CT features in patients with MPA of the lung are an air bronchogram, areas of ground-glass attenuation, areas of air-space consolidation, and interlobular septal thickening. An air bronchogram, likely caused by parenchymal invasion by tumor cells and mucus secretion, was present to some degree in 37 study patients.

Areas of ground-glass attenuation were present in 36 (75.0%) of our 48 patients with MPA of the lung and correlated pathologically with lepidic growth of the tumor along alveolar septa (replacement growth) or with the presence of mucus. These findings are similar to those reported for mucinous BAC in previous studies,8-12 which also showed that areas of ground-glass attenuation can progress to areas of air-space consolidation on sequential CT scans. Multivariate analysis showed no association between ground-glass attenuation and the presence or absence of intrapulmonary metastases or prognosis, however.

Areas of air-space consolidation identified in 75.0% of our cases correlated pathologically with a mixture of tumor cells, mucus, and decreased air content in alveolar spaces. Our results suggest that areas of air-space consolidation can result from dense growth of tumor cells or accumulation of mucus within the lesion. In the current study, a significant difference was found in occurrence of areas of air-space consolidation among the patients with and without intrapulmonary metastases. These results are in keeping with those for mucinous BAC in previously published studies.8-12 Multivariate analysis showed that areas of air-space consolidation are not an independent predictor of intrapulmonary metastasis and prognosis, however.

Bubble-like lucencies on thin-section CT are characterized by the presence of small focal areas of air attenuation within the lesion. The presence of bubble-like lucencies in our study was similar to that reported for mucinous BAC in another study.11 In our study, bubble-like lucencies on thin-section CT corresponded histologically to a mixture of mucus, tumor cells, thickened bronchi or bronchioles, and small amounts of air in alveolar spaces. Although bubble-like lucencies were seen in 47.9% of our cases, this finding was not a predictor of intrapulmonary metastasis or survival.

Centrilobular nodules were present in 45.8% of our cases. This prevalence is in agreement with that reported for mucinous BAC in previous studies.8-12 In our study, 81.8% of patients with centrilobular nodules had intrapulmonary metastases. Multivariate analysis demonstrated that centrilobular nodules were an independent predictor of poor prognosis. These results may reflect multifocal abnormalities of mucus lining and true metastases on CT.

Mucus plugging was identified in 39.6% of our cases on thin-section CT. This finding had a significant association with the presence of intrapulmonary metastases and survival in univariate analysis. Multivariate analysis demonstrated that mucus plugging was not an independent predictor of poor prognosis, however. Mucus plugging is considered to be more nonspecific compared with centrilobular nodules, which can manifest the presence of true metastases on thin-section CT.

The limitation of our study is that bias was probably introduced by including 45.8% of patients who had intrapulmonary metastases and underwent surgical treatment and chemotherapy. These patients had the smallest rate of 5-year disease-free survival, leading to possible selection bias that would tend to overestimate the prevalence of intrapulmonary metastases.

In conclusion, the presence of centrilobular nodules and mucus plugging on thin-section CT is associated with a greater likelihood of intrapulmonary metastases. The presence of centrilobular nodules is also a predictor of a poor prognosis in patients with MPA of the lung.

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Key Words: mucin-producing tumor; adenocarcinoma; lung; computed tomography

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特集

癌緩和医療

癌緩和医療におけるInterventional radiology (IVR)

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Interventional radiology is image-guided percutaneous treatment and it can revise intra-physical abnormal structural or physiological conditions without major invasion. Thus, interventional radiology has much potential for better management of various symptoms caused by cancer progression, such as ductal stenosis, fluid collection, unremoval tubes, etc. Additionally, using techniques of interventional radiology, many kinds of procedure for palliative care can be done more safety, easier and less invasive. Medical stuffs who are concerned in palliative care should have knowledge about interventional radiology and make full use it for their daily works.

Key words: Interventional radiology, Palliative care, QOL, Metallic stent, Drainage
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はじめに

インターベンショナル・ラジオロジー（Interventional radiology）は従来画像診断に用いられていた装置や器具を用いて，画像誘導下に外科的に身体を開けることなく治療を行うものである．Interventional radiologyの語源はMargulisが1967年に提唱したInterventional Diagnostic Radiology[1]に由来しており，現在のような体系づけとInterventional radiologyという言葉の紹介は1976年にWallaceがCancerに載せた総説[2]に始まる．日本語訳として普及したものがないため，インターベンショナル・ラジオロジーあるいは略してIVR, IRと呼称される場合が多い（本稿では以下IVRと略す）．わが国では1980年代より普及し，その後画像診断機器ならびに器材の急速な進歩に伴い広い範囲で活用されるに至っている．その特長は何といっても外科治療に比べ侵襲の少ない点であり，このためQOLが重視されるがん治療での活用範囲は広く，緩和医療（active palliation）において重要な役割を担うに至っている．本稿では癌緩和医療におけるIVRについて述べる．

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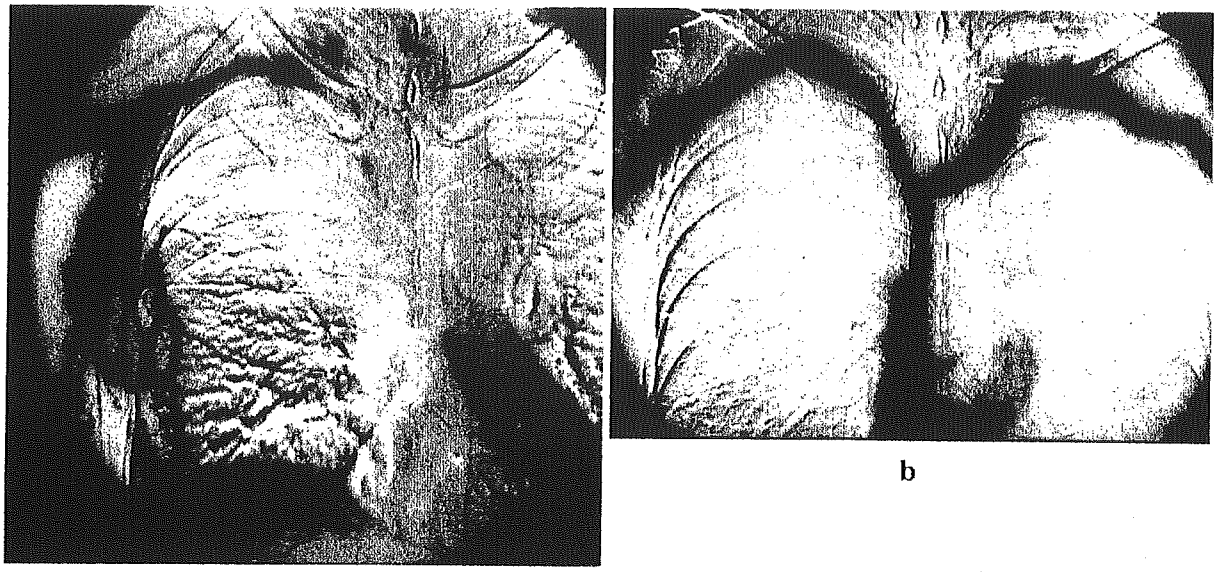
1. 癌緩和医療におけるIVRの原理

IVRにおける画像誘導下での病巣への到達は，カテーテルを用いて血管をはじめとする既存の管腔臓器を介する場合と，針を用いて穿刺により直線的に到達する場合とに大別される．到達した病巣部で行う処置は，液体・気体の注入，吸引あるいは移動，器具を用いた管腔臓器の閉塞，拡張，凝固，凍結などであり，数多いIVRも基本的にはこれらの手技の組み合わせによって行われ



a　b

図1　上大静脈症候群に対するステント留置
a：肺がんにより右鎖骨下静脈-上大静脈は閉塞し，右上肢から注入された造影剤は右房に戻ることなく，胸壁の静脈に逆流している．
b：右鎖骨下静脈-上大静脈へのステント留置により，左右上肢から注入された造影剤は速やかに右房に還流している．

るものである．癌緩和医療におけるIVRはこれらの手技を用いて，癌の進展により身体の正常構築や生理的状態が破綻して生じた「異常な状態」をより正常に近い，より生理的な状態に戻すことにより，その「異常な状態」に起因する症状を軽減，消失させようとするものである．このため，症状の原因自体に対する治療という点で，他の症状を対象とする治療とは原理的に大きく異なっている．

