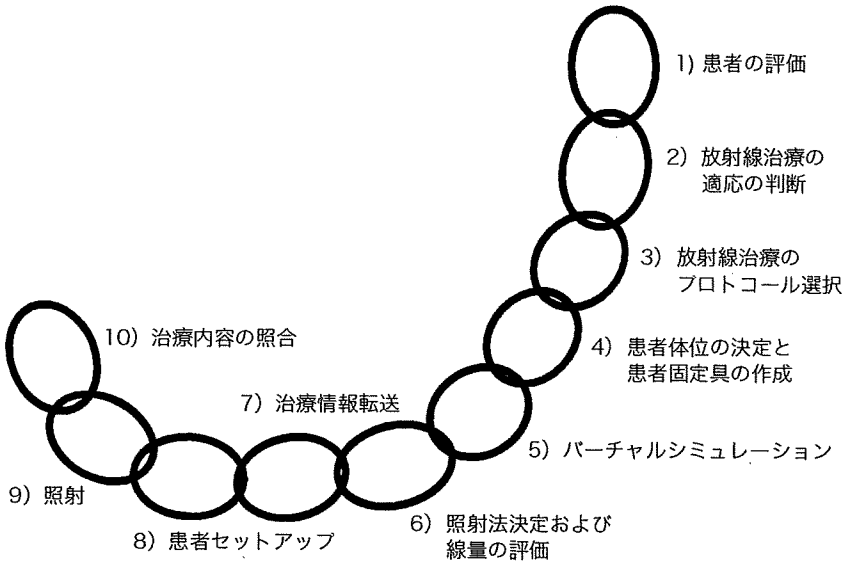

図1　放射線治療のプロセス
放射線治療のプロセスは連鎖状であり，各ステップの一つでもエラーが生じると鎖が切れ事故につながる危険がある．

治療（IMRT）などへと急速に高度化が進んでいる．これらの先進的技術を安全に臨床導入するためにも各技術に応じた適切なQC/QAプログラムの実施が求められている．

A. 国外におけるQC/QA活動

米国においては，放射線治療のQC/QAプログラムが確立されている．1969年にNational Cancer Institute（NCI）の補助金を受けて設立されたRadiological Physics Center（RPC）が物理技術的QC/QAに関する代表的な組織であり，郵送可能な線量計を用いたoff-site auditによる線量モニタリングや，施設訪問による線量測定およびQC/QAプログラムの確認といったon-site auditを全米に約2100存在する放射線治療施設のうち約1500の施設を対象に実施している．さらにはNCIにより臨床試験に参加するためにはRPCによるauditを受けることが必須とされている[7]．最近では，放射線治療技術の高度化に伴い，3D-CRT，SRT，IMRTなどの臨床試験の参加施設，参加医師などにこれらを正しく使用できる知識と経験があること，およびその治療精度を保証するための事前承認制度が導入されている[8]．治療精度の評価においてはRPCで作成された人体腫瘍模擬ファントム（以下RPCファントム：図2）を使用して治療計画を立て，治療

図2　RPCファントム
頭部用（奥）および頭頸部用（手前）

表1　RPCファントムによる治療精度の評価結果[9)]

ファントム	頭頸部	前立腺	胸部	肝臓
照射回数/のべ施設数	250（100%）	64（100%）	24（100%）	4（100%）
許容範囲内	179（ 72%）	55（ 86%）	17（ 71%）	3（ 75%）
許容範囲外	71（ 28%）	9（ 14%）	7（ 29%）	1（ 25%）
開始年	2001	2004	2004	2005

計画装置で計算された放射線の線量分布と実際に投与された線量を比較している．頭頸部がんに対するIMRTの評価では，約30%の施設で一定の基準をクリアできなかったとの結果があるが（表1），これらを通して放射線治療計画装置へのデータ入力の誤り，線量分布計算精度の確認不足，治療計画装置の誤用，治療用寝台の位置表示や患者位置決めエラー，治療計画ソフトのエラーなどが発見され，それぞれの修正が可能であった．同時にこれら事前承認制度が導入された臨床試験においては，導入されていない臨床試験に比べてプロトコール規定からの逸脱・違反割合が少ないことも報告されており，このような事前承認制度は質の確保にきわめて有効である[9)]．

物理技術的QC/QAプログラムとは別に，放射線を照射する標的となる腫瘍の体積やいわゆる照射野の設定方法など治療内容に関する臨床的QC/QAプログラムがあり，こちらも主として臨床試験を通して実施されてきた．Quality Assurance Review Center（QARC）は多施設共同研究グループであるAcute Leukemia Group B（ALGB）の放射線治療委員会により1972年に設立された臨床試験の放射線治療QC/QA活動を実施している米国最古の組織である[10)]．その後，他の多施設共同研究グループにおいて複数のQA組織によりQC/QAプログラムが実施されるようになり，放射線治療の質の改善が示された[11, 12)]．2002年には，米国内に5つあった放射線治療のQA組織：Image-Guided Therapy Center（ITC），Resource Center for Emerging Technology（RCET），RPC，Radiation Therapy Oncology Group（RTOG），QARCを統括する組織としてAdvanced Technology Consortium（ATC）が設立され，QC/QA手順の標準化，効率化がはかられている[13)]．

欧州においてもEuropean Organisation for Research and Treatment of Cancer（EORTC）で同様のプログラムが導入されており[14)]，放射線治療のQC/QAを行うことはglobal standardと認識されているのみならず，教育的観点ならびに均てん化の面からも重要である．現在ではATCとNational Cancer Institute Canada（NCIC），EORTC，日本臨床腫瘍研究グループ（Japan Clinical Oncology Group: JCOG）との間でも標準化のための共同プロジェクトが実施されている[15)]．

B. 国内の状況

わが国においては，従来より「治療用線量計の校正」活動により各施設の線量測定機器の精度は管理されてきたが，リニアックなどの治療装置の線量管理を行う物理技術的QC/QAおよび放射線治療の内容に関する臨床的QC/QAを全国規模で体系的に実施するシステムは近年まで構築されていなかった．物理技術的QC/QAについては2002年より厚生労働科学研究費補助金による研究班が米国RPCで実施されている手法に準じ，ガラス素子線量計の郵送によるoff-site auditを試験的に実施し[16)]，2007年11月にはoff-site audit事

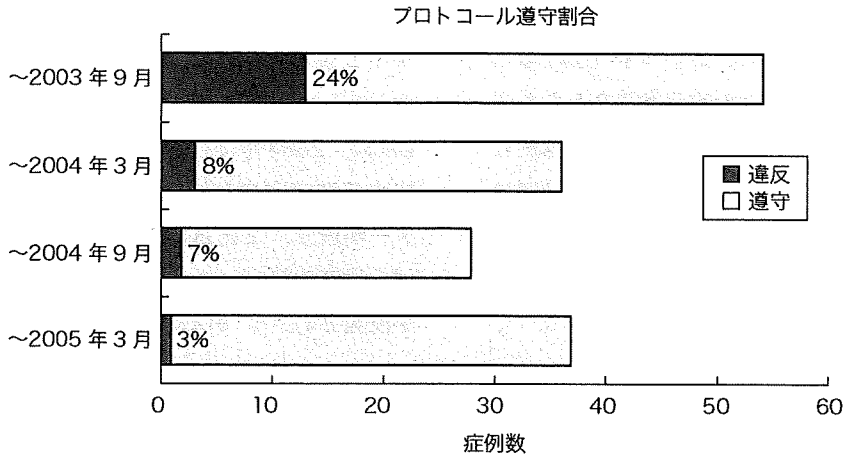

図3　臨床試験におけるプロトコール放射線治療規定遵守割合の変化
開始当初は違反割合が高かったが，その後急速に遵守割合の改善がみられた．

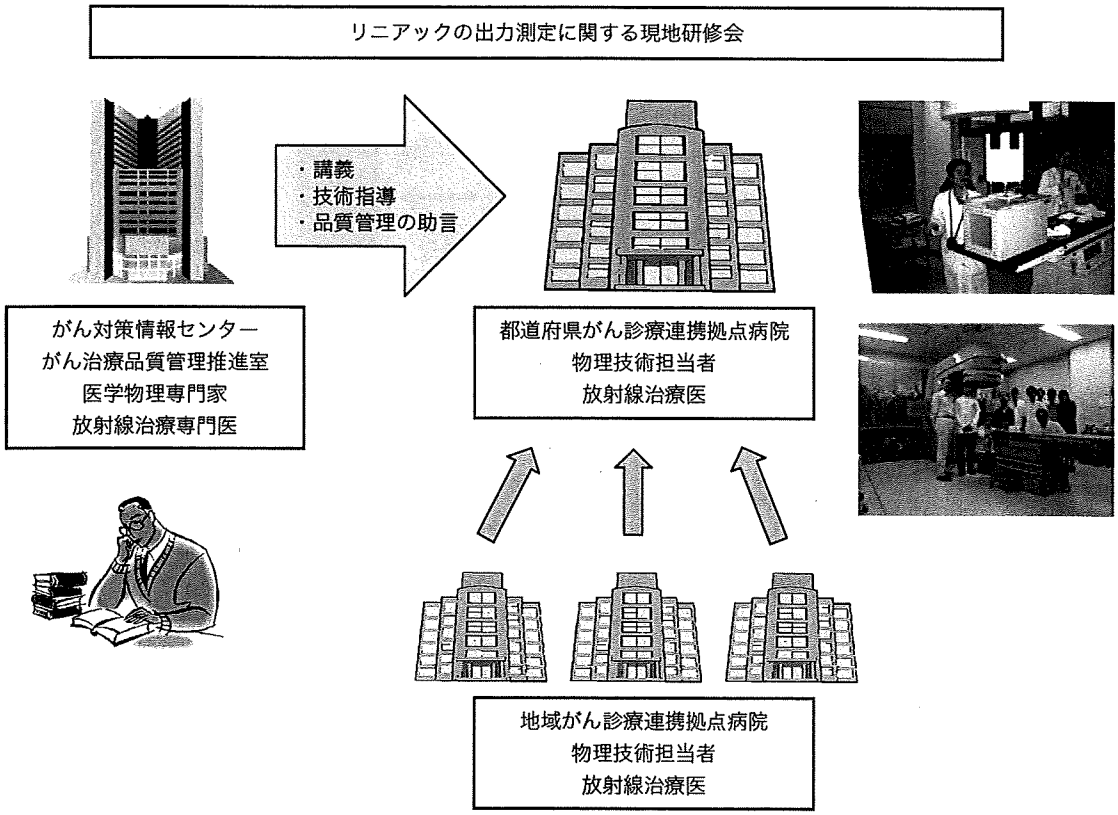

図4a)　がん診療連携拠点病院に対する研修会の開催

業が全国の放射線治療施設を対象に開始された.

