sampling design. An external audit team of radiation oncologists who were recruited from academic institutions surveyed 84 institutes from 1996 to 1998 and 76 institutes from 1999 to 2001, respectively (2). PCS96-98 and PCS99-01 stratified these institutions into either academic (university hospital or cancer centre) or non-academic institutions (other hospitals) according to a facility master list created by the Japanese Society of Therapeutic Radiation Oncology in 1997 and 2001, respectively. The following patient criteria were used in the process survey: (i) the patients had adenocarcinoma of the prostate without distant metastases; (ii) the patients were treated with RT during the period 1996–98 and 1999–2001; (iii) the patients had neither been diagnosed with any other malignancy nor treated with RT previously (4).

The PCS96-98 and PCS99-01 surveys in Japan contain detailed information on a total of 835 patients with prostate cancer treated with RT during the respective survey periods (PCS96-98: 307 patients, PCS99-01: 528 patients). A total of 169 patients who received RT after radical prostatectomy (RP) were selected for this analysis (PCS96-98: 64 patients; PCS99-01: 105 patients). In addition to the analysis of changing trends in national practice between PCS96-98 and PCS99-01, the type of RT used (adjuvant or salvage setting) was revealed in the 1999–2001 survey. Seventy-three of the 105 patients were treated with adjuvant RT and the other 32 received salvage RT.

For statistical analysis, the differences between the proportions were tested by the χ^2-test. A P-value < 0.05 was considered statistically significant difference.

RESULTS

Patients and disease characteristics in the PCS96-98 and PCS99-01 surveys are shown in Table 1. Proportion of non-academic to academic hospitals was significantly different between the two surveys (PCS96-98 and PCS99-01) ($P = 0.004$). We found a significantly lower fraction of patients with clinical T3–4 tumours (26%: $P = 0.0004$) and with positive surgical margins (56%: $P = 0.042$) between 1999 and 2001 than between 1996 and 1998 (T3–4: 63%, positive surgical margins: 78%). Although the distribution of the pre-treatment prostate-specific antigen (PSA) level was not different between the 1996–98 and 1999–2001 surveys ($P = 0.44$), the distribution of the pre-RT PSA level was significantly different between the surveys ($P = 0.0002$). In the 1999–2001 survey, 71% of the patients received RT at a <1 ng/ml level of PSA compared with 28% in the 1996–98 survey.

The treatment characteristics are shown in Table 2. The use of ≥10 MV was significantly decreased in the PCS99-01 (73%) group compared with the PCS96-98 (92%) ($P = 0.0059$) one. The frequency of conformal therapy was also significantly lower in the PCS99-01 (23%) than in the PCS96-98 (65%) ($P < 0.0001$). The percentage of pelvic irradiation was not significantly different between the two survey periods (1996–98: 52%, 1999–2001: 41%) ($P = 0.18$). The distribution of radiation doses is shown in Fig. 1. The median radiation doses during 1996–98 and 1999–2001 did not change (60 Gy).

Although the percentage of patients who received hormonal therapy was not different between the surveys (1996–98: 83% versus 1999–2001: 72%) ($P = 0.18$), a lower number of patients were treated with chemotherapy in the 1999–2001 survey (8%) than in the 1996–98 survey (27%) ($P = 0.0045$).

Table 3 shows the comparison of patient characteristics and the treatment process according to the type of RT administered (adjuvant versus salvage setting) in the PCS99-01. The fraction of patients with a pre-RT PSA < 0.4 ng/ml in the adjuvant setting was significantly higher than that in the salvage setting, and the percentage of patients with a positive surgical margin in the adjuvant setting was higher than that in the salvage setting. The fraction of patients who received pelvic irradiation was significantly higher in the adjuvant setting than in the salvage setting ($P < 0.0001$). The distribution of the total dose to the prostatic bed is shown in Fig. 2. We observed a significant difference in median doses to the prostatic fossa between the adjuvant (56 Gy) and salvage settings (60 Gy) ($P = 0.0015$). However, more than half of patients in the salvage setting received total doses of <64 Gy.

DISCUSSION

Patients' Characteristics

In this analysis, we revealed changes in the practice of postoperative RT for patients with prostate cancer in Japan. The fraction of patients with T3–4 tumours was significantly decreased from the PCS96-98 survey to the PCS99-01 one. This result might indicate that high-risk patients with clinical T3–4 tumours tend not to be subjected to RP. However, Ogawa et al. (6,7) documented that significantly earlier T-stages (T1–2) were found between 1999 and 2001 than between 1996 and 1998 in their analysis of the patients who received radical RT for prostate cancer. These results may indicate the recent expansion of the indications for RT in patients with prostate cancer in Japan.

The pre-RT PSA level was significantly lower in the PCS99-01 patients than in the PCS96-98 ones. This might be a reflection of the accumulating evidence that lower pre-RT PSA is associated with success in the treatment of patients with PSA failure after prostatectomy (8,9). However, in the 1996–98 survey, we did not identify whether each patient received RT in the adjuvant or salvage setting because of the lack of data. The fraction of patients who received adjuvant RT as opposed to salvage RT might differ between the surveys.

Treatment Process

We observed significantly lower fractions of the use of ≥10 MV and conformal therapy in the PCS99-01 survey than in the PCS96-98 one. However, Ogawa et al. (6) documented that the changes in the use of ≥10 MV and conformal therapy for patients with primary prostate cancer were not significant between the PCS96-98 and PCS99-01 surveys.

