表5　cetuximab 療法の海外第Ⅲ相臨床試験

Stage	試験 No.	症例数	レジメン	
1st line	CALGB 80405	2289 (症例集積中)	FOLFOX または FOLFIRI	cetuximab vs ベバシズマブ vs cetuximab + ベバシズマブ
	CRYSTAL (EMR-013) PFS	1080	FOLFIRI ± cetuximab positive PFS : Jan.10, 07	
2nd line4	EPIC (BMS-006) OS, PFS/RR	1300	CPT-11 ± cetuximab positive PFS/RR : Nov.6, 06	
Refractory	BMS-025 OS	572	BSC ± cetuximab positive OS : Nov.6,06	

サリプラチンすべてに不応な症例に対して NCIC-CO.17 試験 (best supportive care vs cetuximab) が，進行中あるいは終了している。このうち，NCIC-CO.17 試験では，全生存期間において cetuximab 群が有意に優れていたとのプレスリリースが 2006 年 11 月に報告された (表5)。

今後，これらの臨床試験成績を受けて，分子標的治療薬の併用療法などが転移性あるいは術後補助療法で検討されることになる。

2．ABX-EGF (panitumumab)

完全ヒト型抗 EGFR 抗体である ABX-EGF (panitumumab) は，キメラ抗体である cetuximab に比べ，infusion reaction などの有害事象の頻度が少ないと報告されている。CPT-11 およびオキサリプラチンに不応となり有効な治療法がない大腸癌患者を対象に，panitumumab 単剤と BSC との比較試験が行われ，無再発生存期間において panitumumab が優れていた[12]。

Ⅲ 増大する医療費と治療選択

これら分子標的治療薬は 5-FU + LV，イリノテカン，オキサリプラチンに続く，第 4 の薬剤として大きな期待が持たれているが，現在，その薬剤費の高価なことが米国においては大きな問題となっている。治療開始 2 カ月間の薬剤費がベバシズマブ併用で 2 万ドル，cetuximab 併用で 3 万ドルという事実[13]は，個々の症例のみならず，社会全体としてこのような症状コントロールと延命を目的とした癌患者に対する高額医療をどのように受け入れるか，コンセンサスを必要とする。

mFOLFOX6 +ベバシズマブ併用療法の薬剤費を概算し，参考までに掲載する(表6)。平均的体格である体表面積 1.7 m^2 の患者をモデルに試算すると，mFOLFOX6 のみで 1 回投与薬剤

表 6　mFOLFOX6 ＋ベバシズマブに関する薬剤費試算

薬剤名	薬剤費
l-LV（アイソボリン®）(25) 1V	3,383 円
オキサリプラチン (100) 1V	74,087 円
5-FU 注 (250) 1A	461 円
グラニセトロン（カイトリル®）注 (3) 1A	7,630 円
デキサメタゾン（デキサート®）注 (8) 1A	123 円
ベバシズマブ（アバスチン®）注 (100) / (400) 1A	50,291/191,299 円
中心静脈ポート設置	108,000 円

170 cm 65 kg BSA 1.7 mFOLFOX6 ＋ベバシズマブの場合の 1 回投与分

	制吐剤	5-FU	LV	オキサリプラチン	ベバシズマブ（/kg）
/m², /kg		2,800 mg	200 mg	85 mg	5/10 mg
/body		4,750 mg	325 mg	140 mg	325/650 mg
A	1A ＋ 1V	19A	13V	2V	1 (400) /1 ＋ 3 V (100)
¥	7,753	8,759	43,979	148,174	191,299/342,172

mFOLFOX6：208,665 円　＋ベバシズマブ 5 mg：399,964 円　＋ベバシズマブ 10 mg：550,837 円

費は 208,665 円，5 mg/kg のアバスチン® 併用では 191,299 円が追加され，合計 399,964 円と 40 万円の高額となる。2 週毎の投与であり，月 80 万円の薬剤費となる。3 割負担，高額医療で 3 カ月後に償還されるなどの負担軽減が適応されるが，患者個人にとっても，社会全体にとっても，医療費が多大な負担になることは間違いない事実である。がん治療を享受する患者個人の利益のみで治療法の評価を行うことの妥当性は，今後十分に議論しなければ，医療全体のバランスを失いかねない状況にまできていると考えられる。