一方, 臨床的QC/QAに関しては1999年にJCOGがALGB同様に放射線治療委員会を立ち上げた. 2001年には一つのランダム化比較試験において放射線治療のプロトコール規定の遵守率はわずか40%であることが判明し, わが国においても臨床試験において積極的にQC/QAプログラムを導入することの重要性が認識された[17].

2002年以降のJCOG臨床試験ではQC/QAプログラムが導入されており[18], 短期間のうちにプロトコール規定の遵守率が飛躍的に向上している(図3). 2004年には臨床試験のQC/QA活動を支援する特定非営利活動法人放射線治療支援センターが設立, また2006年には国立がんセンターがん対策情報センターにがん治療品質管理推進室が設置され[19], がん診療連携拠点病院および臨

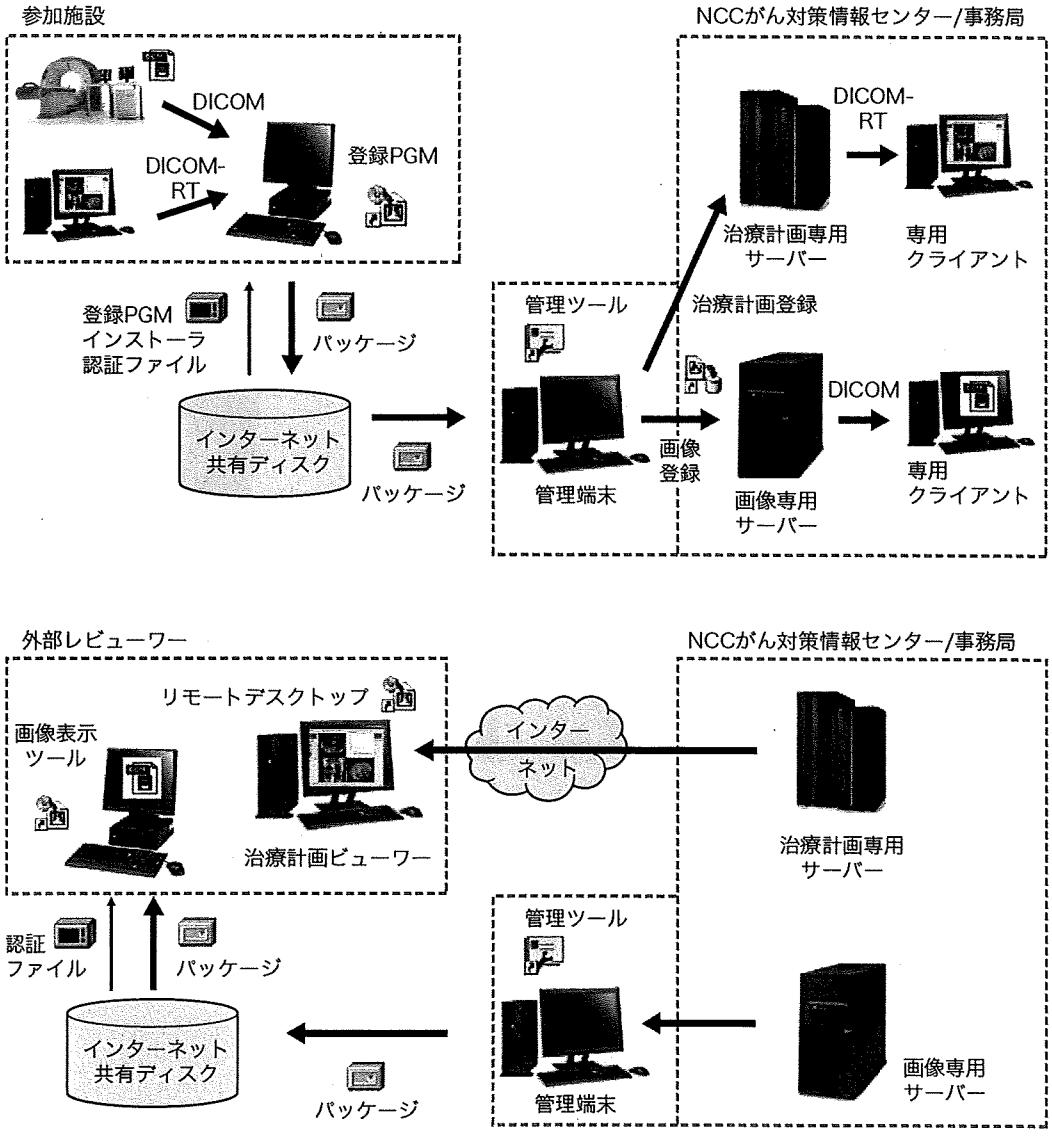

図4b)　放射線治療計画遠隔評価システム

床試験参加施設を中心に物理技術的QC/QAおよび臨床的QC/QAを支援する体制が整備されつつある（図4a，b）.

C. 今後の展望

近年の技術革新による先進的放射線治療の導入により，従来のQC/QAガイドラインでは一部不完全あるいは時代遅れとなっている．特に肺癌の呼吸による腫瘍の移動を考慮した四次元放射線治療のような画像誘導による放射線治療計画および治療，あるいはコンピュータ制御による治療の実施に当たっては，新たなQC/QAガイドラインの作成が急務となっている．主なポイントをあげると，1）IMRTおよび画像誘導による放射線治療計画がコミュニティーに浸透するスピードに比べ，それらのQC/QAガイドラインの作成は遙かに遅れており，医学物理士および放射線腫瘍医は治療の質と安全性を確保するための明確な方針を打ち出せていない状況となっている．先述のRPCファントムを用いた治療精度の評価において少なからず精度を保てていない施設が存在したことは，わが国に比し人的資源が豊富といわれる米国においてすらIMRTの質が思いのほか保たれていないことを示唆しており，深刻な医療事故のリスクが高まっている．2）包括的なQC/QAガイドラインのタイムリーな更新ができるよう，関連学会は体制整備を急ぐ必要がある．3）各施設においては，確率が低い医療事故を予防し限られたQC/QA資源を効率的に利用するためには，産業技術分野の手法に準じプロセスを重視したQC/QAプログラムを作成するなど，新たなパラダイムが必要である．

これらを踏まえて，International Atomic Energy Agency（IAEA）による国際シンポジウム[20] “Quality Assurance and New Techniques in Radiation Medicine” や，米国放射線腫瘍学会によるシンポジウム[21] “Quality Assurance of Radiation Therapy and the Challenges of Advanced Technologies” などが相次いで開催され，対応策の検討が行われている．また，World Health Organization（WHO）でも，“World Alliance for Patient Safety” というプロジェクトチームが作られ，これまでの放射線治療事故事例の分析とともにリスクの高いプロセスを明らかにし，より効率的に患者の安全確保をはかる方策，たとえば，1）治療計画プロトコールチェックリスト，2）放射線治療機器のQC/QAプログラム，3）ピアレビューによる第三者評価の導入など，ガイドラインの作成が進められている．今後これらの活動が実を結び，先進的放射線治療技術が安全かつ効果的に導入され，がんの治療成績の向上に寄与することを期待したい．

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頭頸部がんの化学放射線療法について

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はじめに

頭頸部は多臓器の集合体であり、その原発の部位と進行度によって治療方針・予後も異なります。頭頸部がんはすでに進行した状態で発見されることも多く、ステージ（Stage） III/IVが約60％を占めており、予後は不良といわれております。そのため、治療成績向上を目指して、外科的切除、放射線療法、化学療法などを組み合わせた集学的治療が行なわれてきました。さらに頭頸部には発声・嚥下・咀嚼などの重要な機能があるために、最近では機能温存を希望して非外科的治療を希望する患者も増加しています。このため、頭頸部がんを治療するうえで、1)組織型、2)原発部位、3)病期、4)根治的外科切除の適応、5)機能温存希望の有無、などを総合的に考慮に入れて治療方針を決定しています。ここでは、頭頸部がんとはどのようながんであり、どのような治療が標準治療（科学的根拠により最も推奨されている治療）であるかを、解説いたします。

1.頭頸部がんとは

（1）頭頸部がんの死亡数、罹患率

本邦のがんの統計[1]によると、2000年度の日本人の頭頸部（口唇、口腔および咽頭、喉頭、鼻腔および中耳、副鼻腔）がん死亡数は7,048人で、がん死亡の2.3 %を占め、がん種別では男性において7番目に多い疾患です。頭頸部がんの死亡率は近年、男女ともに増加しています。