Table 1. Patient background and characteristics

	PCS		*P*-value
	1996–98 (n = 64)	1999–2001 (n = 105)	
Number of institutes	84	76	
Number of patients	64	105	0.004
Academic	54	67	
Non-academic	10	38	
Median age (year) at RT	67	67	0.27
Range	50–83	36–89	
Pre-treatment PSA (ng/ml)			0.44
Median (range)	12.24 (0.0–379.8)	0.50 (15.35–268.2)	
<10	17/44 (39%)	29/88 (33%)	
⩾10 to <20	10/44 (22%)	21/88 (24%)	
⩾20	17/44 (39%)	38/88 (43%)	
Missing	20	17	
Differentiation			0.16
Well (G1)	11/62 (18%)	27/99 (27%)	
Moderate (G2)	23/62 (37%)	44/99 (45%)	
Poor (G3–4)	24/62 (39%)	23/99 (23%)	
Unknown	4/62 (6%)	5/99 (5%)	
Missing	2	6	
Gleason combined score			0.41
2–6	19/34 (56%)	24/45 (53%)	
7	8/34 (24%)	8/45 (18%)	
8–10	7/34 (20%)	13/45 (29%)	
Missing	30	60	
Clinical T-stage			0.0004
T1	2/57 (3%)	9/97 (9%)	
T2	14/57 (25%)	49/97 (51%)	
T3	34/57 (60%)	20/97 (21%)	
T4	2/57 (3%)	5/97 (5%)	
Unknown	5/57 (9%)	14/97 (14%)	
Missing	7	8	
Clinical N-stage			0.78
N0	52/61 (85%)	82/97 (85%)	
N1	4/61 (7%)	4/97 (4%)	
Unknown	5/61 (8%)	11/97 (11%)	
Missing	3	8	
Pathological T-stage			0.029
T1	1/59 (1%)	5/98 (5%)	
T2	8/59 (17%)	27/98 (28%)	
T3	47/59 (79%)	53/98 (54%)	
T4	1/59 (1%)	7/98 (7%)	
Tx	2/59 (2%)	6/98 (6%)	
Missing	5	7	
Pathological N-stage			0.27
N0	45/56 (80%)	80/99 (81%)	
N1	9/56 (16%)	9/99 (9%)	
Unknown	2/56 (4%)	10/99 (10%)	
Missing	8	6	
Last pre-RT PSA (ng/ml)			0.0002
<1	3/11 (28%)	60/84 (71%)	
⩾1 to <10	4/11 (36%)	16/84 (19%)	
⩾10	4/11 (36%)	8/84 (10%)	
Hormonal therapy			0.18
Yes	53/64 (83%)	76/105 (72%)	
Chemotherapy*			0.0045
Yes	17/64 (27%)	8/100 (8%)	
Extent of disease on prostatectomy			0.042
Confined to prostate	4/60 (7%)	18/103 (17%)	
Confined to specimen	7/60 (12%)	15/103 (15%)	
Positive surgical margin	47/60 (78%)	58/103 (56%)	
Unknown	2/60 (3%)	12/103 (12%)	
Missing	4	2	

PCS, Patterns of Care Study; RT, radiotherapy; PSA, prostate-specific antigen.
*Including estramustine.

This discrepancy might have arisen from the significantly higher fraction of patients who had received postoperative RT in non-academic hospitals in the 1999–2001 survey than in the 1996–98 survey in our analysis (P = 0.004). Ogawa et al. (10) also documented in their other report that the institutional stratification significantly affected the patterns of RT, such as the beam energy and the administration of conformal therapy.

The most appropriate radiation dose in the post-prostatectomy setting is controversial, as indicated by the wide range of doses noted in previous reports (45–75 Gy) (11). The American Society for Therapeutic Radiation Oncology (ASTRO) consensus panel recommended doses of ⩾64 Gy for patients with PSA failure after RP (12). On the other hand, Petrovich et al. (13) demonstrated that a median dose of 48 Gy in adjuvant RT reduced the risk of local recurrence in patients with pathological T3 prostate cancer. Our results also demonstrated that various doses were applied to the patients who had undergone RP, whether in the adjuvant or salvage setting.

Employing a conformal 3D planning system and promoting a dose escalation of >64 Gy may improve local control and biochemical relapse-free survival for patients with prostate cancer who receive postoperative RT alone (11,14). Ogawa et al. (7) showed that the radiation doses for patients with primary prostate cancer were higher in the PCS99-01 survey than in the PCS96-98 one, and discussed that the use of an increasing

Table 2. Treatment characteristics in RT

	PCS		*P*-value
	1996–98 (n = 64)	1999–2001 (n = 105)	
Energy of X-ray (local)			0.0059
<10 MV	4/51 (8%)	23/86 (27%)	
≥10 MV	47/51 (92%)	63/86 (73%)	
Missing	13	19	
All fields treated each day			–
Yes	–	87/105 (83%)	
Pelvis irradiation			0.18
Yes	33/64 (52%)	43/105 (41%)	
Conformal therapy			<0.0001
Yes	31/48 (65%)	24/103 (23%)	
Radiation dose (Gy)			0.082
Median	60	60	
Range	40–74.6	20–70	

PCS, Patterns of Care Study.

