と比較し，晩期有害事象が増加することが報告されている．臨床医は，放射線療法後の患者を外来で経過観察する際，再発と同時に晩期有害事象を常に念頭に置くべきである．

放射線による二次発がんについては，広島，長崎の原爆被爆者のデータに負うところが大きい．リスクが高い臓器は骨髄，乳腺，甲状腺，肺，胃で，一方，子宮，直腸ではリスクは変化しなかった．白血病は被曝後2～3年経てから増加し始め，6～7年でピークに達する．白血病以外のがんでは潜伏期が長く，一般的には5年以上（5～35年：平均14年）である．

一般にがん患者は生活習慣，遺伝的素因などにより二次発がんを起こしやすく，これらのリスクのほうが放射線による発がんよりはるかに高い．また抗がん薬も二次発がんの原因となる．そのため，放射線療法による発がんの頻度は二次発がんの5%以下である．

7 高精度放射線療法

a. 定位放射線照射（脳，体幹部）

定位放射線照射（stereotactic irradiation：STI）はnarrow beamで線量を集中的に照射する技術で，1回照射を行う定位手術的照射（stereotactic radiosurgery：SRS）と分割照射を行う定位放射線治療（stereotactic radiotherapy：SRT）とに分類できる．健康保険上，照射中心の固定精度は脳・頭頸部の場合2 mm以内，体幹部の場合5 mm以内とされている．主に転移性脳腫瘍に対してはガンマナイフを用いたSRSが広く普及しており，脳動静脈奇形，聴神経腫瘍，さらに焦点性てんかんや三叉神経痛といった機能性疾患へ臨床応用されている．SRTではリニアックを用いて分割照射の利点（正常細胞の亜致死的障害からの回復や再増殖，腫瘍細胞の再酸素化や細胞周期の同調）を生かして，比較的大きな病変や体幹部への応用も可能となっている．

肺，肝腫瘍を中心とした体幹部腫瘍へのSRTはSBRT（stereotactic body radiation therapy）とも呼ばれ，急速に広まっている．2008年の全国調査ではすでに170施設で施行されていた．特にⅠ期非小細胞肺がんに対するSBRTは現在の日常臨床の現場において手術不能な症例では標準的に，手術可能例では手術の代替治療として行われている．

また，前向き試験ではT1N0M0非小細胞肺がんに対する第Ⅱ相試験（JCOG0403）において手術可能例64例において3年全生存率76%と良好な成績であった．このような現状から海外では手術高リスク群におけるランダム化比較試験（ACOSOG Z4099/RTOG 1021）も進行中である．

b. 粒子線療法

粒子線療法とは陽子や重粒子（主に炭素イオン）などの荷電粒子を用いた放射線療法のことで，体表面近くでは線量を出さずに荷電粒子が停止する直前に線量を放出するブラッグピークと呼ばれる線量分布を利用することが特徴である．このピークに病巣を一致させることで優れた線量分布での治療が可能となる．また，相対生物学的効果比（relative biological effectiveness：RBE，通常のX線を1とした場合のその他の放射線における同じ線量の及ぼす生物学的効果の比率）は，陽子線はX線やγ線とほぼ同等の1.1であるが，重粒子線である炭素イオンではRBE 3.0である．このため，特に重粒子線ではX線や陽子線と異なる生物学的特徴を有する．すなわち，亜致死障害（sub-lethal damage：SLD）からの回復が少なく，細胞周期や酸素濃度による感受性の差が少ないことから，従来のX線では難治性であった骨軟部腫瘍，肉腫，悪性黒色腫，頭頸部腺がん系腫瘍などに良好な成績を示している．

2012年10月現在，わが国で稼働している陽子線ないし重粒子線をもついわゆる粒子線施設は9施設に及び，今後さらに数施設での稼働が予定されており，世界に類をみない粒子線大国である．一方で，エビデンスの蓄積が不十分である点や巨額な建設費用など社会的問題も含んでおり，今後いかに有効利用していくかが問題である．

c. 強度変調放射線療法（IMRT）

放射線を集中させる方法としては，病巣部の形状に合った照射野を用い，多方向より放射線を照射する3次元原体照射（three-dimensional conformal radiotherapy：3D-CRT）が一般的に行われている．この3D-CRTをさらに進化させたより高度な方法として強度変調放射線療法（intensity modulated radiation therapy：IMRT）が考案された．IMRTとは，3D-CRTにおける各照射野内の線量強度を不均一にすることで，病巣部への放射線の集中性をさらに増すとともに特定の重要臓器の照射線量を低下させる方法である．病巣部に重要正常臓器が隣接し，かつ腫瘍制御に高線量を要する腫瘍が本治療のよい適応である．IMRTの治療計画には逆方向治療計画（inverse planning）を用いる．これは，治療体位で撮影した治療計画専用のCT画像を用いて，標的体積と重要正常臓器の輪郭を入力し，標的体積の必要線量と重要臓器の耐

用線量を条件として入力し，最適な照射野と照射野内線量強度をコンピューターに繰り返し計算させ決定する方法である．不均一な照射野内線量強度の照射は，リニアックに付属した多分割絞り（MLC）を細かく動かしながら照射することで実現される．さらに作成される線量分布は非常に複雑なものとなるため，ファントムと線量計を用いて線量の実測を行い治療計画の実現性を検証する作業が必要である．また，治療位置のずれは治療効果と有害事象に直結するため，毎回の照射直前には放射線治療器自体あるいは治療室内に装備されたX線撮影装置を用いた2方向の照準写真やCT画像（コーンビームCT）などにより，治療位置の確認と修正を行い，治療位置を高精度に維持する必要がある．このIMRTの適応疾患は，限局性の固形悪性腫瘍の患者に拡大された．IMRTでは，従来の方法に比べ，より良好な線量分布の作成が可能で，副作用を増強することなくがん病巣への照射線量の増量が可能である．今後は，標的腫瘍内のより放射線抵抗性の領域を描出する画像診断法が開発されてきており，この画像を用いてその領域にさらなる高線量を投与するdose painted IMRTや，IMRTを用いて標的腫瘍の1回線量を増加し，治療期間を短縮する寡分割照射など，有害事象を増やすことなく腫瘍制御向上が期待できるIMRTを用いた手法がさらに展開していくものと考える．

強度変調回転放射線療法（volumetric modulated arc therapy：VMAT）は，ガントリ角度ごとにガントリ回転速度，MLC形状，線量率を変化させながら照射を行う新しいIMRT技術である．前述の従来法と同等の線量分布を達成しながら，従来法に比し線量投与に要する時間が著しく短く，また全身被曝線量の低減も図ることができる．

d. 画像誘導放射線療法（IGRT）

画像誘導放射線療法（image-guided radiation therapy：IGRT）とは，治療装置ないし治療室内に付設された画像撮影装置を用いて放射線療法時の位置決め精度を高める技術をいう．安全に放射線療法を行うために，肉眼的腫瘍体積（gross tumor volume：GTV），臨床標的体積（clinical target volume：CTV），内的標的体積（internal target volume：ITV），計画標的体積（planning target volume）の設定が推奨されている．ここでITVとは，呼吸，嚥下，心拍動などの影響による腫瘍の体内移動の影響（internal margin：IM）を加味した標的体積，PTVとは毎回の照射における設定誤差（set-up margin：SM）を含めた標的体積と定義される．IGRTの目的はこれらのマージンを安全に縮小にすることである．

腫瘍の体内移動で大きな誤差要因となるものが呼吸性移動である．以前はこの呼吸性移動はX線透視画像にて確認していたが，最近では時間的要素を加味した4次元CT（4DCT）を使用して，呼吸位相ごとの腫瘍の動きを正確に把握できるようになった．この4DCT画像と呼吸をモニターするシステムを用いることで4次元放射線治療が可能となり，ある呼吸位相に腫瘍が存在する間のみ放射線を照射する迎撃照射や治療ビーム自体を移動させ，腫瘍を追いかけながら照射をする追尾照射が可能となり，すでに臨床使用されている．

最新の放射線治療システムでは，毎回の照射直前に患者体位の設定誤差（SM）を測定し，解剖学的位置ずれを補正したのちに治療を行うことが可能となっている．患者体位の位置誤差を測定するための画像取得には，放射線治療器自体から照射されるMV-X線や，最新の放射線治療器に装備される，または治療室に設置されたkV-X線が用いられる．また，体内の腫瘍や解剖学的構造を3次元的に測定可能なコーンビームCTを装備した放射線治療器も登場した．これら最新の放射線療法を支援する機器を用いて，IMやSMをできる限り最小にし，マージンを縮小することができるようになった．これにより，周囲正常臓器への照射線量を減らし，さらに標的腫瘍への線量増加が可能となり，治療成績向上あるいは有害反応の減少が期待できる．

参考文献

1) Nagata Y et al : Survey of stereotactic body radiation therapy in Japan by the Japan 3-D Conformal External Beam Radiotherapy Group. Int J Radiat Oncol Biol Phys **75** : 343, 2009
2) Onishi H et al : Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer : updated results of 257 patients in Japanese multi-institutional study. J Thorac Oncol **2** : S94, 2007
3) Nagata Y et al : A phase II trial of stereotactic body radiation therapy for operable T1N0M0 non-small cell lung cancer : Japan Clinical Oncology Group (JCOG0403). Int J Radiat Oncol Biol Phys **78** (Suppl) : S27, 2010

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 953–959, 2012

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2011.01.008

CLINICAL INVESTIGATION **Thoracic Cancer**

PHASE I STUDY OF CONCURRENT HIGH-DOSE THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY WITH CHEMOTHERAPY USING CISPLATIN AND VINORELBINE FOR UNRESECTABLE STAGE III NON-SMALL-CELL LUNG CANCER

IKUO SEKINE, M.D., PH.D.,* MINAKO SUMI, M.D.,PH.D.,† YOSHINORI ITO, M.D.,† HIDEHITO HORINOUCHI, M.D.,* HIROSHI NOKIHARA, M.D., PH.D.,* NOBORU YAMAMOTO, M.D., PH.D.,* HIDEO KUNITOH, M.D., PH.D.,* YUICHIRO OHE, M.D., PH.D.,* KAORU KUBOTA, M.D., PH.D.,* AND TOMOHIDE TAMURA, M.D.*

*Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; and †Division of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan

Purpose: To determine the maximum tolerated dose in concurrent three-dimensional conformal radiotherapy (3D-CRT) with chemotherapy for unresectable Stage III non–small-cell lung cancer (NSCLC).
Patients and Methods: Eligible patients with unresectable Stage III NSCLC, age ≥20 years, performance status 0–1, percent of volume of normal lung receiving 20 GY or more (V_{20}) ≤30% received three to four cycles of cisplatin (80 mg/m^2 Day 1) and vinorelbine (20 mg/m^2 Days 1 and 8) repeated every 4 weeks. The doses of 3D-CRT were 66 Gy, 72 Gy, and 78 Gy at dose levels 1 to 3, respectively.
Results: Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were enrolled at dose levels 1 to 3, respectively. The main reasons for exclusion were V_{20} >30% (n = 10) and overdose to the esophagus (n = 8) and brachial plexus (n = 2). There were 26 men and 5 women, with a median age of 60 years (range, 41–75). The full planned dose of radiotherapy could be administered to all the patients. Grade 3–4 neutropenia and febrile neutropenia were noted in 24 (77%) and 5 (16%) of the 31 patients, respectively. Grade 4 infection, Grade 3 esophagitis, and Grade 3 pulmonary toxicity were noted in 1 patient, 2 patients, and 1 patient, respectively. The dose-limiting toxicity was noted in 17% of the patients at each dose level. The median survival and 3-year and 4-year survival rates were 41.9 months, 72.3%, and 49.2%, respectively.
Conclusions: 72 Gy was the maximum dose that could be achieved in most patients, given the predetermined normal tissue constraints. © 2012 Elsevier Inc.

Lung cancer, Chemotherapy, Radiotherapy, High dose, Conformal.