Ⅳ 国内治験，承認に関する情報

現在までの，未承認抗がん剤に関しての承認および承認申請の状況を以下にまとめた。

厚生労働省の未承認薬使用問題検討会議で取り上げられた薬剤のうち，大腸癌に関連する医薬品は，オキサリプラチン（エルプラット® 注射用 100 mg）2005 年 3 月 18 日承認，ベバシズマブ（アバスチン® 点滴注射用 100 mg，400 mg）2007 年 4 月 18 日承認。cetuximab（申請中）の 3 剤である。前 2 剤の承認適応症は，「治癒切除不能な進行・再発の結腸・直腸癌」である。

2007年6月の最新更新版でも，これ以外の薬剤は掲載されていない。今後検討される新薬に関しては，海外での第Ⅲ相試験により臨床的意義を検証した臨床成績を元に国内申請が行われることが予想されている。

これら以外の新薬では，国内で乳癌のみの適応症を持つカペシタビンが，2006年3月に結腸癌術後補助療法を適応症として，海外X-ACT試験を元に申請している。100%ヒト化抗EGFRモノクローナル抗体であるABX-EGF (panitumumab) が，国内臨床試験中である。

Ⅳ 国内臨床現場での課題と対策

以前は，国際的な標準治療薬が国内で使用できない問題点が指摘されてきたが，厚生労働省，企業，研究者の協力により，現在では多くの必須抗がん剤が国内で使用できるようになった。しかしながら，従来と異なり，国内治験での経験がほとんどない状況で，一般臨床現場で使用を開始するというリスクを背負うようになる。従来の市販後調査で安全性情報を収集しても，国内における標準的治療を確立し，根付かせることは難しい。より早い段階から，国内において研究者主導で，企業との共同研究という形態で，臨床試験が実施される体制作りが強く望まれる。この過程において，新規治療法に慣れ，治療法による副作用の管理や安全性情報を共有することにより，短期間で新規治療法を臨床現場に浸透させることが可能と考えられる。治験で得られる限られた情報だけでなく，より一般化した条件での新規治療法の育成が必要である。

臨床現場では，新規薬剤の特徴を十分に理解し，薬剤効果が最大限に発揮できる患者群に適切に使用することにより，治療成績を向上させる努力が必要になっている。新薬は決して魔法の薬ではないが，確実に治療成績を向上させたことも事実である。いかに新薬を使いこなすかが，大腸癌患者に最大の恩恵を提供することにつながると確信する。

（島田 安博）

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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.

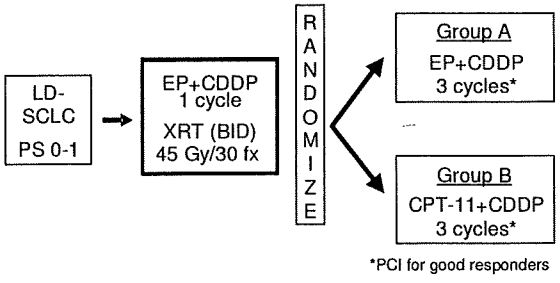

Figure 1
Schema of JCOG 0202. Abbreviations. LD-SCLC, limited-disease small cell lung cancer; PS, performance status; EP, etoposide; CDDP, cisplatin; XRT, thoracic radiotherapy; BID; bis in die/twice a day; CPT-11, irinotecan; PCI, prophylactic cranial irradiation.

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.

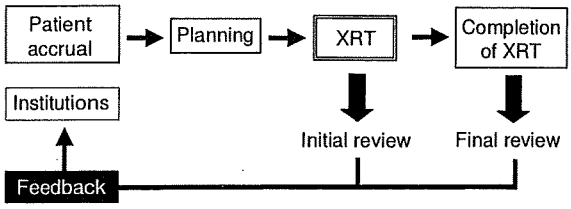

Figure 2
Flow of QA review. After the QA review, feedback was given to the institutions. Treatment planning was modified when possible.

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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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.

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%.

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.

