Histology	
Differentiated	30
Undifferentiated	25
Nodal status	
Para-aortic nodes and bulky N2	19
Only para-aortic nodes	11
Only bulky N2	25

ECOG, Eastern Cooperative Oncology Group.

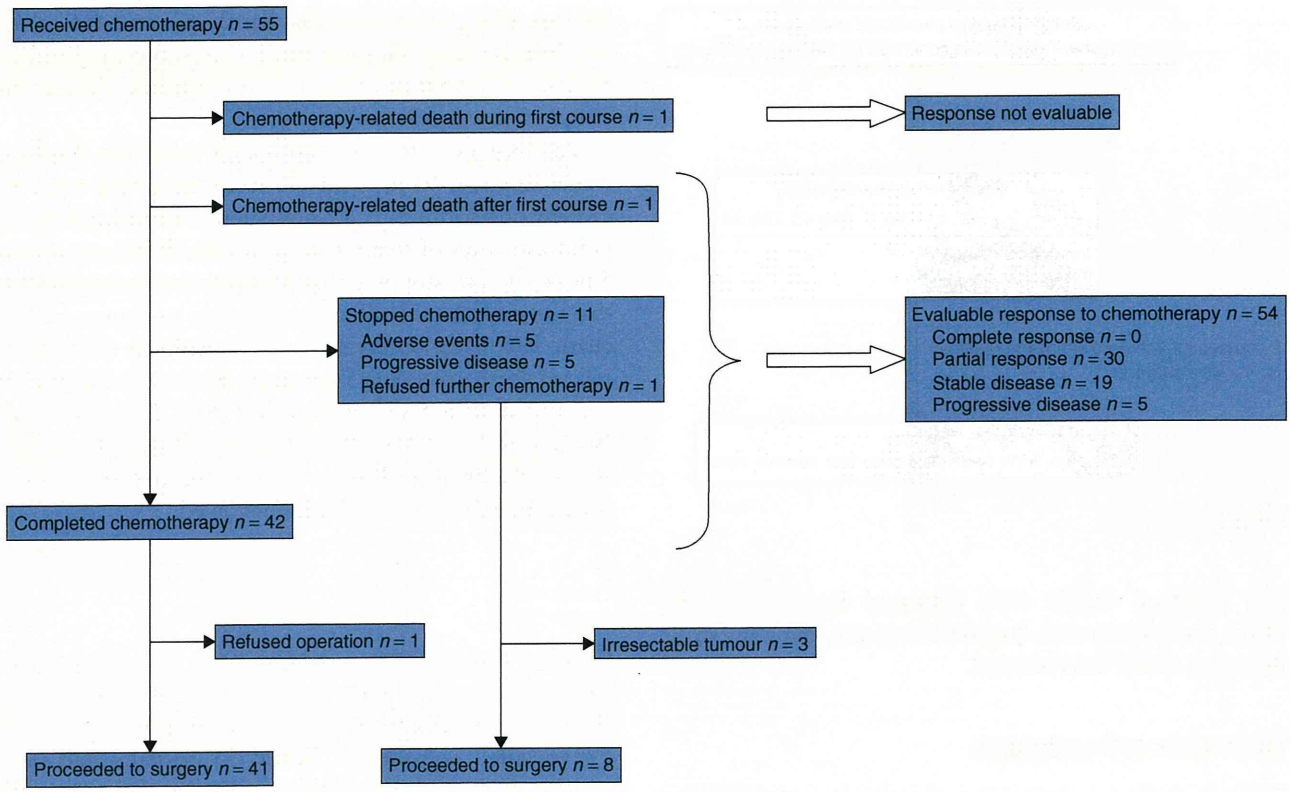

Fig. 3 Flow diagram from chemotherapy to surgery in 55 eligible patients

Table 2 Details of 49 patients who underwent surgery

	No. of patients
Peritoneal cytology	
Negative	45
Positive	4
Type of resection	
Total gastrectomy	32
Distal gastrectomy	15
Bypass	1
Exploratory laparotomy	1
Dissection of nodes along splenic artery	
With splenectomy and distal pancreatectomy	14
With splenectomy	16
Without splenectomy	13
No nodal dissection	6†
Operating time (min)*	370 (40–930)
Blood loss (ml)*	1050 (0–5650)
Blood transfusion	34
No. of para-aortic nodes dissected*	26 (0–86)
No. of nodes dissected*	87 (45–179)

*Values are median (range). †Exploratory laparotomy in one patient, bypass in one, palliative resection in one and non-curative resection in three patients.