INTRODUCTION

Approximately one third of patients with non–small-cell lung cancer (NSCLC) present with locally advanced Stage III disease at the initial diagnosis (1). Of this category, Stage IIIA disease with bulky N2 and Stage IIIB disease without pleural effusion are characterized by a large primary lesion and/or involvement of the mediastinal or supraclavicular lymph nodes. In addition, the majority of these patients have occult systemic micrometastases. Concurrent thoracic radiotherapy and chemotherapy has been the standard care for these patients with unresectable disease (2, 3). A platinum doublet with a third-generation anticancer agent combined with thoracic radiotherapy was reported to yield a median overall survival time (OS) of more than 2 years and long-term survivors (4–6), but the effect of platinum-based chemotherapy has reached a plateau.

The failure pattern in patients with Stage III NSCLC treated by concurrent chemoradiotherapy was roughly local recurrence alone in one third of the patients, both local and distant recurrence in another third of patients, and distant metastasis without local failure in the remaining third of patients (2, 5).

Reprint requests to: Ikuo Sekine, M.D., Ph.D., Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. Tel : (+81) 3-3542-2511; Fax: (+81) 3-3542-3815; E-mail: isekine@ncc.go.jp

Presented at the 45th Annual Meeting of the American Society of Clinical Oncology, May 29—June 2, 2006, Orlando, Florida.

Supported in part by Ministry of Health, Labour and Welfare, Health and Labour Science Research Grants, Research on Clinical Trials' Infrastructure Development, H21-RINKEN (Kikan)-IP-PAN-005.

Conflict of interest: none.

Acknowledgment—The authors thank Asako Sakamoto for her work as data manager and Mika Nagai for manuscript preparation.

Received June 7, 2010, and in revised form Dec 27, 2010. Accepted for publication Jan 10, 2011.

Thus, improvement of local control and suppression of distant metastasis are essential for prolongation of patient survival.

The conventional total dose of thoracic radiotherapy in patients with inoperable NSCLC has been 60 Gy administered in 30 fractions. This dose was established in 1987 by randomized Radiation Therapy Oncology Group trials that demonstrated better 3-year survival with a radiation dose of 60 Gy than with lower doses (7). In these trials, two-dimensional treatment planning was used, wherein the tumor volume was defined on kilovoltage radiographs (7). Thereafter, the standard initial target volume included the primary tumor, metastatic lymph nodes, and adjacent uninvolved ipsilateral hilar and mediastinal regions (elective nodal irradiation: ENI). Except for selected patients, excessive toxicity hampered an increase of the total dose to over 60 Gy in patients with locally advanced NSCLC.

It is, however, time now to reconsider the optimal dose of thoracic radiotherapy using new techniques in patients with locally advanced NSCLC, for the following reasons. First, positron emission tomography (PET) provides more accurate diagnosis of mediastinal lymph node metastases (8) and more accurate quantification of the tumor volumes, especially when atelectasis is present (9). Second, three-dimensional conformal radiation therapy (3D-CRT) enables radiation oncologists to delineate the tumor and adjacent normal tissue more sharply and to choose beam angles to maximize tumor coverage with minimum irradiation of normal tissues (10). Third, omission of the ENI resulted in improvement of radiation-associated toxicity without worsening the local control rate of the tumor (11, 12). Thus, by use of these new techniques, the optimal dose of thoracic radiation could exceed the conventional 60 Gy.

Two dose escalation studies in patients with locally advanced NSCLC showed that the total dose of thoracic radiotherapy could be increased up to 90 Gy in concurrent chemoradiotherapy using the 3D-CRT technique combined with weekly carboplatin and paclitaxel chemotherapy (13, 14). In these trials, chemoradiotherapy was administered after induction chemotherapy. However, it remained unclear whether these doses could be delivered safely to the majority of patients with locally advanced NSCLC, because it is not known how many patients were screened for the trials and how many of them were actually registered, and because some of the registered patients were excluded from the chemoradiotherapy phase after induction chemotherapy. The total number of patients evaluated in the two trials was also limited. Furthermore, chemotherapy other than weekly carboplatin and paclitaxel has not been evaluated in the setting of combined chemotherapy with high-dose thoracic radiotherapy, to our knowledge. The objectives of the current study were (1) to evaluate the toxicity of concurrent high-dose 3D-CRT without ENI with cisplatin and vinorelbine for unresectable Stage III NSCLC, (2) to determine the maximum tolerated dose (MTD) of thoracic radiotherapy, and (3) to observe the antitumor effects of this regimen.

PATIENTS AND METHODS

Study design

This study was designed as a Phase I study at the National Cancer Center Hospital. The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center on July 28, 2005. We planned to treat 12 patients at a dose level and follow them up at least 6 months, and then escalate to the next level if 67% of the patients did not experience dose-limiting toxicity (DLT). We followed widely accepted normal tissue dose constraints. Patients with percent volume of the normal lung receiving 20 Gy or more (V_{20}) of greater than 30% were excluded and treated outside the study. Other dosimetric constraints were applied at the discretion of the treating radiation oncologist. Maximum doses exceeding 50 Gy to the spinal cord, 66 Gy to the esophagus, or 66 Gy to the brachial plexus were generally excluded.

Patient selection

Previously untreated patients with locally advanced NSCLC without effusion were screened for entry into this study. The eligibility criteria were (1) histologically or cytologically proven NSCLC, (2) unresectable Stage IIIA or IIIB disease confirmed by both computed tomography (CT) and PET, (3) no previous treatment, (4) measurable disease, (5) $V_{20} \leq 30\%$, (6) age ≥ 20 years, (7) Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, and (8) adequate bone marrow function (white blood cell [WBC] count $\geq 4.0 \times 10^9$/L, hemoglobin ≥ 9.5 g/dL, and platelet count $\geq 100 \times 10^9$/L), liver function (total bilirubin ≤ 1.5 mg/dL and transaminase ≤ 80 IU/L), renal function (serum creatinine ≤ 1.5 mg/dL), and pulmonary function ($PaO_2 \geq 70$ Torr under room air). Patients were excluded if (1) they had malignant pleural or pericardial effusion or (2) they had a concomitant serious illness such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonitis or lung fibrosis identified by a chest x-ray, infection, or other diseases contraindicating chemotherapy or radiotherapy, or (3) they were pregnant or breast feeding. All patients gave their written informed consent.

Pretreatment evaluation

The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest x-rays, chest CT scan, brain CT scan or magnetic resonance imaging, abdominal CT, and PET.

Treatment schedule

Chemotherapy consisted of cisplatin 80 mg/m^2 on Day 1 and vinorelbine 20 mg/m^2 on Days 1 and 8, repeated every 4 weeks for three to four cycles. Cisplatin was administered by intravenous infusion for 60 minutes with 2,500 to 3,000 mL of intravenous fluid for hydration and prophylactic antiemetic therapy consisting of a 5-hydroxytriptamine-3 antagonist on Day 1 and a corticosteroid on Days 1 to 5. Vinorelbine, diluted in 50 mL of normal saline, was administered intravenously.

Radiation therapy started on Day 1 of the first cycle of chemotherapy and was delivered with megavoltage equipment (6–10 MV) once daily for 5 days a week. The total dose was 66 Gy in 33 fractions at level 1, 72 Gy in 36 fractions at level 2, and 78 Gy in 39 fractions at level 3. All patients underwent a 3D treatment planning CT 3 to 7 days before the start of the treatment, and the eligibility was finally confirmed based on evaluation using the

dose–volume histogram (DVH). The gross tumor volume (GTV) was defined as the primary tumor delineated on pulmonary windows of the chest CT or on the diagnostic PET scans. Atelectasis or secondary changes in the peripheral lung region of the primary tumor were not included. Metastatic lymph nodes defined as nodes of 1 cm or larger visualized on mediastinal windows of the CT images or PET-positive lymph nodes were also included in the GTV. The clinical target volume (CTV) was equivalent to the GTV. Uninvolved mediastinum or supraclavicular fossae were not included in the CTV. The planning target volume (PTV) was determined as the CTV plus 1.0 cm for the anterior, posterior, medial, and lateral margins and a 1.0 to 2.0 cm for the superior and inferior margins, taking account of setup variations and internal organ motion. The spinal cord dose was typically limited to 44 Gy, but a maximum of 50 Gy was allowed. The lung V_{20} was limited to 30% in all patients. The maximum dose to the brachial plexus and esophagus did not exceed 66 Gy. The 100% dose was prescribed to the reference point located in the central part of the PTV, and the entire PTV was covered with 95–107% of the prescribed dose principally, but variation of ±10% was allowed. Lung heterogeneity corrections using the equivalent path length algorithm were applied in all patients.

Toxicity assessment and treatment modification

Complete blood cell counts and differential counts, routine chemistry determinations, and a chest x-ray were performed once a week during the course of treatment. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0). The lung toxicity grade was defined as the highest grade among cough, dyspnea, obstruction/stenosis of airways, pneumonitis/pulmonary infiltrates, and pulmonary fibrosis in the pulmonary/upper respiratory section (15).

Vinorelbine administration on Day 8 was omitted if any of the following were noted: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, Grade 2–3 elevation of the serum hepatic transaminase level or total serum bilirubin levels, Grade 2–3 infection, Grade 2–3 pneumonitis, other ≥Grade 3 nonhematologic toxicity, body temperature ≥38°C, or PS of 2–3. Subsequent cycles of cisplatin and vinorelbine chemotherapy were delayed if any of the following toxicities were noted on Day 1: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, serum creatinine level ≥1.6 mg/dL, Grade 2–3 elevation of the serum hepatic transaminase level or total serum bilirubin levels, Grade 2–3 infection, Grade 2–3 pneumonitis, other ≥Grade 3 nonhematologic toxicity, body temperature ≥38°C, or PS of 2–3. If these toxicities did not recover within 6 weeks from Day 1 of the previous cycle of chemotherapy, subsequent cycles of chemotherapy were stopped. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level rose to 2.0 mg/dL or higher. The dose of vinorelbine was reduced by 25% in all subsequent cycles if any of the following toxicities were noted: WBC count $<1.0 \times 10^9$/L, platelet count $<25 \times 10^9$/L, or Grade 3 infection or liver dysfunction. Thoracic radiotherapy was suspended if any of the following were noted: body temperature ≥38°C, Grade 3 esophagitis, PS of 3, or suspected radiation pneumonitis. Thoracic radiotherapy was terminated if any of the following were noted: Grade 4 esophagitis, Grade 3 or 4 pneumonitis, PS of 4, or duration of radiotherapy of over 62 days (level 1), 67 days (level 2), or 70 days (level 3). Any protocol-defined treatments were terminated if Grade 4 nonhematologic toxicities other than transient electrolyte disturbances or a PS of 4 was noted.

Dose-limiting toxicity and maximum tolerated dose

The DLT was defined as the following toxicities observed during a 6-month period from the start of treatment: (1) Grade 3 esophagitis, lung toxicity, myelitis, dermatitis associated with radiation, and cardiac toxicity associated with radiation, (2) Grade 4 nonhematologic toxicity, or (3) treatment termination due to prolonged toxicity. Twelve patients were enrolled at each dose level. All patients were followed up for at least 6 months to evaluate DLT. During the period, if none to 4 of the 12 patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If 5 or more of the 12 patients experienced DLT, that level was considered to be the MTD. The recommended dose for Phase II trials was defined as the dose preceding the MTD.

Response evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0 (16).

Follow-up

Patients who completed the protocol therapy were followed up to monitor toxicity, response, and recurrence. CT of the chest was performed every 2 to 4 months for 1 year, every 6 months for 2 years, and then yearly for 2 years. The relapse pattern was categorized into (1) local alone, including relapse from the primary site or the hilar, mediastinal, or supraclavicular lymph nodes, (2) distant metastasis alone, including pleural dissemination, pleural and pericardial effusions, and distant metastases, and (3) local and distant.