また、日本のがん罹患率（年齢調整罹患率）の推移によると、1975年度に口腔・咽頭がんでは男4.2、女1.6（人口10万対・以下同）、喉頭がんでは男3.3、女0.3であったのに対し、1999年度には口腔・咽頭がんで男8.4、女2.7、喉頭がんで男4.0、女0.2でした。すなわち、近年、口腔・咽頭がんの罹患率は男女ともに約2倍に増加し、喉頭がんの罹患率は男性で増加、女性は横ばいの傾向にあります。

（2）頭頸部がんの組織型と頻度

日本頭頸部がん学会による頭頸部悪性腫瘍全国登録（2001年度、登録患者1,335名）によれば、組織型の頻度は、扁平上皮がん92.7%、未分化がん1.5%、腺様嚢胞がん1.2%、粘表皮がん0.8%、悪性黒色腫0.7%、腺がん0.6%でした。[2] 欧米においても頭頸部がんの組織型は多彩ですが、90%以上を扁平上皮がんが占めています。このため、頭頸部がんの治療開発は扁平上皮がんを中心に行なわれてきました。

（3）頭頸部がんの原発部位と頻度

頭頸部がんの原発部位は、口腔、鼻副鼻腔、上咽頭、中咽頭、下咽頭、喉頭、唾液腺に大別されます。頭頸部悪性腫瘍全国登録（2001年度）によれば、頭頸部がん原発部位別頻度は、口腔35.8%、鼻副鼻腔6.9%、上咽頭3.8%、中咽頭12.1%、下咽頭16.3%、喉頭25.0%でした。

（4）頭頸部がんのステージ別の頻度

頭頸部悪性腫瘍全国登録（2001年度）によれば、頭頸部がんのステージ別頻度は、0期0.8%、I期19.3%、II期20.3%、III期18.2%、IV期39.2%、不明2.5%であり、III、IV期の進行がんが約60%を占めていました。さらに初診時にすでに遠隔転移を有するもの（M1）の頻度は、2.8%でした。

（5）頭頸部がんの発症要因

飲酒、喫煙が頭頸部がん全体の80%に関与しています。発症のリスクは、喫煙が5～15倍、飲酒が5.5～33.8倍、さらにヘビースモーカーかつヘビードリンカー（heavy smoker & drinker）が200倍以上と報告されています。一方、頭頸部がん全体の2.4～19%は非飲酒・非喫煙であることも報告されています。ＥＶウイルス（Epstein-Barr virus：EBV）が上咽頭がんの、ヒトパピローマウイルス（Human papillomavirus ：HPV）が中咽頭がん、口腔がんの発症に関与しています。

資料1　頭頸部がんの原発部位別、ステージ別の予後

	原発部位別　5年生存割合（%）						
stage	口腔	上顎洞	上咽頭	中咽頭	下咽頭	喉頭	唾液腺
I	59.8	54.5	56.0	50.0	35.2	69.8	74.9
II	46.3	43.8	45.4	47.5	31.3	57.5	58.7
III	36.3	39.5	49.0	37.9	31.8	48.1	46.5
IV	23.3	27.0	34.1	26.1	17.4	32.2	27.9

（6）頭頸部がんの原発部位別、ステージ別の予後

米国National Cancer Institute（NCI）のデータベースによる原発部位、ステージ別の5年生存割合を**資料1**に示します。III、IV期において下咽頭がんが最も予後不良であり、上咽頭がんが最も予後良好です。

2.中咽頭・口腔・喉頭・下咽頭を原発とする局所進行頭頸部扁平上皮がんの治療

前述の通り、発症要因、予後などが異なるため、頭頸部がんの原発亜部位と進行度によって治療方針が異なります。しかし、頭頸部がんはまれながんであるために、中咽頭・口腔・喉頭・下咽頭を原発とするがんはいっしょに治療開発（臨床試験）が行なわれてきました。また前述の通り、組織型の90%以上が扁平上皮がんであるため、頭頸部扁平上皮がんのみの治療開発が行なわれてきました。したがって、ここからは、中咽頭・口腔・喉頭・下咽頭を原発とする局所進行(stage III, IV)頭頸部扁平上皮がんの治療について解説いたします。

局所進行頭頸部扁平上皮がんには、従来から放射線療法が行なわれてきましたが、治療成績は満足できるものではありませんでした。そこで、治療成績向上を目指して抗がん剤を放射線療法に加える治療法の開発が行なわれてきました。その結果、化学放射線療法は、放射線療法単独に比べて根治切除不能な頭頸部扁平上皮がんにおける局所制御率(原発巣あるいは頸部リンパ節のがんが消失し、再発していない状態)、無再発生存率（局所再発、遠隔転移再発なく生存している状態）、および生存率を向上させることが示されました。また、喉頭温存希望の頭頸部がんにおける喉頭温存率を向上させ、術後ハイリスク（high risk）の頭頸部がんにおける無再発生存率、および生存率を向上させることが示されました。以上のことから、化学放射線療法は、以下の場合の標準治療と認識されています。

1） 根治切除不能な局所進行頭頸部扁平上皮がん
2） 喉頭温存希望の局所進行頭頸部扁平上皮がん
3） 術後high riskの局所進行頭頸部扁平上皮がん

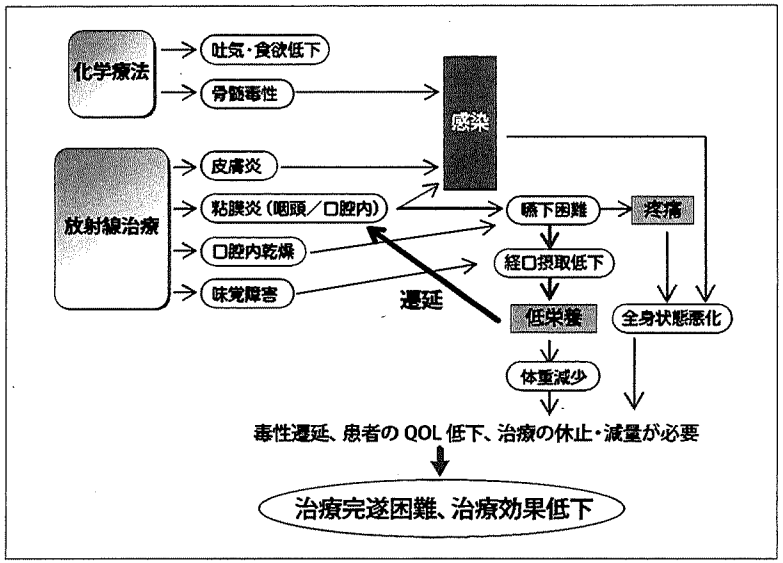
資料2　頭頸部がんにおける放射線照射（RT）休止の治療成績に与える影響[3)~9)]

著者（年）	患者数	対象	治療	結果
Herrmann (1994)	192	頭頸部がん	放射線療法	RT休止にて5年生存率↓ (61% vs 18-25% p<0.01)
Robertson (1998)	352	喉頭がん	放射線療法	3日以上RT休止にて局所制御↓ （ハザード比：1.75　1.20-2.55）
Groome (2006)	704	喉頭がん	放射線療法	T1N0：4日以上のRT休止にて局所制御↓ (RR:2.43　1.00-5.91) T2N0：後半の休止にて局所制御↓ (RR2.19　1.09-4.41)
Barton (1992)	1012	喉頭がん	放射線療法	総治療期間は局所制御と相関 (p=0.02) 1日休止すると局所再発率 4.8%↑ 完遂困難な場合、局所制御が1日毎に1.4%↓
Fowler (1992)	3834	喉頭がん	放射線療法	12論文中10論文で総治療期間と局所制御が相関(p<0.05) 1週間休止すると局所制御が14%↓(3-25%)
Parson (1997)	134	口腔内がん	術後補助放射線療法	High risk群では全治療期間が100日を越えると局所制御率↓ (60%vs14%　p=0.04)
Ang K (2001)	151	頭頸部がん	術後補助放射線療法	全治療期間　局所制御　生存 <11週　76%　48% 11-13週　62%　27% >13W週　38%　25%

しかし、化学放射線療法は、放射線療法単独に比べて、白血球減少などの骨髄毒性、粘膜炎、嚥下障害などの毒性（副作用）を増強させます。

このため、毒性軽減を目的として、放射線照射の休止をあらかじめ設定した化学放射線療法が汎用されるようになりました。しかし、放射線照射の休止は局所制御率を低下させ、治療成績を低下させることがわかってきました（**資料2**）。このような結果から、現在では放射線照射を休止せず化学放射線療法を行なうことが推奨されています。

資料3　頭頸部がんの化学放射線療法における副作用



3.頭頸部がんの化学放射線療法における支持療法の意義

（1）頭頸部がんの化学放射線療法における副作用

頭頸部がんの化学放射線療法には、さまざまな副作用があります（**資料3**）。化学療法によって吐気、食欲低下、骨髄毒性などが生じ、放射線療法により皮膚炎、粘膜炎、口腔内乾燥、味覚障害などが生じます。骨髄毒性、皮膚炎、粘膜炎が生じることにより感染のリスクが高くなり、感染すると全身状態は悪化します。粘膜炎が悪化すると嚥下困難、疼痛も出現し、経口摂取も低下し、栄養状態までも悪化します。また口腔内乾燥、味覚障害が起きることにより、疼痛管理にて嚥下困難が改善しても「食事がおいしくないから、食べたくない」という状況になり、栄養状態はさらに悪化します。このようにして低栄養状態に陥ると粘膜炎も遷延し、さらに低栄養状態に陥ります。これらの副作用が遷延し、重篤化すると、患者のQOLが低下するのみならず、治療の休止・化学療法の減量も必要となり、治療が完遂困難になり、さらに治療効果まで低下させてしまいます。

