20130902-1A

厚生労働科学研究費補助金

医療技術実用化総合研究事業

進展型小細胞肺癌に対する予防的全脳照射の実施の有無を比較するランダム化比較第Ⅲ相試験

平成25年度 総括研究報告書

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平成26 (2014) 年 5月

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Ⅰ. 総 合 研 究 報 告

厚生労働科学研究費補助金（医療技術実用化総合研究事業）

進展型小細胞肺癌に対する予防的全脳照射の実施の有無を比較するランダム化比較第III相試験に関する研究

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研究要旨：進展型小細胞肺癌に対する予防的全脳照射（PCI）に関しては，初回治療の効果が完全寛解(CR)の症例に対しては標準的治療と考えられている。一方、これまでCRに至らなかった症例でのPCIの意義は明らかではなかったが、2007年にCR例以外に対してPCIを行うことにより、生存率が有意に改善することが欧州より報告され、世界的にはこれが標準となっている。しかし、この報告では、CT・MRIにより脳転移の有無を確認した症例は29%にすぎない。我が国ではMRIの普及は海外と比較し抜きんでており、脳転移の有無をMRIにて初回治療開始前、および治療経過中に検索することが一般的である。そのため、このエビデンスを我が国の日常診療にそのまま導入すること困難である。そこで我が国の日常臨床に則して、治療前および治療後の経過観察中に脳画像診断にて脳転移の検索を行うことを必須として、進展型小細胞肺癌症例に対するPCIの有効性を検討する第3相試験を実施した。Primary endpoint：全生存期間、Secondary endpoints：脳転移発症率，無増悪生存期間，PCIの毒性として、無治療群と比較してPCI群の優越性を検討するものである。予定登録数を330例とし2回の中間解析を予定した。 1回目の中間解析により、PCI群で生存期間が有意に延長する可能性が0.00011と示されたため、2013年7月17日、登録数224例にて症例登録を中止した。今後は、予定された症例追跡を実施し、Primary endpointである生存期間、および各種Secondary endpointsを確定する。

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A．研究目的

進展型小細胞肺癌（ED-SCLC）に対する予防的全脳照射（PCI）に関しては，初回治療の効果が完全寛解(CR)の症例に対しては標準的治療と考えられている。一方、これまでCRに至らなかった症例でのPCIの意義は明らかではなかったが、2007年にED-SCLCにおいて初回治療奏効例(CR以外も可)に対してPCIを行うことにより、生存率が有意に改善することが欧州より報告された(N Engl J Med: 357, 664-72, 2007)。しかしながらこの報告については
(1)治療開始時にCT・MRIにより脳転移の有無を確認した症例は29%にすぎない。
(2)我が国ではMRIあるいはCTにより脳転移の有無を初回治療開始前、および治療経過中に検索することが一般的である。また、脳転移検出能に優れるMRIの普及は海外と比較し抜きんでている。
(3)PCIの照射線量，照射回数に大きなばらつきがあり、化学療法レジメンも統一されていない。
(4)脳転移再発時の治療についても、定位脳放射線治療が広く普及している。
などの理由から、我が国の日常診療にそのまま導入すること困難である。そこで我が国の日常臨床に則して、治療前および治療後の経過観察中に脳画像診断にて脳転移の検索を行うことを必須として、ED-SCLC症例に対するPCIの有効性を検討する第3相試験を計画した。

本試験の結果は、国内の多くの施設で日常臨床に導入可能な我が国発のエビデンスであり、参加施設が全国に広がることから質の高いがん医療水準の均てん化を推進することにもつながる。また、日本における脳MRIによる画像診断等の浸透を世界に対してアピールすることが可能となる。

B．研究方法

＜研究対象＞

1. 初回化学療法開始前に脳画像検査にて明らかな脳転移を認めない進展型小細胞肺癌症例
2. 2コース以上の初回化学療法に対して腫瘍縮小がみられた症例
3. 初回化学療法終了後かつ登録前4週以内の脳MRI画像検査で脳転移が認められない。
4. 同意取得時年齢が20 歳以上
5. 登録時PS（ECOG）が0－2
6. 初回化学療法最終コース開始日から登録までが６週以内
7. 頭部あるいは頸部への放射線治療の既往がない。
8. 臨床上問題となる精神疾患あるいは身体的合併症を有さない。
9. 試験参加について患者本人から文書で同意が得られている 。

