表❶ 有痛性骨転移に対する放射線療法の分割法のランダム化比較試験における鎮痛効果

著者	国名/対象	年	n	分割法	CR	RR
RTOG 7402[1]	米国	1982				
	単発性骨転移		74	40Gy/15回	61%	85%
			72	20Gy/5回	53%	82%
	多発性骨転移		167	30Gy/10回	57%	87%
			143	15Gy/5回	49%	85%
			155	20Gy/5回	56%	83%
			148	25Gy/5回	49%	78%
Bone Pain Trial Working Party[7]	英国 ニュージーランド	1999	378	20Gy/5回 30Gy/10回	51%	68%
			383	8Gy/1回	52%	72%
Dutch Bone Metastases Group[8]	オランダ	1999	586	24Gy/6回	30%	62%
			585	8Gy/1回	34%	67%
RTOG 9714[9]	米国	2003	443	30Gy/10回	18%	66%
			455	8Gy/1回	15%	65%

CR：疼痛完全消失割合；RR：疼痛緩和割合
RTOG：Radiation Therapy Oncology Group

ついて，これまでおこなわれた臨床試験の結果をまとめ，各国の日常臨床における分割法の実態や今後の取り組みについて解説する．

1．骨転移痛に対する放射線療法の現状

1）放射線療法の分割法に関する臨床試験

骨転移に対する放射線療法の分割法として，さまざまなスケジュールがあり，疼痛緩和割合は70～90％と報告されている．疼痛緩和を目的とした場合の線量－効果関係，すなわち線量が多くなればなるほど，緩和される割合が増えるかどうかについて議論になっていた．有痛性骨転移に対する放射線療法の臨床試験として，古くは1970年代に米国のRadiation Therapy Oncology Group（RTOG）が1,016例を対象とした大規模なランダム化比較試験（RTOG 7402）をおこない，各分割法による疼痛緩和割合および疼痛緩和持続期間，疼痛再燃割合の差は認められなかった[1]（表❶）．しかし，その後の再分析で単発性と多発性骨転移をあわせた759例に対し，鎮痛薬の使用を加味した場合，疼痛完全消失は分割回数が多いほうが得られることが報告された[2]．

1回（1日）で治療がおわる1回照射は，1969年に1回4～18Gyでの疼痛緩和割合が90％と良好な結果としてその有用性がはじめて報告された[3]．1回照射のメリットとして，治療期間を短縮できることで，患者の時間的・肉体的負担を軽減でき，また全身的治療の日程調整の簡便化，患者側・医療者側のコスト削減などがあげられる．線量別の2つのランダム化比較試験の結果から，現状では8Gy/1回が有痛性骨転移に対する1回照射の最小の最適な線量と考えられている[4][5]．有痛性骨転移に対する分割照射と1回照射のランダム化比較試験は1986年にPriceら[6]によってはじめて報告された．30Gy/10回と8Gy/1回にランダム化され，鎮痛が得られるまでの期間，疼痛緩和持続期間，治療後90日および1年の疼痛緩和割合は両群に差を認めなかった．さらに1999年には2つの大規模なランダム化比較試験が報告された．英国を主体とするBone Pain Trial Working Party[7]は有痛性骨転移を有する765例を無作為に8Gy/1回と20Gy/5回または30Gy/10回に割り付けて治療した．両群において疼痛緩和割合，疼痛完全消失割合，疼痛緩和持続期間，全生存期間，脊髄圧迫または

表❷ 有痛性骨転移に対する放射線療法の分割法のランダム化比較試験における有害事象

著者	対象	分割法	急性期有害反応（嘔気，嘔吐）	遅発性有害事象	病的骨折	脊髄圧迫
RTOG 7402[1]	単発性骨転移	高線量群	NR	NR	18%	NR
		低線量群			4%	
	多発性骨転移	高線量群	NR	NR	8%	NR
		低線量群			5%	
Bone Pain Trial Working Party[7]		20Gy/5回	32%	NR	0.5%	1.1%
		30Gy/10回				
		8Gy/1回	30%		2%	1.7%
Dutch Bone Metastases Group[8]		24 Gy/6回	有意差なし	NR	2%	2%
		8Gy/1回			4%	2%
RTOG 9714[9]		30Gy/10回	19%*	有意差なし	4%	NR
		8 Gy/1回	12%*		5%	

RTOG：Radiation Therapy Oncology Group
NR：報告なし
＊消化器症状

病的骨折の頻度，急性期有害反応（嘔気，嘔吐）に差を認めなかった（表❷）．Dutch Bone Metastases Group[8]は1,171例を対象とし，8Gy/1回と24Gy/6回に無作為に割り付けて治療した．疼痛緩和効果とともにQOL評価および急性期有害反応の頻度においても両群に差を認めなかった．また，病的骨折の頻度が1回照射で分割照射にくらべ有意に多かったが（4% vs 2%，$p<0.05$），脊髄圧迫の頻度は両群に差を認めなかった（2% vs 2%）．

これまでの臨床試験はおもにヨーロッパを中心としておこなわれたものであるが，米国では20年ぶりに骨転移に対する8Gy/1回と30Gy/10回の大規模なランダム化比較試験（RTOG 9714）をおこない，その結果が最近報告された[9]．対象は，比較的予後がよいとされ，前回のRTOG 7402で他の原発巣にくらべ疼痛緩和効果が良好であった乳癌，前立腺癌に限定した．949例が登録され，適格例の898例がランダム化された．結果は，3ヵ月の評価で両群に鎮痛効果の差はなく，Grade2～4の急性期有害事象は分割照射で有意に頻度が高く（10% vs 17%，$p=0.02$），遅発性有害事象，病的骨折の頻度は両群に差は認めなかった．この試験では疼痛評価に鎮痛薬使用量の増減を加味し，疼痛完全消失は0点のみとしていたため，これまで報告された臨床試験の結果にくらべ，疼痛完全消失割合や疼痛緩和割合がやや低い結果となっているが，これまでの試験で最も正確な評価であり，今後の指標になると考えられる（表❶）．またこの試験ではQOL，health utilitiesなどの調査もおこなっており，今後の報告が待たれる．以上の3つの大規模なランダム化比較試験は，病的骨折や骨折のリスクがなく，脊髄麻痺兆候がない有痛性骨転移を対象としたものである．

2003年には有痛性骨転移に対して2000年までに報告されたさまざまな分割法を含む16のランダム化比較試験のメタアナリシスがはじめて報告された[10]．2つの1回照射による線量別の比較試験，8つの1回照射と分割照射の比較試験，6つの分割照射の分割法別の比較試験において，疼痛緩和をエンドポイントとして，1回線量，分割回数，総線量などを考慮した生物学的等価線量（biologically equivalent dose：BED）を用いた線量-効果関係を分析し，線量分割の違いによる線量-効果関係は認められなかった．

これらの結果より，病的骨折や骨折のリスクが

なく，脊髄麻痺兆候や神経因性疼痛がない有痛性骨転移に対する放射線療法において，疼痛緩和を目的とした場合に明らかな線量-効果関係は示されていないと考えられる．また，長期生存が期待できる場合には，局所制御も目的として，40～50Gy/20～25回などの分割法も考慮される．いずれにしても患者ごとに病状，PSなどを考慮して分割法を決定するのが望ましい．

2）海外とわが国での放射線療法の実態

実際に世界でどのような分割法が用いられているかについて，いくつか報告がある．米国における1998年のアンケート調査の報告では，放射線療法の分割法は30Gy/10回が64％の症例に用いられるとの結果であった[11]．また，1998年のAmerican College of Radiologyの提言では20Gy/5回，30Gy/10回，35Gy/14回の分割法を推奨している[12]．この理由として，多くの短期照射の臨床試験が米国以外でおこなわれていること，米国の放射線腫瘍医は1回4Gy以上の経験があまりないこと，ほとんどの放射線腫瘍医は治療方針の決定に費用は考えていないことなどがあげられている．西ヨーロッパでの1998年の大規模なアンケート調査では，30Gy/10回が50％で利用され，1回照射は11％であった[13]．大きな施設ほどその他の施設にくらべ，有意に分割回数が少なく，単純な照射方法を用いていた．さらに医療保険制度も加味したアンケート調査の結果，医療保険制度と分割法との間に相関を認めた[14]．すなわちスペイン，オランダ，英国などの包括医療の国では分割回数が少なく，ドイツ，スイスなどの出来高払いの国では分割回数が多かった．カナダでは1998年のアンケート調査で病的骨折，神経症状などがない有痛性骨転移に対して64％が20Gy/5回，17％で8Gy/1回照射がおこなわれている[15]．オーストラリア，ニュージーランドの1998年のアンケート調査では30Gy/10回が最も多く，1回照射は肺癌，前立腺癌，乳癌でそれぞれ42％，28％，15％で用いるとの結果であった[16]．1999年のヨーロッパおよび2005年の米国での大規模なランダム化比較試験や2003年のメタアナリシスの結果から，各国での日常臨床の分割法がどのようにかわっているか興味のあるところである．