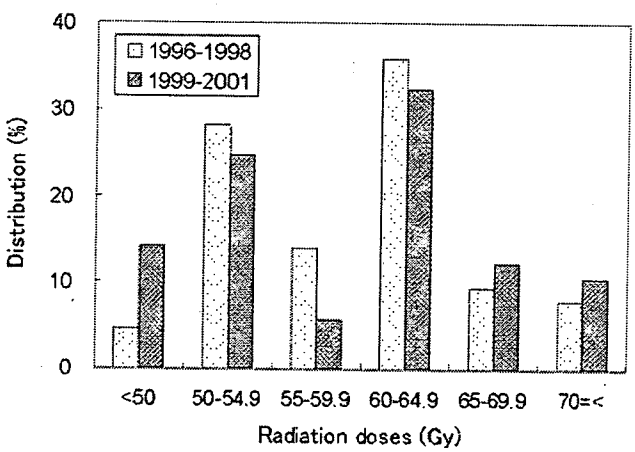

Figure 1. Distribution of radiation doses in patients who received RT after RP between 1996–98 and 1999–2001.

radiation dose might reflect the widespread dissemination of clinical trial results. However, our analysis revealed that the median dose for patients who received postoperative RT in Japan did not change from 1996–98 to 1999–2001. Furthermore, only half of the patients who were subjected to salvage RT in the PCS99-01 received doses of over or equal to 64 Gy, the dosage which was recommended by ASTRO (Fig. 2). Although previous reports of postoperative RT for patients with prostate cancer are rare in Japan, the next PCS may reveal the dissemination of evidence for dose escalation.

There have been no randomized trials to define the field sizes of postoperative irradiation for patients with prostate cancer, and no consensus about the best radiation therapy volume. Pelvic irradiation was performed in 40–50% of

Table 3. Comparison between patients in adjuvant and salvage setting in the 1999–2001 survey

	Adjuvant (n = 73)	Salvage (n = 32)	*P*-value (n = 32)
Age (median) (year) at RT	66	68	0.06
Range	36–77	58–89	
Interval between RP and RT			
Median (range)	1.3 (0.53–26.8)	20.3 (0.82–61)	
Last pre-RT PSA (ng/ml)			0.0046
<0.4	35/56 (62%)	8/28 (29%)	
≥0.4 to <1	6/56 (11%)	11/28 (39%)	
≥1 to <10	11/56 (20%)	8/28 (29%)	
≥10	4/56 (7%)	1/28 (3%)	
Missing	17	4	
Extent of disease			<0.0001
Confined to prostate	7/68 (10%)	11/23 (48%)	
Confined to specimen	10/68 (15%)	5/23 (22%)	
Positive surgical margin	51/68 (75%)	7/23 (30%)	
Missing	5	9	
Conformal therapy			0.0041
Yes	11/73 (15%)	13/32 (41%)	
Pelvic irradiation			<0.0001
Yes	39/73 (53%)	4/32 (13%)	
Radiation dose (Gy)			0.0015
Median	56	60	
Range	20–70	40–70	

RT, radiotherapy; RP, radical prostatectomy; PSA, prostate-specific antigen.

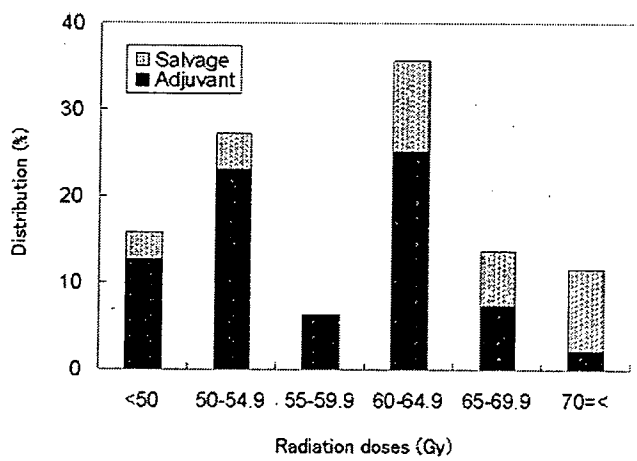

Figure 2. Comparison of dose distributions according to the type of RT administered in the 1999–2001 survey.

the patients, and no significant difference was found in the percentage of patients treated with pelvic irradiation between the PCS96-98 and PCS99-01 surveys. According to the previous analyses, the prostate and immediately adjacent

tissues have been considered to be a reasonable clinical target volume in the adjuvant setting (15,16). However, some previous reports documented the significant benefits of pelvic irradiation for patients in a salvage setting, showing a trend towards better PSA control in those patients with adverse pathological features (including a positive surgical margin, etc.) (17,18). However, the PCS99-01 survey revealed that a higher fraction of the patients received pelvic irradiation in the adjuvant setting than in the salvage setting in Japan.

Adjuvant versus Salvage

The role of postoperative RT for prostate cancer has been controversial. The previous retrospective analyses showed improvement in the local control and disease-free survival of the patients with high-risk pathological features who received adjuvant RT compared with similar patients treated with RP alone (15,19,20). Recently, the first randomized study evaluating the benefits of postoperative RT in prostate cancer was reported by Bolla et al. (21), who documented a significant benefit of postoperative RT in the biochemical relapse-free survival rate and clinical locoregional failure rate in patients with high risk factors after RP by the analysis of a total of 1005 patients who were allocated to postoperative RT or observation. There is no data based on randomized trials favouring adjuvant over salvage RT. The fraction of patients in the adjuvant setting was higher than that in the salvage setting from among all patients who received postoperative RT in the PCS99-01 survey. However, this result may not reflect the actual trend towards postoperative RT in Japan, so further investigation into more cases is needed in the future.