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

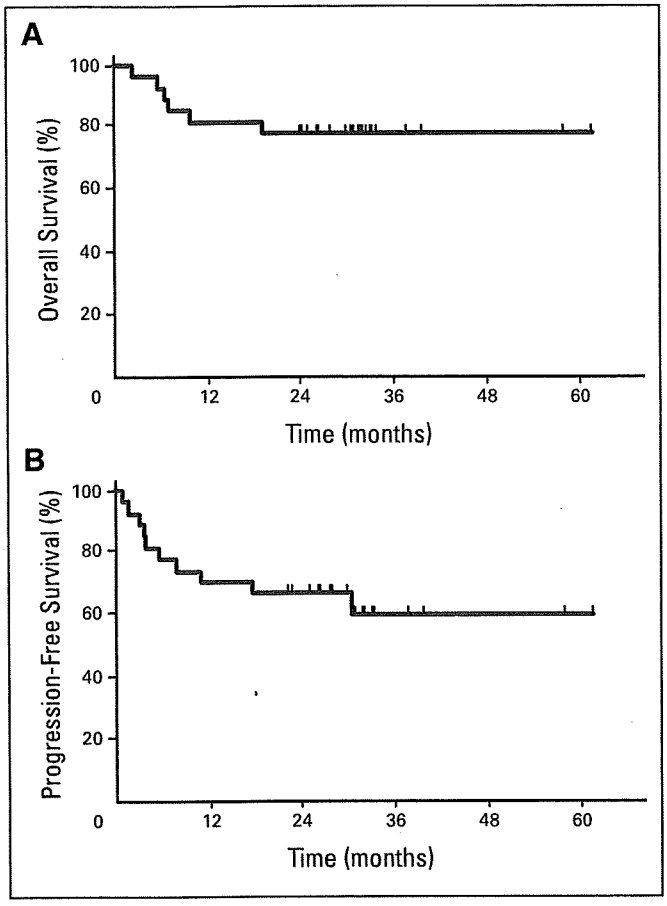

Fig 1. (A) Overall survival and (B) progression-free survival of patients treated with radiotherapy and two thirds dose of dexamethasone, etoposide, ifosfamide, and carboplatin.

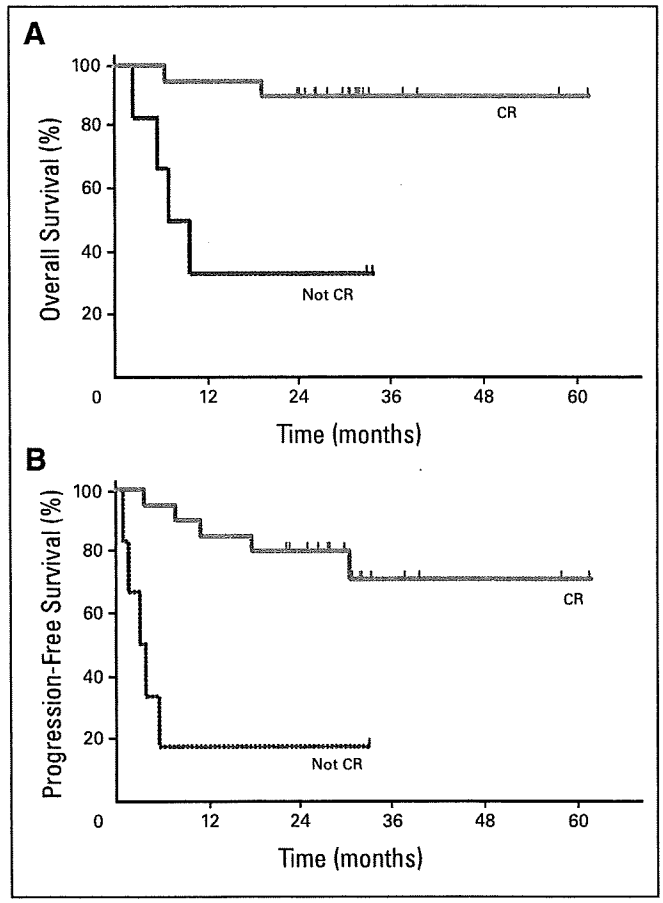

Fig 2. Effect of complete response (CR) on (A) overall survival and (B) progression-free survival of patients treated with radiotherapy and two thirds dose of dexamethasone, etoposide, ifosfamide, and carboplatin.