わが国においてはこれまでアンケート調査はおこなわれていないが，30Gy/10回などの分割照射が一般的におこなわれている．1回照射に関しては，少数例での報告で良好な鎮痛効果を認め，重篤な有害事象も認められていないなど，その有用性が述べられているが[17)～19)]，多くの放射線腫瘍医は1回照射の経験があまりなく，施行している施設においてもPS3, 4などの予後の限られた症例に対してのみ施行されていることが多いようである．現在われわれは厚生労働省がん研究助成金の研究班にて，PS0～2で，2ヵ月以上の生存が期待できるなどの症例に対して，わが国での8Gy/1回照射が日常臨床に適応できる有効性と安全性を有するかどうかの多施設共同の前向き臨床試験を施行中である．

3）骨転移に伴う神経因性疼痛に対する放射線療法

骨転移に伴う神経因性疼痛を対象とした分割法別のランダム化比較試験はTrans-Tasman Radiation Oncology Group（TROG）がおこなったTROG 9605のみであり，その結果が2005年に報告された[20]．神経因性疼痛を有する272例の骨転移症例が登録され，20Gy/5回と8Gy/1回にランダム化された．両群において疼痛緩和割合に有意差は認めなかったが（61％ vs 53％，p = 0.08），無増悪生存期間の中央値が20Gy/5回の3.7ヵ月に対し，8Gy/1回は2.4ヵ月で，ハザード比は1.35（95％CI 0.99～1.85）で有意差はないものの，分割照射群でよい傾向にあった（p = 0.056）．結論として，この対象群では1回照射と分割照射の効果の差は少なかったが，1回照射群の成績が全般に悪い傾向にあり，分割照射が標準的であるとし

表❸ 「国際的コンセンサス（international consensus）」における一般的合意点

1. 0～10ポイントの疼痛スケールを使用する．
2. 疼痛評価は患者側の評価（patient based）にすべきである．
3. 身体図（body diagram）の使用を推奨する．
4. 鎮痛薬の使用量と使用頻度はエンドポイントとして報告されるべきである．
5. ITT解析（intention to treat）をおこなうべきである．
6. 全身的治療（ビスフォスフォネート製剤を含む）の変化や外科的固定術などは報告されるべきである．
7. QOL評価と有害事象は報告されるべきである．
8. 骨密度の変化はエンドポイントにするべきではない．

ている．この対象群に対して1回照射による少ない総線量で効果が弱かった理由として，神経因性疼痛の原因に骨転移巣によるmass effectの関与（腫瘍による神経圧迫）が多くあり，症状緩和のためには腫瘍縮小をめざして中等度以上の総線量が必要なのかもしれない．

2．骨転移に対する放射線療法の新しい試み

1）骨転移に対する放射線療法の臨床試験の問題点と今後の実施に向けてのコンセンサス

これまで施行された骨転移の臨床試験の報告ではつぎのように各試験によって一定でないという問題点が指摘されている．治療対象（痛みの程度がひどい痛みのものだけか軽いものも含まれているのか），疼痛評価方法（医師側の評価か患者側の評価か），使用する疼痛スケール（4段階か5段階か11段階か），疼痛緩和の定義（1点以上の低下か2点以上の低下か），鎮痛薬使用量（疼痛評価に加味しているかどうか）などがあげられている．これらの問題点を解決する目的で，2001年，2002年に今後実施される骨転移に関する放射線療法の臨床試験のエンドポイントをまとめた「国際的コンセンサス（international consensus）」が提示された[21) 22)]．いくつかの合意点があり，痛みの評価は0～10ポイントスケールを使用すること，患者側の評価であること，身体図（body diagram）の使用を推奨すること，鎮痛薬の使用量もエンドポイントとして報告されることなどである（表❸）．これらを統一しておけば，今後実施される臨床試験の結果の比較がこれまでよりも正確になり，さらに系統的レビューやメタアナリシスなどの解析の際もより精度が増すであろう．

2）再照射に関する取り組み

現在，骨転移に対する再照射の時期，適応，線量，分割法のスケジュールなどの明確な基準はなく，今後，骨転移に対する放射線療法において解決すべきことの1つとして再照射があげられている．再照射の適応として，①初回治療無効例に対する鎮痛目的，②疼痛再燃例に対する鎮痛目的，③疼痛緩和有効例に対する更なる鎮痛目的，があげられる．これまで報告された分割照射と1回照射のランダム化比較試験において再照射率が1回照射で11～25％と分割照射の3～10％とくらべ2～4倍に認められている[3) 6) 8) 9)]．この理由として，これらの臨床試験における再照射の明確な適応基準はなく，1回照射にくらべて分割照射では再照射ができないであろうという医療者の考えがおもに反映されていると考えられている．

再照射の効果に関するこれまでの後ろ向き解析の報告では，さまざまな分割法での疼痛緩和割合が50～84％とその有効性が示唆されるが[23)～25)]，初回治療の分割法の違いや有害事象のデータが少なく，今後の前向きでの評価が必要である．再照射施行にあたっては照射野内に含まれる正常組織

の放射線有害反応のリスクが問題となり，とくに重篤な症状が出る可能性のある脊髄や腸管に対する配慮が必要である．初回治療にわが国でもよく用いられている30Gy/10回の分割法を用いた場合，正常組織の残された耐容線量は少なく，一般的に再照射はおこなわないことが多い．しかしおもに30Gy/10回の分割法後の再照射として10Gy/5回から26Gy/13回の分割法をおこなった30例の後ろ向き解析の報告では，重篤な有害事象は認めておらず[25]，今後至適な分割法についての前向きな検討も必要かもしれない．

海外ではすでに再照射の分割法に関して，カナダを中心として英国，オランダ，トランスタスマンが共同して「疼痛再燃例に対する1回照射と分割照射のランダム化比較試験」を初のinternational trialとして現在施行中である(NCIC SC20)．この試験は上述の「国際的コンセンサス」に準拠して評価をおこなっている．

3）放射線療法による鎮痛作用機序

骨転移による疼痛発生機序の全貌はいまだ明らかでないが，近年，骨吸収調節機構などの分子生物学的な解明が進んでいる[26]．放射線療法による鎮痛作用についてもまだ明確にはなっていないが，破骨細胞や前駆細胞，神経終末などを破壊する直接的な作用と，腫瘍細胞を死滅させることにより，サイトカインの放出を抑制したり，mass effect（腫瘍の増大）による骨膜の伸展に伴う痛みを減じるなどの間接的な作用が考えられている．放射線療法による鎮痛効果のために腫瘍量を減じることだけをめざすのであれば，多くの線量が必要となるはずであるが，前述した少ない線量でも鎮痛効果が得られるのは，その他の多くの作用機序も関与しているためであると解釈できる．骨吸収抑制薬であるビスフォスフォネート製剤は破骨細胞に特異的に作用することがわかっているが，放射線療法は破骨細胞の主要な形成・活性化因子であるNF-κB活性化受容体（receptor activator of nuclear factor κB：RANK）にも作用することがわかってきた．今後の分子生物学的研究の発展による更なる骨転移痛のメカニズムの解明にて，放射線療法またはそれに限らず，より選択性の高い治療の開発も可能となるかもしれない．

4）放射線療法の技術的進歩

骨転移の放射線療法計画として，骨の輪郭はX線透視で比較的把握しやすく，疼痛のために治療体位の保持が困難な場合もあり短時間で計画できるX線シミュレータを用いての二次元の治療計画が従来からおこなわれている．近年CT画像データを用いた三次元治療計画が普及してきており，二次元による治療計画にくらべ，より高精度の治療が可能となり，周囲正常組織への線量を少なくして，腫瘍に高線量を投与することが可能となった．骨転移に関しては，CT画像でより的確に腫瘍の位置を把握したい場合や多方向からの照射をおこなう場合やリスク臓器をできるだけ避ける場合などに三次元治療計画がおこなわれることが多い．

さらにここ数年，高度のコンピュータ最適化技術を駆使して理想的な線量分布の実現が可能となる強度変調放射線療法（intensity modulated radiotherapy：IMRT）の有用性が頭頸部癌や前立腺癌などにおいて認められてきている．骨転移を対象とした報告として，椎体に対する再照射の際に定位照射やIMRTを安全かつ有効におこなえたとの報告があるが[27]，現状では骨転移に対しての適応は明確ではない．これらの治療には高度の位置精度の確保が要求されるため，患者の固定が重要であり，疼痛が激しい場合には長時間の体位保持は困難であろう．適応症例として，腫瘍がリスク臓器を含むあるいは近接する再照射例や原発巣が制御され，他に転移のない，単発性の骨転移症例に対する局所制御を目的とした場合に定位照射やIMRTが考慮されるかもしれない．しかし，骨転移に対する定位照射やIMRTの適応の選択，

有効性などは費用面も含めて今後の前向きな評価が必要である．

おわりに

疼痛対策としての放射線療法の役割は大きく，QOL改善を図ることができる．これまで得られたエビデンスをもとに患者ごとに目的，病気の進行状況，PSに応じて医療者と患者が相談して分割法を選択することが必要であろう．その際，有害事象も考慮し，照射範囲，照射方法についても個別に検討することも大事である．今後開発される新しい治療法については共通の基準(ものさし)を用いて，QOL，費用面の評価なども含めてよく計画された臨床試験で検討していくことが望まれる．