Conclusions

Our results revealed national trends in the treatment of prostrate cancer and changes in the practice of postoperative RT for patients in Japan with this disease. The management and strategies (including radiation field and dosages) varied, and the role of postoperative RT for patients with prostate cancer remains controversial (adjuvant RT versus salvage RT). Further evidence needs to be accumulated on postoperative RT for patients with prostate cancer in order to establish appropriate treatment strategies. In addition, continuous nationwide surveys should be performed to evaluate the dissemination of the results that have been collected.

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放射線治療部門システム(RIS)の問題点とその解決法

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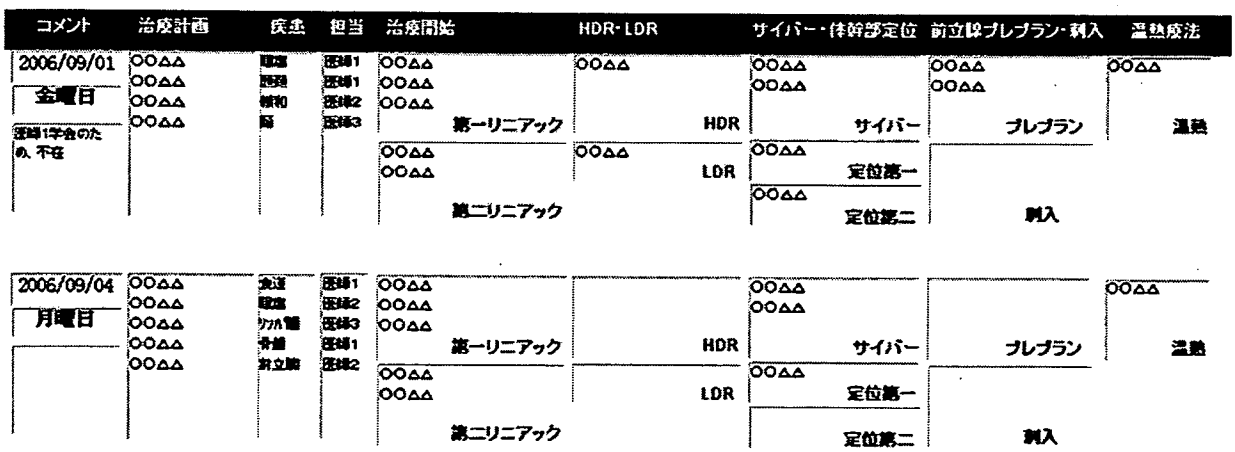
当院の放射線治療部門では，平成14年に新病院開院にあわせて放射線治療部門データの電子化が行われた。当院全体としての電子カルテ化は実施されていないため，あくまで放射線治療部門内のみの，二次システムとしての電子化である。その詳細については，平成14年のJASTRO NEWSLETTERにて「電子カルテ二次システム作成上の問題点」として寄稿させていただいた。導入当初，忙しい日常業務の中での電子化による業務量のさらなる増加に対応できるか非常に心配していたが，今のところ電子化された二次システムとして比較的スムーズに運用されている。

電子化の利点としては，1)最も使用頻度の高いリニアックについて，リニアック上で発生した照射履歴をそのまま治療部門RISに吸い上げ，自動的に記録できるようになった。これにより，技師は日々の照射履歴を診療録に記載する必要がなくなり，同時に人的な記載ミスが生じる可能性がきわめて少なくなった，2)治療で発生した画像データは，すべて治療部門サーバに保存されるようになった。いったん保存すれば，CT，MRIなどの診断用画像，プランごとの線量分布やDRR画像などが参照でき，非常に便利になった，3)どのRIS端末からでも患者情報を参照できるので，診療録を探し出す手間が省けるようになった，などが挙げられる。確かに入力の手間などの業務は増大したものの，利便性が上回っており，もう紙のカルテには戻れないというのが本音である。

一方，今後解決すべき問題点としては，1)いったんソフトウェアの作り込みが終わったら細かい修正がきかず，(高額の予算を獲得してソフトウェアの修正をしない限り)導入後の変化に対応できない，2)検索機能が弱い，3)紹介状，治療同意書など，現在のところ電子化が難しいものでは紙ベースでの保管を併用せざるを得ない，4)紙カルテの時のように持ち運べるわけではないので，各科とのカンファレンスの時には科ごとの治療記録のサマリーを打ち出さなければならない，などがある。

その中で，特に問題となっていたのが，放射線治療の予約についてである。導入当初，放射線治療部門で行っていた治療としては，外照射，HDR小線源治療，セシウム針や放射性金粒子などのLDR小線源治療，そして温熱療法であった。当初から治療部門RISには予約表を作り込んでいたが(われわれの予約表の作成に関する指示が悪かったことも一因かもしれないが)，治療部門RISでは1日のすべての予定患者を一目で見渡せるものではなく，非常に使い勝手の悪いものとなってしまっていた。結局，A3の紙にカレンダーを作り，治療計画予定者，治療開始予定者をカレンダーに書き込んで，予定表としていた。これをわれわれは"紙RIS予定表"と呼び，予定を加えるたびに，この"紙RIS予定表"を探し回らなければならないという，笑うに笑えないような事態となっていた。やむなく，平成16年より自前でFilemakerPro8.0にて予定表を作成し(図1)，治療部門RIS端末にインストールし，使用することとした。FilemakerProは，必ずしもソフ



一日の予定をひとつのレコードとし、リスト形式で表示している。数ヶ月先までの月～金のみのレコードをスクリプトにより自動作成して用いている。FilemakerProの共有設定により、閉鎖されたネットワーク上でこのデータベースを共有している。もし、サンプルファイルがご希望であれば、nakam@radiol.med.kyushu-u.ac.jpまで、メールしてください。