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

is an effective and safe treatment for patients with newly diagnosed, localized nasal NKTCL. The results of this study should serve as a basis for future clinical trials for this disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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JASTRO NEWSLETTER

一般社団法人
日本放射線腫瘍学会

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JRRS/JASTRO合同学術雑誌発行に向けて

JASTRO編集委員長
中野隆史

6月から日本放射線影響学会(JRRS)／日本放射線腫瘍学会(JASTRO)の合同学術誌として新Journal of Radiation Research(JRR)誌の編集を開始しました。現JASTRO誌への投稿は2009年5月31日で終了し，新JRR誌への投稿受付を2009年6月1日から開始しました。新JRR誌は2010年1月号51号から発行を開始する予定です。

新JRR誌が実現に至った背景には，JASTRO誌をさらに国際的な学術情報の発信の場に発展させることがあります。最も早くこの目的を達成するための方法として，JASTRO誌を廃刊し，JRR誌をJRRS/JASTROの合同学術誌として再スタートすることを編集委員会ならびにJASTRO理事会の総意として決定しました。運営はJRRS(主幹事)とJASTRO(副幹事)を幹事学会として，今後はその他の放射線関連学会も参画して行う予定です。

JASTRO准会員も正会員と同じ条件で扱われます。勿論，非会員も新JRR誌への投稿が可能です。JASTRO会員にはJRRS会員と同様に，学会加盟年数により頁チャージ料を最大50％割引という特典がありますので，投稿規定を一度お読みください。

論文審査については，投稿論文の著者名等はブラインドにしないで審査を行い，JASTRO会員の投稿論文は原則JASTRO側のVice Editor in Chiefが対応致しますので，医学博士予定論文の投稿などに積極的に活用していただければ幸いです。JRR誌としては基本的には原著論文を重視致します。症例報告については，相当なインパクトのある内容でないと受理することは困難ですので，投稿に際して留意してください。JASTRO会員の投稿が増えますと，それだけJASTROのJRR誌に対する貢献が評価されますし，JASTROの国際的な学術評価も上がりますので，積極的にご投稿をお願い致します。JASTRO編集委員会としても新JRR誌を盛り立て，より評価の高い国際学術誌となるよう努力致しますので，ご協力を宜しくお願い致します。

と，このがん診療連携拠点病院の整備は，がん診療の均てん化が目的であったはずだが，東京都内においても拠点病院は都心部に集中している傾向はあり，一部の地域では放射線治療認定医の不在など，必ずしも十分な体制が整備されていない部分も残されている。今後の取り組みを期待したい。

がん拠点病院の実態―島根県の場合―

島根大学放射線治療科　内田伸恵

島根県のがん対策の現状

島根県は全国で最も高齢化率が高い県であり，がんは島根県における死亡原因の第１位となっています。島根県のがん患者さんが東京に抗がん剤治療に通いながら，新規抗がん剤の早期承認やがん医療水準の地域格差の是正を社会や行政に訴えました。これが，がん医療の均てん化の促進を大きな柱とする『がん対策基本法』の制定のきっかけとなったことは記憶に新しいことです。当時の島根大学病院長とがん患者さんの団体の会談での「今すぐ島根県にがん治療医を増やしてください」との訴えに，病院長が「専門医の育成には10年かかります」と答え，「われわれにはそんな時間はないのだ」と患者さんが憤慨された光景が放映されたことを覚えています。病院長の言うことも真実なのですが，事態はもっと切迫していました。

こうした経緯から2007年９月，島根県は全国自治体で最初に『島根県がん対策推進条例』を制定しました。さらに患者代表，医療関係者，学識経験者等による『島根県がん対策推進協議会』を設置し，2008年３月に『島根県がん対策推進計画』を策定するなど，全国に先んじたがん対策を進めています。がん患者団体の動きも活発で，県内の主な病院には「がん患者サロン」があり，自主的な運営や病院との連携を行っています。がん拠点病院長とがん患者団体との意見交換会，がんの診断や治療のための医療機器整備等を目的とした「がん対策募金」なども行われています。このように，島根県はがん医療をめぐる患者，自治体のアクションは近年大変活発となり，全国的にも注目されているものと思います。医療政策に関するシンクタンク日本医療政策機構(本部・東京都)が昨年行った都道府県のがん対策推進計画の比較調査では，島根県の計画が全国１位でした。これは国の目標値を上回るがん死亡率の引き下げ，がん薬物療法や放射線治療の専門医の倍増計画など，積極的な数値目標が評価されたものと思われます。今後，計画の実現が大きな課題です。