Statistical analyses

Progression-free survival time (PFS) and OS were estimated by the Kaplan-Meier method. The PFS was measured from the date of registration to the date of disease progression or death resulting from any cause or date of last follow-up. The OS was measured from the date of registration to the date of death resulting from any cause or date of last follow-up. Patients who were lost to follow-up without events were censored at the date of their last known follow-up. A confidence interval (CI) for the response rate was calculated by the method used for exact binomial CIs. The Dr. SPSS II 11.0 software package for Windows (SPSS Japan Inc., Tokyo, Japan) was used for the statistical analyses.

RESULTS

Registration and characteristics of the patients

From August 2005 to September 2008, 57 patients were deemed to initially be eligible. Of these, 3 patients were excluded because idiopathic interstitial pneumonitis ($n = 1$) and anemia ($n = 2$) developed. Explanation of the study using the consent form was given to 54 patients, and informed consent was obtained in 51 patients. The 51 patients underwent 3D treatment planning, and eligibility was finally confirmed in 31 patients. Those 31 were enrolled into this study. A total of 20 patients were excluded as a result of the DVH evaluation: because of V_{20} higher than 30% in 10 patients, overdose to the esophagus in 8 patients, and overdose to the brachial plexus in 2 patients. Eventually, of 17 patients assessed as to their eligibility for dose level 1, 16 patients for dose level 2, and 24 patients to dose level 3, 13 (76%), 12 (75%), and 6 (25%) patients were actually enrolled into levels 1 to 3, respectively (Fig. 1).

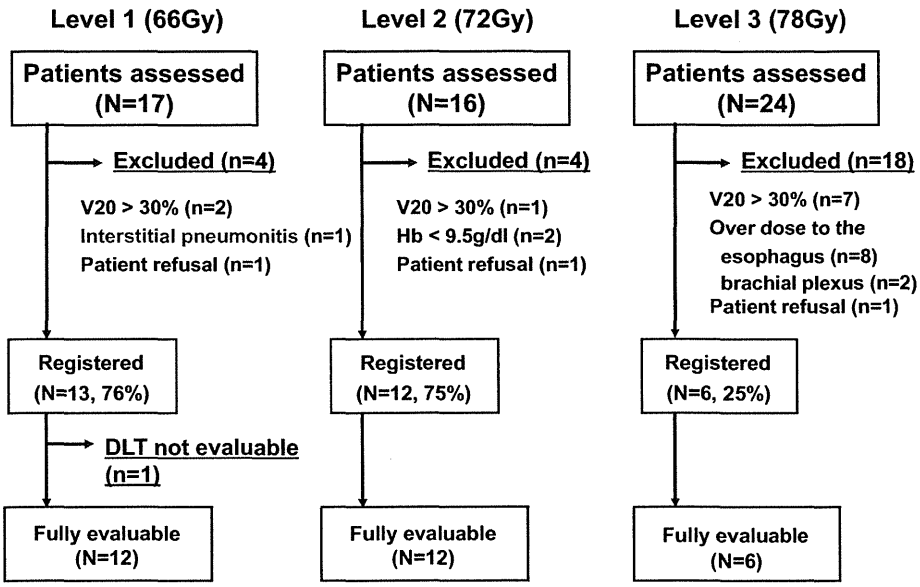

Fig. 1. Algorithm illustrating the flow of the patients. Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were actually enrolled at dose levels 1, 2, and 3, respectively.

The pretreatment characteristics of the patients enrolled in this trial are shown in Table 1. The majority of the patients were in good general condition, with a PS of 0 in 25 (81%) and no weight loss in 26 (84%) patients. Adenocarcinoma was the predominantly encountered histological characteristic, seen in 23 (74%) patients.

Treatment delivery

The treatment delivery to the patients was fairly good (Table 2). The planned dose of radiotherapy was administered to all patients of all the three dose levels. More than 80% of the patients received three to four cycles of chemotherapy without or with only one omission of vinorelbine on Day 8, regardless of the dose levels.

Toxicity and DLTs

The hematologic toxicity was comparable to that of other concurrent chemoradiotherapy (Table 3). Grade 4 septic shock was encountered during the fourth cycle of chemotherapy in 1 patient enrolled at dose level 1, but it was manageable by standard care with antibiotics. Other nonhematologic toxicities were mild and acceptable.

Table 1. Patient characteristics

Characteristic	*n*	(%)
Sex		
M	26	(84)
F	5	(16)
Age (y)		
Median (range)	60	(41–75)
Performance status		
0	25	(81)
1	6	(19)
Body weight loss (%)		
0	26	(84)
0.1–5.0	2	(6)
≤5.0	3	(10)
Histology		
Adenocarcinoma	23	(74)
Squamous cell carcinoma	4	(13)
NSCLC, not otherwise specified	4	(13)
Stage		
IIIA	20	(65)
IIIB	11	(35)

Abbreviation: NSCLC = non–small-cell lung cancer.

Table 2. Treatment delivery

	Level 1 (n = 13)	Level 2 (n = 12)	Level 3 (n = 6)
Radiotherapy			
Total dose (Gy)			
66	13 (100)	–	–
72	–	12 (100)	–
78	–	–	6 (100)
Delay (days)			
≤5	11 (85)	5 (42)	5 (83)
6–10	2 (15)	6 (50)	0
11–15	0	1 (8)	1 (17)
Chemotherapy			
No. of cycles			
4	6 (46)	6 (50)	4 (67)
3	6 (46)	4 (33)	2 (33)
2	0	1 (8)	0
1	1 (8)	1 (8)	0
No. of VNR omissions			
0	10 (77)	7 (58)	2 (33)
1	2 (15)	4 (33)	3 (50)
2	0	0	1 (17)
3	1 (8)	1 (8)	0

Abbreviation: VNR = vinorelbine administered on Day 8.

Table 3. Toxicity

	Grade										
	Level 1			(n = 13)	Level 2			(n = 12)	Level 3			(n = 6)
Toxicity	2	3	4	(3+4 %)	2	3	4	(3+4 %)	2	3	4	(3+4 %)
Leukopenia	4	6	2	(62)	1	3	8	(92)	1	3	2	(83)
Neutropenia	4	4	4	(62)	0	1	10	(92)	1	3	2	(83)
Anemia	8	2	2	(31)	7	3	1	(33)	2	2	0	(50)
Thrombocytopenia	0	0	0	(0)	1	1	0	(8)	0	0	0	(0)
Febrile neutropenia	–	1	0	(8)	–	3	0	(25)	–	1	0	(17)
Infection	0	0	1	(8)	0	1	0	(8)	2	0	0	(0)
Esophagitis	1	1	0	(8)	2	1	0	(8)	0	0	0	(0)
Lung toxicity	2	0	0	(0)	0	0	0	(0)	0	1	0	(17)
Anorexia	3	0	0	(0)	2	2	0	(17)	0	0	0	(0)
Nausea	3	0	0	(0)	3	0	0	(0)	0	0	0	(0)
ALT elevation	1	1	0	(8)	0	0	0	(0)	1	0	0	(0)
CRN elevation	7	0	0	(0)	4	0	0	(0)	0	0	0	(0)

Abbreviations: ALT = alanine aminotransferase; CRN = creatinine.

Of the 13 patients at dose level 1, one was excluded from the analysis of the DLT because he received only one cycle of chemotherapy as a result of the development of cisplatin-induced renal toxicity. Two (17%) of the remaining 12 patients at this dose level developed DLT: Grade 3 esophagitis in 1 patient and Grade 4 septic shock in the other. At dose level 2, two (17%) DLTs were noted: Grade 3 esophagitis in 1 patient and treatment delay by more than 15 days in the other. One (17%) of the 6 patients at dose level 3 developed Grade 3 bronchial stenosis without local recurrence of the disease. This was considered to be a Grade 3 lung toxicity and was counted as DLT. No other DLTs were noted. Thus, inasmuch as the incidence of DLT was below 33% at all dose levels, MTD was not reached.

Preliminary efficacy results

Objective responses and survival were evaluated in the 31 patients. Two patients showed complete responses and 27 showed partial responses, which represented a response rate (95% CI) of 94% (79–99). Disease progression was noted in 23 patients, and the median PFS was 11.6 months with a median duration of follow-up of 30.5 (range, 9.0–49.5) (Fig. 2). The first relapse sites aresummarized in Table 4. Brain metastasis alone as the first relapse site was noted in 7 (23%) patients. The median OS was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively (Fig. 3).

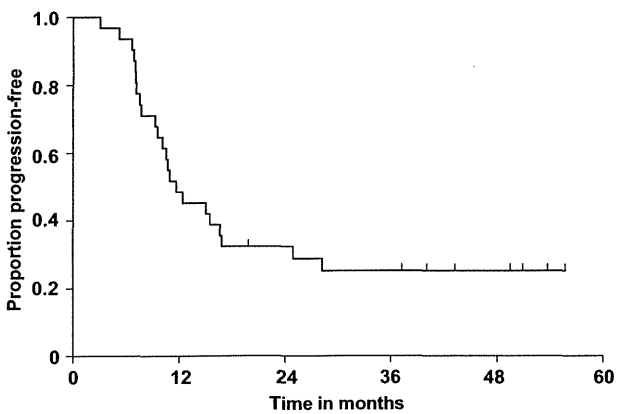

Fig. 2. Progression-free survival (n = 31). The median progression-free survival was 11.6 months, with a median duration of follow-up of 30.5 months (range, 9.0–49.5 months).

DISCUSSION

This study showed that concurrent 3D-CRT to the thorax with cisplatin plus vinorelbine chemotherapy was safe even up to 78 Gy in patients with unresectable Stage III NSCLC. This does not mean, however, that doses as high as 78 Gy can be given to all patients with this disease, because the safety in this study was shown only in highly selected patients by a PET/CT and DVH evaluation and by the standard staging procedure. Twenty-five of the 33 patients met the eligibility criteria for enrollment at dose levels 1 and 2, whereas only 6 of the 24 patients could be enrolled at dose level 3 in this study—that is, only one fourth of the patients could be treated with 78 Gy. Thus, this study showed that 72 Gy was the maximum dose that could be achieved in most patients given the predetermined normal tissue constraints, which forced three quarters of the enrolled patients at the 78-Gy level to not

Table 4. First relapse sites (n = 31)

Sites	n	(%)
Local recurrence alone	6	(19)
Local and distant metastasis	6	(19)
Distant metastasis alone	11	(35)
Brain alone	7	(23)
No relapse	8	(26)

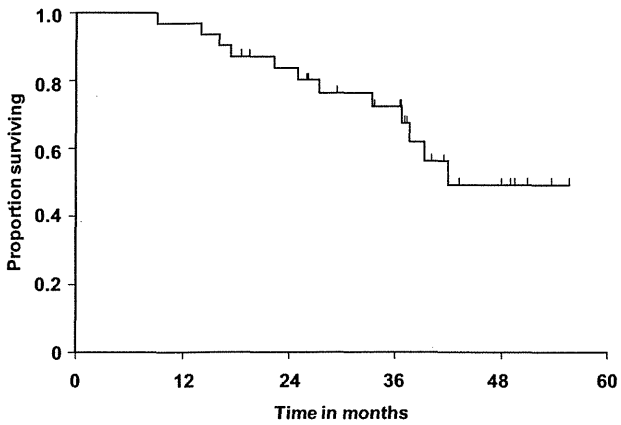

Fig. 3. The median overall survival was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively.

be eligible on the basis of those normal tissue constraints, and that the maximum tolerated dose was not determined because of this issue.