＜試験方法＞

PCI 非施行群に対し PCI 群の生存期間に対する優越性を検討するランダム化第 III 相試験

○評価項目

Primary endpoint：全生存期間
Secondary endpoints：脳転移発症率，無増悪生存期間，PCIによる毒性

○症例数設定

PCI非施行群の2年生存率を10～15%と仮定し、ハザード比=0.71のもとでは、PCI施行群は20

～26%の２年生存率を達成できることになる。このとき、α＝0.05（両側），検出力85%のもとで、必要な総イベント数（死亡数）は約300例と計算される（Freedmanの方法による）。登録期間、追跡期間を考慮し、片群165例，両群計330例を予定登録数とする。

○中間解析・効果安全性評価委員会

本試験では 2 回の中間解析を実施する。 1 回目の中間解析は予定登録数の 1/2 の登録が得られた時点のデータを用いて行い、2回目の中間解析は登録が終了し全ての登録患者のプロトコール治療が終了する時点のデータを用いて行う。原則として中間解析中も登録は停止しない。

中間解析の結果は、独立効果安全性評価委員会に報告し、継続の可否について検討する。

○登録，割付

委託契約を締結して非営利活動法人西日本がん研究機構（WJOG）のデータセンターを使用する．登録はWJOGデータセンターでの中央登録方式とする．ランダム割り付けに際しては年齢（70歳以上/70歳未満）を調整因子とし、PS(0-1/2)、施設、化学療法に対する効果（CR・Partial Response(PR)/ Minor Response(MR)）を動的割り付け因子とする。

＜治療方法＞

最終化学療法開始から4－6週以内に以下の方法でPCIを行う。

１回2.5Gy，１日1回，週5 日，計10 回，総線量25Gy，総治療期間12日間，許容総治療期間28日間とした。

＜効果・毒性の評価＞

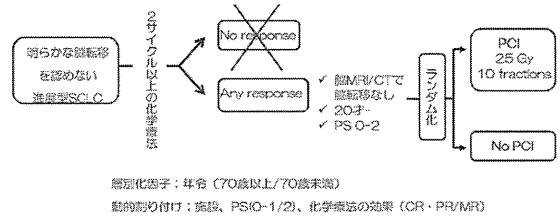
PCIにより予期される有害反応には、PCI 治療中の有害事象として脱毛，皮膚炎，頭痛，食欲不振，悪心・嘔吐，めまい，倦怠感，眠気などがあり、PCI 後の晩期障害として認識力低下，歩行障害，排尿障害，白質脳症などが知られている． PCI終了後3カ月後、6か月後，9か月後，12か月後，18か月後，24ヶ月後に、PCI関連有害事象，脳転移の有無，認知機能，PSを評価する。

＜倫理面への配慮＞

試験に関係するすべての研究者は、ヘルシンキ宣言および臨床研究に関する倫理指針にしたがって本試験を実施し，以下の事項を厳守した。登録に先立って、すべてに患者に施設の倫理審査委員会で承認が得られた説明文書を用いて十分な説明を行い、考慮の時間を設けた後に患者自身の自由意志による同意を文書にて取得する。

個人情報および診療情報などのプライバシーに関する情報は個人の人格尊重の理念の下、厳重に保護され慎重に取り扱われるべきものと認識し、万全な管理対策を講じ、プライバシー保護に努める。データの取り扱いに関しては直接個人を識別できる情報を用いず，データベースのセキュリティーを確保し、個人情報の保護を厳守する。

効果安全性評価委員会を組織し、研究者の第三者的監視を行う。



Ｃ．研究結果

本試験については Japan Clinical Oncology Group(JCOG)肺がん内科グループ及び WJOG 呼吸器グループの主要施設を網羅する研究体制を確立し（全国で 57 施設が参加）、 平成 21 年 4 月から症例登録を開始しており、本事業開始前の段階で 153 例が登録されていた。本事業 1 年目（平成 24 年度）には、55 例の登録があり総計 208 例と予定通りの進捗であった。事業 2 年目（平成 25 年度）に入り、中間解析を実施したところ、PCI 施行群で生存期間が有意に延長する可能性が 0.00011 であったため、2013 年 7 月 17 日、登録数 224 例にて症例登録を中止した。脳転移の発生率は PCI 実施により優位に減少した(P<0.001)。

○患者背景

	PCI 施行群 n=84	PCI 未施行群 n=79
年齢		
範囲	43-83	37-86
中央値	69 歳	68 歳
性別		
男性	68 人	70 人
女性	16 人	9 人
PS		
0-1	80 人	77 人
2	4 人	2 人
化学療法の効果		
CR	10 人	12 人
PR・MR	74 人	67 人