島根県内のがん診療連携拠点病院は，島根大学病院が都道府県がん拠点病院，がん拠点病院が５カ所の合計６施設です(図１)。その概要を表１にお示しします。

がん薬物療法専門医やがん薬物療法認定薬剤師，専門看護師等も全く不足している状態です。県西部のE病院は放射線治療装置を有していません。内科・外科の医師不足が深刻となっており，放射線治療の開始は困難ということで，今年の更新において，がん拠点病院の指定を外れる見通しです。これにより，県中西部のがん拠点病院は２カ所から１カ所に減り，県内のがん医療格差が進むことが懸念されています。病院長とも何度か意見交換をしたことがありますが，胃がん等の症例は比較的多く治療されており，緩和医療やがん患者支援にも熱心に取り組まれています。今後がん拠点病院から外れても，県民にとって重要な病院であることには相違ないと思います。がん拠点病院の認定要件に放射線治療の項目があることは，がん医療にとっても，放射線治療の推進にとっても大変重要なことです。しかしながら，地域のがん医療の現状は，このようにまだまだ厳しい状況です。

がん医療に限定される話ではありませんが，卒後臨床研修制度の必修化に伴う研修医の県外流出，地域医療機関から大学への医師の引き上げ，地域の医療崩壊という構図も非常に厳しい現実となっています。2008年度の文部科学省調査では，島根県

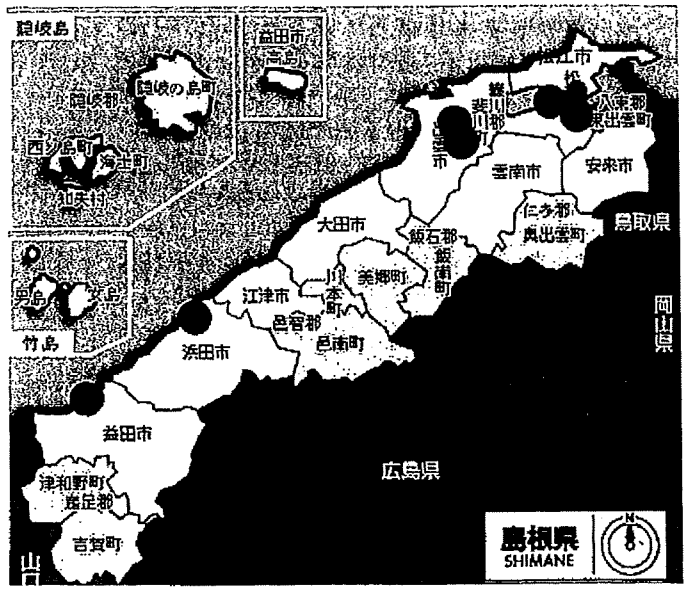

図１

表 1

	A	B	C	島根大学病院	D	E
病床数	710	470	687	616	354	327
医師数	113	79	149	264	42	45
がん薬物療法専門医(暫定指導医)	(1)	-	(1)	1+(2)	(1)	-
JASTRO認定医	-	2	1	4	-	-
がん薬物療法認定薬剤師	1	1	1	1	1	-
放射線治療装置	○	○	○	○	○	×
密封小線源放射線治療装置	×	×	×	○	×	×
外来化学療法室	○	○	○	○	○	○
緩和ケア病棟	×	○	×	×	×	×
院内緩和ケアチーム	○	○	○	○	×	○
年間がん登録数	970	715	1,184	805	483	377

島根県HP，島根県がん登録集計等より抜粋改変
主たるデータは2007年度分

の研修医定着率は20％台で，全国最低レベルでした。地域での医療教育の充実，地域入学枠の拡大など医師不足・偏在の是正が大きな課題です。島根大学も自治体と協力して，県内出身者への奨学金，地域医療教育学講座の設置など，さまざまな対策を講じていますが，医療の現場で成果が出るのにはまだ時間がかかります。