2.　管腔臓器の狭窄・閉塞に対する治療

身体は血管，消化管，気管，胆管など基本的に管腔臓器の集合体であり，このため，癌の進展によりこれらの管腔臓器が狭窄・閉塞することにより種々の症状が発現する．IVRによる治療はこれら管腔臓器の狭窄・閉塞をメタリック・ステントの留置により解除するもので，管腔臓器の生理的機能を回復することにより症状を軽減するものである．現在対象とされる管腔臓器は，上下大静脈，気道，食道を主とする上部消化管，直腸に近い下部消化管，胆道などである．

1）大静脈の狭窄に対する治療（図1）

肺癌，乳癌などによる上大静脈症候群，肝腫瘍の増大などにより生じた下大静脈の狭窄に起因する腹水・下肢の浮腫などが対象となる．通常は局所麻酔下に大腿静脈から挿入したカテーテルを介して，狭窄部にステントを留置する（図1, 2）．119症例を対象とした厚生省がん研究助成金（荒井班）[3~7]による共同研究では，技術的成功率100%，重篤な合併症はなく，明らかな臨床症状の改善が84%で得られている．本治療は大静脈系の狭窄・閉塞に対する唯一の原因除去療法であり，その安全性，有効性の点からも試みるべき治療法といえる．

2）気道の狭窄に対する治療（図2）

メタリック・ステントの挿入により気道狭窄に伴う呼吸困難を改善するものであり，狭窄部が気管，左右主気管支レベルで末梢肺の機能が維持されている場合が対象となる．89例を対象に行われた厚生省がん研究助成金（荒井班）による共同研究では，技術的成功率100%，重篤な合併症はなく，臨床症状の改善が83%にみられている．うち60%の症例ではHugh-Jones分類で2段階以上の改善が得られ，治療前人工呼吸器が使用されていた7例全例が呼吸器管理から離脱，また，術前酸素吸入を要した29例中17例が酸素

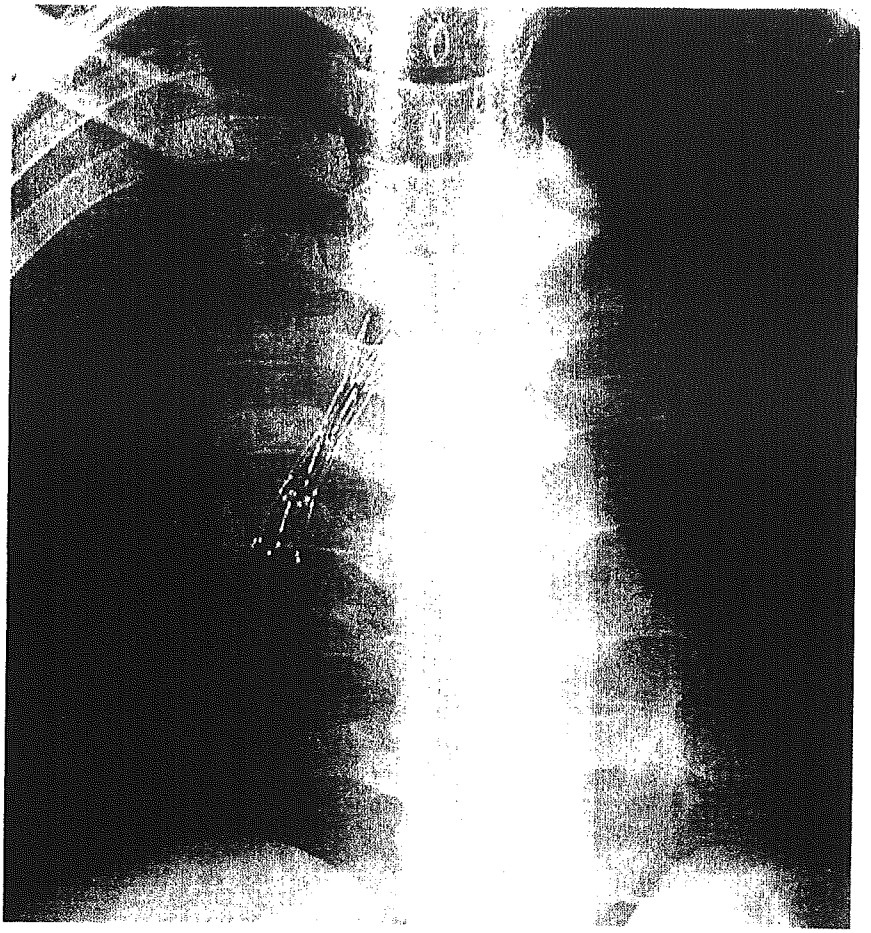


図2　右主気管支狭窄に対し挿入されたステント
ステントにより右上気管支の狭窄部は拡張し，十分な口径が確保されている．

不要となっている．

3）胆道の狭窄に対する治療

胆道の狭窄に対する治療は，現在最も多くメタリック・ステントが使用されている領域であり，PTCDルートを介して挿入する方法と内視鏡的に逆行性に挿入する方法とがある．メタリック・ステントは側枝を閉塞しないため，肝門部胆肝癌のような複数の胆管枝が狭窄している症例にも対応できる．398例を対象に行われた厚生省がん研究助成金（荒井班）による共同研究では，技術的成功率100%，重篤な合併症はなく，90%の症例で外瘻チューブが抜去されている．累積開存期間は6カ月74%，1年55%，2年32%であった．

4）消化管の狭窄に対する治療（図3）

消化管の狭窄は蠕動運動があるためメタリック・ステントが移動しやすく，また圧排による粘膜面のびらんや潰瘍形成，穿孔などの危険性があるため，他の領域に比べ合併症が問題となる頻度が高い．現在，最も汎用されているのは食道あるいは食道-胃・空腸吻合部の狭窄に対する治療であり，この他に直腸，左半結腸，十二指腸などが対象とされている．食道狭窄の場合にはcovered stentが用いられる場合が多い．183例を対象とした厚生省がん研究助成金（荒井班）による共同研究では，技術的成功率97%，臨床症状の改善が84%にみられている．反面，縦隔炎などの重篤な合併症がみられ，8%の症例の死因がメタリック・ステント留置と関連したものであった．消化管狭窄に対するメタリック・ステント留置はがん末期症例の経口摂取を可能にする点で有用である反面，重篤な合併症の危険性が少なくないため，施行にあたっては十分な検討と危険性についての情報開示を徹底する必要がある．

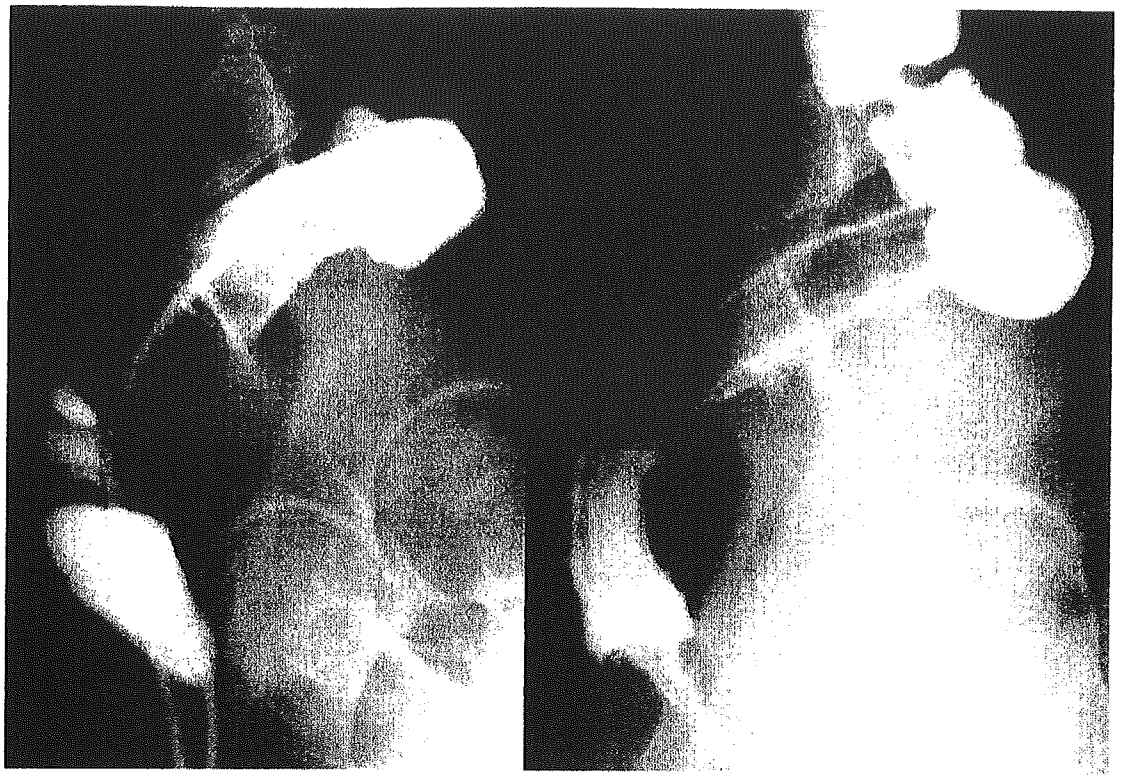


図3　腹膜播種による直腸狭窄に対し留置された直腸ステント

3. チューブ留置からの開放

病態の点で止むを得ないとはいえ，長期に留置されるチューブは患者のQOLを著しく低下させるものであり，これらのチューブの抜去を可能とすることも癌緩和医療におけるIVRの重要な役割のひとつである．経鼻チューブ，輸液や薬剤投与のための中心静脈カテーテル，ドレナージチューブなどがその対象となる．