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Treatment of lung damage

Retrospective analysis of steroid therapy for radiation-induced lung injury in lung cancer patients

Ikuo Sekine[a,*], Minako Sumi[b], Yoshinori Ito[b], Hiroshi Nokihara[a], Noboru Yamamoto[a], Hideo Kunitoh[a], Yuichiro Ohe[a], Tetsuro Kodama[a], Nagahiro Saijo[a], Tomohide Tamura[a]

[a]*Division of Internal Medicine and Thoracic Oncology, and* [b]*Division of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan*

Abstract

***Purpose*: To disclose characteristics of lung cancer patients developing radiation-induced lung injury treated with or without corticosteroid therapy.**

***Methods and materials*: Radiographic changes, symptoms, history of corticosteroid prescription, and clinical course after 50–70 Gy of thoracic radiotherapy were retrospectively evaluated in 385 lung cancer patients.**

***Results*: Radiation-induced lung injury was stable without corticosteroid in 307 patients (Group 1), stable with corticosteroid in 64 patients (Group 2), and progressive to death despite corticosteroid in 14 patients (Group 3). Fever and dyspnea were noted in 11%, 50% and 86% ($p < 0.001$), and in 13%, 44% and 57% ($p < 0.001$) patients in Groups 1–3, respectively. Median weeks between the end of radiotherapy and the first radiographic change were 9.9, 6.7 and 2.4 for Groups 1–3, respectively ($p < 0.001$). The initial prednisolone equivalent dose was 30–40 mg daily in 52 (67%) patients. A total of 16 (4.2%) patients died of radiation pneumonitis or steroid complication with a median survival of 45 (range, 8–107) days.**

***Conclusion*: Development of fever and dyspnea, and short interval between the end of radiotherapy and the first radiographic change were associated with fatal radiation-induced lung injury. Prednisolone 30–40 mg daily was selected for the treatment in many patients.**

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Keywords: Radiation pneumonitis; Radiotherapy; Lung cancer; Corticosteroid

Thoracic radiotherapy is widely used for the curative and palliative treatment of lung cancer. Radiation-induced lung injury was first described as early as 1922 [1,2], and two types of lung injury, radiation pneumonitis and radiation fibrosis, were recognized in 1925 [3]. Radiation pneumonitis occurs in 5–15% of patients who have received radiation therapy for lung cancer. Its clinical symptoms are characterized by cough, dyspnea and fever developing between 1 and 3 months after the end of radiotherapy. Distinctive radiographic changes of radiation pneumonitis are a ground-glass opacification or diffuse haziness in early phase, and then alveolar infiltrates or dense consolidation in late phase in the region corresponding to the irradiated area [4–7]. Radiation pneumonitis may persist for a month or more and subside gradually. In severe cases, however, pneumonitis progresses to death due to respiratory failure within few weeks [4].

Use of adrenocorticotropic hormone (ACTH) and cortisone for radiation pneumonitis in a case was first reported in 1951 [8], and 9 cases of radiation pneumonitis treated with cortisone therapy in the literature were reviewed in 1968 [9]. Although no case series or clinical trials of corticosteroid therapy have been reported since that time, prednisolone has been given in patients with severe pneumonitis in clinical practice. The initial dose of prednisolone, approximately 30–100 mg daily, and very slow tapering schedule are in agreement among experts [4–6,10], because early withdrawal results in aggravation of pneumonitis [11–13]. There is no consensus, however, about criteria to define when steroids are required for radiation-induced lung injury. The objective of this study is to disclose general characteristics of lung cancer patients developing radiation-induced lung injury treated with or without corticosteroid therapy, to obtain data on the initiation criteria, dose, and taper schedule of corticosteroid therapy for further prospective trials.

Patients and methods

Consecutive lung cancer patients treated with thoracic radiotherapy at a total dose of 50–70 Gy in National Cancer

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Center Hospital between January 1998 and December 2003 were subjects of this study. We retrospectively reviewed all chest X-ray films taken during 6 month period from the end of thoracic radiation to identify the first radiographic change and its progress. History of corticosteroid prescription, symptoms at the time of and one-month period after the first radiographic change in a chest X-ray film, and clinical course of radiation-induced lung injury were obtained from medical charts. The diagnosis of radiation-induced lung injury was defined as radiographic changes including opacification, diffuse haziness, infiltrates or consolidation conforming to the outline of the sharply demarcated irradiated area in a chest X-ray film. During clinical course, scarring (fibrosis) was developed within the irradiated area leading to a reduction in lung volume. In contrast, pulmonary infection spreads through anatomical structure of the lung, and the boundary of infiltrates corresponds to anatomical boundary of the lung. For patients with fever, the radiographical response to antibiotics was also evaluated. Observed differences in the proportions of patients in various patient subgroups were evaluated using Chi-square test. Differences between continuous variables were compared using Mann–Whitney tests. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for all statistical analyses.

Results

Of 544 lung cancer patients receiving thoracic radiotherapy at a total dose of 50–70 Gy, 111 patients were excluded from this study because they were not evaluable: loss of follow-up in 88 patients, early lung cancer progression in 18 patients, chemotherapy-induced neutropenic fever and pneumonia in three patients, death of bleeding from the esophageal stent in one patient, and no chest X-ray films available in one patient. In addition, 48 patients (11% of 433 evaluable patients) were also excluded because no radiation-induced lung injury was noted. Thus, the subject of this study was 385 patients.

Of the 385 patients, 78 (20%) received corticosteroid therapy for radiation-induced lung injury, and 307 did not. Radiation-induced lung injury was stable without corticosteroid in the 307 (80%) patients (Group 1), stable or in remission with corticosteroid in 64 (17%) patients (Group 2), and progressive to death despite corticosteroid in 14 (4%) patients (Group 3). No difference in sex, total dose, intent of radiotherapy, and combination chemotherapy was noted among three Groups, but median age of patients was higher in Group 3 (Table 1). Fever was developed in 50% of patients in Group 3 at the initial radiographic change, and in 86% of them during subsequent clinical course, while it was developed in only 11–12% of patients in Group 1 through their clinical course (Table 2). Dyspnea was developed in 57% of patients in Group 3 and in 44% of patients in Group 2 during clinical course, while it was developed in only 14% of patients in Group 1 (Table 2). A total of 88 patients developed fever at the initial change in chest X-ray and/or during subsequent clinical course. Of these, 43 patients received antibiotics, but no radiographical response was obtained in these patients. Five (2%) and seven (2%) patients in Group 1 developed bloody sputum and chest pain, respectively, but none in Group 2 or 3 developed these symptoms. The average interval of chest X-rays taken between the start of radiotherapy and the first appearance of radiographic change was 1.7 weeks for group 1, 1.3 weeks for group 2, and 0.9 weeks for group 3 ($P < 0.001$, Table 3). Interval between the end of radiotherapy and the first change in a chest X-ray was shorter in Group 3 than in Group 2 or Group 1 (Table 3). Of 57 patients in whom the first radiographic change was noted within three weeks, 9 (16%) died of pneumonitis, while radiation-induced lung injury that occurred 10 weeks or later after the end of radiation was easily managed with or without steroid therapy (Table 3). Oxygen content in the blood at the start of steroid therapy was examined in 70 patients of Groups 2 and 3. Oxygen content

Table 1
Patient demographics and radiotherapy performance

Characteristics	Total *N* (%)	Group 1	Group 2	Group 3	*p*-value
		N (%)	*N* (%)	*N* (%)	
Total	385 (100)	307 (80)	64 (17)	14 (4)	
Sex					
Male	300 (78)	240 (78)	47 (73)	13 (93)	0.28
Female	85 (22)	67 (22)	17 (27)	1 (7)	
Age median (range)	65 (28–87)	63 (28–87)	65 (37–83)	71 (65–84)	0.008
Total dose (Gy)					
Median (range)	60 (50–70)	60 (50–70)	60 (50–61)	60 (50–60)	0.50
Intent of radiotherapy					
Curative	298 (77)	232 (76)	52 (81)	14 (100)	0.074
Palliative	87 (23)	75 (24)	12 (19)	0 (0)	
Chemotherapy					
None	121 (31)	101 (33)	15 (23)	5 (36)	0.48
Sequential	121 (31)	93 (30)	25 (39)	3 (21)	
Concurrent	143 (37)	113 (37)	24 (38)	6 (43)	

Table 2
Symptoms through clinical courses

Symptom	At the initial change in chest X-ray				During subsequent clinical course			
	Group 1	Group 2	Group 3	p	Group 1[a]	Group 2[b]	Group3[b]	p
Cough	96 (31)	35 (56)	5 (36)	0.001	85 (28)	38 (59)	5 (36)	<0.001
Sputum	32 (10)	11 (18)	4 (29)	0.049	30 (10)	11 (17)	3 (21)	0.12
Hemosputum	5 (2)	0 (0)	0 (0)	0.53	4 (1)	0 (0)	0 (0)	0.60
Chest pain	7 (2)	0 (0)	0 (0)	0.40	2 (0.6)	0 (0)	0 (0)	0.78
Fever								
None	269 (88)	35 (56)	7 (50)	<0.001	272 (89)	32 (50)	2 (14)	<0.001
37.0–37.9 °C	18 (6)	11 (18)	2 (14)	24 (8)	16 (25)	5 (35)		
38 °C≤	13 (4)	14 (22)	5 (36)	8 (3)	13 (20)	7 (50)		
Not specified	7 (2)	3 (4)	0 (0)	3 (1)	3 (4)	0 (0)		
Dyspnea	43 (14)	14 (22)	6 (43)	0.007	40 (13)	28 (44)	8 (57)	<0.001
Fever or dyspnea	75 (24)	37 (58)	10 (71)	<0.001	65 (21)	49 (77)	14 (100)	<0.001
Any	150 (49)	51 (81)	13 (93)	<0.001	118 (38)	60 (94)	14 (100)	<0.001

[a] During one month period following the initial change in the chest X-ray.
[b] At the start of steroid therapy.