図1　FilemakerProで作成した予約表

トウェアをインストールしなくてもMicrosoft Internet Explorer v6.0にて5ユーザまで同時アクセスが可能で，データの入力および参照ができる。実際にはFilemakerPro同士でアクセスした方が操作性は良好であるため，使用頻度が高い端末2台にFilemakerProをインストールし，それ以外の端末からはInternet Explorerを通して予定表にアクセスしている(図2)。これにより，医師，技師，看護師，受付事務の全員が，治療RIS部門端末から最新の予定表を参照・入力できるようになった。当院の場合，治療部門RISは外部から閉鎖されたネットワークで構築されているため，データが外部に漏れることはないが，念のためパスワードでも保護している。残念ながら，FilemakerProで作成した予定表自体は，治療部門RISとは連携していないので，患者氏名などを手入力する必要がある。しかし，治療部門RIS端末上で作業できるため入力自体はそれほどたいしたことはなく，1日の治療予定が一目で把握でき，業務が非常にスムーズにいくようになった。さらに，体幹部定位照射，前立腺小線源，サイバーナイフIIなど，治療部門RIS導入後に新しく始まった治療予定枠を自由に作成することができ，新規治療の増加にも即座に対応することが可能となった。

予定表の問題点は解決されたが，もう1つの欠点である検索機能が非常に弱いことに関しても，やはりFilemakerProなどでの自作のデータベースを再構築する必要性を感じている。

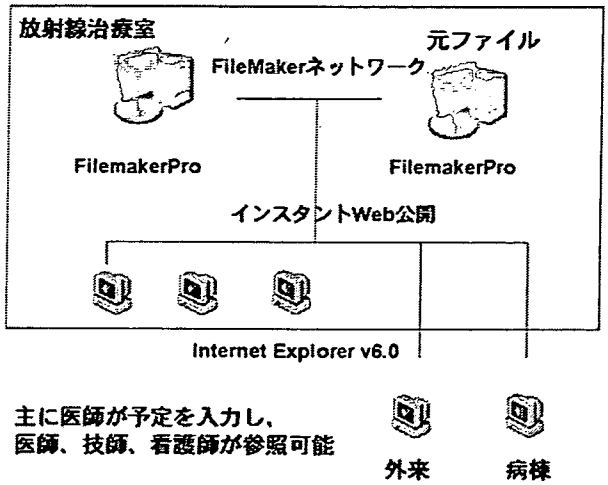


図2 FilemakerProでのネットワーク

治療部門RISに限らず，メーカーによって作成された電子カルテにおいては要求通りの機能は一応作成してくれるはずであるが，その後の細かい変更にはなかなか対応してくれない。結局，メーカーによって作成した電子カルテをうまく補うような，自作のデータベースを作成して初めて実用上うまくいくのではないかと思う。もちろん，病院端末に個別のソフトウェアを導入してよいかどうか，セキュリティは保たれているかなどの問題をクリアする必要はあるけれども。

米国の現状および将来に向けて

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背景

IT化が進み，各放射線治療部門でより詳細な情報を保管，管理できるようになってきた。部門システムの充実を優先する段階を経て，病院全体への情報還元も図ることにより，放射線治療部門への信頼をさらに高める好機である。JASTROは過去10年以上にわたり放射線腫瘍学広域データベース(ROGAD)を構築・運営し，調査項目の標準化にそれなりに貢献してきた。定期的施設構造調査も行い，装備・人員・患者負荷などの状況を全国規模でモニタしてきた。上記の流れの一方で，患者数増加，治療技術高度化による日常業務の増加，スタッフ不足などのために，治療部門では調査項目を縮小した簡易登録に留めざるを得ない施設もかなり存在する。厚生労働省はがん診療連携拠点病院の指定基準として院内がん登録の整備を進めている。各地域がん登録の標準化も進みつつある。これらのいわゆる疫学分野のがん登録は個人情報保護法の問題がクリアされている。しかし標準調査項目から見る限り，日常臨床に役立つデータは追跡情報を除き考慮されていない。それに代わって各学会で運営されている臓器別がん登録や，かつてのROGADは臨床医に有用な治療法詳細を把握できるように意図されている。しかし個人情報保護法の問題があり，倫理委員会審査を経た連結可能匿名化，経ない連結不可能匿名化，拒否への対応など，クリアすべき問題を残している。登録を中断している学会も多い。がん対策基本法では，がん登録に相当する記載はあるものの，「がん登録」という呼称は使われていない。これには，個人情報保護法との整合性の議論や予算面での制約があったからときく。

米国の現状

欧米で1つ明確になってきているのは，がん登録を含む診療科DBは，より多くのデータ項目を含む詳細な方向に向かっていることである。日本の多忙な臨床現場でのより簡易的な方法で済ませようという方向とは逆の動きであることを注意しておく必要がある。米国はがん登録に関しては，カナダ，オーストリア，デンマーク，スウェーデン，ドイツ(半数の州)とともに，法律によって登録が義務づけられている。10数社

前立腺癌に対する小線源治療

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はじめに

前立腺癌の放射線治療は急速に進歩している。近年のコンピュータ技術の発達により、前立腺に線量を集中し、その周囲への被ばくを低減する種々の技術が開発され、治療成績は手術とほとんど変わらないと考えられている。前立腺癌に対する最新の放射線治療として、3次元放射線治療、強度変調放射線治療、粒子線治療、小線源療法などが用いられるようになり、副作用を少なく、安全に、そしてより効果的に治療できるようになっている。