○PCI 実施状況

総線量	n=81*
= 25 Gy	81
< 25 Gy	0
> 25 Gy	0
PCI の期間	
中央値	14 days
範囲	10-23 days

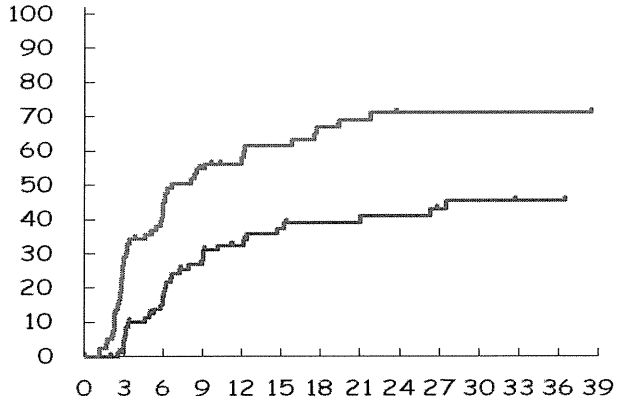
*: PCI 群の 3 人は PCI 実施せず

○脳転移の発現状況

青線：PCI 未施行群、赤線：PCI 施行群

横軸：無作為化からの時間（月）

縦軸：脳転移発生率（%）

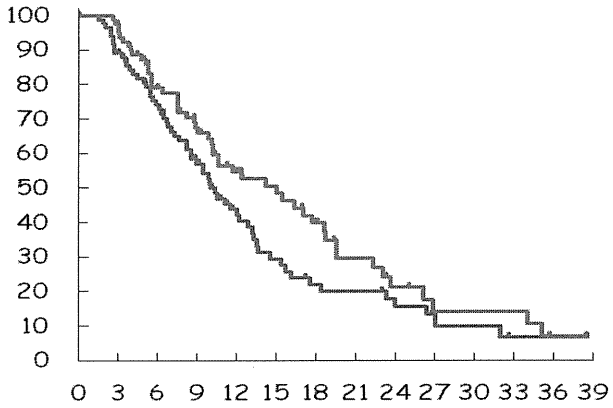


○全生存期間

青線：PCI 未施行群、赤線：PCI 施行群

横軸：無作為化からの時間（月）

縦軸：生存率（%）



今後は、予定された症例追跡を実施し、Primary endpoint である生存期間、および各種 Secondary endpoints を確定する。また、事業 3 年目（平成 26 年度）は、中間解析結果の各種主要学会及び論文での公表も併せて実施する予定である。

D．考察

わが国の医療環境下でのED-SCLCに対するPCIの有用性を検討するランダム化比較試験を実施した。前述のように、本治療に関しては、欧州のグループよりNew England Journal of Medicineに報告され(N Engl J Med: 357, 664-72, 2007)、米国や欧州の主なガイドラインに、標準的治療として記載されている。しかしながら、その実施状況がわが国の日常診療の医療現場と大きくかけ離れていたこと、ED-SCLCの腫瘍特性から（がんの増大スピードが速い）、抗がん剤治療後で他に画像で確認できる腫瘍が残存していた場合、PCIの実施により生存期間の延長が得られることが論理的に考えにくいこと、などよりわが国での再現性を確認する必要があると考え実施した。

欧米のガイドラインで記載されている治療であったため、有効中止を考慮し2回の中間解析を予定していたが、実際には1回目の中間解析で無効中止と判断され、登録を中止している。本試験ではPCIの有用性が示されなかったため、抗がん剤治療後に脳MRIで真に脳転移がないことが確認された症例で、他の臓器に腫瘍が残存している場合にはPCIが不要であることが証明

されたと考えている。
前報の欧州の試験では、PCI施行前のMRI実施率が低頻度であったため、実際は既に脳転移を有していた症例が一定頻度で含まれており、それらの症例に放射線治療を行うことで脳転移の治療になり、結果として生存期間が延長された可能性があるのではないかと類推される。
欧米では、MRIの普及率はわが国と比較して低率であり、治療後の脳転移の有無を全症例でMRIを用いて確認することは困難である。逆に、放射線治療医はわが国と比較して充足しているため、放射線治療を実施することに困難を感じることは少ない。そのため、MRIで脳転移を確認することなく脳症状がないものを脳転移がない症例としてPCIを実施するのは、日常臨床に則していると思われる。しかしながら、わが国では逆に放射線治療医は少なくMRI装置は潤沢に普及している。そのため、化学療法後にMRIを実施して脳転移の有無の確認することは普通に実施できるのに対し、放射線治療の実施件数を増やすことは容易ではない。
それぞれの地域の医療事情に則した臨床試験を実施することが重要であることは言うまでもない。また、海外で報告された重要なエビデンスを全てわが国で確認する必要がないことも自明である。しかしながら、明らかにわが国の医療環境と異なった状況下で得られたエビデンスについては、海外の結果を鵜呑みにせず、再確認する必要があるということが確認されたことも今回の試験の重要な成果の一つであると考えている。
中間解析の結果ではPCI施行群で未施行群と比較して逆に生存期間で劣っているような生存曲線が得られている。追跡期間が不十分であるためPCIで有意に生存期間を短縮してしまうかどうかは現時点では不明である。今後、予定の追跡を行い最終的な生存期間を確定し、さらに毒性、QOLなどのデータも検討して、Secondary Endpointも含めた最終方向を行う予定である。