Table 3
The chest X-ray intervals and first radiographic change

Weeks	Group 1	Group 2	Group 3	p-value
The average interval of chest X-rays (weeks)[a]				
Median (range)	1.7 (0.7 to 6.0)	1.3 (0.5 to 4.4)	0.9 (0.5 to 3.8)	<0.001
Duration between the end of radiotherapy and the first radiographic change (weeks)				
Median (range)	9.9 (−2.9 to 45.1)	6.7 (0 to 24.9)	2.4 (0.4 to 10.1)	<0.001
<6	82 (27)	26 (41)	11 (79)	<0.001
6–11.9	116 (38)	29 (45)	3 (21)	
12–17.9	71 (23)	7 (11)	0 (0)	
18≤	38 (12)	2 (3)	0 (0)	

[a] Calculated as follows: the average interval of chest X-rays = (the first radiographic change − the start of radiotherapy)/the number of chest X-rays taken during this period/7).

was slightly decreased (PaO2 = 70–74.9 Torr) in 12 (19%) patients of Group 2 and one (7%) patient of Group 3, and moderately to severely decreased (PaO2 ⩽ 69.9 Torr or SpO2 ⩽ 92%) in 21 (33%) patients of Group 2 and 7 (50%) patients of Group 3 ($p = 0.38$).

Prednisolone was administered as the initial therapy in 69 (88%) patients of Groups 2 and 3. The initial prednisolone equivalent dose of steroid was 30–40 mg daily in 52 (67%), and 60 mg of higher only in 8 (10%) patients (Table 4). The median duration of the initial dose was 10 (range, 2–64) days, and the dose was reduced within 14 days in 57 (77%) patients. The median duration of steroid therapy was 10 (range, 2–28) weeks (Table 4). Steroid pulse therapy (methylprednisolone 1000 mg daily for three days) was administered as the initial therapy in one patient, and as salvage therapy in six patients at the time of pneumonitis aggravation. Among the seven patients, six died of respiratory failure due to progressive radiation pneumonitis.

Outcome of steroid therapy was evaluated in 76 patients (Fig. 1). Symptomatic relief was obtained and the steroid dose was reduced in 71 (93%) of the 76 patients, while no effect was noted in the remaining five patients, who all died of radiation pneumonitis despite escalated steroid administration. Of the 71 patients, 15 (21%) developed recurrent symptoms at the median daily prednisolone dose of 20 mg (range, 10–40 mg) within median 33 days (range, 21–42 days) from the start of the steroid therapy, and required steroids to be escalated. Of the 15 patients, nine died of radiation pneumonitis and one died of complication of steroid therapy. A total of 54 (71%) patients were in remission from pneumonitis and steroid therapy was terminated. The remainder 22 patients died during steroid therapy, 14 of radiation pneumonitis, two of infectious complication (bacterial pneumonia in one, and lung aspergillosis in another patient), five of lung cancer progression, and one of hemoptysis. Thus, 16 patients, who accounted for 4.2% of 385 patients receiving 50–70 Gy of thoracic radiotherapy, and who accounted for 21% of 78 patients treated with steroid therapy, died of radiation pneumonitis or complication associated with steroid therapy. Median survival from the start of steroid therapy in these patients was 45 (range, 8–107) days.

Discussion

Patients with radiation-induced lung injury have been managed in compliance with the expert opinions, because there has been no case series or clinical trial report on clinical course and corticosteroid use for this lung injury. This

Table 4
Corticosteroid, dose and duration of steroid therapy

	N (%)
Corticosteroid	
Prednisolone	69 (88)
Dexamethasone	4 (5)
Betamethasone	4 (5)
Methylprednisolone	1 (1)
Initial dose, mg/body daily (prednisolone equivalent)	
Pulse therapy	1 (1)
60	7 (9)
50	1 (1)
40	10 (13)
30	42 (54)
10–25	17 (22)
Duration of the initial dose, days	
Median (range)	10 (2–64)
⩽14	57 (77)
15–28	9 (12)
29⩽	8 (11)
Not evaluable	4
Total duration of steroid therapy, weeks	
Median (range)	10 (2–28)
⩽6	16 (30)
6.1–12	19 (35)
12.1–18	14 (26)
18.1⩽	5 (9)
Not evaluable	24

study is the first systemic review of these patients both who received corticosteroid therapy and who did not. Comparison between the expert opinions and the results of this study is given below. First, radiation-induced lung injury is severer when a radiographic change appears earlier [5]. In this study, the initial change in a chest X-ray film was observed in 9.9 (range, −3 to 45) weeks in Group 1, in 6.7 (range, 0–25) weeks in Group 2, and 2.4 (range, 0–10) weeks in Group 3 after the end of thoracic radiotherapy. If patients present with symptoms, presumably they receive a chest X-ray. Thus, the patients with symptoms may have radiographic findings seen sooner, since they receive an X-ray when they complain of symptoms. The average interval of chest X-rays taken between the start of radiotherapy and the first appearance of radiographic change was longer in Group 1 than that in groups 2 and 3. The difference, however, was negligibly small when compared with the difference in duration between the end of radiotherapy and the first radiographic change. Second, steroid administration is determined generally based on the severity of symptoms [5]. In this study steroid was used when patients developed dyspnea or fever. Dyspnea has been thought to be the cardinal symptom of radiation pneumonitis but fever to be unusual [5,10]. In this study, however, fever was highly associated with fatal radiation pneumonitis; fever was noted in 12% patients of Group 1, in 58% patients of Group 2, and 86% patients of Group 3. This study failed to show utility of blood gas analysis. An oxygen content in the blood was decreased moderately to severely in only 28 (36%) patients in Groups 2 and 3, and did not differ between the two groups. The oxygen content in Group 1 was measured in only small number of patients, and therefore it was not evaluable in this study. Third, 30–100 mg/day of prednisolone has been recommended as the initial dose [4–6,10]. In our practice, a dose of 30–40 mg was the most frequently used. We selected this relatively low dose of steroid mostly because steroid therapy was started in out patient clinic. Forth, duration of the initial dose was within two weeks in 73% of patients, which is consistent to most expert opinions [6,10]. In contrast, tapering schedules varied between a pa-

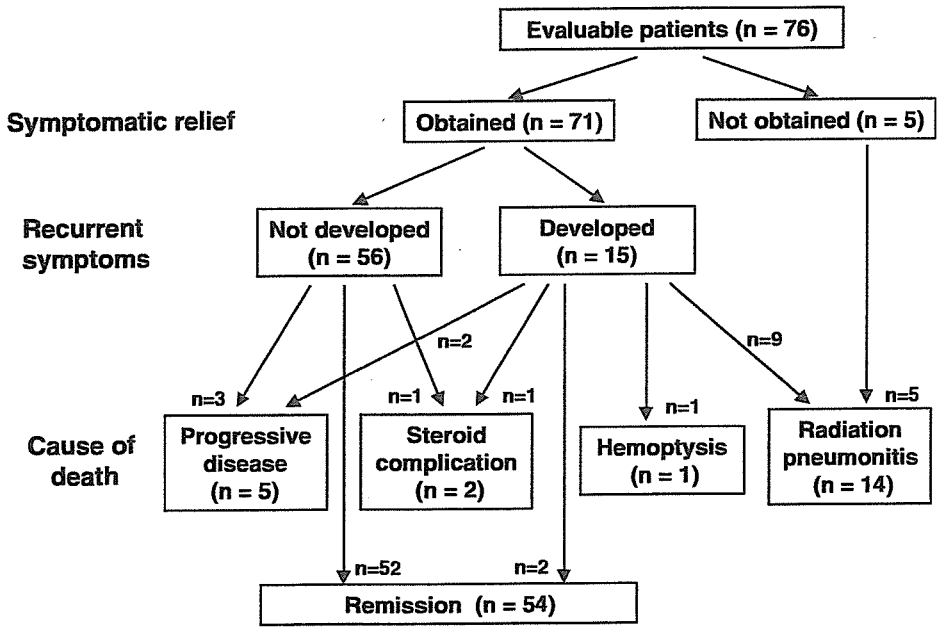

Fig. 1. Outcome of patients who received steroid therapy. Two patients were excluded because of loss of follow-up. Of 76 evaluable patients, 71 (93%) experienced symptomatic relief by steroid therapy.

tient and another in this study. This may be partly due to the diversity in clinical course of radiation pneumonitis, but mostly due to lacking in available recommendation for tapering schedules. In this study, median total duration of steroid therapy was 10 weeks, which may be a tentative guide. A guideline of taper schedule appeared in the latest textbook: the dose should be tapered by 10 mg every two weeks, and be terminated in 12 weeks [10].