本稿では、そのうちの一つ、小線源療法(ブラキテラピー、brachytherapy)について解説する。ブラキとは「小さい」と言う意味で、小さい金属容器に密封された放射性同位元素から放出されるγ線などを治療に用いる。

前立腺癌に対する小線源療法は、1980年代に経直腸的超音波のガイド下で会陰部より線源を前立腺に正確に挿入できるようになって、急速に進歩をとげた(図1)。図2に、外部照射と小線源療法との線量分布の違いを示す。前立腺に正確に線源が挿入できれば、周囲の被ばくは少なくなり、理想的な治療が可能となることがわかる。

前立腺癌に対する小線源治療には二種類の方法がある(図3)。一つは、ヨウ素125密封小線源(^{125}I)などを前立腺に直接挿入する低線量率小線源治療である。術者などの医療従事者の被ばくを少なくするために、低線量率、すなわち単位時間当たりの照射線量の少ない線源を用いる。米国では、すでに手術、外照射と並ぶ、安全かつ効果的な治療として定着しているが、我が国でも2003年に^{125}Iの使用が許可されて以後、急速に普及している。

もう一つは、前立腺にアプリケータ針を挿入し、アフターローディング法にて、イリジウム192線源(^{192}Ir)をアプリケータ針内に一時的に挿入する、高線量率小線源治療である。これは、線量の挿入を治療室外から操作でき、医療従事者の被ばくがないため、単位時間当たりの照射線量の多い高線量率線源を用いることができる。高線量率小線源治療は、外照射と併用したブースト照射として使用されることが多い[1]。

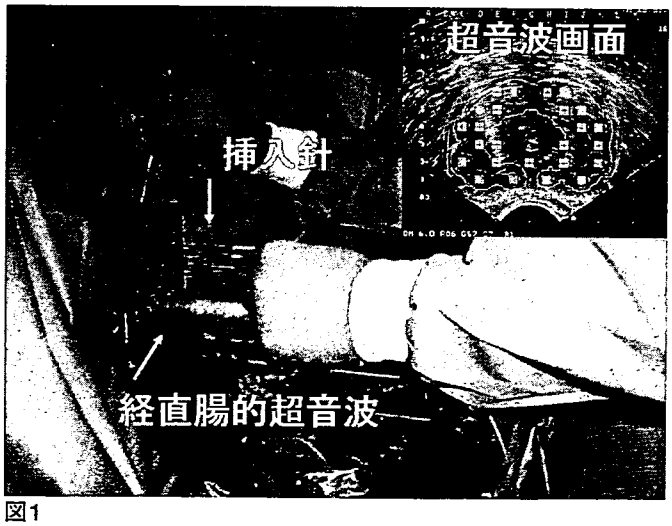
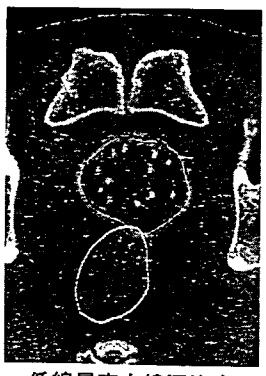


図1
肛門より挿入された経直腸的超音波にて前立腺を確認しながら(右上図)、会陰部より挿入針を刺入して、線源を正確に挿入していく。

巻頭カラー参照

3次元原体放射線治療(6門照射)



低線量率小線源治療

図2

巻頭カラー参照

低線量率小線源治療

1. 原理

線源には、直径0.8mm、長さ4.5mmの小さいチタン性カプセルに密封された放射性ヨウ素^{125}Iを用い、放出される約28keVの弱いエネルギーのγ線を治療に用いる。本邦では^{125}Iのみが認可されているが、欧米では他にパラジウム(^{103}Pd)も使用されている。治療の大まかな流れは以下の通りである。

①プレプラン

線源挿入一ヶ月前に手術時と同様の体位にて前立腺の体積を測定し、治療に必要な線源数を発注する。同時に、恥骨弓干渉がないか、強い石灰化病変がないかなど、線源挿入時の問題点をチェックする。

②線源挿入

原則腰椎麻酔を行う。体位を(強)砕石位にとり、経直腸的超音波とX線透視にて確認していきながら、経会陰的に、前立腺内に線源を挿入していく。線源挿入デバイスは、本邦ではMickアプリケータが使用されているが、米国ではその他に穿刺針に線源がプレロードされたものも使用されている。

線源挿入の手法には、プレプラン時の線源配置に従って線源を挿入するpreplanning法、術中に再度プランを行い、それに従って線源を挿入するintraoperative planning法の二つがある。実際にプレプランの位置と同じ位置に前立腺を再現することが難しいため、最近はintraoperative planning法が用いられることも多い。

線源挿入後は、単純X線写真にて線源数を確認する(図4)。その後、管理区域内にて経過観察を行い、法令で定められた退出基準を満たした後に一般病棟へ退出する。通常は1日で退出できることが多い。

③ポストプラン

線源配置の最終的な評価は、挿入一ヶ月後にCTを撮影して行う。この際、D90(前立腺体積の90%を囲む線量)が治療効果を予測する指標として用いられ、線源治療単独においては145Gy、外照射と併用時は100～110GyがAmerican Brachytherapy Societyより推奨されている[2]。