Table 3 Pathological findings in resected patients

	No. of patients (n = 47)
Depth of tumour invasion	
T1	3
T2	18
T3	19
T4	6
Unknown	1*
JGCA, nodal status	
N0	1
N1	7
N2	9
N3	30
JGCA, pathological response	
Grade 0	6
Grade 1a	33
Grade 1b	2
Grade 2	5
Grade 3	1

*Not evaluable as no residual cancer cells. JGCA, Japanese Gastric Cancer Association.

Surgical findings and surgical pathology

Forty-nine patients proceeded to surgery (*Table 2*). Resection with curative intent was undertaken in 46 patients. One patient had only exploratory laparotomy because of peritoneal metastases, one underwent gastrojejunostomy, and one required palliative resection to stop bleeding from the primary tumour. Of the 46 patients who had resection with curative intent, R0 resection was performed in 36, R1 in four (positive surgical margin, three; positive peritoneal cytology, one) and R2 in six with unresectable tumours (*Table 3*). Thus, the proportion of R0 resections in the 55 eligible patients was 65 (95 per cent c.i. 51 to 78) per cent.

The pathological response rate in resected patients was 15 (95 per cent c.i. 7 to 27) per cent.

Adverse events from chemotherapy

Toxicity of grade 3 or above included leucopenia (31 per cent), neutropenia (55 per cent), anaemia (24 per cent), febrile neutropenia (16 per cent), nausea (36 per cent), vomiting (13 per cent) and diarrhoea (5 per cent). Two patients died from myelosuppression after the initial chemotherapy course, giving a chemotherapy-related mortality rate of 4 per cent (two of 55 patients).

Surgical complications

Surgical complications are shown in *Table 4*. One (2 per cent) of 49 patients died from multiple organ failure 3 days after thoracoabdominal surgery for oesophageal invasion in addition to a total gastrectomy with pancreaticosplenectomy.

Overall survival

The 3-year survival rate was 27 (95 per cent c.i. 15 to 39) per cent, and thus the lower limit of the 95 per cent c.i. was higher than the prespecified threshold (*Fig. 4*). Median survival was 14·6 (95 per cent c.i. 10·1 to 24·1) months.

Table 4 Surgical complications in the 49 operated patients

	No. of patients
Leakage	1 (2)
Pancreatic fistula	6 (12)
Abdominal abscess	2 (4)
Pneumonia	2 (4)
Ileus	0 (0)
Wound infection	2 (4)
Stenosis of anastomosis	1 (2)
Cardiac failure	1 (2)
Renal dysfunction	1 (2)
Other	6 (12)

Values in parentheses are percentages.

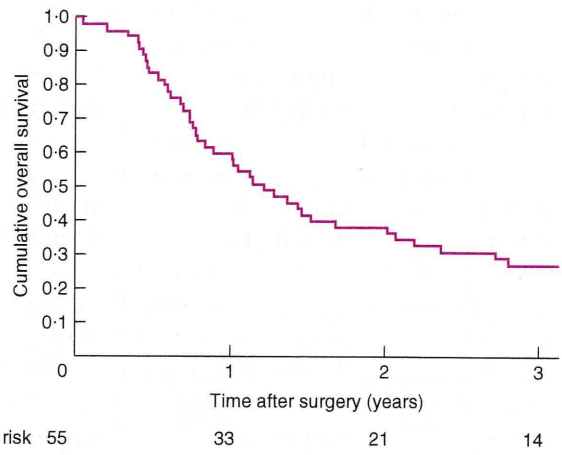

Fig. 4 Kaplan–Meier overall survival curve for the 55 eligible patients

Discussion

This multi-institutional phase II prospective trial of neoadjuvant chemotherapy in locally advanced gastric cancer with extensive lymph node metastases showed that multimodality treatment can achieve a high 3-year survival rate of 27 per cent. Usually these patients rarely survive for more than 3 years when treated by chemotherapy alone or by surgery followed by postoperative chemotherapy. Thus, the protocol treatment was effective for these patients, but was achieved at the cost of considerable morbidity and mortality, and the study had to be stopped prematurely because of treatment-related deaths.