Although our clinical practice mostly followed the expert opinions on the management of radiation-induced lung injury as mentioned above, there is little evidence that our steroid use, dose and duration for radiation-induced lung injury were correct. In this study, 21% of patients received steroid therapy and 4% of patients died of radiation pneumonitis among lung cancer patients treated with thoracic radiotherapy at a total dose of 50 Gy or higher. These figures are comparable to the incidence of grade 3 pneumonitis, 3–20%, and that of fatal pneumonitis, 1–4%, in other reports [10].

In conclusion, development of fever and dyspnea, and short interval between the end of radiotherapy and the first radiographic change were associated with fatal radiation-induced lung injury. Prednisolone 30–40 mg daily for two weeks followed by slow taper was selected for the treatment in many patients.

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* **Corresponding author. Ikuo Sekine**, Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. *E-mail address:* isekine@ncc.go.jp

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Docetaxel Consolidation Therapy Following Cisplatin, Vinorelbine, and Concurrent Thoracic Radiotherapy in Patients with Unresectable Stage III Non-small Cell Lung Cancer

Ikuo Sekine, Hiroshi Nokihara,* Minako Sumi,† Nagahiro Saijo,‡ Yutaka Nishiwaki,§ Satoshi Ishikura,|| Kiyoshi Mori,¶ Iwao Tsukiyama,# and Tomohide Tamura**

Background: To evaluate the feasibility and efficacy of docetaxel consolidation therapy after concurrent chemoradiotherapy for unresectable stage III non–small cell lung cancer (NSCLC).

Patients and Methods: The eligibility criteria included unresectable stage III NSCLC, no previous treatment, age between 20 and 74 years, and performance status 0 or 1. Treatment consisted of cisplatin (80 mg/m^2 on days 1, 29, and 57), vinorelbine (20 mg/m^2 on days 1, 8, 29, 36, 57, and 64), and thoracic radiotherapy (TRT) (60 Gy/30 fractions over 6 weeks starting on day 2), followed by consolidation docetaxel (60 mg/m^2 every 3 to 4 weeks for three cycles).

Results: Of 97 patients who were enrolled in this study between 2001 and 2003, 93 (76 males and 17 females with a median age of 60) could be evaluated. Chemoradiotherapy was well tolerated; three cycles of chemotherapy and 60 Gy of TRT were administered in 80 (86%) and 87 (94%) patients, respectively. Grade 3 or 4 neutropenia, esophagitis, and pneumonitis developed in 62, 11, and 3 patients, respectively. Docetaxel consolidation was administered in 59 (63%) patients, but three cycles were completed in only 34 (37%) patients. The most common reason for discontinuation was pneumonitis, which developed in 14 (24%) of the 59 patients. During consolidation therapy, grade 3 or 4 neutropenia, esophagitis, and pneumonitis developed in 51, 2, and 4 patients, respectively. A total of four patients died of pneumonitis. We calculated a V_{20} (the percent volume of the normal lung receiving 20 Gy or more) on a dose–volume histogram in 25 patients. Of these, five patients developed grade 3 or more severe radiation pneumonitis. A median V_{20} for these five patients was 35% (range, 26–40%), whereas the median V_{20} for the remaining 20 patients was 30% (range, 17–35%) (p = 0.035 by a Mann–Whitney test). The response rate was 81.7% (95% confidence interval [CI], 72.7–88.0%), with 5 complete and 71 partial responses. The median progression-free survival was 12.8 (CI, 10.2–15.4) months, and median survival was 30.4 (CI, 24.5–36.3) months. The 1-, 2-, and 3-year survival rates were 80.7, 60.2, and 42.6%, respectively.

Conclusion: This regimen produced promising overall survival in patients with stage III NSCLC, but the vast majority of patients could not continue with the docetaxel consolidation because of toxicity.

Key Words: Non-small cell lung cancer, Chemoradiotherapy, Consolidation, Docetaxel.

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Locally advanced unresectable non–small cell lung cancer (NSCLC), stage IIIA with bulky N2 and stage IIIB disease without pleural effusion, is characterized by large primary lesions and/or involvement of the mediastinal or supraclavicular lymph nodes and occult systemic micrometastases. A combination of thoracic radiotherapy and chemotherapy is the standard medical treatment for this disease, but the optimal combination has not been established.[1] Although the available data are insufficient to accurately define the size of a potential benefit,[2] concurrent chemoradiotherapy using a platinum doublet has been shown to be superior to the sequential approach in phase III trials of this disease.[3–5] However, third-generation cytotoxic agents, which have provided better patient survival with extrathoracic spread than the old-generation agents, must be reduced when administered concurrently with thoracic radiotherapy.[6] Thus, it has been hypothesized that the addition of systemic dose chemotherapy with a new cytotoxic agent to concurrent chemoradiotherapy, either as induction or as consolidation chemotherapy, might further improve patient survival.[1]

The consolidation chemotherapy with docetaxel was based on the observation that this drug was highly active in the primary treatment of metastatic NSCLC, producing a response rate (RR) as high as 20% after platinum-based chemotherapy failed.[7–9] Highly encouraging results of a me-

Divisions of *Internal Medicine and Thoracic Oncology, and †Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan; Divisions of ‡Internal Medicine, §Thoracic Oncology, and ||Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Japan; and Divisions of ¶Thoracic Oncology and #Radiotherapy, Tochigi Cancer Center, Utsunomiya, Japan.

Address for correspondence: Ikuo Sekine, Division of Thoracic Oncology and Internal Medicine, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. E-mail: isekine@ncc.go.jp

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dian survival time (MST) of more than 2 years and a 3-year survival rate of nearly 40% were obtained in a phase II trial of docetaxel consolidation after chemoradiotherapy with cisplatin and etoposide in patients with stage IIIB NSCLC (SWOG study S9504).[10]

We have developed a combination chemotherapy schedule with cisplatin and vinorelbine concurrently administered with thoracic radiotherapy at a total dose of 60 Gy in 30 fractions in patients with unresectable stage III NSCLC. The results of a phase I study in 18 patients were very promising, with a RR of 83%, a MST of 30 months, and a 3-year survival rate of 50%.[6] Thus, addition of docetaxel consolidation to this regimen is a particularly interesting therapeutic strategy. The objectives of the current study were to evaluate the feasibility of docetaxel consolidation therapy after concurrent chemoradiotherapy with cisplatin and vinorelbine and to evaluate the efficacy and safety of the whole treatment regimen including both the chemoradiotherapy and consolidation therapy in patients with unresectable stage IIIA and IIIB NSCLC.

PATIENTS AND METHODS

Patient Selection

The eligibility criteria were histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease; no previous treatment; measurable disease; tumor within an estimated irradiation field no larger than half the hemithorax; age between 20 and 74 years; Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; adequate bone marrow function (12.0×10^9/liter $\geq$ white blood cell [WBC] count $\geq 4.0 \times 10^9$/liter, neutrophil count $\geq 2.0 \times 10^9$/liter, hemoglobin ≥ 10.0 g/dl, and platelet count $\geq 100 \times 10^9$/liter), liver function (total bilirubin ≤ 1.5 mg/dl and transaminase no more than twice the upper limit of the normal value), and renal function (serum creatinine ≤ 1.5 mg/dl and creatinine clearance ≥ 60 ml per minute); and a PaO_2 of 70 torr or more under room air conditions. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonia or lung fibrosis identified by a chest x-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or if they were 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 computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan or ultrasonography, and radionuclide bone scan.

Treatment Schedule

Treatment consisted of a chemoradiotherapy phase with three cycles of cisplatin and vinorelbine followed by a consolidation phase with three cycles of docetaxel (Figure 1). Cisplatin 80 mg/m^2 was administered on days 1, 29, and 57 by intravenous infusion for 60 minutes with 2500 to 3000 ml of fluid for hydration. Vinorelbine diluted in 50 ml of normal saline was administered intravenously on days 1, 8, 29, 36, 57, and 64. All patients received prophylactic antiemetic therapy consisting of a $5HT_3$-antagonist and a steroid.