2. 適応

小線源治療単独の適応は、T1・T2a、GleasonスコアG以下、かつPSA10未満の低リスク群である。小線源療法では、線源から離れるに従って放射線強度は急速に低減するため、精嚢や被膜外浸潤があるものに対しては治療成績が落ちる可能性がある。そのため、中等度リスク群を治療する場合には、小線源療法に外照射を組み合わせることが多い。

適応除外項目は、期待余命5年未満、経尿道的前立腺切除術(TURP)による組織欠損が大きい前立腺などである。相対的禁忌として、中葉肥大、以前の骨盤内照射歴、多数の骨盤内手術歴、重度糖尿病、前立腺容積60cc以上などがあげられる。

3. メリット

短期入院での治療が可能で、本邦では平均2～4日、米国では日帰りで行われることが多い。有害事象として尿路系傷害、直腸出血などがあるが、一般的には小線源治療に伴う副作用は軽微なことがほとんどである。勃起機能障害は手術に比較して少ないとされている[3]。

上記のメリットの反面、挿入した線源の移動・術中前立腺の浮腫といった不確定要素も多く、線量分布の善し悪しは術者の挿入技術にも依存する。効果的な線量分布を得るための線源配置を実現するには、術者及び計画者の一定の経験と熟

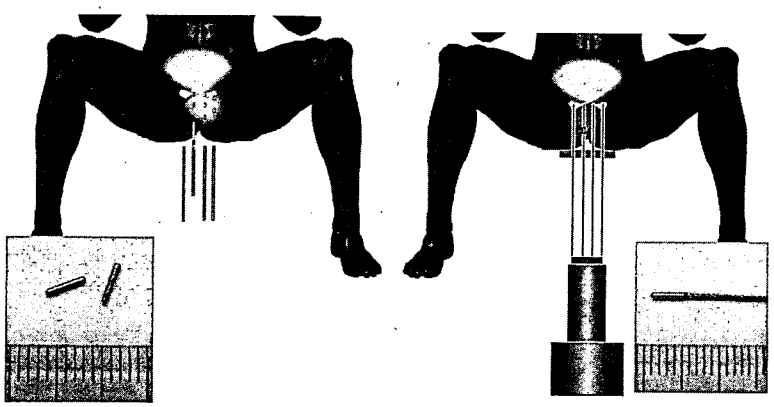


図3　低線量率小線源治療(左)と高線量率小線源治療の模式図と線源(右)
低線量率小線源治療では、80～100個程度の線源を永久的に挿入する。高線量率小線源治療では、ワイヤの先に固定された一つの線源をアプリケータ針内に送り込むことにより、前立腺に線量を投与する。

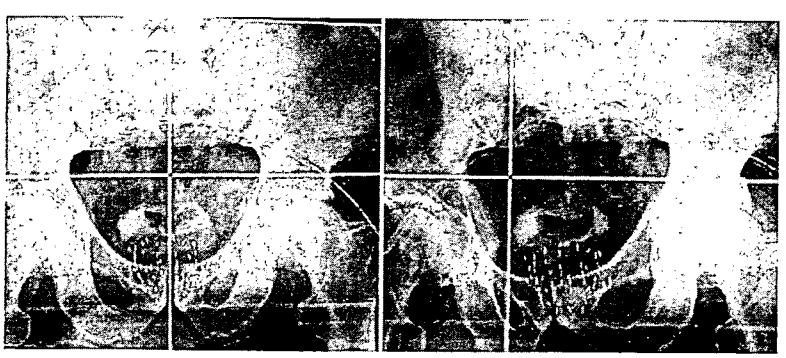


図4　線源挿入直後の単純X線写真

練が必要である。

治療成績は、低リスク群にて生化学的無再発率は80～90%程度である[4]。

4. 運用条件

本治療の施行には、放射線源取り扱いに関する関係法令の遵守が重要である。日本放射線腫瘍学会、日本泌尿器科学会、日本医学放射線学会より安全管理に関するガイドラインが作成されており、十分に理解しておく必要がある。

高線量率小線源治療

1. 原理

^{192}Irを前立腺内及び周囲に挿入されたアプリケータ針に送り込んで治療を行う。アプリケータ針は、経直腸的超音波ガイド下に経会陰的に刺入する。その後、CTを撮影し、治療計画を行う。前立腺への投与線量、尿道や直腸の線量を治療計画用コンピュータで最適化し、線源停留時間を計算して、治療を行う。

高線量率のため、実際の照射時間は短く、医療従事者の被ばくもないが、アプリケータ針は治療期間中(1～数日)会陰部より挿入されたままの状態にしておく必要がある。そのための疼痛管理及び排便のコントロールが重要となり、低線量率小線源療法と比較して、相対的に患者侵襲が大きいことを念頭に置く必要がある。

照射線量や治療期間は、施設によって異なるが、前立腺周囲や骨盤腔への40～50Gyの外照射後、ブースト照射として高線量率小線源治療15～30Gyを行うことが多い。

2. 適応

限局性前立腺癌が適応となる。被膜外や精嚢にも十分な線量を投与できるため、低線量率小線源療法と比べて高いリスク群の前立腺癌にも治療適応がある。

3. メリット

高線量率小線源治療のメリットは、大線量、少数分割で投与するため、高い放射線生物学的効果が期待でき、高リスク群にも適応できることである。また、医療従事者の被ばくがないこと、照射時間以外は一般病棟で管理できることなども利点としてあげられる。

本治療では、アプリケータ針挿入後に、治療計画用コンピュータにてある程度の線量分布の最適化は可能であるが、それでもアプリケータ針の配置が治療成績を左右するため、術者の技術の習熟が必要となる。