（2）放射線照射休止なく治療完遂するためには

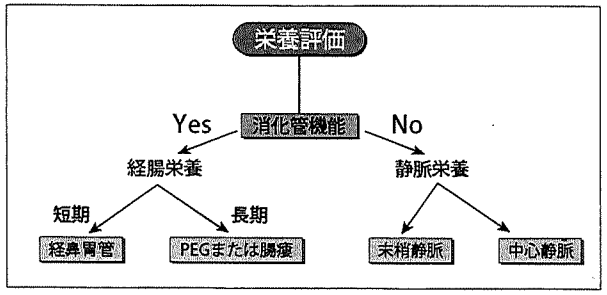
以上のことから、頭頸部がんの化学放射線療法における副作用のマネージメント（支持療法）には、①感染の管理、②疼痛の管理、③栄養管理が必須です。

①感染の管理

骨髄毒性による感染には抗生剤、G-CSFを適切に使用し、粘膜炎には口腔ケアを積極的に行ない、皮膚炎にも適切な処置を行なうことが必要です。

②疼痛の管理

資料4　アメリカ静脈経腸栄養学会（ASPEN）のガイドライン



麻薬などの鎮痛剤を積極的に使用することが必要です。

③栄養管理

アメリカ静脈経腸栄養学会（ASPEN）のガイドライン（**資料4**）において、消化管機能が問題なく、長期間の経管栄養が必要である場合は、胃瘻（PEG）あるいは腸瘻からの経管栄養を行なうことが推奨されています。

局所進行頭頸部がんに対する化学放射線療法は、重篤な粘膜炎、嚥下困難、さらに低栄養状態をもたらす頻度が高いので、化学放射線療法を予定している局所進行頭頸部がん、特に切除不能例には、治療前に胃瘻造設することが推奨されています。

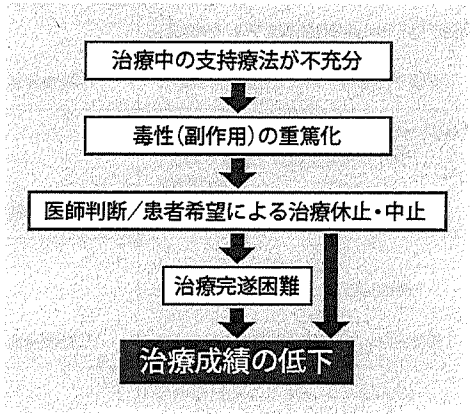
〔3〕支持療法の重要性

頭頸部がんにおける化学放射線療法中の支持療法が不充分であると、毒性（副作用）は重篤化し、医師の判断あるいは患者の希望にて治療の休止・中止を余儀なくされ、治療完遂困難になることもあり、治療成績は低下します（**資料5**）。すなわち、支持療法は、患者のQOLのみならず治療成績にも影響を与えることがわかります。

おわりに

頭頸部がんの化学放射線療法は、さまざまなところで標準治療として行なわれていますが、治療の副作用が重篤化することで、治療休止・治療完遂が困難になることが懸念されます。したがって、頭頸部がんの化学放射線療法には充分な支持療法が必須であり、これが治療成績に影響を与えることを充分に理解して、患者のケアにあたってほしいと思います。

資料5　支持療法の重要性



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Radiotherapy quality assurance review in a multi-center randomized trial of limited-disease small cell lung cancer: the Japan Clinical Oncology Group (JCOG) trial 0202

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Abstract

Background: The purpose of this study was to analyze the radiotherapy (RT) quality assurance (QA) assessment in Japan Clinical Oncology Group (JCOG) 0202, which was the first trial that required on-going RT QA review in the JCOG.

Methods: JCOG 0202 was a multi-center phase III trial comparing two types of consolidation chemotherapy after concurrent chemoradiotherapy for limited-disease small cell lung cancer. RT requirements included a total dose of 45 Gy/30 fx (bis in die, BID/twice a day) without heterogeneity correction; elective nodal irradiation (ENI) of 30 Gy; at least 1 cm margin around the clinical target volume (CTV); and interfraction interval of 6 hours or longer. Dose constraints were defined in regards to the spinal cord and the lung. The QA assessment was classed as per protocol (PP), deviation acceptable (DA), violation unacceptable (VU), and incomplete/not evaluable (I/NE).

Results: A total of 283 cases were accrued, of which 204 were fully evaluable, excluding 79 I/NE cases. There were 18 VU in gross tumor volume (GTV) coverage (8% of 238 evaluated); 4 VU and 23 DA in elective nodal irradiation (ENI) (2% and 9% of 243 evaluated, respectively). Some VU were observed in organs at risk (1 VU in the lung and 5 VU in the spinal cord). Overall RT compliance (PP + DA) was 92% (187 of 204 fully evaluable). Comparison between the former and latter halves of the accrued cases revealed that the number of VU and DA had decreased.

Conclusion: The results of the RT QA assessment in JCOG 0202 seemed to be acceptable, providing reliable results.

Introduction

Quality assurance (QA) and quality control are an integral part of multi-center clinical trials involving radiotherapy (RT). Several reports have shown that failure to adhere to the treatment protocol deteriorated the outcome in clinical trials [1-5]. To provide reliable results in clinical trials, it is important to keep each treatment as uniform as possible. In addition, a QA program is indispensable for patient safety, preventing increased or unexpected toxicity, and ensuring a certain effect.

In 1999, Japan Clinical Oncology Group (JCOG) trial 9812 was started to evaluate whether RT with carboplatin would result in longer survival than RT alone in elderly patients with unresectable stage III non-small cell lung cancer; however, due to excessive serious adverse events, the trial was terminated early when 46 patients were registered. By retrospective RT QA review, a protocol violation was revealed in 60% of the cases [6].

JCOG 0202 was a multi-center phase III trial comparing two types of consolidation chemotherapy after concurrent chemoradiotherapy for limited-disease small cell lung cancer (Figure 1).

The primary endpoint of JCOG 0202 was overall survival and the secondary endpoints included disease-free survival and the toxicity profile of each treatment. This trial was the first in JCOG to require on-going RT QA to improve the quality of clinical trials. This is a retrospective evaluation of the protocol compliance of JCOG 0202.

Methods

Study design and RT requirements

After enrolling in this trial, patients received cisplatin 80 mg/m^2 on day 1 and etoposide 100 mg/m^2 on days 1–3, with concurrent RT. Patients were randomized after chemoradiotherapy and received either 3 cycles of the same chemotherapy of cisplatin and etoposide every 3 weeks, or cisplatin 60 mg/m^2 on day 1 and irinotecan 60 mg/m^2 on days 1, 8 and 15 every 4 weeks.

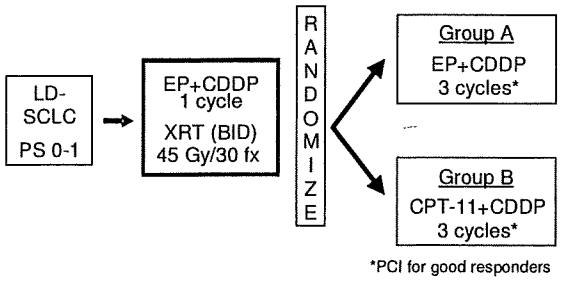

Figure 1
Schema of JCOG 0202. Abbreviations. LD-SCLC, limited-disease small cell lung cancer; PS, performance status; EP, etoposide; CDDP, cisplatin; XRT, thoracic radiotherapy; BID; bis in die/twice a day; CPT-11, irinotecan; PCI, prophylactic cranial irradiation.

RT requirements included a total dose of 45 Gy in 30 fractions (bis in die, BID/twice a day) with an interfraction interval of over 6 hours. For treatment planning, both conventional 2-dimensional (2-D) X-ray simulation and 3-dimensional (3-D) CT simulation were allowed. PET scanning was not required in RT planning. Gross tumor volume (GTV) was defined as the primary tumor demonstrated by CT scan as well as metastatic lymph nodes measuring 1 cm or greater in short axis. In this trial, the clinical target volume (CTV) for the primary tumor and metastatic lymph nodes was created without adding any margins to GTV. CTV also included a regional (elecitve) nodal area which consisted of ipsilateral hilum and bilateral mediastinal (pretracheal, paratracheal, tracheobroncheal, and subcarinal) lymph nodes. Contralateral hilar lymph nodes were not included in the CTV. The planning target volume (PTV) was created by adding margins at the discretion of radiation oncologists (typically 0.5–1 cm for lateral margin and 1–2 cm for cranio-caudal margin, depending on respiratory motion and patient fixation). A dose of 30 Gy was prescribed at the center of the PTV, including elective nodal irradiation (ENI), followed by a boost dose of 15 Gy to the primary tumor and metastatic lymph nodes. Tissue heterogeneity correction was not used for monitor unit calculation, because if heterogeneity correction was required and different calculation algorithms were allowed, inter-institutional variation of the delivered dose would have been significant, and the convolution-superposition algorithm was not available in some participating institutions at the beginning of this trial.

Dose constraints were defined in regard to the dose to the spinal cord and the lung. The dose to the spinal cord was kept at ≤ 36 Gy. A posterior spinal shield was not allowed. The percentage of normal lung volume minus PTV receiving 20 Gy or greater (V_{20}) was kept ≤ 35%. In 2-D planning, the field size was limited to ≤ half of the ipsilateral lung (for upper lobe tumors, ≤ 2/3).