1）経皮経食道胃管挿入術（図4）

経腸栄養あるいは消化管閉塞に対するドレナージ目的で留置される経鼻チューブの苦痛を解除するために，頸部食道を直接穿刺し，ここからチューブを留置するものである．イレウスチューブを挿入することも可能であり，改善の見込みのない末期の癌性腹膜炎によるイレウス症例などがきわめてよい適応と言える．

2）中心静脈カテーテルの埋め込み

治療のための血管確保としての観点から中心静脈カテーテルにポート（リザーバー）を接続して皮下に埋め込み，カテーテル管理の煩わしさや感染リスクを減らそうとするもので，すでに広く行われている．特に，在宅での輸液を継続する場合や持続的な抗癌剤投与を外来ベースで行う場合には必須の処置と言える．

3）ドレナージルートの内瘻化（図5）

胆管狭窄におけるメタリック・ステントによる内瘻化や尿管狭窄におけるW-Jカテーテルによる内瘻化など以外に遷延する膿瘍なども本来の流出下流側の狭窄が原因である場合には，メタリック・ステントによる内瘻化でチューブを抜去できる場合がある．

4）骨転移による疼痛に対する治療（図6）

骨転移による疼痛や骨変形の進行を阻止する目的で，経皮的に骨転移巣へ針を刺入して骨セメントを注入する方法であり，下部胸椎，腰椎，骨盤骨などが対象となる．骨の強化による疼痛の軽減に加え，病的骨折を予防する点も期待されるが，放射線照射や化学療法など既存の抗癌治療との併用についての検討は未だなされていない．この他にラジオ波凝固を用いた骨転移の疼痛に対する治療も行われているが，未だ臨床試験の段階である．