Ｅ．結論
進展型小細胞肺癌(ED-SCLC)で化学療法で腫瘍縮小を認めた症例に対しては、予防的全脳照射（PCI）の実施で生存期間の延長は認めなかった

Ｆ．健康危険情報
治療関連死亡などの重篤な有害事象は認められていない。

Ｇ．研究発表
2014年のAmrican Society of Clinical Oncology Meetingで口演演題として採択された。

Ⅱ．研究成果の刊行に関する一覧表

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Ⅲ. 研究成果の刊行物・別刷

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2013;43(2)176–183
doi:10.1093/jjco/hys197
Advance Access Publication 5 December 2012

Chemoradiotherapy for Limited-disease Small-cell Lung Cancer in Elderly Patients Aged 75 Years or Older

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Received September 14, 2012; accepted October 28, 2012

Background: As clinical trials for limited-disease small-cell lung cancer often exclude elderly patients due to comorbidities and a decline in organ function, the most suitable treatment for limited-disease small-cell lung cancer patients aged 75 years or older still remains unclear.
Methods: From July 2002 to June 2011, 20 consecutive patients aged 75 years or older, with Stage II to IIIB limited-disease small-cell lung cancer, were scheduled to be treated with concurrent or sequential chemoradiotherapy at the Shizuoka Cancer Center. We reviewed the medical charts of the patients and evaluated their characteristics, treatment compliance, toxicity and antitumor efficacy.
Results: Five patients were treated with concurrent chemoradiotherapy and the other 15 patients were scheduled to be treated with sequential chemoradiotherapy. Of these 15 patients, 12 were treated with four cycles of etoposide (80 mg/m^2, days 1–3, q3–4w) plus carboplatin (area under the curve 5, day 1, q3–4w), followed by thoracic radiotherapy. Of the five patients treated with concurrent chemoradiotherapy, discontinuation of chemotherapy/thoracic radiotherapy occurred in two patients due to toxicity and they suffered a prolonged decrease in performance status. Of the 12 patients treated with etoposide plus carboplatin followed by sequential thoracic radiotherapy, the response rate, median progression-free survival and median overall survival time were 91%, 244 and 601 days.
Conclusions: These results suggest that concurrent chemoradiotherapy is not feasible for all limited-disease small-cell lung cancer patients aged 75 years or older. The alternative of four cycles of etoposide plus carboplatin followed by thoracic radiotherapy is a candidate for the standard treatment of limited-disease small-cell lung cancer patients in this age group. A further trial is warranted to develop and evaluate the optimal treatment for elderly patients with limited-disease small-cell lung cancer.

Key words: small-cell lung cancer – limited-disease small-cell lung cancer – elderly – chemoradiotherapy – chemotherapy – radiotherapy – feasibility – efficacy

INTRODUCTION

Small-cell lung cancer (SCLC) accounts for 10–15% of all lung cancer cases, with individuals aged 70 years or older constituting 25–40% of SCLC patients (1,2). Limited-disease SCLC (LD-SCLC) is confined to one hemithorax and its regional lymph nodes, and can be treated using a

single radiation therapy port. Approximately 30–40% of all SCLC patients present with LD-SCLC (1,2). The proportion of elderly SCLC patients continues to increase with the growing geriatric population (1,3).

The combination of chemotherapy and radiotherapy, particularly etoposide plus cisplatin with early concurrent twice-daily thoracic radiotherapy (TRT), is regarded as the standard treatment for LD-SCLC, provided the patients are in a good general condition (4–6). However, many clinical trials for LD-SCLC have excluded elderly patients for reasons, such as comorbidities or a decline in organ function (7,8). Takada et al. (6) reported that etoposide plus cisplatin and concurrent TRT are more effective for the treatment of LD-SCLC than are etoposide plus cisplatin and sequential TRT, but patients aged 75 years or older were excluded from this trial.