Quality assurance review

For initial QA review, copies of pre-treatment diagnostic chest X-ray and CT, simulation and portal films, worksheets for monitor unit calculation of the prescribed dose, and RT charts with the record of the irradiated time were collected. Information on the initial RT plan was required to be sent to the QA review center within 7 days after the start of RT. Information on the total course of RT, including the boost treatment plan, was required to be sent within 30 days after completion of RT. These were reviewed periodically at least twice a month by the RT

principal investigator (S.I.), and also by an independent radiation oncologist (N.S.) after patient accrual. RT QA for prophylactic cranial irradiation was not performed. After the review of the initial RT plan, the RT principal investigator sent each institution a letter reporting whether they had complied with the treatment protocol as well as an inquiry about QA documentation when necessary (Figure 2). Progress remarks and problems were reported at periodical meetings for investigators.

To assess protocol compliance for RT, the following parameters were reviewed: the dose and field border placement for PTV (adequacy of margins for GTV and ENI), doses to organs at risk, such as the spinal cord and the normal lung, overall treatment time, interfraction interval, and dose calculation without heterogeneity correction. The QA assessment was given as per protocol (PP), deviation acceptable (DA), violation unacceptable (VU), and incomplete/not evaluable (I/NE). The criteria were set for each parameter as follows. For the dose and field coverage of GTV, VU was defined as a dose less than 40.5 Gy, more than 49.5 Gy, or the distance between the field edge of the blocks or multileaf collimators and the rim of GTV less than 1 cm or more than 3.5 cm. For the dose and field coverage of ENI, a dose less than 27 Gy, more than 36 Gy or inclusion of the contralateral hilum was judged as VU. If hererogeneity correction was used for dose calculation and the recalculated uncorrected dose deviated more than 10%, it was judged as VU. Other criteria for the QA assessment are listed in Table 1. These criteria were arbitrary rather than based on the literature. We set these criteria based on the patterns of practice in Japan at the start of this trial. After parameter compliance was assessed, overall RT compliance was determined as PPoverall, no DA or VU in any parameter; VUoverall, at least one VU in any parameter; or DAoverall, neither PP nor VU. The proportion of 2-D X-ray simulation vs. 3-D CT simulation was analyzed, and a comparison was also made between compliance in the first half vs. the second.

Results

From September 2002 to September 2006, 283 cases were accrued. Of these, 204 (72%) were fully evaluable, excluding 79 cases (Table 2). Partially evaluable cases were included to evaluate each item.

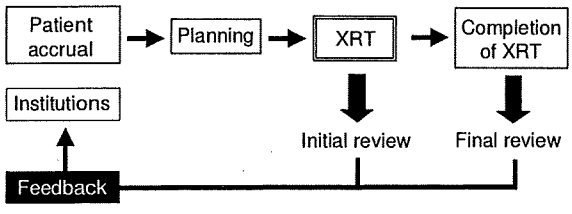

Figure 2
Flow of QA review. After the QA review, feedback was given to the institutions. Treatment planning was modified when possible.

Among 258 patients evaluable for the treatment planning method, conventional 2-D X-ray simulation was performed in 62 (24%) patients, while 196 (76%) had 3-D CT simulation. Of 35 participating institutions, 24 institutions had introduced 3-D CT simulation, 6 used only 2-D X-ray simulation, and 5 used both.

RT compliance for each parameter is listed in Table 3. There were 18 VU in GTV (8% of 238 evaluated), of which, 14 (78%) had insufficient lateral margins, while 3 (17%) and 2 (11%) had insufficient caudal and cranial margins, respectively (one case, both lateral and caudal margins). There was no VU in the GTV dose. With regard to ENI, 4 VU and 23 DA (2% and 9% of 243 evaluated, respectively) were observed. Of these 4 VU, a total dose of 45 Gy instead of 30 Gy was given in 3, and the contralateral hilum was irradiated in one case. Of these 23 DA, 17 had larger field placement than required in the protocol, such as the inclusion of uninvolved supraclavicular fossa, upper mediastinum, or subaortic/paraaortic lymph node area, etc, whereas 3 had insufficient margins. Three had both larger field placement and insufficient margins. No VU was found in overall treatment time, interfraction interval and dose calculation, while some VU were observed in organs at risk (1 VU in the lung and 5 VU in the spinal cord). Overall RT compliance (PP + DA) was 92% (187 of 204 fully evaluable).

In regard to the 35 participating institutions, 17 (49%) had no VU. In 18 institutions with VU, 15 (83%) had only one VU and 3 (17%) had 2 or more VU. Sixteen institutions (89%) had VU in their first 3 cases.

Comparison between the former and latter halves of the accrued cases (141 and 142 cases, respectively) revealed that the number of VU and DA had decreased: for GTV, the number of VU was 13 in the early period (9%; 95% CI, 5%–15%), while 5 in the late period (4%; 95% CI, 1%–8%). In regard to ENI, DA decreased from 20 (14%; 95% CI, 9%–21%) to 3 (2%; 95% CI, 0.4%–6%), respectively.

Discussion

In clinical trials, patients must receive optimal treatment. Since the 1980s, a number of reports have focused on the relationship between RT compliance and treatment outcomes in various types of malignancy [1-5]. These results suggested that failure to adhere to RT protocol guidelines compromises survival. Overall compliance of 92% in the current trial seemed acceptable to provide reliable results. More than half of the participating institutions did not have VU, and even with VU, the majority had only one VU; however, there is room for improving compliance in

Table 1: Criteria for QA scores

	PP	DA	VU
GTV			
distance to field borders	1 – 3.5 cm	NA	< 1 cm or > 3.5 cm
prescribed dose	45 Gy	Neither PP nor VU	< 40.5 Gy or > 49.5 Gy
ENI			
distance to field borders	1 – 3.5 cm	Neither PP nor VU	contralateral hilum included
prescribed dose	27 – 36 Gy	NA	< 27 Gy or > 36 Gy
Overall treatment time	21 – 42 days	NA	> 42 days
Interfraction interval	≥ 5.5 hrs	4 – 5.5 hrs or <4 hrs (once)	< 4 hrs more than once
Organs at risk			
Spinal cord	≤ 36 Gy	Neither PP nor VU	> 39 Gy
Lung	≤ 1/2 ipsilateral hemithorax (≤ 2/3, upper lobe tumor) or V_{20} ≤ 35%	Neither PP nor VU	> 1/2 ipsilateral hemithorax (> 2/3, upper lobe tumor) or V_{20} > 40%
Heterogeneity correction	No	Yes (≤ 10% total dose difference)	Yes (> 10% total dose difference)

Abbreviations: PP, per protocol; DA, deviation acceptable; VU, violation unacceptable; GTV, gross tumor volume; ENI, elective nodal irradiaton; NA, not applicable; hrs, hours; V_{20}, percentage of the total lung minus PTV receiving ≥ 20 Gy.

future trials incorporating RT. GTV and ENI violations and/or deviations were more frequent in the early period. In addition, among institutions with VU, the majority had VU in the first 3 cases. This may be because the institutions received feedback on how to better comply with the treatment protocol by the RT principal investigator, which enabled participants to follow the protocol guidelines in their later cases.

In the current study, more suboptimal treatments were observed in field placement than in the dose for tumors or risk organs. A similar trend was reported in other studies [7,8]. The majority of VU consisted of smaller lateral margins. The reason may have been a discrepancy between the protocol guidelines and their daily practices. The physicians tended to reduce lateral margins rather than craniospinal margins for fear of radiation pneumonitis. The varied ENI coverage also suggested a discrepancy. In this trial, a dry-run procedure was not attempted and therefore the radiation oncologists in each institution might not have been familiar with the protocol guidelines in the initial period of this trial. Wallner et al. [4] speculated the influence of clinical trial experience by reviewing a large number of cases in RTOG studies for lung and head and neck cancer. They reported that adequate primary and lymph node margins and dose prescriptions had progressively improved over the years, suggesting long-lasting learning experiences in clinical trials. As the need for immediate monitoring was described by Schaake-Koning et al. [9] from a quality control study in the EORTC lung cancer trial, some early interventions, such as a dry-run and immediate feedback before the start of treatment, will be more effective to improve compliance in clinical trials involving RT.

Table 2: Number of evaluable cases and overall RT compliance

	number	(%)
Total	283	
Data insufficient/partially evaluable	62	
Off-protocol	12	
Ineligible	5	
Fully evaluable	204	(100)
PPoverall	158	(77)
DAoverall	29	(14)
VUoverall	17	(8)
Compliance (PPoverall+DAoverall)	187	(92)

Abbreviations: PP, per protocol; DA, deviation acceptable; VU, violation unacceptable

There were several limitations of our study. We did not perform 3-D volumetric data analyses due to technical limitations. Other factors, such as inter-observer contouring variations, 2-D vs. 3-D planning, may have had a much greater impact on the outcome of this trial than protocol compliance. The transition from 2-D to 3-D treatment planning is now almost complete in Japan, and more precise QA analyses using digital data, exported from treatment planning systems with the DICOM-RT format, have been introduced in recent JCOG 3-D RT trials.