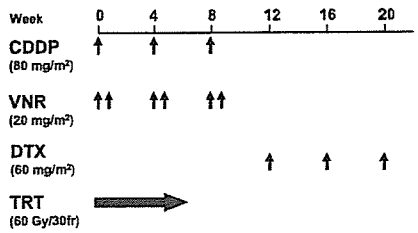

FIGURE 1. Treatment schema. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

Radiation therapy was delivered with megavoltage equipment ($\geq$6 MV) using anterior/posterior opposed fields up to 40 Gy in 20 fractions including the primary tumor, the metastatic lymph nodes, and the regional nodes. A booster dose of 20 Gy in 10 fractions was given to the primary tumor and the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique fields. A CT scan–based treatment planning was used in all patients. The clinical target volume (CTV) for the primary tumor was defined as the gross tumor volume (GTV) plus 1 cm taking account of subclinical extension. CTV and GTV for the metastatic nodes (>1 cm in shortest dimension) were the same. Regional nodes, excluding the contralateral hilar and supraclavicular nodes, were included in the CTV, but the lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The planning target volumes for the primary tumor, the metastatic lymph nodes, and regional nodes were determined as CTVs plus 0.5- to 1.0-cm margins laterally and 1.0- to 2.0-cm margins craniocaudally, taking account of setup variations and internal organ motion. Lung heterogeneity corrections were not used.

The criteria for starting consolidation chemotherapy were completion of three cycles of cisplatin and vinorelbine and a full dose of thoracic radiotherapy, the absence of progressive disease, adequate general condition within 6 weeks of the start of the third cycle of cisplatin and vinorelbine (PS 0 or 1, WBC count $\geq 3.0 \times 10^9$/liter, neutrophil count $\geq 1.5 \times 10^9$/liter, hemoglobin ≥ 9.0 g/dl and platelet count $\geq 100 \times 10^9$/liter, total bilirubin ≤ 1.5 mg/dl and transaminase no more than twice the upper limit of the normal value, and a PaO_2 of 70 torr or more at room air). Docetaxel (60 mg/m^2) was administered intravenously for 1 hour every 3 to 4 weeks for three cycles.

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. Acute toxicity was graded according to the NCI Common Toxicity Criteria, and late toxicity associated with thoracic radiother-

apy was graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. Vinorelbine administration on day 8 was omitted if any of the following were noted: WBC count $<3.0 \times 10^9$/liter, neutrophil count $<1.5 \times 10^9$/liter, platelet count $<100 \times 10^9$/liter, elevated hepatic transaminase level or total serum bilirubin of at least grade 2, fever ≥38°C, or PS ≥2. Subsequent cycles of cisplatin and vinorelbine chemotherapy were delayed if any of the following toxicities were noted on day 1: WBC count $<3.0 \times 10^9$/liter, neutrophil count $<1.5 \times 10^9$/liter, platelet count $<100 \times 10^9$/liter, serum creatinine level ≥1.6 mg/dl, elevated hepatic transaminase level or total serum bilirubin of at least grade 2, fever ≥38°C, or PS ≥2. 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 or docetaxel was reduced by 25% in all subsequent cycles if any of the following toxicities were noted: WBC count $<1.0 \times 10^9$/liter, platelet count $<10 \times 10^9$/liter, or grade 3 or 4 infection or liver dysfunction. Thoracic radiotherapy was suspended if any of the following were noted: fever ≥38°C, grade 3 esophagitis, PS of 3, or PaO_2 <70 torr. 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 60 days. The use of granulocyte colony-stimulating factor during radiotherapy was not permitted unless radiotherapy was on hold. The criteria for termination of docetaxel consolidation were not defined in the protocol.

Response Evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumor.[11] Local recurrence was defined as tumor progression in the primary site and in the hilar, mediastinal, and supraclavicular lymph nodes after a partial or complete response; regional recurrence as the development of malignant pleural and pericardial effusions; and distant recurrence as the appearance of a distant metastasis.

Study Design, Data Management, and Statistical Considerations

This study was conducted at three institutions: the National Cancer Center Hospital, National Cancer Center Hospital East, and Tochigi Cancer Center. The protocol and consent form were approved by the institutional review board of each institution. Registration was conducted at the registration center. Data management, periodic monitoring, and the final analysis were performed by the study coordinator.

The primary objective of the current study was to evaluate the feasibility of docetaxel consolidation therapy. The secondary endpoints were toxicity observed during chemoradiotherapy and consolidation therapy, the best response, and overall survival in all patients eligible to participate in this study. Because no standard method to evaluate consolidation chemotherapy after chemoradiotherapy has been established, we arbitrarily defined the primary endpoint of this study as a ratio (R) of the number of patients receiving docetaxel without grade 4 nonhematological toxicity or treatment-related death to the total number of patients receiving docetaxel. The sample size was initially estimated to be 34 patients with a power of 0.80 at a significance level of 0.05, under the assumption that a R of 0.95 would indicate potential usefulness, whereas a R of 0.8 would be the lower limit of interest, and that 85% of patients would move into the consolidation phase. An analysis of the first 13 patients, however, showed that only 8 (61%) patients advanced into the consolidation phase. The reasons for not receiving docetaxel were disease progression in one, delay in completion of chemoradiotherapy in two, grade 3 esophagitis in one, and death due to hemoptysis in one patient. Considering that the SWOG trial S9504 included 83 patients, we decided to revise the number of patients in the current study. According to Simon's two-stage minimax design, the required number of patients was calculated to be 59 with a power of 0.80 at a significance level of 0.05, under the assumption that a R of 0.85 would indicate potential usefulness, whereas a R of 0.7 would be the lower limit of interest.[12] Assuming that 61% of registered patients would move into the consolidation phase, the sample size was determined to be 97 patients.

Overall survival time and progression-free survival time were estimated by the Kaplan–Meier method, and confidence intervals (CI) were based on Greenwood's formula.[13] Overall survival time was measured from the date of registration to the date of death (from any cause) or to the last follow-up. Progression-free survival time was measured from the date of registration to the date of disease progression, death (from any cause), or the last follow-up. Patients who were lost to follow-up without event were censored at the date of their last known follow-up. A CI for RR was calculated using methods for exact binomial CIs. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for statistical analyses.

RESULTS

Registration and Characteristics of the Patients

A total of 97 patients were enrolled in this study between April 2001 and June 2003. Four patients were excluded from this study before the treatment was started because the radiation treatment planning disclosed that their tumors were too advanced for curative thoracic radiotherapy. Thus, 93 patients who received the protocol-defined treatment were the subjects of this analysis (Figure 2). There were 76 males and 17 females, with a median age of 60 (range 31–74). Body weight loss was less than 5% in 77 patients; adenocarcinoma histology was noted in 57 patients, and stage IIIA disease was noted in 41 patients (Table 1).

Treatment Delivery

Treatment delivery was generally well maintained in the chemoradiotherapy phase (Table 2). Full cycles of cisplatin and vinorelbine and the full dose of thoracic radiotherapy were administered in 80 (86%) and 87 (94%) patients, respectively. Delay in radiotherapy was less than 5 days in 61 (66%) patients. In contrast, the delivery of docetaxel was poor (Table 2). A total of 59 (63%) patients could enter the consolidation phase, and only 34 (37%) patients completed three cycles of docetaxel chemotherapy. The reasons for not

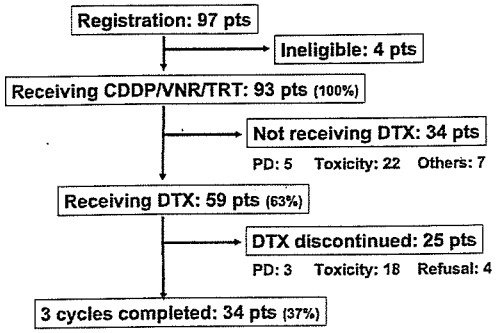

FIGURE 2. Patient registration. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

receiving consolidation were toxicity in 22 (65%) patients including pneumonitis in seven patients, myelosuppression in five patients, esophagitis in four patients, liver dysfunction in two patients, infection in two patients, other toxicity in two patients, progressive disease in five (15%) patients, patient refusal in three (9%) patients, early death due to hemoptysis in one (3%) patient, and other reasons in three (9%) patients. Of the 59 patients, 18 (31%) discontinued docetaxel consolidation because of toxicity, including pneumonitis (n = 14) and esophagitis, infection, gastric ulcer, and allergic reaction (n = 1 each), four (7%) because of patient refusal, and three (5%) because of progressive disease.