One obstacle to enrolling patients at dose level 3 was that the lung V_{20} often exceeded 30% when the total dose was increased to 78 Gy. This lung V_{20} dose constraint might have been too strict. According to a recent review, it is prudent to limit V_{20} to ≤30–35% with conventional fractionation, but there is no sharp dose threshold below which there is no risk for severe radiation pneumonitis (17). This is partly because DVH-based parameters will change at specific phases of the respiratory cycle when CT images for DVH evaluation have been obtained, there is uncertainty regarding how much of the bronchus should be defined as lung, and the lung edges may vary with the CT window level setting. In addition, patient-associated factors such as age, smoking status, lung function, and preexisting lung damage may influence the incidence and severity of radiation pneumonitis (18). If the threshold of V_{20} were set at higher than 30% (*e.g.*, 35%), then more patients would meet the eligibility criteria, but safety might not be guaranteed. Given that the definite threshold cannot be determined, a strict constraint should be introduced. This study showed that the lung toxicity was acceptable when the V_{20} was kept within 30%; therefore, we decided to use this eligibility criterion for concurrent chemotherapy and high-dose radiotherapy for a subsequent Phase II study.

Another obstacle was overdose to the esophagus and brachial plexus, which were close to the subcarinal (No. 7) and supraclavicular lymph nodes, respectively, that were frequently involved in patients with advanced NSCLC; therefore, the volume of these serial organs were included, in part, in the PTV in many patients with Stage III disease. The radiation tolerance doses of these organs have been defined as no higher than 72 Gy when one third of the organs are included in the irradiation volume (19). However, few data are available on the radiation tolerance doses of normal organs in humans; therefore, whether or not radiation doses above 72 Gy may be tolerated is unknown, especially when only small percentages of the organs are actually included in the irradiation volume. Notwithstanding, we do not agree that the radiation dose can be increased close to the intolerable level, because serious radiation toxicity to these serial organs could be irreversible, frequently leaves severe sequelae, and is fatal in some cases.

The toxicity observed in this trial was comparable to that in our previous study of concurrent chemoradiotherapy with vinorelbine and cisplatin chemotherapy plus thoracic radiation at a total dose of 60 Gy administered in 30 fractions: Grade 3–4 neutropenia in 77% and 67% of patients, Grade 3–4 esophagitis in 6% and 12% of patients, and Grade 3–5 lung toxicity in 3% and 7% in the current and previous studies, respectively (5). This suggests that patient selection using PET/CT and DVH evaluation may be useful to keep the toxicity associated with high-dose thoracic radiation within the range of toxicity induced by conventional-dose thoracic radiation.

In this study, a remarkably high proportion (74%) of subjects had adenocarcinoma, which may provide an explanation for the high rate of subsequent brain metastases. Patient selection also affects the treatment efficacy considerably; therefore, it is difficult to compare it between the current and previous studies. However, the median PFS of 11.6 months and median OS of 41.9 months sound promising. We are conducting a Phase II study of concurrent 3D-CRT at a total dose of 72 Gy and chemotherapy with cisplatin and vinorelbine.

In conclusion, concurrent 3D-CRT with cisplatin and vinorelbine chemotherapy was feasible up to 72 Gy, in patients with unresectable Stage III NSCLC. At the level of 78 Gy, however, only 25% of the patients assessed for eligibility were found to be actually eligible. Thus, 72 Gy in 36 fractions was the maximum dose that could be achieved in most patients given the predetermined normal tissue constraints when administered concurrently with cisplatin and vinorelbine.

REFERENCES

1. Yang P, Allen MS, Aubry MC, *et al.* Clinical features of 5,628 primary lung cancer patients: Experience at Mayo Clinic from 1997 to 2003. *Chest* 2005;128:452–462.
2. Furuse K, Fukuoka M, Kawahara M, *et al.* Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17: 2692–2699.
3. Curran WJ, Scott C, Langer C, *et al.* Phase III comparison of sequential vs concurrent chemoradiation for patients with unresectable stage III non-small-cell lung cancer (NSCLC): Initial report of the Radiation Therapy Oncology Group (RTOG) 9410. *Proc Am Soc Clin Oncol* 2000;19: 484a.
4. Sekine I, Noda K, Oshita F, *et al.* Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for

unresectable stage III non-small cell lung cancer. *Cancer Sci* 2004;95:691–695.
5. Sekine I, Nokihara H, Sumi M, *et al.* Docetaxel consolidation therapy following cisplatin, vinorelbine, and concurrent thoracic radiotherapy in patients with unresectable stage III non-small cell lung cancer. *J Thorac Oncol* 2006;1:810–815.
6. Kiura K, Takigawa N, Segawa Y, *et al.* Randomized phase III trial of docetaxel and cisplatin combination chemotherapy versus mitomycin, vindesine and cisplatin combination chemotherapy with concurrent thoracic radiation therapy for locally advanced non-small cell lung cancer: OLCSG 0007. *J Clin Oncol* 2008;26(Suppl):400s (abstr. 7515).
7. Perez CA, Pajak TF, Rubin P, *et al.* Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* 1987; 59:1874–1881.
8. Birim O, Kappetein AP, Stijnen T, *et al.* Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer. *Ann Thorac Surg* 2005;79:375–382.
9. Nestle U, Walter K, Schmidt S, *et al.* 18F-deoxyglucose positron emission tomography (FDG-PET) for the planning of radiotherapy in lung cancer: High impact in patients with atelectasis. *Int J Radiat Oncol Biol Phys* 1999;44:593–597.
10. Purdy J. Three-dimensional conformal radiation therapy: Physics, treatment planning, and clinical aspects. In: Halperin E, Perez C, Brady L, editors. Principles and practice of radiation oncology. 5th ed. Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins; 2008.
11. Rosenzweig KE, Sura S, Jackson A, *et al.* Involved-field radiation therapy for inoperable non small-cell lung cancer. *J Clin Oncol* 2007;25:5557–5561.
12. Sanuki-Fujimoto N, Sumi M, Ito Y, *et al.* Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses. *Radiother Oncol* 2009;91: 433–437.
13. Socinski MA, Morris DE, Halle JS, *et al.* Induction and concurrent chemotherapy with high-dose thoracic conformal radiation therapy in unresectable stage IIIA and IIIB non-small-cell lung cancer: A dose-escalation phase I trial. *J Clin Oncol* 2004;22: 4341–4350.
14. Rosenman JG, Halle JS, Socinski MA, *et al.* High-dose conformal radiotherapy for treatment of stage IIIA/IIIB non-small-cell lung cancer: Technical issues and results of a phase I/II trial. *Int J Radiat Oncol Biol Phys* 2002; 54:348–356.
15. Miller KL, Shafman TD, Marks LB. A practical approach to pulmonary risk assessment in the radiotherapy of lung cancer. *Semin Radiat Oncol* 2004;14:298–307.
16. Therasse P, Arbuck SG, Eisenhauer EA, *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92: 205–216.
17. Marks LB, Bentzen SM, Deasy JO, *et al.* Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys* 2010;76(3 Suppl):S70–S76.
18. Mehta V. Radiation pneumonitis and pulmonary fibrosis in non-small-cell lung cancer: Pulmonary function, prediction, and prevention. *Int J Radiat Oncol Biol Phys* 2005;63:5–24.
19. Emami B, Lyman J, Brown A, *et al.* Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991; 21:109–122.

Risk Factors for Treatment-Related Death Associated with Chemotherapy and Thoracic Radiotherapy for Lung Cancer

Yuko Minami-Shimmyo, MD, Yuichiro Ohe, MD, PhD,* Seiichiro Yamamoto, PhD,† Minako Sumi, MD, PhD,‡ Hiroshi Nokihara, MD, PhD,* Hidehito Horinouchi, MD,* Noboru Yamamoto, MD, PhD,* Ikuo Sekine, MD, PhD,* Kaoru Kubota, MD, PhD,* and Tomohide Tamura, MD**

Introduction: The aim of the study is to evaluate the current status of treatment-related death (TRD) in lung cancer patients.

Methods: We retrospectively analyzed the incidence and risk factors of TRD in lung cancer patients who received chemotherapy and/or thoracic radiotherapy using logistic regression analyses.

Results: Between January 2001 and December 2005, 1225 (222 small cell and 1003 non-small cell lung cancers) patients received chemotherapy and/or thoracic radiotherapy as the initial treatment. Of these, 43 patients receiving chemotherapy followed by thoracic radiotherapy were included into both the chemotherapy-alone and radiotherapy-alone groups. There were a total of 23 (1.9%) TRDs. Chemotherapy-related deaths occurred in 7 of 927 (0.8%) patients, including 4 from drug-induced lung injury, 2 from pneumonia, and 1 from unknown cause. Concurrent chemoradiotherapy-related deaths occurred in 12 of 245 (4.9%) patients, including 11 from radiation pneumonitis and 1 from pneumonia. Thoracic radiotherapy-related deaths occurred in 4 of 96 (4.2%) patients. The incidence of chemotherapy-related death was correlated with poor performance status (odds ratio [OR]: 11.4, 95% confidence interval [CI]: 3.53–37.1), the presence of hypoxia (OR: 19.3, CI: 6.06–61.7), hyponatremia (OR: 45.5, CI: 13.4–154), and treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (OR: 8.56, CI: 2.48–29.5), whereas the incidence of concurrent chemoradiotherapy-related death was correlated with pulmonary fibrosis (OR: 22.2, CI: 5.61–87.8). Radiotherapy results were not analyzed because there were too few patients.

Conclusions: TRD occurred in 1.9% of the patients as a result of treatment-related lung injury in the majority of the cases.

Key Words: Lung cancer, Treatment-related death, Risk factor, Chemotherapy, Thoracic radiotherapy.

(*J Thorac Oncol.* 2012;7: 177–182)

*Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital; †Division of Cancer Information and Epidemiology, National Cancer Center Research Institute; and ‡Division of Radiation Oncology, National Cancer Center Hospital, Tsukiji, Chuo-ku, Tokyo, Japan.

Disclosure: The authors declare no conflict of interests.

Address for correspondence: Ikuo Sekine, MD, PhD, Department of Medical Oncology, Graduate School of Medicine, Chiba University, Inohana 1-8-1, Chuo-ku, Chiba 260-8670, Japan. E-mail: isekine@chiba-u.jp

ISSN: 1556-0864/12/0701-0177

Before any medical interventions are undertaken in patients with lung cancer, they must be clearly informed about the risks and benefits of the intervention(s) and about alternative treatment options. Careful delivery of this is particularly important if the planned treatment may not only result in cure but may also be harmful. Provision of accurate information to help patients make the most appropriate decision is therefore crucial. However, the risks of death from drug toxicity and the incidences of such events tend to be uncertain[1–4] and also constantly change with the wide use of newer agents, such as third-generation chemotherapy agents, and molecular-targeted agents. In addition, the incidence of treatment-related deaths (TRDs) has not been thoroughly examined in clinical settings outside of clinical trials. Prospective clinical trials for poor-risk patients are often difficult to perform because of poor accrual, reflecting the reluctance of physicians to subject patients with underlying comorbid illness to the toxic effects of chemotherapy and radiation.

Our ultimate goal is to prospectively identify individuals who are at a high risk of TRD so as to provide the most precise estimation of the possible risks to each patient. In this study, we retrospectively examined the data of patients with locally advanced or metastatic lung cancer who were treated at the National Cancer Center Hospital, Tokyo, Japan, focusing on the risks and incidences of TRD associated with chemotherapy and radiotherapy.

PATIENTS AND METHODS

Patients

Between January 2001 and December 2005, a total of 1623 lung cancer patients were admitted to the thoracic oncology ward at the National Cancer Center Hospital. All patients were admitted in this period to be treated as part of standard practice in Japan. Patients who received chemotherapy alone usually stayed in the hospital for 7 to 10 days for one cycle of chemotherapy, and those who received concurrent chemoradiotherapy stayed for 6 weeks. Among these, a total of 1225 patients who had received first-line chemotherapy and/or radiotherapy on an inpatient basis were extracted from the institutional database. Additional details about the patients, including the diagnostic imaging findings, were then reviewed from the patients' medical records. The data of patients receiving chemotherapy and/or thoracic radiotherapy

as the initial treatment were evaluated. They included patients with stage III to IV disease and postoperative recurrent disease who received chemotherapy; those with stage III disease who received chemoradiotherapy or radiotherapy alone; and those with stage III disease who received preoperative induction therapy or postoperative adjuvant therapy. All the patients had been followed for at least 4 weeks after the completion of treatment.