The combination chemotherapy of irinotecan plus cisplatin was chosen because it had achieved a high response rate of 59 per cent in a previous phase II study of chemotherapy-naive patients with metastatic gastric cancer[11]. At the start of the present study in 2000, this was considered to be the most effective and promising regimen for gastric cancer. In Japan, based on these data, a phase III trial was initiated to determine the superiority of irinotecan plus cisplatin compared with 5-fluorouracil (5-FU) alone for metastatic gastric cancer[17]. In the present study, the clinical response to preoperative chemotherapy was 55 per cent, comparable with previous results using this regimen in patients with metastatic gastric cancer[11]. Although the above-mentioned Japanese phase III trial (JCOG 9912) did not demonstrate superiority for this regimen compared with 5-FU alone, a subset analysis for tumours with target lesion defined by RECIST

showed that combination chemotherapy of irinotecan plus cisplatin gave a median survival of 12·1 months, which was significantly longer than for 5-FU alone[17]. This suggested that irinotecan plus cisplatin was especially active against tumours forming bulky masses[17]. In contrast to the impressive clinical response of metastatic nodes, the pathological response in the primary tumours was relatively low in the present study. In gastric cancer, the pathological response rate is usually less than 20 per cent for any chemotherapeutic regimen, suggesting the importance of appropriate local control by surgery. The relatively good overall survival at 3 years in the present study appears to be due to the effects of neoadjuvant chemotherapy in two ways: downstaging of lymph node metastases, which enabled R0 resection in 65 per cent of patients, and good control of micrometastases.

Treatment-related death was observed in 5 per cent of patients in this study, indicating that this treatment protocol is hazardous. Of three patients, two died from chemotherapy-induced myelosuppression. Neutropenia and diarrhoea were the major toxicities of this regimen, as reported previously[11,17]. Compared with these trials, toxicity in the present study was relatively low, but the mortality rate was high. In two treatment-related deaths from chemotherapy, severe myelosuppression appeared immediately after the first administration of irinotecan plus cisplatin. Boku and colleagues[17] observed severe diarrhoea only during the first course of the same regimen in patients with unresectable gastric cancer. Noda and co-workers[18] reported on the efficacy of combination therapy with irinotecan plus cisplatin for small cell lung cancer, using a different schedule and dosage than those in the present study. They observed treatment-related deaths in three patients (4 per cent) during the first or second cycle of chemotherapy. Taken together, all of these results indicate that severe haematological toxicity and diarrhoea should be managed carefully, especially during the initial cycles of chemotherapy.

Recently, genetic polymorphism of UTG1A1, which is involved in glucuronidation of SN-38 or is an active metabolite of irinotecan, has been reported to be associated with irinotecan toxicity[19,20]. Polymorphisms of UGT have also recently been suggested as a risk factor for irinotecan-induced neutropenia[21]. These factors might have been involved in the treatment-related deaths observed in the present study, although genetic analysis was not performed. Patient risk may be reduced not only by careful management of myelosuppression, but possibly also by patient selection based on genetic analysis. However, further studies are needed to confirm this. Because the combination chemotherapy regimen employed in this study is difficult to manage in terms of toxicity, a new phase II study has been initiated to evaluate a preoperative S-1 (oral anticancer drug that combines tegafur, a prodrug of fluorouracil, with 5-chloro-2,4-dihydropyrimidine and potassium oxonate) plus cisplatin regimen, which is considered less toxic for patients with extensive nodal metastases. S-1 and cisplatin showed a high response rate of over 50 per cent with mild toxicity in recent trials of patients with metastatic gastric cancer[22,23].

The operative mortality rate in this study was 2 per cent. In the JCOG 9501 trial, which compared D2 with D2 plus para-aortic nodal dissection, the mortality rate was 0·8 per cent for D2 plus para-aortic nodal dissection[13], whereas in the JCOG 9502 trial, which compared an abdominal approach with a left thoracoabdominal approach for gastric tumours invading the oesophagus, mortality rates were 0 and 4 per cent respectively[24]. Thus, the thoracoabdominal approach was the more hazardous of the two procedures. Because the influence of preoperative chemotherapy on surgery is unclear, patients who require such an extensive thoracoabdominal operation should probably be excluded from future studies.

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