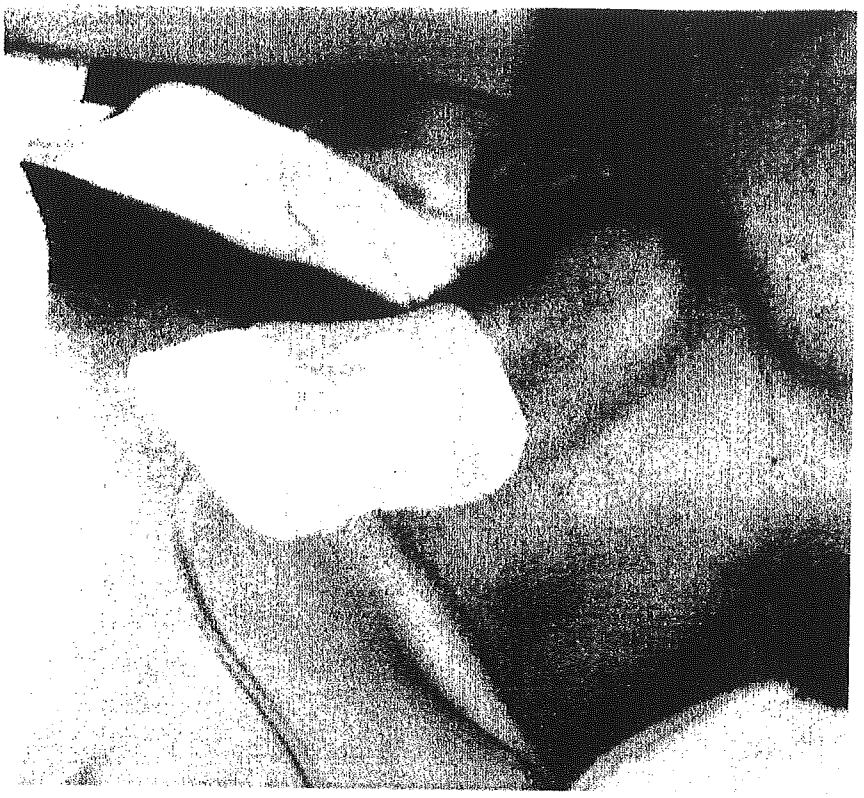


図4　頸部食道から直接挿入された胃管

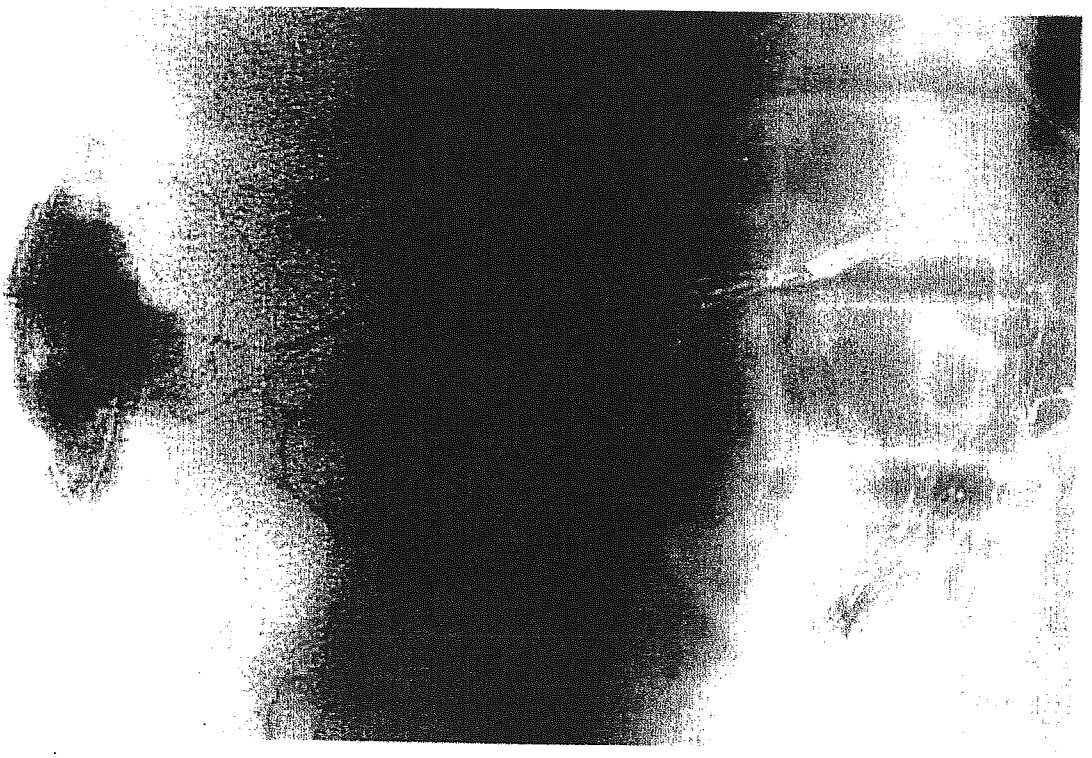


図5　遷延する肝膿瘍に対する内瘻化

当該部位の胆管狭窄をステントで拡張することにより，肝膿瘍は速やかに改善しチューブが抜去された．

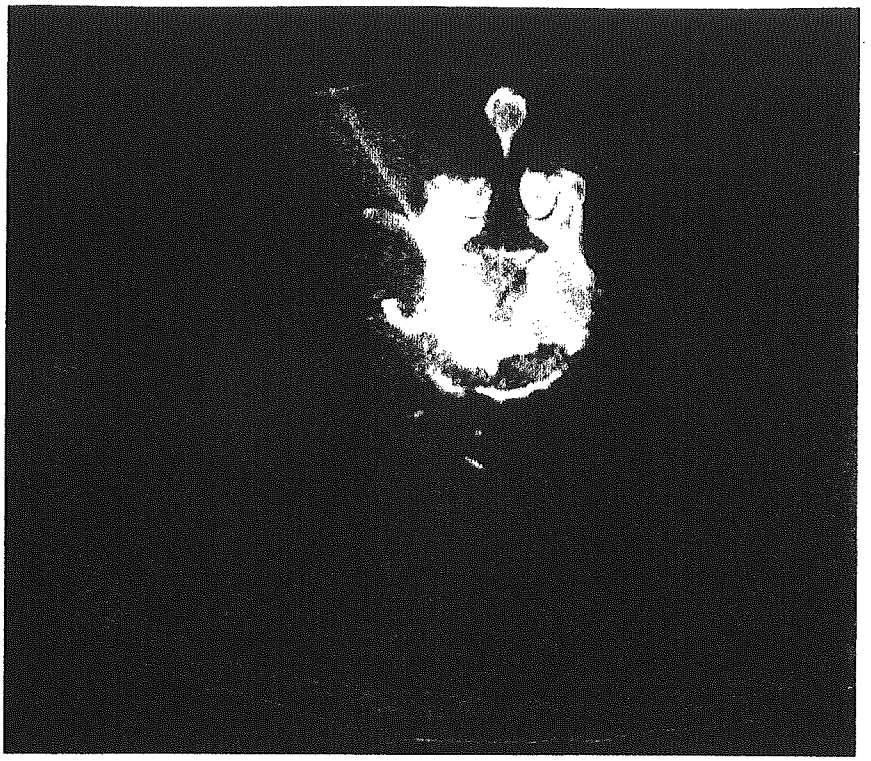


図6　椎体形成術
CTガイド下に椎体の骨転移部に針が刺入され，骨セメントが注入されている．

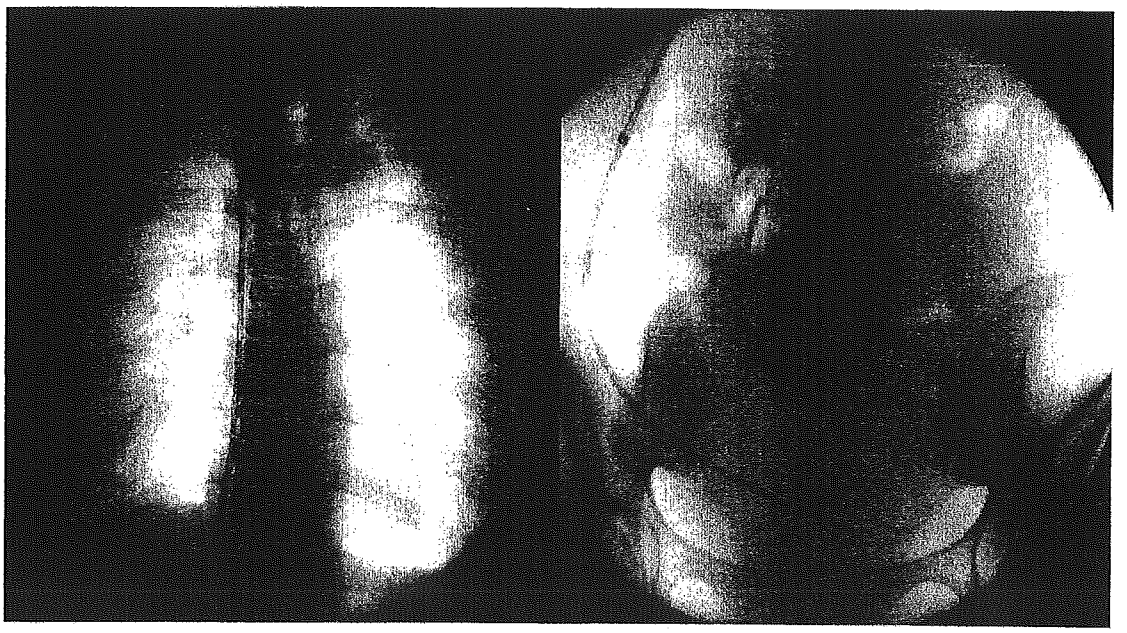


図7　経頸静脈経肝的腹水—静脈シャント
右頸静脈から挿入したカテーテルが，右肝静脈を通り，肝表面を穿破して骨盤腔に達して留置されている．腹水はカテーテル内部を上行し，逆流防止機能付側孔弁より右房に還流する．

4.　難治性腹水に対する治療（図7）

腹水を中心静脈に還流させるチューブを留置することにより，腹水を減少させるとともに，循環血漿量を増加させ全身状態の改善を図る方法である．従来からあるデンバーシャント（皮下トンネ

ルを介してシャントチューブを留置するもの）以外にも，肝静脈を介する血管経由で中心静脈と腹腔を結ぶ方法も開発されている．

5. IVR技術の応用

本来画像誘導なしでも可能な領域に画像誘導やIVR技術を導入することにより，手技に伴う侵襲を少なくし，またQOL向上を図ろうとするものである．例えば，通常ベッドサイドで盲目的に行われる鎖骨下静脈からの中心静脈カテーテルの挿入を，肘静脈から少量の造影剤を注入しながら透視下に行うことで安全性，確実性を高め，さらに手技に要する時間を短縮するなどが挙げられる．また，胸水や腹水のドレナージに際しても，セルジンガー法を用いることにより，より苦痛の少ない柔軟なチューブ留置することが可能であり，末期症例の胸水ドレナージのために大口径のトロッカー・カテーテルを留置するなどは到底許容し難い．このようにQOL向上のためにIVRが活用できる領域はきわめて広い．

6. IVRの問題点

IVRの問題点としては，以下の点が挙げられる．

①個々の症例の解剖や状況に即応しての器材と手技の選択が必要であるため手技の標準化が難しい，②術者の技量や使用する画像機器の性能が結果に大きく影響する，③臨床試験による評価が難しい，④新しい器材を使用する新しい治療であるため，しばしば規制当局の承認や保険対応等が間に合わず適正な医療報酬に繋がらない，⑤医療関係者における認知度が低く，十分に活用されていない．特に⑤の医療関係者における認知度が低い点は大きな問題であり，少なくとも緩和医療においては，その必須知識としてIVRが認知されるべきと思われる．ちなみに，わが国の臨床腫瘍学のテキストブックでは海外のものに比べ多くの頁がIVRに割かれている[7]．

7. IVRの臨床試験

IVRが十分に活用されるためには，臨床試験により明確なエビデンスが示され，IVRが癌緩和医療における標準的治療の一環に組み込まれる必要がある．IVRの臨床試験は，欧米も含め薬物療法などに比べ未だ大きく立ち遅れているのが，国内では海外に先行して厚生労働省がん研究助成金による研究班を母体に，2002年にがんのIVRについての臨床試験組織JIVROSG（Japan Interventional Oncology Study Group）が結成され，現在33組織が参加し，10の臨床試験が進められている（表1）[8]．また，欧米でもMedical OncologistをえInterventional OncologyとしてIVRを臨床試験により評価しようとする活動が本格化している．よって近い将来，臨床試験で示されたエビデンスに基づいてIVRが癌診療における標準的治療の一角として認知されることが期待される．

表1　JIVROSGにおける臨床試験

Phase Ⅰ/Ⅱ	
	経頸静脈経肝的腹水—静脈シャント造設術（進行中）
	経皮的椎体形成術（進行中）
	肺腫瘍に対するラジオ波凝固療法（進行中）
	骨腫瘍に対するラジオ波凝固療法（進行中）
	骨盤内腫瘍に対するラジオ波凝固療法（進行中）
	肝内胆管がんに対する塩酸ゲムシタビン肝動注療法（進行中）
	子宮筋腫に対するゼラチンスポンジによる動脈塞栓療法（進行中）
	肝細胞がんに対するシスプラチン＋ゼラチンスポンジによる動脈塞栓療法（計画中）
Phase Ⅱ	
	経皮経食道胃管挿入術（進行中）
	大腸狭窄に対するステント治療（進行中）
	大静脈狭窄に対するステント治療（計画中）
Phase Ⅲ	
	胆道狭窄に対するベア・ステントとカバード・ステントの比較試験（進行中）

まとめ

癌緩和医療に関わるIVRを紹介した．IVRは癌緩和医療においてきわめて有用な治療手段であるが，このIVRが活用されるか否かは，緩和医療に携わる医療従事者が眼前の患者を診たときにIVRを思いつくか否かにかかっている．いまや癌緩和医療における必須の治療手段として，常にIVRを思い起こしていただくことに本稿が役立

てば幸いである．

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Pro-Gastrin–Releasing Peptide as a Factor Predicting the Incidence of Brain Metastasis in Patients with Small Cell Lung Carcinoma with Limited Disease Receiving Prophylactic Cranial Irradiation

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BACKGROUND. Prophylactic cranial irradiation (PCI) reduces the incidence of brain metastasis with an effect on overall survival in patients with small cell lung carcinoma (SCLC). In spite of multidisciplinary intensive treatment approaches, many patients still experience brain metastasis. The authors retrospectively analyzed the characteristics of the first failure event due to brain metastasis (FBM) in patients treated with PCI.