Treatment Selection

After a thorough evaluation of the operability and/or curability, the eligibility of each patient for enrollment in an open clinical trial was determined. Although patient recruitment for protocol treatments is a priority of ours, patients were free to refuse treatment. If no appropriate clinical trials were scheduled or under way, the known best standard treatments were administered.

Best Standard Treatments

For first-line treatment, patients with non-small cell lung cancer (NSCLC) who were deemed inoperable but curable with good local control with chemoradiotherapy received three to four cycles of cisplatin (CDDP) 80 mg/m^2 on day 1 + vinorelbine (VNR) 20 mg/m^2 on days 1 and 8, every 4 weeks, along with early concurrent thoracic radiotherapy, usually at a total dose of 60 Gy/30 fractions.[5] Sequential chemoradiotherapy, rather than concurrent chemoradiotherapy, was offered if the calculated percentage of the total lung volume receiving radiation in excess of 20 Gy (V_{20}) was more than 40%.[6] Thoracic radiotherapy alone was selected if chemotherapy could not be given due to comorbidity. If the radiation field involved the contralateral hilum or if the patients had malignant effusion and/or distant metastasis, platinum doublet therapy was administered; the most common combination was four cycles of carboplatin (CBDCA) area under the curve = 6 on day 1 + paclitaxel (PTX) 200 mg/m^2 on day 1, every 3 weeks.[7] For limited-disease SCLC, four cycles of a combination of CDDP 80 mg/m^2 on day 1 + etoposide 100 mg/m^2 on days 1 to 3, every 4 weeks, were administered concurrently with hyperfractionated thoracic radiotherapy at a total radiation dose of 45 Gy in fractional doses of 1.5 Gy, administered twice a day.[8] In patients with extensive-disease SCLC, four cycles of a combination of CDDP 60 mg/m^2 on day 1 and irinotecan (CPT) 60 mg/m^2 on days 1, 8, and 15, every 4 weeks, were usually administered.[9] Radiotherapy was given using megavoltage photons (6–15 MV). The routine radiation schedule without chemotherapy for locally advanced NSCLC was a total radiation dose of 60 to 66 Gy, or as high as 70 Gy, administered in fractional doses of 2.0 Gy once a day.

Definition of TRD

Chemotherapy-related death was defined as death occurring within 4 weeks of the completion of treatment, without clear evidence of any other cause of death, or death obviously caused by treatment toxicity. Radiotherapy-related death was defined as death secondary to hypoxia or to complications of corticosteroid administration after the diagnosis of radiation pneumonitis. Steroid therapy was administered based on the attending physician's discretion, without a standardized treatment dose or duration, for the management of radiation-induced lung injury.[10]

Definition of Treatment-Induced Lung Injury

The criteria of drug-induced lung injury in this study were as follows: (1) appearance of new symptoms and radiological abnormalities in the course of chemotherapy with the onset within a few months of the start of the therapy; (2) diffuse or multifocal ground-glass opacities and intralobular interstitial thickening without segmental distribution in computed tomography (CT) scans of the chest; and (3) no evidence of underlying heart disease, infection, or lymphangitic carcinomatosis. Lung biopsy was not routinely performed in our hospital because patients were frequently too frail to undergo biopsy. The criteria of radiation-induced lung injury were (1) appearance of new symptoms and radiological abnormalities with the onset within 6 months of the end of thoracic radiotherapy; (2) opacification, diffuse haziness, infiltrates, or consolidation conforming to the outline of the sharply demarcated irradiated area in CT scans; and (3) a reduction in lung volume within the irradiated area and linear, ground-glass opacities or reticular shadows beyond the irradiated area developing during clinical course. In contrast, the criteria of bacterial pneumonia were (1) clinical suspicion of pneumonia including rapidly developing fever and/or productive cough; and (2) consolidation spreading through anatomical structure of the lung in CT scans.

Statistical Analysis

We investigated the associations between chemotherapy-related or concurrent chemoradiotherapy-related death and the potential risk factors at the time of diagnosis. The following potential risk factors were investigated: sex, age (≥70 years versus <70 years), performance status (Eastern Cooperative Oncology Group criteria; 2–4 versus 0–1), smoking history (presence versus absence), partial pressure of oxygen (70 mmHg ≤ PO_2 versus >70 mmHg), hemoglobin (Hgb < 13.7 g/dl versus ≥ 13.7 g/dl), platelet (Plt > 367 × 10^9/L versus ≤367 × 10^9/L), albumin (Alb < 3.7 g/dl versus ≥3.7 g/dl), sodium (Na < 138 mEq/L versus ≥138 mEq/L), clinical trial (in versus out), and chemotherapy regimen (The cutoff values of hemoglobin, platelet, albumin, and sodium are the institutional normal limits [above or below]). For concurrent chemoradiotherapy-related factors, the presence of coincidental diseases such as emphysema (with versus without) or pulmonary fibrosis (with versus without) and the location of the primary tumor (lower lobe versus other lobes) were also included in the analyses. The diagnostic criteria of pulmonary fibrosis were a linear, ground-glass attenuation or reticular shadows on chest radiographs and CT scans before treatment that were predominant in the lower zone of the lung. Also, the influence of the chemotherapy regimens was evaluated.

In the univariate preliminary analysis, the relation between previously defined variables at the time of presentation and the occurrence of the outcome variable (toxic death) was assessed using the χ^2 test. To adjust for each factor, multivariate logistic regression analyses were planned. When the number of observed events was less than 10, multivariate

analysis was not performed. When the number of patients for each factor was small, the factor was excluded from the model, even when it appeared to be statistically significant. All the analyses were performed using the STATISTICA 4.1J program (StatSoft, Inc., Tulsa, OK).

RESULTS

Patient Characteristics

The patient characteristics before treatment are listed in Table 1. Of the 1225 patients (SCLC: 222; adenocarcinoma: 652; squamous cell carcinoma: 194; NSCLC not otherwise specified: 111; large cell carcinoma: 7; others: 39), chemotherapy alone was administered in 884 patients, concurrent chemoradiotherapy in 245, sequential chemoradiotherapy in 43, and thoracic radiotherapy alone in 53 patients. To evaluate the incidence of TRD among the patients who received chemotherapy, radiotherapy, or a combination of these modalities, we included the 43 patients who received sequential chemoradiotherapy into both the chemotherapy-alone group and the thoracic radiotherapy-alone group. Therefore, the patients who received sequential chemoradiotherapy were regarded as having been exposed to the risks of treatment twice. The groups were therefore analyzed as chemotherapy alone in 927 patients, concurrent chemotherapy in 245 patients, and thoracic radiotherapy alone in 96 patients. In these groupings, the percentages of patients enrolled in clinical trials were 62, 53, and 23%, respectively.

Cumulative Incidence and Causes of TRD

The cumulative incidence and causes of TRD are listed in Table 2. Of the 1225 patients, a total of 23 (1.9%) TRDs occurred. Chemotherapy-related deaths occurred in 7 of 927 (0.8%) patients, including 4 (0.4%) from drug-induced lung injury (gefitinib, $n = 3$ and CBDCA + gemcitabine, $n = 1$), 2 (0.2%) from pneumonia (CBDCA + PTX, $n = 2$), and 1 (0.1%) from unknown cause. The patient who died of unknown cause experienced hemodynamic instability (shock) of unknown etiology within 24 hours of ingestion of the first dose of gefitinib (250 mg). No TRDs from sepsis occurred in this series.

Concurrent chemoradiotherapy-related deaths occurred in 12 of 245 (4.9%) patients, including 11 (4.5%) from radiation pneumonitis and 1 (0.4%) from pneumonia during the last planned cycle of CDDP + VNR. Radiotherapy-

TABLE 1. Patient Characteristics

Characteristics	Chemotherapy Alone[a] ($n = 927$)	Concurrent Chemoradiotherapy ($n = 245$)	Radiotherapy Alone[a] ($n = 96$)
Sex			
Male	639	201	43
Female	288	44	53
Age			
Median (range)	64 (27–86)	59 (18–77)	67 (35–81)
Performance status			
0–1	871	245	88
2	140	0	8
3–4	16	0	0
Stage			
III	297	235	71
IV	454	2	17
Postoperative recurrence	176	8	8
Histology			
Non-small cell carcinoma	760	191	88
Small cell carcinoma	167	54	8
Coincidental lung disease			
Pulmonary fibrosis	34	1	4
Pulmonary emphysema	69	30	1
Chemotherapy regimen			
Platinum + taxane	368	21	—
Platinum + irinotecan	133	1	—
EGFR-TKI	125	0	—
Platinum + etoposide	95	54	—
Platinum + antimetabolite	85	0	—
Platinum + vinca alkaloid	37	168	—
Others	84	1	—

[a] Forty-three patients who received sequential chemotherapy followed by radiotherapy are included in the analysis of both the chemotherapy-alone group and radiotherapy-alone group, as described in the text.

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

TABLE 2. Treatment-Related Death and Its Cumulative Incidence

Characteristics	Chemotherapy Alone[a] (n = 927)	Concurrent Chemoradiotherapy (n = 245)	Radiotherapy Alone[a] (n = 96)
No. of treatment-related deaths	7	12	4
Cumulative incidence (%)	0.8	4.9	4.2
Sex			
Male	5	11	4
Female	2	1	0
Age of patients who died of treatment (yr)			
Median (range)	69 (46–77)	68 (50–77)	75 (65–77)
Causes			
Treatment-induced lung injury	4	11	4
Infectious pneumonia	2	1	0
Unknown	1	0	0
Chemotherapy regimen			
Platinum + taxane	2	2	—
EGFR-TKI	4	—	—
Platinum + antimetabolite	1	—	—
Platinum + etoposide	0	1	—
Platinum + vinca alkaloid	0	8	—
Others	0	1	—

[a] Forty-three patients who received sequential chemotherapy followed by radiotherapy are included in the analysis of both the chemotherapy-alone group and radiotherapy-alone group, as described in the text.
EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

related deaths occurred in 4 of 96 (4.2%) patients: all 4 (4.2%) patients died of radiation pneumonitis.

Risk Factors for TRD from Chemotherapy

Statistically significant factors identified by the univariate analysis were a performance status of 2 to 4, hypoxia, hypoalbuminemia, hyponatremia, out of clinical trials, and treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) (Table 3). Although statistically significant, the degrees of hyponatremia in the events were neither clinically significant nor symptomatic for the range of 133 to 137 mEq/L. Pulmonary fibrosis and emphysema were noted in 34 and 69 patients, respectively, among the 927 patients. None of these patients with lung disease died of treatment in this study. Multivariate analysis was not performed because the number of observed events was too small (n = 7).

Risk Factors for TRD from Concurrent Chemoradiotherapy

None of the factors, except for pulmonary fibrosis, were found to be statistically significant in the univariate analysis, although a trend toward increase in the risk of TRD was observed in patients of advanced age (>70 years) and with lower lobe as the primary tumor site (Table 4). Pulmonary fibrosis appeared to be a statistically significant risk factor for TRD; however, it was excluded from the multivariate analysis because of its limited incidence. Thus, we did not perform multivariate analysis for chemoradiotherapy group, and an analysis of the risk of TRD associated with thoracic radiotherapy alone was not conducted because of the limited number of cases.