Retrospective subset analyses of patients with LD-SCLC treated with etoposide plus cisplatin and concurrent early chemoradiotherapy (CRT) in Phase III trials have shown that severe hematological toxicity, pneumonitis of Grade 4 or more and treatment-related death occurred much more often among patients aged 70 years or older than among younger patients (9,10). Although the response rate and 5-year event-free survival rate did not significantly differ between these two subgroups, there was a trend for them to be worse in older patients, and significant difference in the 5-year overall survival rate favored patients younger than 70 years in one trial (9,10). These results suggest that this regimen is too toxic for elderly LD-SCLC patients and the most suitable method of treatment remains unclear.

The objective of our retrospective analysis was to discover the optimal treatment method for elderly patients with LD-SCLC aged 75 years or older. We compared the patient characteristics, treatment compliance, toxicity and antitumor efficacy between those undergoing concurrent and sequential CRT. Then, we focused on etoposide plus carboplatin and sequential TRT, as this is the most common method for treating elderly LD-SCLC patients in our institute, and evaluated their characteristics, treatment compliance, toxicity and antitumor efficacy of this regimen.

PATIENTS AND METHODS

Patient Selection

We reviewed 20 consecutive patients with Stage II–IIIB LD-SCLC, aged 75 years or older, whose treatment plan involved concurrent or sequential CRT at the Shizuoka Cancer Center between July 2002 and June 2011. The TNM stage was classified using TNM stage version 6 (11). Chest CT, abdominal CT, bone scintigram or FDG-PET, and brain magnetic resonance imaging (MRI)/CT were performed before treatment in all patients.

The inclusion criteria for concurrent or sequential CRT in our institution are generally as follows: a performance status (PS) of 0–2; white blood cell count, $\geq 3.0 \times 10^3/mm^3$; neutrophil count, $\geq 1.5 \times 10^3/mm^3$; platelet count, $\geq 1.0 \times 10^5/mm^3$; serum creatinine, ≤ 1.5 mg/dl; total bilirubin, ≤ 1.5 mg/dl and a transaminase level less than twice the upper limit of the normal value. The exclusion criteria were interstitial lung disease identified by a chest radiograph; the presence of malignant pleural or pericardial effusion prior to radiotherapy and serious complications, such as severe respiratory failure, active infectious diseases, serious heart diseases and poorly controlled hypertension/diabetes mellitus. The study protocol was approved by the institutional review board of Shizuoka Cancer Center.

Chemotherapy

The combination of etoposide (80 or 100 mg/m^2) on days 1–3 plus cisplatin (80 mg/m^2) on day 1, cisplatin (25 mg/m^2) on days 1–3, or carboplatin [area under the curve (AUC) 5] on day 1 were administered intravenously to elderly LD-SCLC patients every 3–4 weeks. The administered drug and its dose were determined by the physician in charge. The treatment cycles were repeated every 3–4 weeks for four cycles. The criteria for starting subsequent cycles of treatment in our institution are generally the same as the inclusion criteria for concurrent or sequential CRT mentioned in the 'Patient selection' section. If these criteria were not met, subsequent cycles were withheld until the noted abnormality had resolved. If there was no resolution of the abnormality after 7 weeks from the first day of the cycle, chemotherapy was stopped. Generally, the doses of etoposide and cisplatin or carboplatin were reduced or chemotherapeutic regimens were changed in the event of Grade 4 anemia, Grade 4 thrombocytopenia, prolonged Grade 4 leukopenia/neutropenia or Grade 3 or more severe non-hematological toxicity during the previous treatment cycle.

Radiotherapy

Generally, TRT was started concurrently in the first cycle of chemotherapy or sequentially after four cycles of chemotherapy in the elderly LD-SCLC patients. The timing and prescribed dose of TRT was determined by the physician in charge. All patients were required to undergo a chest CT to facilitate treatment planning. The primary tumor (gross tumor volume; GTV primary) was delineated in the pulmonary windows, and the nodal involvement (GTV node) was delineated in the mediastinal windows. The clinical target volume (CTV) included the GTV primary; GTV node; ipsilateral hilum and the elective mediastinum, for which the lower border was 3.0 cm below the carina up to 40 Gy in a once-daily fraction of 2 Gy per fraction or 30 Gy in twice-daily fractions of 1.5 Gy per fraction. Thereafter, CTV included the GTV primary and GTV node. The planning target volume was the CTV plus a margin to ensure that the planned dose was actually delivered to the CTV. The total planned dose was usually 50 Gy in a once-daily fraction or 45 Gy in twice-daily fractions. The initial field in the sequential arm was also based on the pretreatment tumor volume.