Toxicity

Acute severe toxicity in the chemoradiotherapy phase was mainly leukopenia and neutropenia, whereas grade 3 or 4 thrombocytopenia was not noted (Table 3). Severe nonhematological toxicity was sporadic, and grade 3 esophagitis and pneumonitis were observed in only 11 (12%) and 3 (3%) patients, respectively. Acute severe toxicity in the consolidation phase also consisted of neutropenia and associated infection (Table 4). In addition, grade 3 or 4 pneumonitis developed in 4 (7%) patients. The R observed in this study was 0.05 (3 out of 57 patients), which was much lower than the hypothetical value. Grade 3 or 4 late toxicities were included lung toxicity in four patients, esophageal toxicity in two patients, renal toxicity in one patient, and a second esophageal cancer that developed 35.4 months after the start of the chemoradiotherapy in one patient. Treatment-related

TABLE 1. Patient Characteristics

Characteristics	n	%
Gender		
Male	76	82
Female	17	18
Age median (range)	60	31–74
Weight loss		
<5%	76	81
5–9%	12	13
≥10%	3	3
Unknown	2	2
Histology		
Adenocarcinoma	57	61
Squamous cell carcinoma	23	25
Large cell carcinoma	12	13
Others	1	1
Stage		
IIIA	41	44
IIIB	52	56

TABLE 2. Treatment Delivery

Variables	n	%
Cisplatin and vinorelbine chemotherapy		
Total number of cycles		
3	80	86
2	10	11
1	3	3
Number of vinorelbine skips		
0	63	68
1	25	27
2–3	5	5
Thoracic radiotherapy		
Total dose (Gy)		
60	87	94
50–59	4	4
<50	2	2
Delay (days)		
<5	61	66
5–9	20	22
10–16	6	6
Not evaluable (<60 Gy)	6	6
Docetaxel consolidation		
Number of cycles		
3	34	37
2	12	13
1	13	14
0	34	34

TABLE 3. Acute Toxicity in Chemoradiotherapy (n = 93)

	Grade			
Toxicity	3	4	3 + 4	%
Leukopenia	54	18	72	77
Neutropenia	33	29	62	67
Anemia	21	0	21	23
Infection	15	1	16	17
Esophagitis	11	0	11	12
Hyponatremia	11	0	11	12
Anorexia	9	1	10	11
Nausea	5	—	5	5
Pneumonitis	3	0	3	3
Syncope	2	0	2	2
Hyperkalemia	2	0	2	2
Ileus	0	1	1	1
Cardiac ischemia	1	0	1	1

TABLE 4. Acute Toxicity in Consolidation Therapy (n = 57)

	Grade			
Toxicity	3	4	3 + 4	%
Leukopenia	33	11	44	77
Neutropenia	24	26	50	88
Anemia	5	0	5	9
Infection	5	1	6	11
Esophagitis	2	0	2	3
Anorexia	1	0	1	2
Pneumonitis	2	2	4	7

death was observed in four (4%) patients. Of these, three received docetaxel, and one did not. The reason for death was pneumonitis in all patients. We calculated a V_{20} (the percent volume of the normal lung receiving 20 Gy or more) on a dose–volume histogram in 25 patients. Of these, five patients developed grade 3 or severer radiation pneumonitis. A median V_{20} for these five patients was 35% (range, 26–40%), whereas that for the remaining 20 patients was 30% (range, 17–35%) (p = 0.035 by a Mann–Whitney test).

Objective Responses, Relapse Pattern, and Survival

All 93 patients were included in the analyses of tumor response and survival. Complete and partial responses were obtained in 5 (5%) and 71 patients (76%), respectively, for an overall RR of 81.7% (95% CI, 72.7–88.0%). Stable and progressive diseases occurred in 12 (13%) and 5 (5%) patients, respectively. With a median follow-up period of 29.7 months, 38 patients developed locoregional recurrence, 32 developed distant recurrence, 4 developed both locoregional and distant recurrences, and 19 did not. The median progression-free survival time was 12.8 (95% CI, 10.2–15.4) months (Figure 3). Two patients underwent salvage surgery for a recurrent primary tumors. Conventional chemotherapy and gefitinib monotherapy were administered after recurrence in 20 and 25 patients, respectively. The median overall survival time was 30.4 (95% CI, 24.5–36.3) months. The 1-, 2-, and 3-year survival rates were 80.7, 60.2, and 42.6%, respectively. (Figure 4).

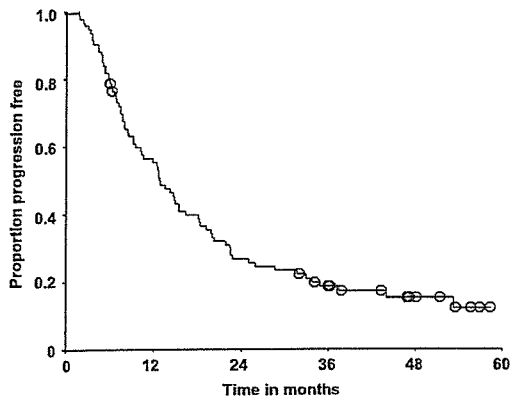

FIGURE 3. Progression-free survival (n = 93). The median progression-free survival time was 12.8 (95% CI, 10.2–15.4) months.

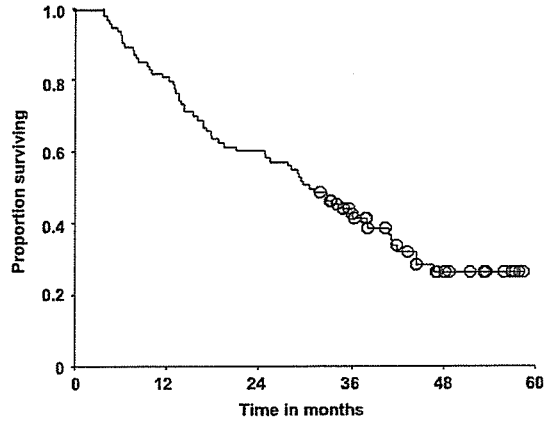

FIGURE 4. Overall survival (n = 93). The median overall survival time was 30.4 (95% CI, 25.4–35.4) months. The 1-, 2-, and 3-year survival rates were 80, 60, and 40%, respectively.

DISCUSSION

This study showed that concurrent chemoradiotherapy with cisplatin, vinorelbine, and standard thoracic radiotherapy was well tolerated, with a high completion rate exceeding 80%. The incidence of acute toxicity, including 67% (62/93) of grade 3 or 4 neutropenia, 12% (11/93) of grade 3 esophagitis, and 3% (3/93) of grade 3 pneumonitis, were comparable with other reports of concurrent chemoradiotherapy.[3,4,10] In contrast, consolidation docetaxel could be administered in only 59 of 93 (63%) patients eligible to participate in this study. Of the remaining 34 patients, 22 (65%) patients did not receive consolidation chemotherapy because of toxicities affecting various organs. Other studies also showed that not all patients proceeded to the consolidation phase after completion of concurrent chemoradiotherapy: 61 to 78% of patients after two cycles of cisplatin and etoposide with radiotherapy,[3,10] and 54 to 75% of patients after weekly carboplatin and paclitaxel with radiotherapy.[14,15] Thus, for 20 to 40% of the patients, concurrent chemoradiotherapy was as much as they could undergo, and the additional chemotherapy was not practical.

Furthermore, the number of patients who fulfilled the three cycles of consolidation docetaxel was only 34 (58%) of the 59 patients, which corresponded to only 37% of those eligible in this study. The reason for the termination of docetaxel in the 25 patients was toxicity in 18 (72%) patients, especially pneumonitis in 14 (56%) patients. The grade of pneumonitis during the consolidation phase was within grade 2 in most cases, and this was probably because docetaxel was discontinued early. Considering that pneumonitis associated with cancer treatment is more common in Japan, docetaxel consolidation is not thought to be feasible in the Japanese population. The MST and the 3-year survival rate in all eligible patients were 33 months and 44% in this study, but docetaxel consolidation was unlikely to contribute to these promising results because only 37% of patients received full cycles of docetaxel. This contrasts clearly with the result of

the SWOG study S9504, a phase II trial of two cycles of cisplatin and etoposide with thoracic radiation followed by three cycles of docetaxel. In this trial, 75% of patients starting consolidation and 59% of those entering the trial received full cycles. In addition, docetaxel consolidation seemed to prolong survival, although this was drawn from a retrospective comparison of the results between the two SWOG studies S9504 and S9019.[10]

There is no widely used definition of consolidation therapy following chemoradiotherapy. Given that consolidation therapy is arbitrarily defined as chemotherapy with three cycles or more after the completion of concurrent chemoradiotherapy, only one randomized trial is available in the literature. The randomized phase III trial of standard chemoradiotherapy with carboplatin and paclitaxel followed by either weekly paclitaxel or observation in patients with stage III NSCLC showed that only 54% of patients proceeded to randomization, and overall survival was worse in the consolidation arm (MST, 16 versus 27 months).[15] Thus, there have been no data supporting the use of consolidation therapy, especially when a third-generation cytotoxic agent such as paclitaxel and vinorelbine is incorporated into concurrent chemoradiation therapy.

The low complete-response rate of 5% in this study may be explained partly by an inability to distinguish between inactive scarring or necrotic tumor and active tumor after radiotherapy. Positron emission tomography (PET) using 18F-fluorodeoxyglucose showed a much higher rate of complete response than conventional CT scanning and provided a better correlation of the response assessment using PET with patterns of failure and patient survival.[16] In addition, the high locoregional relapse rate in this study clearly showed that the conventional total dose of 60 Gy was insufficient. Three-dimensional treatment planning, omission of elective nodal irradiation, and precise evaluation of the gross tumor volume by PET may facilitate the escalation of the total radiation dose without enhanced toxicity.

In conclusion, cisplatin and vinorelbine chemotherapy concurrently combined with standard thoracic radiotherapy and followed by docetaxel consolidation produced promising overall survival in patients with stage III NSCLC, but the vast majority of patients could not continue with the docetaxel consolidation because of toxicity.