In addition, all described QA activities focused on the medical aspects and treatment planning. Another important aspect is dosimetric QA. It is well known from the reports and scientific publications of the WHO/IAEA network [10], the ESTRO-EQUAL network in Europe [11] and the NCI network in the US [12] that external dosimetric audits are a powerful tool to avoid systematic errors. Dosimetric audits are generally recommended as integral parts of QA activities for clinical trials. In Japan, dosimetric audits were introduced in 2003, and were therefore not available at the beginning of this trial, and have been implemented in recent JCOG radiotherapy trials [13]. We

Table 3: RT compliance for each parameter

	Evaluable cases	PP	(%)	DA	(%)	VU	(%)
GTV	**238**	**220**	(92)	**NA**		**18**	(8)
ENI	**243**	**216**	(89)	**23**	(9)	**4**	(2)
Overall treatment time	**227**	**227**	(100)	**NA**		**0**	(0)
Interfraction interval	**205**	**195**	(95)	**10**	(5)	**0**	(0)
Organs at risk							
Spinal cord	**236**	**231**	(98)	**0**	(0)	**5**	(2)
Lung	**246**	**245**	(100)	**0**	(0)	**1**	(0.4)
Heterogeneity correction	**244**	**228**	(93)	**16**	(7)	**0**	(0)

Abbreviations: PP, per protocol; DA, deviation acceptable; VU, violation unacceptable; GTV, gross tumor volume; ENI, elective nodal irradiaton; NA, not applicable.

also believe that these activities will have run-on effects in routine practice and lead to higher quality cancer care.

Conclusion

In conclusion, the results of the RT QA assessment of JCOG 0202 seemed to be acceptable, providing scientifically reliable results. The time trend toward improved compliance in this trial showed the importance of introducing an RT QA program. A dry-run procedure and intensive feedback to participating institutions are being implemented to further improve JCOG trials.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

NS performed the QA evaluation. SI was in charge of the QA program and performed the QA evaluation. KH participated in the design of the QA program and helped to draft the manuscript. KK, and YN and TT conceived the study and helped to draft the manuscript.

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ORIGINAL REPORT

Phase I/II Study of Concurrent Chemoradiotherapy for Localized Nasal Natural Killer/T-Cell Lymphoma: Japan Clinical Oncology Group Study JCOG0211

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ABSTRACT

Purpose
To explore a more effective treatment for localized nasal natural killer (NK)/T-cell lymphoma, we conducted a phase I/II study of concurrent chemoradiotherapy.

Patients and Methods
Treatments comprised concurrent radiotherapy (50 Gy) and 3 courses of dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC). Patients with a newly diagnosed stage IE or contiguous IIE disease with cervical node involvement and a performance status (PS) of 0 to 2 were eligible for enrollment. The primary end point of the phase II portion was a 2-year overall survival in patients treated with the recommended dose.

Results
Of the 33 patients enrolled, 10 patients were enrolled in the phase I portion and a two thirds dose of DeVIC was established as the recommended dose. Twenty-seven patients (range, 21 to 68; median, 56 years) treated with the recommended dose showed the following clinical features: male:female, 17:10; stage IE, 18; stage IIE, 9; B symptoms present, 10; elevated serum lactate dehydrogenase, 5; and PS 2, 2. With a median follow-up of 32 months, the 2-year overall survival was 78% (95% CI, 57% to 89%). This compared favorably with the historical control of radiotherapy alone (45%). Of the 26 patients assessable for a response, 20 (77%) achieved a complete response, with one partial response. The overall response rate was 81%. The most common grade 3 nonhematologic toxicity was mucositis related to radiation (30%). No treatment-related deaths were observed.

Conclusion
Concurrent chemoradiotherapy using multidrug resistance-nonrelated agents and etoposide is a safe and effective treatment for localized nasal NK/T-cell lymphoma and warrants further investigation.

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INTRODUCTION

Extranodal natural killer (NK)/T-cell lymphoma (NKTCL), nasal type,[1,2] accounts for 3% to 10% of malignant lymphomas in East Asia.[3,4] Incidence is lower in Western countries, where it comprises less than 1% of lymphomas.[5] Two thirds of patients have stage I or II disease in the nasal cavity and its adjacent sites,[6,7] which is commonly referred to as nasal NKTCL.[1] This disease is an Epstein-Barr virus (EBV) –associated lymphoid malignancy[8,9] and tumor cells express P glycoprotein, resulting in tumor multidrug resistance (MDR).[10-12]

Few prospective trials for NKTCL have been reported[13,14] and a standard therapy for newly diagnosed, localized nasal NKTCL remains to be established. Cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) therapy followed by involved-field radiotherapy (RT) has been established as the standard therapy for localized aggressive lymphomas.[15] Reported 5-year overall survival (OS) for patients with localized nasal NKTCL treated with this standard therapy is lower than 50%,[16-19] suggesting that this treatment is not effective. RT alone is also not sufficient, with 5-year OS ranging from 30% to 40%.[20,21]

Concurrent chemoradiotherapy is expected to improve both local and systemic disease control and has been established as a standard therapy for several types of solid tumors.[22-24] However,

chemoradiotherapy is not a standard practice in lymphoma treatment and only a limited number of cases have been reported of its use in the treatment of localized nasal NKTCL.[18,21] Yamaguchi et al[18] reported two cases of localized nasal NKTCL successfully treated with concurrent chemoradiotherapy. These patients showed high serum levels of lactate dehydrogenase (LDH) and B symptoms, which are known as unfavorable prognostic factors in NKTCL.[25] In this report, dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC) chemotherapy was selected for the concurrent chemoradiotherapy (RT-DeVIC). DeVIC was designed as a salvage chemotherapeutic regimen for aggressive lymphoma[26] comprised of MDR-nonrelated agents and etoposide, which is known to be effective against EBV-associated hemophagocytic syndrome.[27]

To explore a more effective therapeutic strategy for newly diagnosed, localized nasal NKTCL, the Lymphoma Study Group of the Japan Clinical Oncology Group conducted a phase I/II study of RT-DeVIC therapy. Based on the results of recent multicenter retrospective studies of optimal RT for this disease,[28-30] we selected an RT total dose of 50 Gy with extended radiation volume including the entire nasal cavity and sinuses. The study addressed the research questions of establishing an optimal dose of DeVIC chemotherapy in combination with RT of 50 Gy and the efficacy of this therapy compared with RT alone.

PATIENTS AND METHODS

Patients: Eligibility Criteria

Patients were eligible for the study if they were 20 to 69 years old and had previously untreated extranodal NKTCL, nasal type as defined by the WHO classification.[1] Patients were also required to have stage IE or contiguous stage IIE disease with cervical lymph node involvement and to have at least one measurable lymphomatous lesion in the nasal cavity, paranasal sinuses, orbit, pharynx, Waldeyer's ring, or oral cavity. Other eligibility criteria included no prior chemotherapy or RT, performance status (PS) of 0 to 2 according to the Eastern Cooperative Oncology Group scale, and preserved organ functions. For example, a WBC count $\geq$ 3,000/μL, an absolute neutrophil count (ANC) $\geq$ 1,200/μL, a platelet count $\geq$ 100,000/μL, AST and ALT $\leq$ 5$\times$ the normal upper limit, total bilirubin $\leq$ 2.0 mg/dL, normal ECG, a cardiac ejection fraction $\geq$ 50%, and $Pao_2 \geq$ 65 mmHg were required. Patients were excluded if they had symptomatic CNS involvement or other concurrent cancers. Patients suffering from severe infection, liver cirrhosis, or psychiatric disorders were also excluded.

Pretreatment staging procedures included a physical examination, a bone marrow aspiration and/or a biopsy, a chest radiograph, a computed tomography (CT) scan of the nasal cavity, neck, chest, abdomen, and pelvis, a magnetic resonance imaging of the nasal cavity, an endoscopy of upper gastrointestinal tract, and a Ga-67 scintigram.

After patient enrollment, hematoxylin and eosin–stained sections were histologically reviewed according to the WHO classification[1] by the central pathology review board. For this purpose, immunohistochemical staining using antibodies against CD3, CD5, CD20, CD56, and in situ hybridization for EBV encoded small RNA-1 were performed at the central pathology office using formalin-fixed paraffin sections.

The study was approved by both the JCOG Protocol Review Committee and the institutional review board of each institution. Written informed consents were obtained.

Chemotherapy

Chemotherapy and RT were simultaneously started within 7 days after registration. The drug doses of level 1 (two thirds DeVIC) and the drug administration schedule were as follows: dexamethasone, 40 mg/d intravenously on days 1 to 3; etoposide, 67 mg/m^2 intravenously over 2 hours on days 1 to 3; ifosfamide, 1.0 g/m^2 intravenously over 3 hours on days 1 to 3; and carboplatin, 200 mg/m^2 intravenously over 30 minutes on day 1. In level 2 (100% DeVIC), doses of etoposide, ifosfamide, and carboplatin were scheduled to escalate to 100 mg/m^2, 1.5 g/m^2, and 300 mg/m^2, respectively. Chemotherapy was planned to repeat every 3 weeks. Granulocyte colony-stimulating factor was initiated if the leukocyte count decreased to lower than 2,000/μL or the ANC count decreased to lower than 1,000/μL, and was discontinued if the leukocyte count exceeded 5,000/μL. Three courses of chemotherapy were planned.

If a patient developed febrile neutropenia, doses of carboplatin, ifosfamide, and etoposide were decreased by two thirds for all following cycles. If grade $\geq$ 3 thrombocytopenia developed, doses of carboplatin were decreased by two thirds for all following cycles. If grade $\geq$ 2 hematuria developed, doses of ifosfamide were decreased by two thirds for all following cycles. If leukocytes lower than 2,000/μL or platelets lower than 100,000/μL were found at the time of starting a next cycle, the cycle was delayed for up to 3 weeks. If the patient's leukocyte and platelet counts did not increase above these levels after 3 weeks, chemotherapy was discontinued. If stomatitis/pharyngitis of grade $\geq$ 3 developed, the cycle was delayed for up to 3 weeks.

RT

All patients were treated with a photon beam of 4 MV or greater. Three-dimensional conformal treatment planning was recommended, but not mandatory. Tissue heterogeneity correction was not used in dose calculations.