DISCUSSION

We identified a total of 23 TRDs out of the 1225 patients (1.9%) enrolled in this study, which is lower than the rate (2.7%) indicated in a previous report, particularly in relation to the number of TRDs from infections, including pneumonia and sepsis.[1] The reason for the decrease in the incidence of infection-related deaths is likely explained by the infrequent use of triplet regimens when compared with previous studies. Especially, mitomycin-C-containing regimens are regarded as effective regimens in the treatment of lung cancer; however, prolonged neutropenia has been observed with these regimens. Ohe et al.[1] reported that combined mitomycin-C + vindesine + CDDP (MVP regimen) therapy is a risk factor for chemotherapy-related TRD (toxic deaths occurred in 9 of 301 patients; odds ratio [OR] = 9.36, 95% confidence interval [CI] = 1.29–68.0, p = 0.027). In this study, only 35 patients, the majority (89%) of whom were enrolled in a clinical trial, received the MVP regimen. In the past, however, the MVP regimen was widely used as part of practice-based regimens (only 28% recorded under clinical trials). In most cases, patients who were not eligible for clinical trials ended up receiving the MVP regimen. Another reason is the relatively frequent use of EGFR-TKI (in 13.5% of the patients in this study) at present, which does not induce myelosuppression. The reduction in the frequency of TRD might also be explained by a progress in supportive care in the treatments given for cancer treatment toxicities.

This study revealed that drug-induced lung injury was the most frequent cause of TRD in the era of molecular-targeted therapy. Three (75%) of four TRDs from drug-induced lung injury were associated with gefitinib. The re-

TABLE 3. Risk Factors for Treatment-Related Death from Chemotherapy

Factors	No. of Patients	Cumulative Incidence (%)	Univariate Analysis OR (95% CI)	p
Sex				
Female	288	0.8	1	
Male	639	0.7	1.13 (0.22–5.76)	0.89
Age				
<70	689	0.6	1	
≥70	238	1.3	2.17 (0.51–9.30)	0.30
PS				
0–1	870	0.5	1	
2–4	57	5.2	11.4 (3.53–37.1)	<0.001
Smoking history				
No	271	0.4	1	
Yes	656	0.9	2.49 (0.30–20.8)	0.40
PaO_2 (Torr)				
≥70	812	0.2	1	
<70	105	4.8	19.3 (6.06–61.7)	<0.001
Hemoglobin (g/dl)				
≥13.7	371	0.5	1	
<13.7	556	0.9	1.67 (0.33–8.39)	0.54
Albumin (g/dl)				
≥3.7	663	0.3	1	
<3.7	264	1.9	6.28 (1.51–26.1)	0.012
AST (IU/L)				
≤33	831	0.6	1	
>33	96	2.1	3.46 (0.75–16.0)	0.11
Na (mEq/L)				
≥138	819	0.1	1	
<138	108	5.6	45.5 (13.4–154)	<0.001
Clinical trial				
No	355	1.7	1	
Yes	572	0.2	0.10 (0.58–0.019)	0.001
Platinum + taxane				
No	559	0.9	1	
Yes	368	0.5	0.61 (0.12–3.14)	0.55
EGFR-TKIs				
No	802	0.4	1	
Yes	125	3.2	8.56 (2.48–29.5)	0.001
Platinum + antimetabolite				
No	842	0.7	1	
Yes	85	1.1	1.66 (0.20–13.9)	0.64

Multivariate analysis was not performed because the number of observed events was too small ($n = 7$).

OR, odds ratio; CI, confidence interval; PS, performance status; AST, aspartate transaminase; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors.

TABLE 4. Risk Factors for Treatment-Related Death from Concurrent Chemoradiotherapy

Factors	No. of Patients	Cumulative Incidence (%)	Univariate Analysis OR (95% CI)	p
Sex				
Female	44	2.3	1	
Male	201	5.2	2.41 (0.35–16.6)	0.37
Age (yr)				
<70	221	4.1	1	
≥70	24	12.5	3.07 (0.92–10.3)	0.069
PS				
0	114	5.3	1	
1	131	4.6	0.87 (0.29–2.62)	0.81
Smoking history				
No	32	3.2	1	
Yes	213	5.2	1.65 (0.23–11.9)	0.24
Fibrosis				
No	244	4.5	1	
Yes	1	100	22.2 (5.61–87.8)	<0.001
Emphysema				
No	215	4.7	1	
Yes	30	6.7	1.43 (0.33–6.25)	0.63
Location of the tumor				
Other lobes	189	3.7	1	
Lower lobe	56	8.9	2.41 (0.82–7.13)	0.11
Histology				
SCLC	54	1.9	1	
NSCLC	191	5.8	3.11 (0.47–20.6)	0.24
Hemoglobin (g/dl)				
≥13.7	146	4.1	1	
<13.7	99	6.1	1.48 (0.49–4.42)	0.48
Albumin (g/dl)				
≥3.7	198	4.5	1	
<3.7	47	6.4	1.40 (0.40–4.99)	0.6
Na (mEq/L)				
≥138	219	5.0	1	
<138	26	3.8	0.77 (0.11–5.60)	0.79
Clinical trial				
No	114	5.3	1	
Yes	131	4.6	0.87 (0.29–2.62)	0.81
Platinum + taxane				
No	224	4.5	1	
Yes	21	9.5	2.25 (0.46–11.0)	0.32
Platinum + vinca alkaloid				
No	77	5.2	1	
Yes	168	4.8	0.91 (0.27–3.13)	0.88

Multivariate analysis was not performed because only fibrosis was significant in univariate analysis.

OR, odds ratio; CI, confidence interval; PS, performance status; NSCLC, non-small cell lung cancer.

ported risk factors for interstitial lung disease in NSCLC patients treated with gefitinib are male sex, history of smoking, and underlying interstitial pneumonitis.[11] In this study, however, none of these factors were associated with TRD from chemotherapy. Another TRD from drug-induced lung injury occurred in a patient who received gemcitabine, but this patient was also free from underlying pulmonary disease or concomitant use of taxanes, which are reported to be risk factors for gemcitabine-associated interstitial lung disease.[12]

For patients who receive concurrent chemoradiotherapy, we would like to emphasize the previous finding that the

presence of evidence of pulmonary fibrosis on a plain chest x-ray is an extremely strong risk factor for TRD (OR = 166, 95% CI = 8.79–3122, $p < 0.001$).[1] In this study, only one patient with pulmonary fibrosis was identified, and pulmonary fibrosis was not included in the multivariate analysis because of the small number of patients with this factor, because we generally exclude patients with evidence of pulmonary fibrosis on the chest x-ray from consideration of concurrent chemoradiotherapy. This study also suggested that advanced age may be a risk factor for TRD. This is consistent with the results of previous studies.[1,13–15] The association between advanced age and fatal radiation-induced lung injury may be explained by the increased likelihood of these patients developing comorbid lung disease, particularly among patients with a history of heavy tobacco exposure. A meta-analysis of chemoradiotherapy using individual data from 1764 patients with locally advanced NSCLC showed that the benefit of chemoradiotherapy was obtained in elderly patients (≥71 years) as well as in younger patients. However, it might be assumed that patients who are included in such trials are fit patients with minimal comorbidities. In addition, despite the increase in toxicity that accompanied chemoradiotherapy in elderly patients, it seemed that they had disease control and survival rates similar to those of younger patients.[16]

In conclusion, TRD occurred in a total of 1.9% of patients and was caused in the majority of the cases by treatment-related lung injury. This finding is in clear contrast with previous reports which suggested that the principal cause of TRD in lung cancer patients was septic shock.

ACKNOWLEDGMENTS

The authors thank Ms. Mika Nagai for her assistance in the preparation of this manuscript.

REFERENCES

1. Ohe Y, Yamamoto S, Suzuki K, et al. Risk factors of treatment-related death in chemotherapy and thoracic radiotherapy for lung cancer. *Eur J Cancer* 2001;37:54–63.
2. Morittu L, Earl HM, Souhami RL, et al. Patients at risk of chemotherapy-associated toxicity in small cell lung cancer. *Br J Cancer* 1989;59: 801–804.
3. Radford JA, Ryder WD, Dodwell D, et al. Predicting septic complications of chemotherapy:an analysis of 382 patients treated for small cell lung cancer without dose reduction after major sepsis. *Eur J Cancer* 1992;29A:81–86.
4. Stephens RJ, Girling DJ, Machin D. Treatment-related deaths in small cell lung cancer trials: can patients at risk be identified? Medical Research Council Lung Cancer Working Party. *Lung Cancer* 1994;11: 259–274.
5. Sekine I, Noda K, Oshita F, et al. Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer. *Cancer Sci* 2004;95:691–695.
6. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1999;45:323–329.
7. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007; 18:317–323.
8. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol* 2002;20: 3054–3060.
9. Noda K, Nishiwaki Y, Kawahara M, et al; Japan Clinical Oncology Group. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;346:85–91.
10. Sekine I, Sumi M, Ito Y, et al. Retrospective analysis of steroid therapy for radiation-induced lung injury in lung cancer patients. *Radiother Oncol* 2006;80:93–97.
11. Ando M, Okamoto I, Yamamoto N, et al. Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. *J Clin Oncol* 2006;24:2549–2556.
12. Barlési F, Villani P, Doddoli C, et al. Gemcitabine-induced severe pulmonary toxicity. *Fundam Clin Pharmacol* 2004;18:85–91.
13. Yuen AR, Zou G, Turrisi AT, et al. Similar outcome of elderly patients in intergroup trial 0096: cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. *Cancer* 2000;89:1953–1960.
14. Schild SE, Stella PJ, Geyer SM, et al. North Central Cancer Treatment Group. The outcome of combined-modality therapy for stage III non-small-cell lung cancer in the elderly. *J Clin Oncol* 2003;21:3201–3206.
15. Schild SE, Stella PJ, Brooks BJ, et al. Results of combined-modality therapy for limited-stage small cell lung carcinoma in the elderly. *Cancer* 2005;103:2349–2354.
16. Aupérin A, Le Péchoux C, Pignon JP, et al; Meta-Analysis of Cisplatin/carboplatin based Concomitant Chemotherapy in non-small cell Lung Cancer (MAC3-LC) Group. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006;17:473–483.

Cancer Science
The official journal of the Japanese Cancer Association JCA

Brain metastases after definitive concurrent chemoradiotherapy in patients with stage III lung adenocarcinoma: Carcinoembryonic antigen as a potential predictive factor

Hidehito Horinouchi,[1,3] Ikuo Sekine,[1] Minako Sumi,[2] Yoshinori Ito,[2] Hiroshi Nokihara,[1] Noboru Yamamoto,[1] Yuichiro Ohe[1] and Tomohide Tamura[1]

[1]Division of Internal Medicine and Thoracic Oncology, [2]Division of Radiation Oncology, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan

(Received September 5, 2011/Revised December 26, 2011/Accepted January 5, 2012/Accepted manuscript online February 9, 2012/Article first published online February 20, 2012)

The predictive factors for the development of brain metastases in patients with stage III non-small-cell lung cancer receiving concurrent chemoradiotherapy remain unclear. Several studies have suggested adenocarcinoma as a predictive factor of brain relapses. In the current analysis, we tried to identify the factors associated with brain metastases in stage III lung adenocarcinoma. The demographic and clinical characteristics, site and date of recurrence, and date of death were reviewed in patients with unresectable stage III lung adenocarcinoma who underwent concurrent platinum-based chemoradiotherapy. In total, 116 patients were identified with a median (range) age of 57 (35–74) years. Of these, 86 (74%) were men, all patients had platinum-based chemotherapy, and 100 (86%) received a total dose of 60 Gy in 30 fractions as definitive thoracic radiotherapy. Of the 95 patients with disease progression or recurrence, 19 (16%) developed brain metastases as the sole site of initial recurrence. A total of 43 (37%) patients developed brain metastases at some time during follow-up. Time to brain metastases was significantly associated with the pretreatment carcinoembryonic antigen (CEA) value, with a hazard ratio (95% confidence interval) of 2.64 (1.39–5.02, $P = 0.003$). Patients who developed brain metastases as the first recurrent site had marginally better survival (log-rank test, $P = 0.066$) than those with metastases other than brain. In conclusion, stage III lung adenocarcinoma patients with an elevated CEA value before treatment had a higher risk of developing brain metastases after chemoradiotherapy. Further effort is mandatory to control brain metastases in this patient population by a therapeutic strategy based on the tumor histology and pretreatment CEA value. (*Cancer Sci* 2012; 103: 756–759)

Recent advances in chemotherapy added to radiotherapy have dramatically improved the prognosis of patients with inoperable stage III non-small-cell lung cancer (NSCLC). The current standard treatment for these patients, concurrent thoracic radiotherapy and platinum-based chemotherapy, yields a 5-year survival rate of 16–23%, with acceptable acute and late toxicity.[1,2] However, many patients still die of recurrent disease. Brain metastases, as well as loco-regional recurrences, are the most frequent types of initial failure. Observational studies in patients with stage III NSCLC who underwent chemoradiotherapy with or without surgery showed that the first recurrent site was the brain in only 8–35% of patients, and brain and other sites in 4–10% of patients, resulting in brain metastases as the first recurrent site in 17–43% of patients.[1,3,4] Prophylactic cranial irradiation (PCI) has been tried to eradicate undetectable micrometastases before they become clinically apparent. Prospective randomized trials comparing PCI and observation in patients with locally advanced NSCLC treated by thoracic radiotherapy with or without chemotherapy showed a significant reduction in the development of brain metastases, but no survival benefit in the PCI arms.[5–8] Thus, PCI is not indicated for all patients with stage III NSCLC treated with chemoradiotherapy, but it would improve prognosis if used to treat selected patients who are more likely to develop brain metastases. Several clinical factors have been identified to predict brain metastases in locally advanced NSCLC patients, but they are inconsistent among studies.[9–11] Of these clinical factors, adenocarcinoma histology was suggested to have a higher risk of brain relapses.[11–16] The objectives of this study were to identify factors associated with development of brain metastases in stage III adenocarcinoma patients who received concurrent chemoradiotherapy and to identify potential candidates for intervention to reduce brain relapses.