TRT was suspended if a patient experienced Grade 4 thrombocytopenia, radiation pneumonitis, fever caused by infection, a decrease in arterial oxygen pressure exceeding 10 mmHg or if a patient had difficulty swallowing a liquid diet. It was ensured that the normal lung volume receiving more than 20 Gy (V20) was $\leq$35% of the total lung volume. The maximum spinal cord dose was limited to 45 Gy in a once-daily fraction or 36 Gy in twice-daily fractions at any level.

After TRT, prophylactic cranial irradiation (PCI) was administered to patients with a complete or near-complete response represented by a scar-like shadow on a chest CT if the physician in charge judged the patient would benefit from PCI. The PCI consisted of 25 Gy/10 fr.

Evaluation of Efficacy and Toxicity

All the patients were evaluated for lesions approximately every 2 months by CT, MRI, bone scintigraphy or PET during the treatment period and every 3–6 months after treatment. The tumor response was evaluated in accordance with the response evaluation criteria in solid tumors (RECIST; version 1.0) (12). Adverse events were evaluated in accordance with the common terminology criteria for adverse events (CTCAE; version 3.0) (13).

Statistical Analyses

To evaluate the difference between concurrent CRT and sequential CRT, in relation to the patients' characteristics, the χ^2 test, Fisher's exact test and the Mann–Whitney *U*-test were performed. To analyze the PFS and OS, survival curves were drawn using the Kaplan–Meier method. The PFS was calculated from the date of initiation of the treatment to the date of detection of disease progression or the date of death from any cause. The PFS was censored at the date of the last visit for those patients who were still alive without any documented disease progression. PFS were compared between concurrent CRT and sequential CRT using the log-rank test. The OS was calculated from the date of initiation of the treatment to the date of death. The OS was censored at the date of the last visit for those patients whose deaths could not be confirmed. *P* values of <0.05 were considered to be statistically significant. All statistical analyses were performed by the application of JMP version 8.0 for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

Characteristics and Treatment Methods of the 20 Patients Treated with Chemoradiotherapy

Twenty patients 75 years of age or older and with Stage II–IIIB LD-SCLC were scheduled to be treated with concurrent or sequential CRT at the Shizuoka Cancer Center. During the same period, seven patients 75 years of age or older and with Stage II–IIIB LD-SCLC were excluded by the inclusion/exclusion criteria of CRT. The reasons for exclusion were interstitial lung disease in six patients and renal failure in one patient. Tables 1 and 2 show the individual patients' characteristics, treatment methods and outcome of the patients treated with concurrent and sequential CRT. Of these patients, 80% were men and their median age was 77 years. Forty percent of the patients had a PS of 0 and the remaining a PS of 1. The majority of the patients were smokers and 80% were Stage IIIA or IIIB.

Five patients were treated with concurrent CRT and 15 were scheduled to be treated with sequential CRT. Of the five treated with concurrent CRT, two received TRT from the first cycle of chemotherapy and three received TRT from the second cycle of chemotherapy. From the beginning, two were scheduled to receive TRT from the second cycle after the confirmation of toxicity in the first cycle. The other patient was also scheduled to receive TRT from the second cycle if the symptom due to tumor compression had not recovered by chemotherapy only. Two patients received etoposide (80 mg/m^2, days 1–3) plus carboplatin (AUC 5, day 1), two were administered etoposide (100 mg/m^2, days 1–3) plus cisplatin (80 mg/m^2, day 1) and one received etoposide (80 mg/m^2, days 1–3) plus cisplatin (25 mg/m^2, days 1–3) as their chemotherapy regimen. Of these patients, one patient switched from etoposide (80 mg/m^2, days 1–3) plus cisplatin (25 mg/m^2, days 1–3) to etoposide (80 mg/m^2, days 1–3) plus carboplatin (AUC 5, day 1) from cycle 2 due to Grade 4 hyponatremia and Grade 3 anorexia.

Of the 15 patients scheduled to be treated with sequential CRT, 12 received etoposide (80 mg/m^2, days 1–3) plus carboplatin (AUC 5, day 1), two received etoposide (80 mg/m^2, days 1–3) plus cisplatin (25 mg/m^2, days 1–3) and one was administered etoposide (100 mg/m^2, days 1–3) plus cisplatin (25 mg/m^2, days 1–3) as chemotherapy. Two patients could not receive TRT due to discontinuation of treatment during the chemotherapy period.

The planned TRT doses were 45 Gy in twice-daily fractions and 1.5 Gy per fraction in 12 patients, 50 Gy in a once-daily fraction and 2 Gy per fraction in three patients, and the other radiation doses in three patients. PCI was performed in Patient #C-5 and #S-13.