METHODS. Between January 1990 and April 2004, 71 patients with limited disease SCLC were treated with PCI after completing systemic treatment at the National Cancer Center Hospital (Tokyo, Japan). Univariate and multivariate analyses were used to identify factors related to FBM and survival.

RESULTS. The FBM and overall incidence of brain metastasis (OBM) were 16.9 % (12 of 71) and 26.8% (19 of 71), respectively. Median time to progressive disease and median survival were 8.4 months and 21.6 months, respectively. Elevation of pro-gastrin–releasing peptide (Pro GRP) level before PCI was found to be a significant predictive and prognostic factor for FBM, OBM, and survival on multivariate analysis ($P = 0.007$, $P = 0.025$, and $P = 0.009$, respectively).

CONCLUSIONS. An elevated Pro GRP level before PCI was found to be significantly related to FBM and survival, and should be considered before PCI is performed. *Cancer* **2005;104:811–6.** © *2005 American Cancer Society.*

KEYWORDS: prophylactic cranial irradiation, small cell lung carcinoma, limited disease, predictive factor, pro-gastrin–releasing peptide.

Small cell lung carcinoma (SCLC) accounts for approximately 20% of all lung carcinomas.[1] Although SCLC rapidly develops distant metastasis, it is very sensitive to chemoradiotherapy, unlike non-SCLC. Limited disease SCLC is clinically confined to the hemithorax, and chemoradiotherapy is the standard treatment. In patients with limited disease SCLC, chemotherapy combined with thoracic radiotherapy yields complete remission (CR) rates of 50–85%, with a median survival time of 12–20 months.[2–4] The 5-year survival rate is reported to be 26% for patients who have CR.[4] Because chemoradiotherapy reduces the risk of intrathoracic disease recurrence, distant metastasis in the brain has been the main cause of disease recurrence. Although only 10% of patients have brain metastasis at the time of diagnosis, the cumulative incidence at 2 years is > 50%.[5,6] As many as 73% of patients develop clinically apparent central nervous system metastases before death,[7,8] and even higher rates are documented in autopsy series.[9] The brain is the initial site of disease recurrence in 5–

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33% of patients, and is the only site of disease recurrence in ≤ 20% of patients.[10,11]

Although several randomized trials of prophylactic cranial irradiation (PCI) have attempted to reduce the risk of brain metastasis and to improve survival, to our knowledge its role in the management of patients with SCLC has remained controversial according to the results of each trial.[12–14]

Recently, the metaanalysis of these trials comparing PCI with no-PCI found that PCI led to a small but significant absolute reduction in mortality (5.4%), and that PCI not only significantly reduced the risk of brain metastasis, but also improved both overall survival (OS) and disease-free survival among patients with SCLC in CR.[15] These results suggest that PCI should be considered as a part of the standard treatment for patients with limited disease SCLC who achieved CR or good partial remission (PR).

Although PCI was performed for patients who achieved CR or good PR as part of the combined treatment that consisted of chemotherapy and thoracic radiotherapy, brain metastasis occurred in 4–24% of the treated patients.[6,12–14] Whole-brain irradiation (WBRT) for brain recurrence was often difficult because these patients had already received PCI to the whole brain. Therefore, we should strictly consider PCI for patients who could achieve a true CR, as assessed with diagnostic imaging. In addition, we should be careful to follow the patients who have a high risk of brain recurrence after PCI.

To our knowledge, there are no previous reports that describe the characteristics of patients with brain metastasis after PCI. In the current study, we analyzed retrospectively predictive factors for brain metastasis in patients with limited disease SCLC treated with PCI.

MATERIALS AND METHODS

Patients

A total of 71 patients with limited disease SCLC were treated with PCI after chemoradiotherapy for primary disease between January 1990 and April 2004 at the National Cancer Center Hospital (Tokyo, Japan). Fifty-four patients were male, and the median age was 62 years old (range, 40–75 years).

Histologic or cytologic examination confirmed the diagnosis of SCLC in all patients. Before the initiation of systemic treatment, staging was performed using computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and brain, as well as radionuclide bone scanning and bone marrow aspiration and biopsy. Limited disease was defined as being limited to one hemithorax, mediastinal, hilar, or supraclavicular area, which could be encompassed within a reasonable single radiation portal. Patients with pleural effusion found on chest films or CT scan were excluded.

Tumor response was classified in accordance with the World Health Organization (WHO) criteria.[16] After systemic treatment, including thoracic radiotherapy, PCI was administered to patients with CR or good PR according to the results of chest radiography and CT or MRI scans of the head, chest, and abdomen.

Thoracic Radiotherapy

The majority of patients (n = 55 [77.5%]) received accelerated twice-daily thoracic radiotherapy comprised of 45 gray (Gy) in 1.5-Gy fractions. The remaining patients (n = 16 [22.5%]) received once-daily radiotherapy, 50 Gy in 2-Gy fractions. Radiotherapy was performed 5 days per week, excluding weekends and holidays. Sixty of the 71 patients received concurrent chemoradiotherapy, which began on Day 2 of the first cycle of combination chemotherapy as cisplatin (80 mg/m^2, Day 1) plus etoposide (100 mg/m^2, Days 1, 2, and 3). The other patients received sequential thoracic radiotherapy after the forth cycle of chemotherapy.

The initial field included the primary tumor volume with a 1.5-cm margin around the mass, the ipsilateral hilum, the entire width of the mediastinum, and the supraclavicular lymph nodes (only if there was tumor involvement).

Chemotherapy

All patients received cisplatin combination chemotherapy. After concurrent chemoradiotherapy, 34 patients received 3 cycles of cisplatin plus etoposide, 17 patients received CODE therapy (cisplatin at a dose of 25 mg/m^2 weekly for 6 weeks; vincristine at a dose of 1 mg/m^2 during Weeks 2, 4, and 6; and doxorubicin at a dose of 40 mg/m^2 and etoposide at a dose of 80 mg/m^2 for 3 days during Weeks 1, 3, and 5), and 9 patients received 3 cycles of cisplatin (60 mg/m^2, Day 1) plus irinotecan (60 mg/m^2, Days 1, 8, 15). In patients treated with sequential radiotherapy, five patients received four cycles of cisplatin plus etoposide, four patients received four cycles of cisplatin plus irinotecan, and two patients received four cycles of cisplatin containing combination chemotherapy, optimized for each patient.

Prophylactic Cranial Irradiation

All patients who achieved CR (n =40 [56.3%]) or good PR (n = 31 [43.7%]) were treated with PCI. The median time between the initiation of systemic induction treatment and the initiation of PCI (duration) was 3.7 months (range, 2.6–7.5 months).

The target volume was the entire intracranial site. Individual shaped ports with multileaf collimators

were used to define the irradiation target volume. Patients were treated using a megavoltage linear accelerator with 4–6 megavolt (MV) photons. Treatment was delivered with equally weighted right and left lateral fields, with the dose calculated on the central ray at mid-separation of the beams.

Of the 71 patients who received PCI, the majority of patients (52 of 71 [73.2%]) received 25 Gy in 2.5-Gy fractions daily, 12 patients received 30 Gy in 2-Gy fractions daily, 6 patients received 24 Gy in 1.5-Gy fractions twice daily, and 1 patient received 36 Gy in 2-Gy fractions daily. All PCI was performed a total of 5 days per week. The treatment was administered with a linear accelerator of 6 MV (n = 53 patients) or 4 MV (n = 18 patients). The median follow-up time after PCI was 16.3 months (range, 1.4–113.6 months).

Statistical Analysis

The first failure event due to brain metastasis (FBM) was defined as brain metastasis as a first event after PCI, and the overall incidence of brain metastasis (OBM) was defined as the overall incidence of brain metastasis found throughout the clinical course after PCI. Clinical and laboratory variables before PCI were chosen by considering possible factors indicated by our own experience. We determined the predictive factors for FBM and OBM using both univariate (Pearson chi-square test/Fisher exact test) and multivariate analysis.

Before PCI, 9 categorized variables for multivariate analysis were selected, as follows: gender (male vs. female), age (< 60 vs. ≥ 60 years), response to systemic treatment (CR vs. good PR), time between the start of systemic treatment and the start of PCI (duration: < 4 months vs. ≥ 4 months), hemoglobin level (< 10 g/dL vs. ≥ 10 g/dL), lactate dehydrogenase level (≤ 229 U/L vs. > 229 U/L), C-reactive protein (≤ 0.1 mg/dL vs. > 0.1 mg/dL), neuron-specific enolase (NSE) (≤ 10 ng/mL vs. > 10 ng/mL), and pro-gastrin–releasing peptide (Pro GRP) (≤ 46 pg/mL vs. > 46 pg/mL).