Materials and Methods

Patient selection. Patients with unresectable stage III lung adenocarcinoma who underwent concurrent platinum-based chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital (Tokyo, Japan) between 1994 and 2005 were eligible for this study. Patients treated with sequential chemotherapy and thoracic radiotherapy were excluded because we have considered the standard care for the stage III NSCLC patients to be concurrent chemoradiotherapy, and therefore, the sequential treatment was given only to patients with poor general condition or to patients who had a tumor too large for radiotherapy initially but decreasing enough for radiotherapy after chemotherapy. All patients underwent a systematic pretreatment evaluation and standardized staging procedures, which included physical examination, chest X-rays, CT scans of the chest and abdomen, a CT scan or MRI of the brain, a bone scintigram, and blood examinations including tumor markers.

Data collection and statistical analyses. Sex, age, performance status, body weight loss, carcinoembryonic antigen (CEA), clinical stage, nodal status, chemotherapy regimens, total dose of radiotherapy, tumor responses to treatment, sites and date of recurrence, and date of death were obtained from a retrospective medical chart review. As a routine clinical practice, tumor markers including CEA were examined in every patient eligible for chemotherapy and chemoradiotherapy before, during,

[3]To whom correspondence should be addressed.
E-mail: hhorinou@ncc.go.jp

doi: 10.1111/j.1349-7006.2012.02217.x

and just after the initiation of treatment. Receiver operator characteristic (ROC) curves and the corresponding area under the curve (AUC) were used to evaluate the cut points of CEA values to predict brain metastasis as the sole, or one of the first, relapse sites. Tumor histological classification was based on the criteria of the World Health Organization.[17] Patients were staged using the 6th edition of Union for International Cancer Control TNM classification for lung cancer.

Time to brain metastases was measured from the start of initial chemoradiotherapy to when the brain metastases were confirmed by a brain CT scan or MRI. Although we monitor brain metastases regularly as a routine follow-up imaging study after chemoradiotherapy, there might be diversity in the frequency and methods of monitoring. Patients who did not develop brain metastases at the last follow-up were censored at that time. Time to brain metastases was evaluated using the Kaplan–Meier method, the log–rank test, and Cox's proportional hazard model.

Sex, age, performance status, body weight loss, smoking status, CEA value, stage, T-factor, and nodal status were included as covariates in the multivariate analyses (Cox's proportional hazard model analyses). All of these analyses were carried out using STATA 11.1 software for Windows (StataCorp, College Station, TX, USA).

This study was approved by the president of the National Cancer Center Hospital. The institutional review board and ethics review committee decided to exempt this study from the usual review process because of its retrospective nature.

Results

In total, 116 patients were identified. Females accounted for 26% of the study group. The median age was 57 years. Almost all patients were in good general condition with a performance status of 0–1. Of the 116 patients, 63% had tumor factor (T-factor) 1–2 disease and 93% had nodal factor (N-factor) 2–3 disease. All patients received platinum-based chemotherapy, and 86% received a total dose of 60 Gy in 30 fractions as definitive thoracic radiotherapy (Table 1). The response rate was 82%, median survival time was 24.5 months, and the 5-year survival rate was 24% in this study group.

Disease progression or recurrence was noted in 95 (82%) patients. Brain metastases as the sole site of initial recurrence were noted in 19 (16%) patients, and both brain and other sites were involved in 17 (15%) patients (Table 2). Of the 19 patients who had isolated brain failure, 10 developed recurrences subsequently at additional sites other than the brain, three died of progressive brain metastases without progression in other sites, and two developed meningitis carcinomatosa. Another two patients also died, but the cause of death was not identified because they were lost to follow-up. Brain metastases were controlled by radiotherapy in the other two patients.

A total of 43 patients (37%) developed brain metastases at some time during the course of follow-up. We examined various cut points of CEA value and found 20 ng/mL gave a relatively better AUC (56.2%) by the ROC analysis. Time to brain metastasis was significantly associated with pretreatment CEA value. The responses of CEA during chemoradiotherapy and the CEA level just after chemoradiotherapy did not have significant correlation with brain relapses. The multivariate analysis using Cox's proportional hazard model showed that the hazard ratio (95% confidence interval [CI], *P*-value) of a CEA value $\geq$20 ng/mL was 2.64 (1.39–5.02, $P = 0.003$, Table 3) compared to a CEA value of < 20 ng/mL. Sex, age, performance status, body weight loss, smoking history, T-factor, nodal status, and stage were not associated with the time to brain metastasis (Table 3). Percentages of patients who developed brain metastases at 12 and 24 months were 37% and 67% in patients with elevated CEA value, and 21% and 32% in the others (log–rank test, $P = 0.01$), respectively (Fig. 1).

Overall survival according to the first relapse site is shown in Figure 2. Patients who developed brain metastases only as the first recurrent site had marginally better survival (log–rank test, $P = 0.066$) compared to those with metastases other than brain.

Table 1. Characteristics of patients with stage III lung adenocarcinoma who participated in this study ($n = 116$)

Characteristic	*n*	%
Sex		
Female	30	26
Male	86	74
Age (years)		
Median (range)	57 (35–74)	NA
Performance status		
0	36	31
1	79	68
2	1	1
Body weight loss		
≤4.9%	95	82
≥5.0%	21	18
Smoking (pack-years)		
≤10	29	25
≥11	87	75
CEA (ng/mL)		
< 20	89	77
≥20	27	23
Stage		
IIIA	57	49
IIIB	59	51
T-factor		
1–2	73	63
3–4	43	37
N-factor		
0–1	8	7
2–3	108	93
Chemotherapy type		
Cisplatin + vinorelbine	75	65
Cisplatin + vindesine + mitomycin	26	22
Nedaplatin + paclitaxel	8	7
Other combinations	7	6
Total radiation dose (Gy)		
60	100	86
<60	16	14

CEA, carcinoembryonic antigen; NA, not applicable; N-factor, nodal factor; T-factor, tumor factor.

Table 2. Sites of first recurrence in patients with stage III lung adenocarcinoma ($n = 95$)

Site of recurrence	*n*	%
Relapses including brain	36	38
Brain only	19	20
Brain and other sites	17	18
Sites other than brain	56	59
Unknown	3	3

Discussion

This study showed that CEA values before treatment were associated with time to brain metastasis in patients with stage III

Table 3. Time to brain metastases according to clinical factors in patients with stage III adenocarcinoma: Cox proportional hazard model analysis

Characteristic	Cox proportional hazard model (HR [95% CI])			
	Univariate	*P*-value	Multivariate	*P*-value
Sex				
Male	1	0.03	1	0.660
Female	2.00 (1.08–3.69)		1.24 (0.48–322)	
Age (years)				
≤57	1	0.17	1	0.110
≥58	0.65 (0.34–1.21)		0.58 (0.30–1.13)	
Performance status				
0	1	0.96	1	0.830
1–2	0.98 (0.53–1.83)		0.92 (0.44–1.92)	
Body weight loss (%)				
≤4.9	1	0.91	1	0.630
≥5.0	1.05 (0.47–2.36)		1.25 (0.51–3.05)	
Smoking (pack-years)				
≤10	1	0.01	1	0.290
≥11	0.43 (0.23–0.79)		0.58 (0.21–1.59)	
CEA				
<20	1	0.01	1	0.003
≥20	2.17 (1.17–3.99)		2.64 (1.39–5.02)	
T-factor				
1–2	1	0.39	1	0.880
3–4	0.75 (0.39–1.44)		0.84 (0.37–1.90)	
N-factor				
0–1	1	0.33	1	0.520
2–3	2.02 (0.49–8.38)		1.40 (0.50–3.88)	
Stage				
IIIA	1	0.93	1	0.770
IIIB	1.03 (0.57–1.87)		0.85 (0.30–2.46)	

CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; N-factor, nodal factor; T-factor, tumor factor.

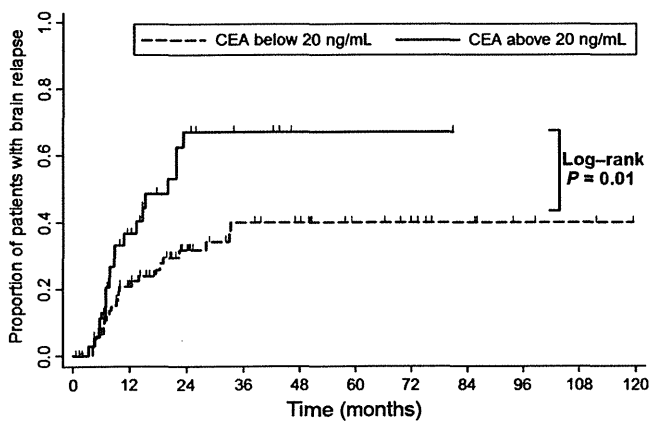

Fig. 1. Cumulative incidence of brain relapse in patients with stage III lung adenocarcinoma by carcinoembryonic antigen (CEA) value (ng/mL). Percentages of patients who developed brain metastases at 12 and 24 months were 37% and 67% in patients with elevated CEA value, and 21% and 32% in the others (log-rank test, $P = 0.01$), respectively.

lung adenocarcinoma who received concurrent platinum-based chemotherapy and thoracic radiotherapy. This is the first report showing that the CEA value might be associated with a higher risk of brain metastases in locally advanced lung adenocarcinoma.

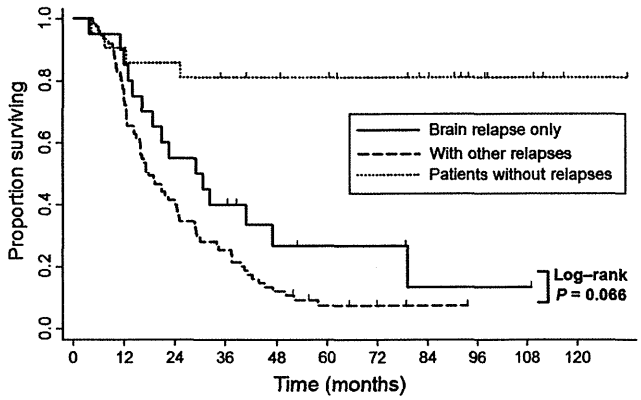

Fig. 2. Overall survival in patients with stage III lung adenocarcinoma according to the first relapse site. Dashed line, patients who developed extracranial recurrence with or without brain metastases; thick line, patients who developed brain relapse only; dotted line, patients who had no relapse. Patients who developed brain metastases as the first recurrent site had marginally better survival (log-rank test, $P = 0.066$) compared to those with metastases other than brain.