Table 3 shows the individual patients' characteristics, past history and complications of the patients treated with concurrent and sequential CRT. Generally, past history and complications were fewer and less severe in concurrent CRT, especially in terms of cardiopulmonary diseases.

Comparison of Patient Characteristics, Response, PFS, Compliance and Adverse Events Between Concurrent CRT and Sequential CRT

In terms of patient characteristics, (gender, age, PS, stage), the difference in age between concurrent CRT and sequential CRT is significant (Mann–Whitney *U*-test $P = 0.041$).

Table 1. Individual patients' characteristics, treatment methods and outcome of the patients treated with concurrent chemoradiotherapy (CRT)

No.	Age (years)	Gender	PS	Stage	CTx	Response	RTx (timing)	RTx (Dose/Fr)	CTx compliance	RTx compliance	Failure site	PFS	OS
C-1	75	F	1	IIIA	CB(5)+ETP(80)2c	PR	From c2	39.6/22	Discontinuation +	Discontinuation +	WT	165	971
C-2	75	M	0	IIIA	CB(5)+ETP(80)3c	PR	From c2	44/22	Discontinuation +	4 days omission	Brain	547	1114
C-3	75	M	1	IIB	CD(80)+ETP(100)4c	PR	From c1	45/30	Dose reduction +	7 days omission	Brain	1790	2393+
C-4	76	M	1	IIB	CD(80)+ETP(100)4c	PR	From c1	45/30	Completed	2 days omission	Brain	214	2485
C-5	77	F	1	IIIB	CD(25)x3+ETP(80)1c→ CB(5)+ETP(80)3c	Near CR	From c2	45/30	Changed CTx regimen and dose reduction	Completed	Liver	201	359

No., number; PS, performance status; CTx, chemotherapy; RTx, radiotherapy; Fr, fraction; PFS, progression-free survival; OS, overall survival; F, female; M, male; CB, carboplatin; ETP, etoposide; c, cycle; CD, cisplatin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; NA, not available; WT, within the thorax; PF, progression-free.
The dose of carboplatin was indicated by area under the curve in parentheses.
The doses of etoposide and cisplatin were indicated by per body surface area in parentheses.

Patients tended to be female, have lower stage and have a poorer PS in concurrent CRT, although there is no significant difference.

All five patients treated with concurrent CRT exhibited a partial response (PR) and the response rate was 100%. Of the 15 patients treated with sequential CRT, 3 had a complete response (CR), 9 exhibited PR, 1 showed stable disease (SD), 1 developed progressive disease (PD) and 1 was not evaluable (NE). The response rate was 80%. The median PFS of concurrent and sequential CRT were 208 and 216 days, respectively (Fig. 1). There was no statistically significant difference between the PFS of the two treatment methods (log-rank $P = 0.9715$) and the two PFS curves almost overlapped each other.

Of the five patients treated with concurrent CRT, discontinuation of chemotherapy occurred in two (40%) and dose reductions were needed in two due to adverse events (40%). Moreover, discontinuation of radiotherapy occurred in one patient (20%) and omissions were needed in three (60%). Among the 15 patients treated with sequential CRT, 11 completed the whole treatment method without discontinuation, dose reduction and omission of chemotherapy/TRT. Dose reductions of chemotherapy were needed in two patients (13%), and one of the two patients was treated with etoposide (100 mg/m^2, days 1–3) plus cisplatin (25 mg/m^2, days 1–3). Discontinuation of chemotherapy occurred in two patients (13%) due to toxicities. Radiotherapy was completed without omission in all 11 patients who received sequential radiotherapy.

Table 4 shows the adverse events in patients treated with concurrent CRT and sequential CRT. Hematological toxicities, febrile neutropenia, fatigue and anorexia tended to be more frequent and severe in concurrent CRT than in sequential CRT. However, Grade 3 or more severe pneumonitis tended to be frequent in sequential CRT (four patients, 27%).

Patients' Characteristics, Tumor Response, PFS, OS and Toxicity in Patients Treated with Etoposide Plus Carboplatin Followed by Sequential TRT

Twelve patients were treated with etoposide plus carboplatin followed by sequential TRT. The number of male patients, 10 (83%), was larger than that of the female patients, and the median age of the patients was 79 years. Eight patients (67%) had a PS of 0 and the remaining a PS of 1. All were smokers, and 10 patients (83%) were Stage IIIA or IIIB and the remaining Stage IIA or IIB.

With regard to the tumor response, CR was achieved by three patients, PR by eight and one patient was NE. The response rate was 91%.