The RT prescription was 50 Gy in 25 fractions over 5 weeks for stage IE disease, and 50.4 Gy in 28 fractions over 6 weeks for stage IIE disease. Clinical target volume (CTV) included gross tumor volume with a margin of at least 20 mm and the entire nasal cavity and parasinuses. Planning target volume (PTV) included CTV with a 5 mm margin. For stage IIE disease, CTV and PTV also included the involved the cervical lymph node area. Use of a mouth spacer and two-step cone down of RT were recommended to reduce local toxicity.

RT was postponed until the toxicity was reduced to grade $\leq$ 2 if one or more of the following adverse events were observed: grade 4 leukopenia or neutropenia, platelet count lower than 25,000/μL, any grade $\geq$ 3 nonhematologic toxicities except for mucositis or dysphagia related to radiation, and PS $\geq$ 3. If the grade of toxicity did not recover to $\leq$ 2 after 2 weeks, the planned treatment was terminated.

All RT planning, verification films, and RT charts were reviewed by the RT Quality Assurance Committee of JCOG0211.[31]

Statistical Analysis

The primary end point of the phase I portion was toxicity for the purpose of estimating a recommended dose of carboplatin, etoposide, and ifosfamide for the subsequent phase II portion. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria 2.0, version 2. A standard 3 + 3 design was used to evaluate dose-limiting toxicities (DLTs) in two dose levels (two thirds DeVIC and 100% DeVIC). DLT included grade 4 leukopenia or neutropenia lasting $\geq$ 5 days; grade 4 thrombocytopenia; any nonhematologic toxicity of grade $\geq$ 3 except for nausea, vomiting, stomatitis, serum amylase elevation, mucositis related to radiation, dysphagia phayngeal, or esophageal related to radiation; more than 14 days delay of RT due to toxicity; more than 21 days delay of DeVIC due to toxicity; patient refusal; and physician's discretion.

The primary end point of the phase II portion was 2-year OS. The secondary end points were 2-year progression-free survival (PFS), complete response (CR) rate, 2-year PTV control rate, pattern of failure, and toxicity. Response was judged using the International Workshop Criteria[32] by the Central CT Review Committee.

The study was designed as a trial with a one-sided hypothesis that the superiority of the historical control to RT-DeVIC was out of concern a priori. This hypothesis was used because RT-DeVIC was expected to be more toxic than the historical control. The required sample size was 24 eligible patients in the phase II portion for an 80% power to detect a 25% difference in the 2-year OS from the historical control of 45%[20] with a one-sided type I error of 0.05. The planned sample size was 27 patients in the phase II portion, with the expectation that 10% would be ineligible.

OS was defined as the time from registration until death from any cause or until the date of last follow-up for patients who were alive. PFS was defined as the time from registration until death from any cause, relapse, progressive disease, or until the last follow-up for patients who were alive. The CR rate was defined as the proportion of all patients assessable for response who experienced CR. The PTV control rate was defined as the proportion of patients with no evidence of disease in PTV. Survival estimates were calculated using the Kaplan-Meier method. In subgroup analyses, survival compared using the log-rank test and hazard ratio (HR) was estimated by Cox regression. All *P* values are two tailed. All analyses were performed using SPSS Statistics 17.0 software (SPSS Japan Inc, Tokyo, Japan).

RESULTS

Patient Characteristics

A total of 33 patients were accrued onto the study between September 2003 and December 2006 from 18 participating institutions. Histologic diagnoses of all patients were confirmed as extranodal NKTCL, nasal type, by the central pathology review. The concordance between institutional diagnosis and central diagnosis was 100% and intrapanel concordance was also 100%.

Baseline patient characteristics are listed in Table 1. All patients with stage II disease had cervical node involvement. Clinical parameters in all 33 patients were comparable with those with the 27 patients treated with the recommended dose.

Dose Escalation and DLTs

During the phase I portion, 10 patients were enrolled (Table 1). Initially, three patients were enrolled at level 1. Since one of them developed progressive disease (PD) before the evaluation of DLT, an additional patient was entered at level 1. All three patients evaluated at level 1 did not develop DLTs. At level 2, two of the first three patients developed DLTs. Two of additional three patients experienced DLTs. Since four of the six patients developed DLTs at level 2, the dose of level 1 was selected as the recommended dose for the phase II portion.[33]

Major toxicity profiles for the 10 patients are presented in Table 2. The DLTs observed in four patients at level 2 were: grade 4 leukopenia or neutropenia lasting ≥ 5 days (n = 2); grade 4 thrombocytopenia (n = 2); grade 3 infection (n = 3); grade 3 weight loss (n = 1); and grade 3 keratitis (n = 1). At level 2, three patients needed a red cell transfusion and two patients needed a transfusion of platelets.

Toxicity and Compliance With the Regimen

Table 3 lists all grade 3 or 4 toxicities for all 33 patients enrolled to the phase I/II study and the 27 patients treated at the recommended dose level of two thirds DeVIC. No treatment-related deaths occurred. Transient and clinically manageable grade 4 hyponatremia and hypokalemia were observed in each individual patient. One patient who experienced grade 4 dermatitis related to radiation had a necrotic mass in the nasal cavity and experienced perforation of the nasal skin. At the

Table 1. Baseline Patient Characteristics

Characteristic	No.							
	Phase I (n = 10)			Phase II (n = 23)	Patients Treated With Two Thirds DeVIC* (n = 27)		All Patients (N = 33)	
	Level 1 (n = 4)	Level 2 (n = 6)	Total				No.	%
Male sex	3	2	5	14	17	63	19	58
Age, years								
Median		44.5		56	56		54	
Range		30-61		21-68	21-68		21-68	
> 60		1		6	7	26	7	21
Stage								
IE	2	4	6	16	18	67	22	67
IIE	2	2	4	7	9	33	11	33
B symptoms	2	2	4	8	10	37	12	36
Elevated LDH	0	2	2	5	5	19	7	21
Performance status								
0	3	4	7	18	21	78	25	76
1	1	2	3	3	4	15	6	18
2	0	0	0	2	2	7	2	6
IPI score								
0	3	4	7	13	16	59	20	61
1	1	2	3	7	8	30	10	30
2	0	0	0	3	3	11	3	9
NK-PI group								
1	1	2	3	8	9	33	11	33
2	1	2	3	7	8	30	10	30
3	2	2	4	5	7	26	9	27
4	0	0	0	3	3	11	3	9

Abbreviations: DeVIC, dexamethasone, etoposide, ifosfamide, carboplatin; LDH, lactate dehydrogenase; IPI, International Prognostic Index; NK-PI, natural killer/T-cell lymphoma Prognostic Index.
*Recommended dose.

Table 2. Adverse Events Observed During the Phase I Portion (N = 10)

Adverse Event	No. of Events by Grade: Level 1 (n = 4) 3	Level 1 (n = 4) 4	Level 2 (n = 6) 3	Level 2 (n = 6) 4
Leukopenia	3	1	2	3
Neutropenia	1	3	0	5
Anemia	0	0	1	3
Thrombocytopenia	0	0	1	2
Weight loss	0	0	1	0
Appetite loss	2	0	2	0
Stomatitis/mucositis	2	0	3	0
Constipation	0	0	1	0
Mucositis related to radiation	2	0	4	0
Dysphagia related to radiation	1	0	2	0
Keratitis	0	0	1	0
Febrile neutropenia	0	0	2	0
Infection with grade 3 or 4 neutropenia	0	0	2	0
Hypokalemia	0	0	0	1

median follow-up period of 32 months, no grade 3 or greater late toxicities were observed.

Among patients treated with the recommended dose, the most common grade 3 nonhematologic toxicity was mucositis related to radiation (30%). Local toxicity was transient and manageable in most patients. Seven patients (26%) experienced 1 or more grade 3 infections. Grade 3 or 4 leukopenia and neutropenia were common. Neither grade 4 anemia nor thrombocytopenia was observed.

Table 3. Incidence and Maximum Severity of Adverse Events

Adverse Event	Patients Treated With 2/3 DeVIC* (n = 27) Grade 3 No.	%	Grade 4 No.	%	All Patients (N = 33) Grade 3 No.	%	Grade 4 No.	%
Leukopenia	23	85	4	15	25	76	7	21
Neutropenia	18	67	7	26	18	55	12	36
Anemia	4	15	0	0	5	15	3	9
Thrombocytopenia	3	11	0	0	4	12	2	6
Weight loss	0	0	0	0	1	3	0	0
Dehydration	1	4	0	0	1	3	0	0
Appetite loss	6	22	0	0	8	24	0	0
Stomatitis/pharyngitis	3	11	0	0	6	18	0	0
Constipation	0	0	0	0	1	3	0	0
Mucositis related to radiation	8	30	0	0	12	36	0	0
Dysphagia related to radiation	4	15	0	0	6	18	0	0
Dermatitis related to radiation	1	4	1	4	1	3	1	3
Conjuctivitis	1	4	0	0	1	3	0	0
Keratitis	0	0	0	0	1	3	0	0
Febrile neutropenia	4	15	0	0	6	18	0	0
Infection with grade 3 or 4 neutropenia	2	7	0	0	4	12	0	0
Infection without neutropenia	2	7	0	0	2	6	0	0
Hypokalemia	0	0	0	0	0	0	1	3
Hyponatremia	0	0	1	4	0	0	1	3

Abbreviation: DeVIC, dexamethasone, etoposide, ifosfamide, carboplatin.
*Recommended dose.

All patients completed RT without any protocol violations.[31] In nine patients, RT was postponed due to toxicity, but was restarted within 7 days of postponement. Thirty-one patients (94%) received three courses of DeVIC. In the remaining two patients, DeVIC chemotherapy was terminated before the third course. Thus, compliance with the planned protocol treatment was 94%.