島根県の放射線治療の現状

島根県内の放射線治療の現状については，2006年のJASTRO NEWSLETTERの「認定医が少ない県の放射線治療の現状と今後」で紹介させていただきました。それから 3 年経過しましたが，当時 2 名であった県内の認定医は現在 7 名，JASTRO認定施設が当院，認定協力施設が 2 施設と，3 倍(!)に増えています。

上述の日本医療政策機構による都道府県別の放射線腫瘍医数の人口比のデータでは，島根県は群馬県に続いて 2 位であり，全国第46位の県人口が影響している結果です。現実には放射線治療も県内の地域格差があります。東西に細長く，離島も有するなか，県東部には 5 カ所 6 台の放射線治療装置があるのに比べ，中西部には 1 カ所 1 台であることが 1 例です。通常なら外来で十分治療可能な前立腺がんの局所照射を，病院への通院時間や交通事情の問題で 7 週間以上の入院が必要となってしまう患者さんが多数おります。限られた医療資源を有効活用し，より多くの患者さんに良質な放射線治療を提供するためには，県内の放射線治療機能の役割分担と連携強化が必要です。放射線腫瘍医の育成とともに大きな課題であると考えています。

がん拠点病院の実態―神戸大学編―

神戸大学医学部附属病院放射線腫瘍科　佐々木良平

神戸大学医学部附属病院は2008年にがん診療連携拠点病院の指定を受けました。また，特定機能病院としての指定も併せて受けております。同病院が期待されている役割と実態を内部に働く一人の医師の視点で紹介させていただきます。

兵庫県は瀬戸内海と日本海に挟まれた縦長の県ですが，神戸市を中心とした阪神地域に人口が集中しているためか，県内に14指定されている「がん診療連携拠点病院」も実に10病院が阪神地域に所在しています。その中でも，われわれの施設の近隣には，兵庫県立がんセンター，兵庫医科大学病院，神戸市立医療センター中央市民病院等の実績があり，有名な大病院群が約 1 時間以内の移動距離の間にひしめき合っている実情があります。

個人的な見解を述べさせていただくと，そのような環境の中でも，神戸大学医学部附属病院は『がん対策基本法』の恩恵を受け，「がん診療連携拠点病院」の指定も含めてドラマチックに整備が進んだと思われます。それまでは，一部のがん診療に関して実績の高い診療科が，大学病院としての周囲関連病院との関係の中でがん診療の中心として活躍しておりましたが，「がん診療連携拠点病院」の指定に併

総説

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非小細胞肺癌の放射線治療

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■ はじめに

非小細胞肺癌治療における放射線治療の役割は多岐にわたるが，大別して，① 医学的に手術不能なI・II期，② 局所進行切除不能III期，③ 術前・術後照射，④ 骨転移・脳転移・上大静脈症候群・再発癌などに対する対症・緩和照射の4つが代表的である。

本稿ではこれらのうち，根治的治療の一環としての①～ ③について，現在までのエビデンスに基づく標準的治療と今後の展望について概説し，さらに三次元治療計画・近年進歩著しい治療技術についても述べる。

❶ 医学的手術不能I・II期

1) 従来型放射線単独治療

早期肺癌の標準的治療は手術であるが，高齢や低肺機能・合併症など医学的理由で手術が不可能な患者には，放射線単独治療が適応となる事が多い。放射線単独治療についての成績をまとめたsystematic reviewを表1[1-3]に示す。通常分割60Gy前後の従来型放射線単独治療では，5年生存率15～20%前後，5年原病生存率25～30%前後と，症例選択のバイアスは大きいと考えられるものの，手術と比較して明らかに不良である。また，これらのreviewにより，再発形式としては局所再発が多いこと，高線量ほど治療成績が良好な傾向にあること，I期肺癌においては縦隔予防照射の利益は低いことが示された。