The median survival time (24.5 months) in the present study seemed better than the results observed in the study of Cox *et al.* (median survival time, 12.2–18.9 months) that included four clinical trials involving chemoradiotherapy.[12,18–21] The proportion of the participants whose first recurrent sites included brain metastases (38%, Table 2) in this study was substantially higher than the results observed in the analysis of Cox *et al.*[12] (16% with adenocarcinoma). Because the concurrent chemoradiotherapy with better survival failed to improve the proportion of brain relapses, the importance of the prevention of brain metastases has increased in this patient group. Furthermore, overall survival in patients who developed brain metastases as the sole site of the initial recurrence was marginally better than in those with metastases to other sites (log-rank, $P = 0.066$, Fig. 2) in our observation of patients with locally advanced lung adenocarcinoma. In fact, some patients with only brain relapses as the first recurrent site survived without further metastases after local treatment for the brain lesions.

Prospective randomized trials evaluating the effect of PCI in patients with locally advanced NSCLC after chemoradiotherapy showed a significant reduction in the development of brain metastases, but no survival benefit in the PCI arms.[5–8] Thus, it is necessary to identify the clinical factors of patients who are more likely to develop brain metastases and would be good candidates for PCI. In retrospective analyses of patients with locally advanced NSCLC, adenocarcinoma histology was suggested to have a higher risk of brain relapses and be worthy of more attention concerning brain metastases.[11–16] Therefore, locally advanced lung adenocarcinoma was specifically analyzed to identify clinical factors predicting brain metastases.

Among patients with disseminated adenocarcinoma without indications for definitive thoracic radiotherapy, a high CEA value (over 40 ng/mL) before treatment might be associated with a higher risk of brain relapses.[22] The present study involving patients with locally advanced lung adenocarcinoma after chemoradiotherapy showed that the CEA value was significantly associated with the time to brain metastasis on multivariate analysis (Table 3). This result suggested that patients with stage III lung adenocarcinoma and elevated CEA values might be good candidates for interventions to prevent brain metastases.

This study had several limitations. First, the number of patients included in the analysis was relatively small because we selected patients with stage III lung adenocarcinoma who

doi: 10.1111/j.1349-7006.2012.02217.x

underwent concurrent chemoradiotherapy. Second, there might be diversity in the frequency and methods of monitoring brain metastases because of the retrospective nature of the analysis. Third, we could not determine significant factors to predict solitary brain relapses which might be cured by prophylactic brain intervention, mainly because the number of patients with solitary brain relapse was too small for efficient statistical analysis.

In conclusion, the present analysis implies that patients with elevated CEA values before treatment have a higher risk of developing brain metastases after chemoradiotherapy for locally advanced lung adenocarcinoma. Further effort is mandatory to evaluate the clinical relevance of CEA value to predict brain relapses and select candidates for prophylactic interventions in future prospective trials.

Acknowledgment

We thank Ms. Mika Nagai for her assistance in the preparation of this manuscript.

Disclosure Statement

The authors have no conflicts of interest.

References

1 Furuse K, Fukuoka M, Kawahara M *et al.* Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999; **17**: 2692–9.
2 Kiura K, Takigawa N, Segawa Y *et al.* Randomized phase III trial of docetaxel and cisplatin combination chemotherapy versus mitomycin, vindesine and cisplatin combination chemotherapy with concurrent thoracic radiation therapy for locally advanced non-small cell lung cancer:OLCSG 0007. *J Clin Oncol* 2008; **26**(Suppl): 400s (abstr7515).
3 Albain KS, Rusch VW, Crowley JJ *et al.* Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. *J Clin Oncol* 1995; **13**: 1880–92.
4 Chen AM, Jahan TM, Jablons DM, Garcia J, Larson DA. Risk of cerebral metastases and neurological death after pathological complete response to neoadjuvant therapy for locally advanced nonsmall-cell lung cancer: clinical implications for the subsequent management of the brain. *Cancer* 2007; **109**: 1668–75.
5 Cox JD, Stanley K, Petrovich Z, Paig C, Yesner R. Cranial irradiation in cancer of the lung of all cell types. *JAMA* 1981; **245**: 469–72.
6 Umsawasdi T, Valdivieso M, Chen TT *et al.* Role of elective brain irradiation during combined chemoradiotherapy for limited disease non-small cell lung cancer. *J Neurooncol* 1984; **2**: 253–9.
7 Russell AH, Pajak TE, Selim HM *et al.* Prophylactic cranial irradiation for lung cancer patients at high risk for development of cerebral metastasis: results of a prospective randomized trial conducted by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1991; **21**: 637–43.
8 Gore EM, Bae K, Wong SJ *et al.* Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. *J Clin Oncol* 2011; **29**: 272–8.
9 Robnett TJ, Machtay M, Stevenson JP, Algazy KM, Hahn SM. Factors affecting the risk of brain metastases after definitive chemoradiation for locally advanced non-small-cell lung carcinoma. *J Clin Oncol* 2001; **19**: 1344–9.
10 Carolan H, Sun AY, Bezjak A *et al.* Does the incidence and outcome of brain metastases in locally advanced non-small cell lung cancer justify prophylactic cranial irradiation or early detection? *Lung Cancer* 2005; **49**: 109–15.
11 Gaspar LE, Chansky K, Albain KS *et al.* Time from treatment to subsequent diagnosis of brain metastases in stage III non-small-cell lung cancer: a retrospective review by the Southwest Oncology Group. *J Clin Oncol* 2005; **23**: 2955–61.
12 Cox JD, Scott CB, Byhardt RW *et al.* Addition of chemotherapy to radiation therapy alters failure patterns by cell type within non-small cell carcinoma of lung (NSCCL): analysis of radiation therapy oncology group (RTOG) trials. *Int J Radiat Oncol Biol Phys* 1999; **43**: 505–9.
13 Andre F, Grunenwald D, Pujol JL *et al.* Patterns of relapse of N2 nonsmall-cell lung carcinoma patients treated with preoperative chemotherapy: should prophylactic cranial irradiation be reconsidered? *Cancer* 2001; **91**: 2394–400.
14 Keith B, Vincent M, Stitt L *et al.* Subsets more likely to benefit from surgery or prophylactic cranial irradiation after chemoradiation for localized non-small-cell lung cancer. *Am J Clin Oncol* 2002; **25**: 583–7.
15 Bajard A, Westeel V, Dubiez A *et al.* Multivariate analysis of factors predictive of brain metastases in localised non-small cell lung carcinoma. *Lung Cancer* 2004; **45**: 317–23.
16 Mamon HJ, Yeap BY, Janne PA *et al.* High risk of brain metastases in surgically staged IIIA non-small-cell lung cancer patients treated with surgery, chemotherapy, and radiation. *J Clin Oncol* 2005; **23**: 1530–7.
17 Travis WD. *Pathology & Genetics of Tumours of the Lung, Thymus And Heart, World Health Organization Classification of Tumours,* 1st edn. Switzerland: WHO Press, 2004.
18 Sause WT, Scott C, Taylor S *et al.* Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst* 1995; **87**: 198–205.
19 Byhardt RW, Scott CB, Ettinger DS *et al.* Concurrent hyperfractionated irradiation and chemotherapy for unresectable nonsmall cell lung cancer. Results of Radiation Therapy Oncology Group 90-15. *Cancer* 1995; **75**: 2337–44.
20 Lee JS, Scott C, Komaki R *et al.* Concurrent chemoradiation therapy with oral etoposide and cisplatin for locally advanced inoperable non-small-cell lung cancer: radiation therapy oncology group protocol 91-06. *J Clin Oncol* 1996; **14**: 1055–64.
21 Komaki R, Scott C, Ettinger D *et al.* Randomized study of chemotherapy/radiation therapy combinations for favorable patients with locally advanced inoperable nonsmall cell lung cancer: Radiation Therapy Oncology Group (RTOG) 92-04. *Int J Radiat Oncol Biol Phys* 1997; **38**: 149–55.
22 Arrieta O, Saavedra-Perez D, Kuri R *et al.* Brain metastasis development and poor survival associated with carcinoembryonic antigen (CEA) level in advanced non-small cell lung cancer: a prospective analysis. *BMC Cancer* 2009; **9**: 119.

Ann Surg Oncol (2012) 19:677–683
DOI 10.1245/s10434-011-1983-x

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Clinicopathological Features and Prognostic Factors of Adenocarcinoma of the Esophagogastric Junction According to Siewert Classification: Experiences at a Single Institution in Japan

Yuichi Hosokawa, MD[1,2], Takahiro Kinoshita, PhD[1], Masaru Konishi, MD[1], Shinichiro Takahashi, PhD[1], Naoto Gotohda, PhD[1], Yuichiro Kato, MD[1], Hiroyuki Daiko, MD[1], Mitsuyo Nishimura, MD[1], Kenji Katsumata, PhD[2], Yasuyuki Sugiyama, PhD[2], and Taira Kinoshita, PhD[1]

[1]Department of Surgical Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [2]Department of Surgery, University Hospital of Mizonokuchi, Teikyo University School of Medicine, Kawasaki, Japan

ABSTRACT

Background. Treatment strategy for adenocarcinoma of the esophagogastric junction (AEG) remains controversial. The aims of this study are to evaluate results of surgery for AEG, to clarify clinicopathological differences according to the Siewert classification, and to define prognostic factors.

Methods. We retrospectively analyzed 179 consecutive patients with Siewert type I, II, and III AEG who underwent curative (R0) resection at the National Cancer Center Hospital East between January 1993 and December 2008.

Results. Patients with AEG were divided according to tumor: 10 type I (5.6%), 107 type II (59.8%), and 62 type III (34.6%). Larger, deeper tumors and nodal metastasis were more common in type III than type II tumors. No significant differences were seen in 5-year survival rates among the three types: type I (51.4%), type II (51.8%), and type III (62.6%). Multivariate analysis showed that depth of tumor and mediastinal lymph node metastasis were independent prognostic indicators. The recurrence rate for patients with mediastinal lymph node metastasis was 87.5%. The risk factors for mediastinal lymph node metastasis were length of esophageal invasion and histopathological grade.

Conclusions. Mediastinal lymph node metastasis and tumor depth were significant and independent factors for poor prognosis after R0 resection for AEG. Esophageal invasion and histopathological grade were significant and independent factors for mediastinal lymph node metastasis.

In Western countries, incidence of adenocarcinoma of the esophagogastric junction (AEG) is rapidly increasing. This trend has not occurred in Eastern countries.[1–4] Siewert's classification into three types of tumors, proposed in 1996, defines AEG tumors according to the location of the tumor center in relation to the anatomical esophagogastric junction (EGJ) line. Characteristics differ for each type, making the classification useful for determining optimal treatment strategies.[5]

Surgical resection with lymphadenectomy is the mainstay of treatment for AEG. Though AEG consists of tumor arising from the proximal stomach and distal esophagus, there are various surgical options. Factors that surgeons need to consider are whether the esophagectomy should be subtotal or distal and if it should be combined with total or proximal gastrectomy via transhiatal or transthoracic approach. Currently, Siewert's classification is used to determine treatment strategy, but the approach is still controversial. An optimal surgical strategy has yet to be established.

The distribution of the three types of AEG differs markedly between Eastern and Western countries. In Eastern countries, type II and III cancers are more common than type I. In Western countries, however, the distribution is nearly equal between the three types of adenocarcinoma.[3,6,7] Only a few studies have addressed clinicopathological features of AEG in Japan, and most involved only type II and III cancers.[8,9] One reason for this might be that type I patients at most Japanese institutions are likely to be treated by the

First Received: 14 January 2011;
Published Online: 6 August 2011

Y. Hosokawa, MD
e-mail: ryu37072002@yahoo.co.jp