Efficacy

Efficacy was assessed in 27 patients who were treated with the recommended dose of two thirds DeVIC (Table 1). One patient was deemed ineligible for response analysis because there was no measurable lesion in the baseline CT scan that was taken after biopsy. Of the 26 patients assessable for response, there were 20 patients with CR (77%; 95% CI, 56% to 91%), one with PR, two with stable disease (SD), and three with PD. The overall response rate (ORR) was 81%. In 92% of patients (24 of 26), lymphomatous involvement disappeared in the field of RT at the time of restaging after the protocol treatment.

Of the 32 total assessable patients, 24 patients achieved CR (75%; 95% CI, 57% to 89%), one with PR, three with SD, and four with PD. The ORR was 78%. Local control was achieved in 91% of patients (29 of 32).

All patients were eligible for survival analysis. The median follow-up time for the 27 patients evaluated in the phase II portion was 32 months, with a range of 24 to 62 months. In these patients, the OS at 2 years was 78% (90% CI, 61% to 88%; 95% CI, 57% to 89%; Fig 1A). PFS at 2 years was achieved in 67% (90% CI, 49% to 80%; 95% CI, 46% to 81%) of patients (Fig 1B). The PTV control rate at 2 years was 96% (26 of 27). During the follow-up period, 10 of 27 patients experienced disease recurrence. Patterns of failure were 4% locoregional (one of 27) and 33% distant (nine of 27). In patients who relapsed after CR, the sites of relapse were lymph node (n = 3), skin (n = 2), bone marrow (n = 2), stomach (n = 1), ascites (n = 1), and spleen (n = 1).

Subgroup Analysis

Although number of events is inadequate for statistical power to detect the difference between subgroups, the score of the International Prognostic Index[34] and the NK/T-cell lymphoma prognostic index[25] group were not statistically correlated with OS and PFS in the study population (data not shown). On the contrary, the induction of CR strongly affected both OS (HR, 0.095; 95% CI, 0.017 to 0.531) and PFS (HR, 0.122; 95% CI, 0.033 to 0.444), as shown in Figure 2.

DISCUSSION

To our knowledge, our study is the first prospective study of concurrent chemoradiotherapy for untreated, localized nasal NKTCL incorporating an adequate sample size, central pathology review, central CT review, and RT quality assurance program.

We compared the efficacy of RT/two thirds DeVIC with that of RT alone in terms of 2-year OS because the reported survival curves of localized nasal NKTCL treated with RT alone declined rapidly and reached to plateau at 2 years after diagnosis.[20] Although median age was higher and incidence of B symptoms and cervical node involvement were more frequent in the current study population than in the

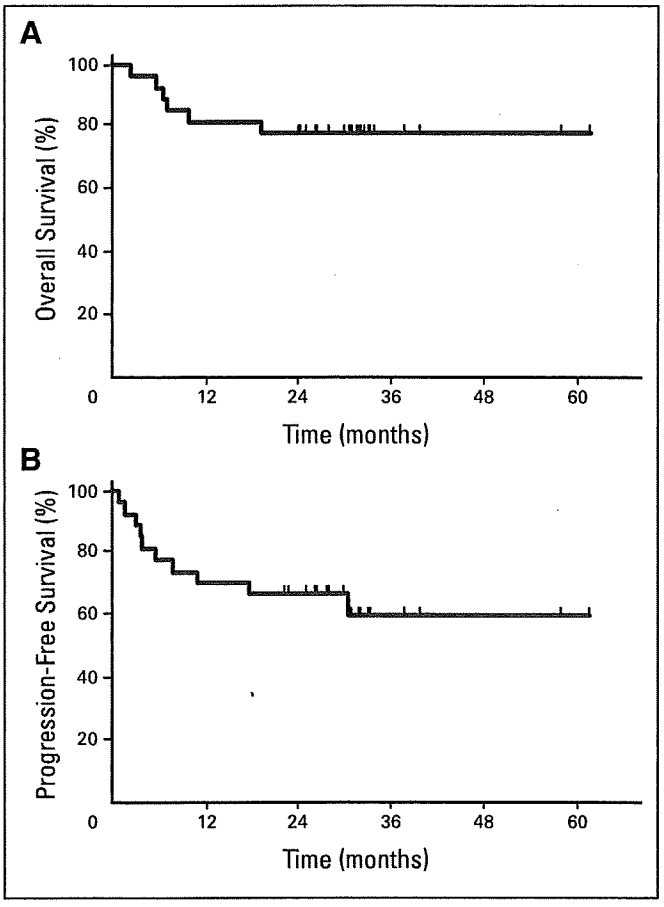

Fig 1. (A) Overall survival and (B) progression-free survival of patients treated with radiotherapy and two thirds dose of dexamethasone, etoposide, ifosfamide, and carboplatin.

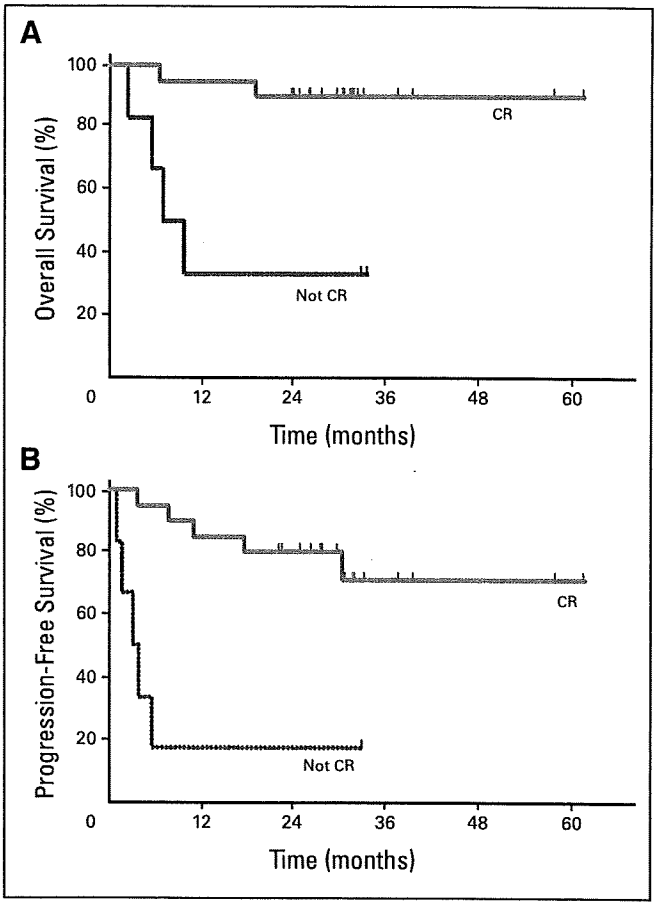

Fig 2. Effect of complete response (CR) on (A) overall survival and (B) progression-free survival of patients treated with radiotherapy and two thirds dose of dexamethasone, etoposide, ifosfamide, and carboplatin.

historical control group[20] (56 *v* 45 years, 37% *v* 8.7%, 33% *v* 17.4%, respectively), 2-year OS (79%; 95% CI, 57% to 89%) was superior to the historical control (45%).[20] Based on these results and the excellent PTV control rate at 2 years (96%), we consider RT-2/3DeVIC to be more effective than RT alone for the treatment of localized nasal NKTCL.

There are few reports describing comparable efficacy to our study using first-line RT followed by CHOP-like chemotherapy.[35,36] It is difficult to evaluate efficacy in those retrospective studies because of heterogeneous treatment protocols and incomplete immunophenotypic tumor cell analyses. The efficacy of CHOP chemotherapy for NKTCL is questionable, because the 5-year OS after first-line CHOP with or without additional RT was less than 50%.[17,19] Since the first publication of RT-DeVIC therapy,[18] several studies and case reports describing the efficacy of DeVIC or DeVIC-like chemotherapies for NKTCL have been presented.[13,14,37-39] The results of this study should serve as a basis for testing these treatment regimens in larger patient populations.

The toxicity profile of concurrent chemoradiotherapy for lymphoma has not been well established. In a phase II study of concurrent chemoradiotherapy for relapsed aggressive lymphoma with bulky mass, hematologic toxicity and infection were frequent and severe.[40] Our results support this observation; therefore, these adverse events should be carefully evaluated in future trials. The incidence of mucositis in this study was 30%, which was lower than reported for concurrent chemoradiotherapy for head and neck cancer (38% to 57%).[41,42] Use of a mouth spacer and two-step cone down of RT were considered to be important, resulting acceptable local toxicities of this study.

Because this study is the first prospective trial of concurrent chemoradiotherapy for localized nasal NKTCL, we cannot make a definitive conclusion regarding the component of RT-2/3DeVIC which had the greatest impact on improvement in 2-year OS. Since the local control was excellent and patients who obtained a CR showed better OS than the other patients, additional chemotherapy such as L-asparaginase–containing regimens,[13,43,44] or high-dose chemotherapy with autologous hematopoietic stem cell transplantation,[45,46] may be beneficial for patients with risk factors for systemic relapse. However, we could not identify risk factors at diagnosis predictive of OS or PFS in subgroup analyses of the current trial. Additional clinicopathologic studies, including Ki-67 expression and platelet count which were identified as the risk factors by an international study,[7] and monitoring EBV DNA load in peripheral blood[47,48] might be useful for identification of risk factors for survival in patients treated with RT-2/3DeVIC.

In conclusion, the results of this phase I/II study indicate that concurrent chemoradiotherapy with non-MDR agents and etoposide