2) 体幹部定位放射線治療

近年の著しい照射技術の発展により，肺原発腫瘍のみに多方向から高精度に集中して短期間に大線量を照射する体幹部定位放射線治療（stereotactic body radiotherapy：SBRT）が可能になった。方法の詳細については他を参照されたい[4]。日本の先行する14施設257症例の治療結果をまとめた報告によると，肺野型のI期非小細胞肺癌のうち，BED（biological effective dose）100Gy$_{10}$以上照射された215例では5年局所制御率84%と良好であった。さらに手術可能だが拒否され，BED100Gy$_{10}$以上照射された86例では，5年生存率70.8%と手術に匹敵する成績であった[5]。現在日本においてはJCOGで，IA期手術不能例・拒否例を対象にした48Gy/4fr/4daysのレジメンでの第2相試験（JCOG0403）の登録がほぼ終了し，IB期に対する線量増加第1相試験（JCOG0702）が開始された。他にもRTOGなど国外においても第1，2相臨床試験が進行中で，さらに手術と比較する第3相試験も計画されており，それらの結果が期待される。

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表1　医学的手術不能 I・II 期に対する従来型照射単独治療の systematic review

報告者・年	文献数	症例数	病期	線量（Gy）	5年生存率（%）	5年原病生存率（%）	備考
Rowell 2001[1]	26	2,003	I, II	BED 59～76	0～42	13～39	局所再発：6～70% IFRT*後の LN 再発：0～3%
Sibley 1998[2]	10	848	I	≈60	≈15	≈30	高線量で成績良好 予防照射意義少ない
Qiao 2003[3]	18	1,532	I	BED 62～76	21±8	25±9	局所再発中央値：40% 領域 LN 再発：0～3%

* IFRT：involved field radiotherapy

表2　照射単独 vs. 順次化学放射線療法についての第3相試験

報告者・年	導入化学療法	放射線療法（Gy）	症例数	MST**（M）	3年生存率（%）
Dillman	—	60	77	9.7	11
CALGB 1996[6]	CDDP/VBL	60	78	13.8	23
Le Chevalier	—	65	177	10.0	4
1991[7]	VCPL*	65	176	12.0	12
Sause	—	60	152	11.4	11
RTOG/ECOG/SWOG	—	69.6HF	154	12.0	14
2000[8]	CDDP/VBL	60	152	13.8	17

* VCPL：VDS, CPA, CDDP, lomustin, ** MST：median survival time

❷ 局所進行切除不能 III 期

1）照射単独治療から化学放射線治療へ

切除不能の定義は定まったものはなく議論のあるところであるが，一般に bulkyN2 または複数ステーション転移を有する IIIA 期以上は切除不能とされ，悪性胸水例を除く，IIIA・B 期が局所進行切除不能癌として根治的放射線治療の対象となる。1980 年代までは，60Gy 程度の胸部照射単独治療が標準治療であったが，80 年代後半以降，胸部放射線治療に導入化学療法を追加することで治療成績の向上（MST 約 10 カ月から約 13 カ月へ）が得られるようになった（表 2）[6-8]。用いられた化学療法はシスプラチン（CDDP）+ビンブラスチン（VBL）などの旧薬（第 2 世代）レジメンであった。さらに大規模な NSCLC collaborative group による meta-analysis によっても，CDDP を含む導入化学療法の追加によって有意な生存期間の延長を認めることが証明され（HR0.87，p = 0.005，死亡リスク 13%減少，5 年生存率 2%上昇）[9]，順次化学放射線治療が標準治療となった。

2）順次化学放射線治療から同時化学放射線治療へ

続いて 90 年代後半～2000 年代にかけて化学療法の併用時期について順次併用と同時併用の比較試験が行われ，同時併用によりさらなる生存期間の延長が証明された（MST 約 13 カ月から約 16 カ月へ）。日本の West Japan Thoracic Oncology Group（WJTOG）の試験を含む代表的な 3 つの第 3 相比較試験の結果を示す（表 3）[10-12]。Rowell らによる meta-analysis によると，同時化学放射線療法は放射線単独療法に対して 2 年で 7%，順次化学放射線療法に対して 2 年で 14%の死亡リスクの減少を認めたが，いずれも食道炎の発症の増加を認めた[13]。また Rolland らによる 7 つの試験，1,307 症例の meta-analysis では，CDDP を含む化学療法を同時に行うことにより，順次併用に比べて，3 年生存率が 5.7%改善した[14]。しかし有害事象の増加も認