The median PFS and OS were 244 and 601 days, respectively (Fig. 2). The median follow-up duration was 496 days. In terms of the first failure site during and after CRT, nine patients (75%) had experienced disease relapse at the time of data analyses. Five (42%) and two (17%) patients

Table 2. Individual patients' characteristics, treatment methods and outcome of the patients treated with sequential CRT

No.	Age (years)	Gender	PS	Stage	CTx	Response	RTx (dose/Fr)	CTx compliance	RTx compliance	Failure site	PFS	OS
S-1	75	M	0	IIIA	CB(5)+ETP(80)4c	PR	45/30	Completed	Completed	PF	2754+	2754+
S-2	75	M	0	IIIA	CD(25)x3+ETP(80)4c	SD	45/30	Completed	Completed	Brain	137	578
S-3	75	M	0	IIIA	CD(25)x3+ETP(100)4c	PD	50/25	Dose Reduction +	Completed	WT	143	769
S-4	76	M	1	IIIB	CB(5)+ETP(80)4c	PR	45/30	Dose Reduction +	Completed	WT and liver	414	652
S-5	76	M	1	IIIA	CB(5)+ETP(80)4c	CR	45/30	Completed	Completed	Brain	137	257
S-6	77	M	1	IIA	CB(5)+ETP(80)4c	PR	45/30	Completed	Completed	PF	442+	442+
S-7	77	M	0	IIIB	CD(25)x3+ETP(80)3c	PR	NA	Discontinuation +	NA	WT	243	454
S-8	78	M	1	IIIA	CB(5)+ETP(80)4c	PR	59/32	Completed	Completed	Brain	181+	181+
S-9	78	M	0	IIIA	CB(5)+ETP(80)4c	PR	45/30	Completed	Completed	Brain	181	550+
S-10	80	F	1	IIIA	CB(5)+ETP(80)1c	NE	NA	Discontinuation +	NA	WT	70	316+
S-11	80	M	0	IIIB	CB(5)+ETP(80)4c	CR	45/30	Completed	Completed	Brain	152	258
S-12	81	F	1	IIB	CB(5)+ETP(80)4c	PR	50/25	Completed	Completed	PF	1892+	1892+
S-13	83	M	1	IIIB	CB(5)+ETP(80)4c	CR	45/30	Completed	Completed	Brain	269	327
S-14	83	F	1	IIIA	CB(5)+ETP(80)4c	Near CR	50/25	Completed	Completed	Liver and lung	408	415+
S-15	92	M	0	IIIA	CB(5)+ETP(80)4c	PR	45/30	Completed	Completed	WT	218	383

The dose of carboplatin was indicated by area under the curve in parentheses.
The doses of etoposide and cisplatin were indicated by per body surface area in parentheses.

Table 3. Individual patients' characteristics, past history and complications of the patients treated with concurrent CRT and sequential CRT

No	Age (years)	Gender	PS	Stage	Past history	Complications
C-1	75	F	1	IIIA	–	Osteoarthritis
C-2	75	M	0	IIIA	–	Anal stenosis
C-3	75	M	1	IIB	Gastric ulcer	COPD, prostatic hypertrophy
C-4	76	M	1	IIB	Gastric ulcer	–
C-5	77	F	1	IIIB	–	Hypertension, hyperlipidemia, osteoporosis
S-1	75	M	0	IIIA	–	Arrhythmia, prostate cancer
S-2	75	M	0	IIIA	–	Gastric ulcer, hypertension
S-3	75	M	0	IIIA	–	Prostatic hypertrophy, abdominal aortic aneurism
S-4	76	M	1	IIIB	Abdominal aortic aneurism	IHD, DM, hypertension
S-5	76	M	1	IIIA	Abdominal aortic aneurism	Aortic dissection
S-6	77	M	1	IIA	Laryngeal cancer, brain hemorrhage	Hypertension
S-7	77	M	0	IIIB	Gout, gastritis	Hypertension, prostatic hypertrophy
S-8	78	M	1	IIIA	Bladder cancer, brain hemorrhage	Hypertension
S-9	78	M	0	IIIA	ASO, IHD, gastric ulcer	–
S-10	80	F	1	IIIA	IHD, pneumothorax, gout, renal failure	COPD
S-11	80	M	0	IIIB	Rectal cancer	–
S-12	81	F	1	IIB	–	IHD
S-13	83	M	1	IIIB	Asthma, gastric ulcer, colon cancer	Hypertension
S-14	83	F	1	IIIA	Uterine cancer	Hypertension
S-15	92	M	0	IIIA	–	Reflux esophagitis, hypertension

COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; DM, diabetes mellitus; ASO, arteriosclerosis obliterans.