Time to progressive disease (PD) was measured from the first day of PCI until PD or the last day of follow-up without PD, and OS time was measured from the first day of PCI until death or the last day of follow-up. Median time to PD and median OS were estimated using the Kaplan–Meier method. Prognostic factors were evaluated by multivariate analysis. All statistical analyses were performed using SPSS version 12.0J (SPSS Inc., Chicago, IL).

RESULTS

Incidence of Brain Metastasis

FBM and OBM were observed in 16.9% (12 of 71; 95% confidence interval [95% CI], 8.2–17.3%) and 26.8% (19 of 71; 95% CI, 16.5–27.3%) of patients, respectively. Nine patients with FBM had multiple brain metastases and the others had solitary lesions. Among these patients, six were reirradiated with WBRT or stereotactic multiarc radiotherapy, five were treated with systemic chemotherapy, and one received best supportive care. The median times to FBM and OBM were 9.4 months (range, 1.1–23.5 months) and 12.0 months (range, 1.1–92.9 months), respectively. In univariate analysis, an elevated Pro GRP level was found to be significantly related to FBM and OBM (Table 1) (P = 0.007 and P = 0.029, respectively). Using a complete dataset from

TABLE 1
Univariate Analyses of Pretreatment Variables for FBM and OBM

Variables	No. of patients	No. of FBM	P value	No. of OBM	P value
Gender			0.27		0.99
Male	54	11		15	
Female	17	1		4	
Age (yrs)			0.71		
≥ 60	38	7		11	0.66
< 60	33	5		8	
Energy (MV)			0.99		0.36
4	18	3		3	
6	53	9		16	
Total dose (Gy)			0.99		0.08
≤ 25	58	10		13	
> 25	13	2		6	
Hyperfraction			0.27		0.33
Twice daily	6	2		3	
Once daily	65	10		16	
Response			0.63		0.70
Good PR	31	6		9	
CR	40	6		10	
Duration (mos)[a]			0.61		0.86
≥ 4	25	5		7	
< 4	46	7		12	
Hemoglobin level (g/dL)			0.75		0.79
< 10	43	8		12	
≥ 10	28	4		7	
LDH level (U/L)			0.99		0.99
> 229	6	1		1	
≤ 229	65	11		18	
CRP level			0.75		0.50
> 0.1 mg/mL	42	8		10	
≤ 0.1 mg/dL	29	4		9	
NSE level (ng/mL)			0.63		0.99
> 10	8	2		2	
≤ 10	59	10		16	
Pro GRP level (pg/mL)			0.007		0.029
> 46	12	5		5	
≤ 46	37	2		4	

FBM: first failure event due to brain metastasis, OBM: overall incidence of brain metastasis, MV: megavolt; Gy: grays; PR: partial remission, CR: complete remission; LDH: lactate dehydrogenase, CRP: C-reactive protein; NSE: neuron- specific enolase; Pro GRP: pro-gastrin-releasing peptide.
[a] Duration indicates the time between the initiation of systemic induction treatment and the initiation of prophylactic cranial irradiation.

TABLE 2
First Progressive Disease Sites after PCI

Site	No. of patients	% of all patients
Local failure (inside the thorax)	20	28.2
Distant metastasis[a]	26	36.6
Abdominal organ	7	9.9
Bone	9	12.7
Spinal cord	1	1.4
Brain	12	16.9
Total	46	64.8

PCI: prophylactic cranial irradiation.
[a] Three patients had more than one progressive disease site in distant metastasis.

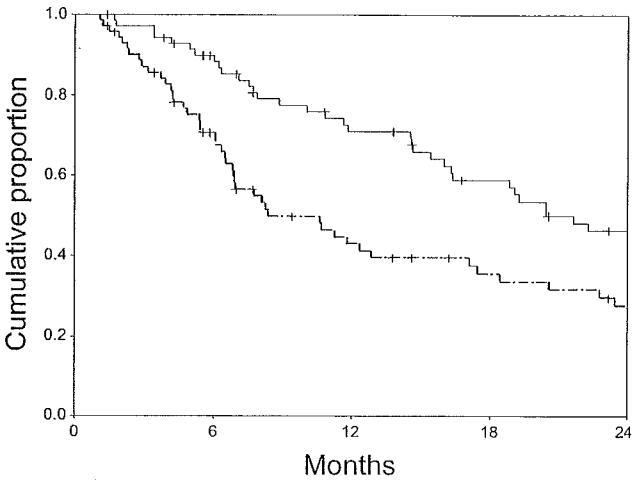

FIGURE 1. Kaplan–Meier analysis of time to disease progression (dotted line) and overall survival (solid line).

49 patients, a multivariate logistic regression model disclosed that an elevated Pro GRP level was a significant predictive factor for both FBM (hazard ratio [HR], 12.5; 95% CI, 2.00–77.9 [$P = 0.007$]) and OBM (HR, 5.89; 95% CI, 1.25–27.7 [$P = 0.025$]).

Time to Progressive Disease and Survival

In the current series, the majority of patients (46 of 71 [64.8%]; 95% CI, 53.7–65.4%) experienced PD in their clinical courses. The first sites of PD are listed in Table 2. The median time to PD and the median survival time were 8.4 months (95% CI, 3.9–12.8 months) (Fig. 1)and 21.6 months (95% CI, 14.1–29.2 months) (Fig. 1), respectively. A multivariate Cox regression model indicated that elevated Pro GRP level before PCI was a prognostic factor (HR, 2.97; 95% CI, 1.31–6.75 [$P = 0.009$]).

DISCUSSION

It is suggested that PCI eradicates subclinical brain metastasis that is protected from cytotoxic drugs by the blood-brain barrier as a pharmacologic sanctuary.[17] A recently reported metaanalysis of seven prospectively randomized trials demonstrated both an OS and disease-free survival advantage for patients with limited disease SCLC who received PCI compared with patients who did not receive PCI.[15] However, the metaanalysis included various trials and often insufficient systemic chemotherapy regimens, different PCI techniques, and a mixed population of patients with limited and extensive disease.[12–15] Therefore, Kotalik et al.[18] found there was insufficient evidence to make a definitive recommendation in terms of the total dose, fractionation, indication, and timing of PCI according to this metaanalysis.

In the current study, 16.9% of patients had brain metastasis as a first site of failure, which is consistent with previous reports of 4–24%.[6,12–14] The salvage treatment for brain metastasis after PCI would be restricted by the number of brain metastases, patient condition, and previous irradiation. To our knowledge, no report has described the predictive or prognostic factors for outcomes after PCI. Therefore, our results could provide useful information concerning the indication of PCI and close follow-up in patients with limited disease SCLC with CR or good PR who received intensive multidisciplinary treatment.

We found that elevated Pro GRP level before PCI was a significant predictive factor for FBM and for OBM ($P = 0.007$ and $P = 0.025$, respectively). The other pretreatment variables such as clinical and laboratory parameters had no influence on FBM or OBM. Among tumor markers, NSE is known to have a high false-positive rate due to hemolysis, whereas Pro GRP is a stable and reliable tumor marker for SCLC.[19] In addition Pro GRP is found to have higher specificity than NSE, and its serum level was frequently elevated at an earlier stage compared with that of the NSE level in patients with SCLC at the time of diagnosis.[20,21] It is reported that Pro GRP reflects tumor volume and the effect of treatment more sensitively than does NSE, and that it is useful in detecting PD because Pro GRP levels increase before disease recurrence becomes evident.[19,21,22] From the results of the current study, the elevation of Pro GRP before PCI might reflect the existence of residual viable tumor cells after a series of induction treatments, even if CR or good PR is indicated by imaging. A PCI would be recommended for patients with limited and extensive disease SCLC with CR.[15] However, PCI might not be sufficiently beneficial for decreasing the incidence of brain metastasis in patients with an elevated Pro GRP level. Therefore, by the completion of whole therapy, we should completely eliminate residual subclinical intracranial

and/or extracranial disease that causes the brain recurrence.

Several evidence-based guidelines for limited disease SCLC described uncertainty in terms of the optimal regimen, schedule of drug administration, duration of chemotherapy, and maintenance chemotherapy.[23,24] Although there is a guideline that recommends a maximum of six cycles of chemotherapy,[23] the trend in clinical trials and practice, including the current study, has been to use only four cycles of cisplatin-based chemotherapy. In patients with CR with elevated Pro GRP after four cycles of chemotherapy, two additional cycles of chemotherapy might be possible to eliminate tumor cells, to normalize Pro GRP levels, and to reduce the risk of brain recurrence.