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SURVEY REPORT

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JASTRO平成15・16年度研究課題報告
医療実態調査研究による放射線治療施設構造基準化（案）の改訂
（日本版ブルーブック）

日本PCS作業部会

手島 昭樹[*1]，立崎 英夫[*2]，光森 通英[*3]，三橋 紀夫[*4]，宇野 隆[*5]，
中村 和正[*6]，角 美奈子[*7]，鹿間 直人[*8]，戸板 孝文[*9]，小口 正彦[*10]，
権丈 雅浩[*11]，小泉 雅彦[*12]，大西 洋[*13]，高橋 豊[*14]，古平 毅[*15]，
山内 智香子[*3]，芦野 靖夫[*16]，小川 和彦[*9]，井上 俊彦[*17]

REVISION OF GUIDELINE FOR STRUCTURE OF RADIATION ONCOLOGY BY THE PATTERNS OF CARE STUDY

Japanese PCS Working Group

Teruki TESHIMA[*1], Hideo TATSUZAKI[*2], Michihide MITSUMORI[*3], Norio MITSUHASHI[*4], Takashi UNO[*5], Katsumasa NAKAMURA[*6], Minako SUMI[*7], Naoto SHIKAMA[*8], Takafumi TOITA[*9], Masahiko OGUCHI[*10], Masahiro KENJO[*11], Masahiko KOIZUMI[*12], Hiroshi ONISHI[*13], Yutaka TAKAHASHI[*14], Takeshi KODAIRA[*15], Chikako YAMAUCHI[*3], Yasuo ASHINO[*16], Kazuhiko OGAWA[*9], and Toshihiko INOUE[*17]

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Abstract: "Guidelines for Structure of Radiation Oncology in Japan" was revised by referring to annual change of structure and process in Japan and to other international guidelines. These results were published as so called "Japanese Blue Book Guidelines". Number of cancer patients who require radiation is increasing by more than 7% annually. The standard guidelines for annual patient load per FTE radiation oncologist were set at 200 (warning level 300), those per FTE radiation technologist 120 (warning level 200), and those per one external beam equipment 250-350 (warning level 400). As the standards of process, establishment of verifiable information system like radiotherapy database and hospital cancer registration was proposed. Economic analysis showed that enough profit to meet with these guidelines became available recently in most radiotherapy institutions except for the smallest group.

Key words: Patterns of Care Study, Radiation Oncology, Structural Guideline, Japanese Blue Book Guideline

[*1] 大阪大学大学院医学系研究科医用物理工学講座（〒565-0871 大阪府吹田市山田丘 1-7）
Department of Medical Physics & Engineering, Osaka University Graduate School of Medicine (1-7 Yamadaoka, Suita, Osaka 565-0871, JAPAN)
[*2] 放射線医学総合研究所国際室 International Cooperation Section, National Institute of Radiological Sciences
[*3] 京都大学大学院医学研究科放射線医学講座放射線腫瘍学・画像応用治療学
Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine Kyoto University
[*4] 東京女子医科大学放射線科 Department of Radiology, Tokyo Women's Medical University
[*5] 千葉大学大学院医学研究院放射線医学 Department of Radiology, Graduate School of Medicine, Chiba University
[*6] 九州大学大学院医学研究院臨床放射線科学 Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University
[*7] 国立がんセンター中央病院放射線治療部 Radiation Oncology Division, National Cancer Center Hospital
[*8] 信州大学医学部画像医学講座 Department of Radiology, Shinshu University School of Medicine
[*9] 琉球大学医学部放射線医学教室 Department of Radiology, University of the Ryukyus School of Medicine
[*10] 癌研究会附属病院放射線治療科 Department of Radiation Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research
[*11] 広島大学大学院医歯薬総合研究科病態情報医科学講座
Division of Medical Intelligence and Informatics, Hiroshima University Graduate School of Biomedical Sciences
[*12] 京都府立医科大学大学院放射線医学教室 Department of Radiology, Kyoto Prefectural University of Medicine
[*13] 山梨大学医学部放射線医学教室 Department of Radiology, University of Yamanashi, School of Medicine
[*14] 癌研究会癌研究所物理部 Department of Physics, Cancer Institute, Japanese Foundation for Cancer Research
[*15] 愛知がんセンター中央病院放射線治療部 Department of Radiology, Aichi Cancer Center Hospital
[*16] シー・エム・エス・ジャパン株式会社 CMS Japan, Co., Ltd.
[*17] 大阪大学名誉教授 Professor Emeritus, Osaka University

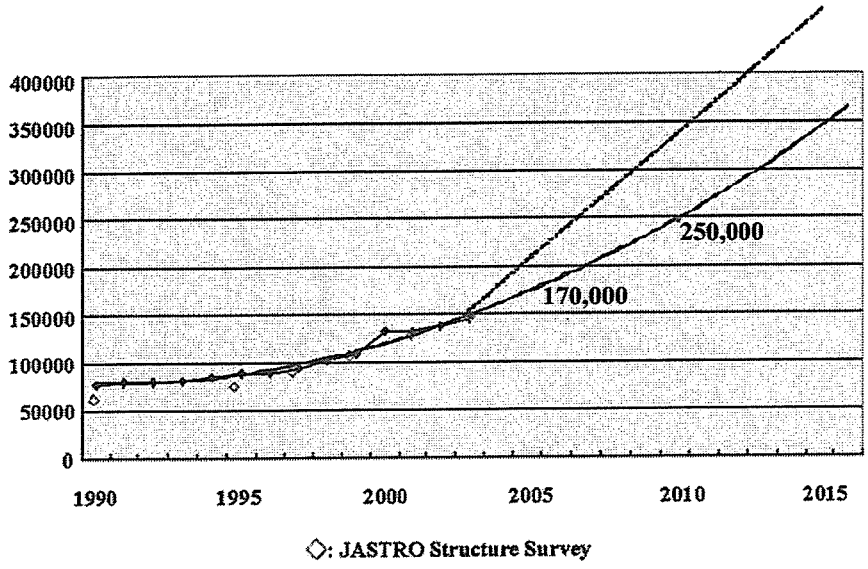

Fig. 1 Estimate of increase in demand for radiotherapy in Japan, based on statistical correction of annual change in the number of new patients per year at PCS survey. Broken line indicates the increasing trend in a case assuming achievement in 2015 of radiotherapy application in approximately 50% of all cancer patients, on par with the US.

はじめに

平成11・12年度研究課題として，厚生労働省がん研究助成金阿部班（8-27）で策定された「放射線治療施設の基準化（案）」[1]を，同井上班（10-17）で行った医療実態調査研究 Patterns of Care Study（PCS）による全国の放射線治療施設の2段階クラスタサンプリングで得た実態データにより検証した[2]．基準化（案）およびPCSによる施設層別化が装備，人員を含む構造を明瞭に識別できていることは検証できたが，1995年から1997年の実態は基準化（案）より1ランク下の条件を満たしているに過ぎなかった．一方，ダイナミックな患者数増加が観察され（今後10年で2倍以上の需要の発生が推定された），同時にIMRT等を含む高精度放射線治療の急速な普及による現場への負荷増大が懸念された．現状のままでは患者サービスの低下を起こす危険性がある．臨床現場により即した早急な基準化（案）の改訂の必要性が示唆された．研究代表者らは平成14年度より同手島班（14-6）として新たなPCS（第3次調査）を開始し，1999年から2001年の実態を把握した．これらのretrospectiveに集積した全国の放射線治療の実態データに立脚して基準化（案）を改定することを本研究の目的とした．その成果を日本版「ブルーブックガイドライン」と名づけた．

ＰＣＳ概要

全国の放射線治療施設の構造（装備，人員），過程（診断，治療内容），結果（生存率，有害事象発生率）の3要素を施設規模（＝構造）に準拠した2段階クラスタサンプリング法により訪問調査によって研究してきた．全国約70～80施設より班員・研究協力者約20名からなる訪問調査チームによって約2年半をかけて診療録の詳細な訪問調査を行った．収集されたデータに統計的加重補正を行い，個々の医療実態の全国的平均値national averageを求めた．施設構造に準拠したデータ抽出なので診療実態内容を照合しながら構造問題を分析できた[3),4)]．

わが国の推定放射線治療患者数

PCSの訪問調査を施行した施設の協力を得て過去の患者数の推移を2度にわたり調査した．統計補正をかけて全国の患者数の推移を推定し，同時にJASTROの定期的構造調査の全数調査データを重ね合わせた（Fig. 1）．その結果，返答率の高い最近の構造調査データはほぼPCSの推定値と一致していた．これらの推移から今後の患者数の増加率を推定した．2005年は17万人，2010年25万人，2015年36万人である．施設構造基準にはこのような将来需要を考慮した新たなものの策定が必要である．

日本版ブルーブック（がんの集学治療における放射線腫瘍学―医療実態調査研究に基づく放射線治療の品質確保に必要とされる基準構造）[5)]の作成

総論として，一般にも理解できる内容でがん治療の目標，放射線治療のがん診療における位置づけ，放射線治療の流れを記載した．各論として，構造基準（装備と人員），過程に関する基準，経済的問題点，用語解説を詳細に述べ