A previous study suggested that there may be a dose-response relation for PCI, and that higher doses were more effective in reducing the risk of brain metastasis.[14] If currently ongoing trials that compare 25 Gy in 10 fractions with 36 Gy in 18 fractions[18] indicate the superiority of high-dose PCI, this will be another option to optimize the PCI procedure for controlling the subclinical disease at pharmacologic sanctuary.

The previous WHO criteria for evaluation of tumor response[11] did not consider the value of tumor markers. However, the Response Evaluation Criteria in Solid Tumors (RECIST) include tumor markers for assessment of CR.[25] Serum laboratory methods more accurately evaluate the evidence of viable tumor cells, and have a complementary role to the imaging studies when macroscopic tumor disappears or residual scar remains. In SCLC, tumor markers are well correlated to the response and tumor volume,[19,21,22] as was observed with Pro GRP in the current study. Therefore, CR according to the RECIST guidelines might be more appropriate in the evaluation of patients with SCLC for PCI.

Several authors reported many prognostic factors of clinical and laboratory parameters for patients with SCLC.[26] Almost all the analyses in the previous reports showed pretreatment factors before the initiation of systemic therapies. We analyzed pretreatment parameters for patients with CR or good PR receiving PCI. In our study, most of the laboratory parameters fell within normal limits before PCI, except for Pro GRP as a prognostic factor.

Local failure occurred in approximately one-half of the patients with disease recurrence, in addition to distant failure. The Southwest Oncology Group reported the pattern of failure in 114 patients with limited disease SCLC treated with cisplatin plus etoposide and concomitant thoracic radiotherapy followed by PCI. Local failure and distant metastasis occurred in 49% and 35% of patients, respectively.[27] These results also suggested that the main cause for disease recurrence was local or distant failure. Therefore, it is crucial to develop new drugs or regimens for improving local and distant control, which achieve a high rate of CR without elevation of tumor markers such as Pro GRP before PCI.

The results of the current study demonstrate that elevation of Pro GRP before PCI is a significant predictive factor for the first failure event due to brain metastasis. With regard to the indication of PCI, the assessment of clinical response according to RECIST might be evaluated more accurately using Pro GRP together with conventional imaging studies.

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A multidisciplinary treatment strategy that includes high-dose chemotherapy for metastatic retinoblastoma without CNS involvement

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Summary:

The prognosis of patients with metastatic retinoblastoma is poor with conventional chemotherapy and radiation. Since retinoblastoma is highly chemosensitive, dose-escalation of chemotherapeutic agents with stem cell support should be promising. We report our experience with high-dose chemotherapy (HDC) and autologous stem cell transplantation (SCT) in patients with metastatic retinoblastoma. Five patients with metastatic retinoblastoma underwent HDC with autologous SCT following conventional chemotherapy and local radiation therapy. Stem cells (bone marrow in four and peripheral blood stem cells in one) were collected after marrow involvement was cleared. Melphalan was a key drug in all patients, and was administered in combination with other agents such as cisplatin, cyclophosphamide, carboplatin or thiotepa. Three patients are currently alive disease-free at 113, 107 and 38 months, respectively, from the time of SCT. They had no central nervous system (CNS) involvement. The two patients who died of disease had CNS involvement. No long-term sequelae of HDC have been noted. Our treatment strategy using HDC appears to be effective for treating metastatic retinoblastoma without CNS involvement.

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Retinoblastoma, the most common ocular malignancy in childhood, develops in infants, and the incidence is one in 160 000–20 000 births in Japan.[1] Many therapeutic modalities have been employed, and retinoblastoma has become one of the curable pediatric solid tumors. Nevertheless, the prognosis of extraocular retinoblastoma with metastasis to bone/bone marrow (BM) or the central nervous system (CNS) remains very poor.[2] Such high-risk populations include involvement of the cut end of the optic nerve, extrascleral spread into the orbit, lymphatic or hematogenous dissemination, CNS involvement and trilateral retinoblastoma. The overall occurrence of extraocular retinoblastoma was 4.8% of all patients at an institution.[3] Since retinoblastoma is highly chemosensitive, a treatment strategy that includes the dose-escalation of chemotherapeutic agents and stem cell support should be promising. We treated five patients with metastatic retinoblastoma using high-dose chemotherapy (HDC) followed by autologous stem cell transplantation (SCT), and three patients are currently alive and disease-free. Although our experience is very limited, our experience suggests the feasibility of a prospective study.

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Patients and methods

Five patients received HDC for extraocular retinoblastoma between March 1986 and November 2000 at the National Cancer Center Hospital of Japan (NCCH), and the data reported reflect the last patient contact as of January 2004. All patients originally were treated with radiation therapy and/or enucleation for intraocular disease at NCCH. The clinical characteristics of the patients are described in Table 1. After completion of the initial series of local ophthalmic therapies in NCCH, four of the five patients developed metastatic recurrence, as reported elsewhere.[4–6] Only one patient had BM metastasis at the initial diagnosis. Staging studies included computed tomography and magnetic resonance imaging of orbits and brain, histopathologic evaluation of BM aspiration and cytologic examination of cerebrospinal fluid (CSF). All patients were classified as having stage III/IV disease by the grading system of Grabowski and Abramson.[7] After the diagnosis of metastatic diseases was established, all patients were treated with conventional chemotherapy with or without radiotherapy and surgical enucleation (Table 2). Systemic chemotherapy included courses of vincristine, cyclophosphamide and doxorubicin with or without cisplatin alternating with cisplatin and cyclophosphamide, or

Table 1 Patients characteristics

UPN	*Sex*	*Age at diagnosis*	*Involvement*	*Metastases at diagnosis*	*Treatment*	*Metastases after therapy*
1	F	3 months	Bilateral	None	Right: 50.7 Gy radiation Left: enucleation	Brain (optic chiasm), spinal cord (L1)
2	M	10 months	Bilateral	None	Right: 49.4 Gy radiation Left: enucleation	Brain (ethmoid and sphenoid sinus), bilateral cervical LNs
3	F	41 months	Left	None	Left: 46 Gy radiation + HIT	Right temporal bone, marrow (70%)
4	F	16 months	Right	Marrow	Right: enucleation + 6 Gy radiation + chemotherapy	
5	F	18 months	Right	None	Right: 46 Gy radiation + enucleation + HIT + PC + CTT + IVI	Right orbit, marrow (50%)

UPN = unique patient number; HIT = heat-inducing thermotherapy; PC = photocoagulation; CTT = chemothermotherapy; IVI = intravitreal injection.

Table 2 Therapy and outcome

UPN	*Cx. after Mets*	*Rx. after Mets*	*SCT from relapse (mos)*	*Conditioning (mg/m²)*	*Stem cell source*	*Result*	*Meta. after SCT (mos)*	*Sequelae*
1	VCR/CY/ADR ×2 CY/CDDP ×1	Spine 40 Gy, cranium 25 Gy + boost 15 Gy	5	CDDP 90, CY 120 mg/kg, L-PAM180	BM	DOD	Spinal cord at Th12-L1 level (24 mos)	NE
2	VCR/CY/ADR ×3 CDDP/ETO ×2	Cranium 40 Gy + boost 20 Gy, spine 21 Gy, cervical LNs 40 Gy	5	CDDP 90, CY 120 mg/kg, L-PAM180	BM	DOD	Rt. cervical LN (4 mos)	NE
3	VCR/CY/ADR ×4 CDDP/ETO ×2	Focal site 40 Gy	7	L-PAM 180, VP-16 800, CBDCA 1600	BM	NED (113+)	None	None
4	VCR/CY/ADR ×3 CDDP/ETO ×3	—	6	L-PAM 180, VP-16 800, CBDCA 1600	BM	NED (107+)	None	None
5	VCR/CY/ADR/ CDDP ×3 CBP/ ETO ×4	—	7	L-PAM 160, CY 120 mg/kg, TEPA 500	PBSC	NED (38+)	None	None

SCT = stem cell transplantation; BM = bone marrow; CNS = central nervous system; LN = lymph node; NED = no evidence of disease; DOD = dead of disease; NE = not evaluable; VCR/CY/ADR = vincristine 1.5 mg/m²/day × 1, cyclophosphamide 600 or 800 mg/m²/day × 2, doxorubicin 40 mg/m²/day × 1; CDDP/CY = cisplatin 90 mg/m²/day × 1, cyclophosphamide 1200 mg/m²/day × 1; CDDP/ETO = cisplatin 20 mg/m²/day × 5, etoposide 100 mg/m²/day × 5; VCR/CY/ADR/CDDP = vincristine 1.5 mg/m²/day × 1, cyclophosphamide 1200 mg/m²/day × 1, doxorubicin 40 mg/m²/day × 1, cisplatin 18 mg/m²/day × 5; CBP/ETO = carboplatin 120 mg/m²/day × 5, etoposide 100 mg/m²/day × 5; L-PAM = melphalan; VP-16 = etoposide; CBDCA = carboplatin; TEPA = thiotepa.

cisplatin and etoposide, or carboplatin and etoposide. After complete response of tumor involvement in the BM, autologous BM cells were collected from four patients, autologous blood stem cells from one patient, respectively. The nonpurged stem cells were cryopreserved. All patients also received one to five intrathecal injections of methotrexate at a variable dose of 5–12.5 mg/dose, concomitant with systemic chemotherapy. Radiation therapy was given in four patients to sites that had harbored bulky disease at early stage after the diagnosis of metastasis. All patients were prepared for HDC with SCT after achieving complete remission, which was evaluated by imaging studies, BM aspiration and/or CSF examination. We harvested BM cells or peripheral blood stem cells, if a BM aspirate had no tumor cells on morphologic analysis before harvesting. We did not apply minimum residual disease (MRD) studies on BM cells or peripheral blood stem cells. Conditioning regimens for all patients contained melphalan 180 mg/m² as a key drug. Concomitant agents were cisplatin 90 mg/m² and cyclophosphamide 120 mg/kg (case 1, 2), etoposide 800 mg/m² and carboplatin 1600 mg/m² (case 3, 4), or thiotepa 500 mg/m² and cyclophosphamide 120 mg/kg (case 5). The collected BM cells ($1.0–1.7 \times 10^8$ total nucleated cells/kg) or peripheral blood stem cells (4.7×10^6 CD34+ cells/kg), which were unmanipulated, were infused approximately 24 h after completion of the conditioning chemotherapy. Granulocyte-colony stimulating factor was administrated intravenously once daily from day +5 or +7, and was continued until engraftment of neutrophils was established (case 3–5).

Results

Engraftment

Engraftment of neutrophils, defined as the first of two consecutive days of an absolute neutrophil count of at least 0.5×10^9/l, occurred 18, 26, 10, 14 and 11 days, respectively, after stem cell rescue. Platelet engraftment, defined as the first of 2 consecutive days of an absolute platelet count of at least 50×10^9/l sustained without transfusion, occurred 67, 32, 11, 51 and 16 days, respectively, after stem cell rescue.

Toxicities

All patients developed severe mucositis with oropharyngeal pain (WHO grade 3) after SCT. Only one patient had elevated transaminase levels greater than five times normal (case 5). All patients developed febrile neutropenia without a detectable pathogen, which subsided within 7 days by antibiotic treatment. No other acute toxicities associated with SCT were observed.

Patient survival

All three patients without CNS metastasis are alive disease-free at 113, 107 and 38 months, respectively, from the time of SCT (case 3–5). They are alive without complications, except for orbital growth retardation because of local irradiation and surgical enucleation. Two patients died of recurrent diseases 4 and 48 months, respectively, after SCT (case 1, 2). There was no second malignancy in this series.

Discussion

The prognosis of patients with metastatic retinoblastoma is poor with conventional chemotherapy and radiation therapy.[2,8] Honavar *et al*[9] have shown that postenucleation adjuvant therapy is safe and effective in significantly reducing the occurrence of metastasis in patients with retinoblastoma manifesting high-risk histopathologic characteristics.[9] Several centers have used conventional-dose chemotherapy and radiation therapy for hematogenously spread extraocular disease. Despite some reports of long-term event-free survival,[7,10] the bulk of the evidence suggests that the prognosis remains poor with such an approach.[11]

A limited number of studies and case reports have suggested that HDC with autologous stem cell rescue might be beneficial for patients with metastatic retinoblastoma (Table 3).[12–20] Namouni *et al*[14] conducted a study of HDC consisting of carboplatin, etoposide and cyclophosphamide (CARBOPEC) followed by autologous SCT in 25 patients, including 12 patients with distant metastases. Among eight children with bone and BM metastases, five survived between 11 and 70 months disease free, while three patients with CNS metastases relapsed in the CNS after HDC and died. Thus, the CARBOPEC regimen appeared to be effective only for patients with bone and/or BM involvement of retinoblastoma. Dunkel *et al*[16] reported four retinoblastoma patients with orbit and BM metastases who underwent HDC consisting of carboplatin and thiotepa with or without etoposide. All patients survived event-free for 46–80 months after the diagnosis of metastatic disease. They concluded that this treatment strategy is effective for metastatic retinoblastoma without CNS involvement. Rodriguez-Galindo *et al*[19] reported four retinoblastoma patients with bone and BM metastases, treated by intensive systemic therapy. Although they did not mention an effectiveness of HDC, they concluded that the use of intensive multimodal approach in patients with metastatic retinoblastoma without CNS involvement could achieve long-term survival.

The important component in HDC is the alkylating agents, which have favorable toxicity profile. There are some reports that thiotepa is effective for high-risk retinoblastoma and other malignancies.[16,19,21,22] As it penetrates well into the brain, as demonstrated by similar drug levels in CSF and in serum after intravenous injection bolus use, we should consider the high-dose thiotepa in the attempts of HDC in disseminated retinoblastoma, particularly with CNS involvement. However, we used not thiotepa but melphalan for HDC. High-dose melphalan and SCT have been used to treat neuroblastoma, rhabdomyosarcoma and Ewing's sarcoma in children.[23–26] In addition, Inomata and Kaneko[27] suggested that retinoblastoma was most sensitive to melphalan based on a colony assay on double agar layers. Kaneko treated six patients with intraocular retinoblastoma that recurred after irradiation therapy by injecting 40 mg/m^2 of melphalan into the ipsilateral intracarotid artery, and by applying ocular hyperthermia (45°C, 1 h).[5] Two patients were cured (no recurrence for more than 10 years) with a single treatment procedure while preserving adequate visual function. Based on their observation, we selected melphalan as a key drug for HDC. We should consider that not only thiotepa but also melphalan is an effective agent of HDC for retinoblastoma. As other agents, busulfan and nitrosurea drugs

Table 3 High-dose chemotherapy for retinoblastoma

Author (year)	*n*	*Marrow involvement (+/−)*	*Bone Metastasis (+/−)*	*CNS Metastatsis (+/−)*	*High-dose chemotherapy*	*Result*
Namouni *et al* (1997)[14]	12	1/11	7/5	4/8	CARBOPEC	6 alive
Dunkel *et al* (2000)[16]	4	3/1	4/0	0/4	CTE 3, TC 1	4 alive
Kremens *et al* (2003)[19]	5	4/1	2/3	0/5	CTE 4, BCyE 1	5 alive[a]
Rodriguez-Galindo *et al* (2003)[20]	4	4/0	4/0	0/4	CE 1, BuCyM 1, CyE 1, CyTopo 1	2 alive
Jubran *et al* (2004)[3]	4	1/3	2/0	1[b]/3	CTE	2 alive
Our cases	5	2/3	2/3	2/3	CDDP-CyM 2, MEC 2, TCyM 1	3 alive

[a]One alive after relapse.
[b]Pineal.
CARBOPEC = carboplatin + etoposide + cyclophosphamide; CTE = carboplatine + thiotepa + etoposide; TC = thiotepa + carboplatin; BcyE = busulfan + cyclophosphamide + etoposide; CE = carboplatin + etoposide; BuCyM = busulfan + cyclophosphamide + melphalan; CyE = cyclophosphamide + etoposide; CyTopo = cyclophosphamide + topotecan; CDDP-CyM = cisplatin + cyclophosphamide + melphalan; MEC = melphalan + etoposide + carboplatin; TCyM = thiotepa + cyclophosphamide + melphalan; DOD = dead of disease.

(nimustine, ranimustine), which are effective because of their capacity to cross the blood–brain barrier, have been used for retinoblastoma.[28,29]

We conclude that our treatment strategy that includes high-dose melphalan with autologous SCT and local irradiation is effective in patients with metastatic retinoblastoma without involvement of the CNS, although a wide variation in the HDC regimen made it difficult to judge the objective safety and efficacy of autologous SCT. A safer and more effective modality is required to better control CNS involvement. The possible risk of late sequelae secondary to additive toxicity by HDC and cranial radiation should be critically evaluated. Since metastatic retinoblastoma is a rare disease, a larger cooperative study is needed to clarify the safety and efficacy of this HDC strategy.

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