高リスク群も含めた生化学的無再発率は70～90%である[1]。

4. 運用条件

刺入技術に熟練した放射線腫瘍医の存在が重要である。

課題

小線源療法は、限局した領域に高い線量を投与することが可能であるため、限局性前立腺癌に対する非常に有効な治療法と考えられる。しかし、麻酔が必要な侵襲的治療であることには間違いなく、治療法の選択には、ほぼ治療成績が同じとされている外照射も十分に検討する必要がある。また、効果的な小線源療法を実施するためには、刺入技術の習得とたゆまない技術向上への努力が必要不可欠である。

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Concurrent Chemoradiotherapy for Limited-disease Small Cell Lung Cancer in Elderly Patients Aged 75 Years or Older

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Background: The optimal treatment for limited-disease small cell lung cancer (LD-SCLC) in patients aged 75 years or older remains unknown.
Methods: Elderly patients with LD-SCLC who were treated with chemoradiotherapy were retrospectively reviewed to evaluate their demographic characteristics and the treatment delivery, drug toxicities and antitumor efficacy.
Results: Of the 94 LD-SCLC patients treated with chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1998 and 2003, seven (7.4%) were 75 years of age or older. All of the seven patients were in good general condition, with a performance status of 0 or 1. Five and two patients were treated with early and late concurrent chemoradiotherapy, respectively. While the four cycles of chemotherapy could be completed in only four patients, the full dose of radiotherapy was completed in all of the patients. Grade 4 neutropenia and thrombocytopenia were noted in seven and three patients, respectively. Granulocyte-colony stimulating factor support was used in five patients, red blood cell transfusion was administered in two patients and platelet transfusion was administered in one patient. Grade 3 or more severe esophagitis, pneumonitis and neutropenic fever developed in one, two and three patients, respectively, and one patient died of radiation pneumonitis. Complete response was achieved in six patients and partial response in one patient. The median survival time was 24.7 months, with three disease-free survivors for more than 5 years.
Conclusion: Concurrent chemoradiotherapy promises to provide long-term benefit with acceptable toxicity for selected patients of LD-SCLC aged 75 years or older.

Key words: elderly – small cell lung cancer – chemotherapy – radiotherapy

INTRODUCTION

Small cell lung cancer (SCLC) accounts for approximately 20% of all pulmonary neoplasms and 25–40% of patients with this disease are 70 years of age or older. The number of elderly patients with such disease are expected to increase with the growing geriatric population (1).

Because SCLC is highly sensitive to chemotherapy and radiotherapy, the standard treatment for limited-disease SCLC (LD-SCLC) has been a combination of platinum and etoposide with concurrently administered thoracic radiotherapy, as long as the patients are in good general condition (2, 3). Such elderly patients, however, may show decreased clearance of the anticancer agents commonly used for the treatment of SCLC, including cisplatin and etoposide, because of the decrease of the lean body mass, hepatic blood flow and renal function that are associated with aging. In addition, myelotoxicity is sometimes more severe in this population than in younger populations, because the absolute area of hematopoietic marrow decreases with age (4). Retrospective subset analyses of patients with LD-SCLC treated with concurrent chemotherapy and radiotherapy in phase III trials have shown that the percentage of patients in whom the planned number of chemotherapy cycles can be completed is usually 10% lower in patients

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70 years of age or older as compared with that in younger patients (5). One study reported that myelotoxicity was more severe in elderly patients than in younger patients (5), while another reported no such difference between the patients of the two age groups (6). The delivery of thoracic radiotherapy was not influenced by age in these patients (7). However, 78–85% of patients in these analyses were aged between 70 and 75 years old and a few were over 80 years old. Thus, the most suitable treatment options for elderly patients with LD-SCLC aged 75 years or older still remain unknown.

The objective of this retrospective analysis was to evaluate the patient characteristics and the treatment delivery, toxicity and antitumor efficacy of the administered treatments in LD-SCLC patients 75 years of age or older who were treated with chemotherapy and thoracic radiotherapy.

PATIENTS AND METHODS

We retrospectively reviewed the medical charts, chest X-rays and computed tomography (CT) scans of LD-SCLC patients aged 75 years or older. To evaluate the thoracic irradiation field, the standard initial field was defined as follows: the field including the primary tumor and involved nodes with a short axis length of 1 cm or more on CT scans with a 1.0–1.5 cm margin, and the subclinical ipsilateral hilum and bilateral mediastinal lymph node regions with a 1.0 cm margin. The supraclavicular lymph node regions were included only if there was tumor involvement of these nodes. Toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 3.0, Japanese edition (8). The objective tumor response was evaluated according to the WHO criteria issued in 1979 (9). The overall survival time was measured from day 1 of chemotherapy to the date of death as a result of any cause or the date of the last follow-up.

RESULTS

Of the 94 LD-SCLC patients treated with chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1998 and 2003, seven (7.4%) were 75 years of age or older (Table 1). During this period, we had three other patients with LD-SCLC who were aged 75 years or older. They were treated with chemotherapy alone because of complications in two patients and refusal of intensive therapy in one patient. There were five males and two females, and four patients were between 75 and 79 years of age and three patients were 80 years old or older. Three patients presented with persistent cough, while the remaining four patients complained of no symptoms and were diagnosed based on the detection of an abnormal shadow on a plain chest X-ray obtained during a mass screening or routine health examination program. All the patients were in good general condition. One patient had a history of inferior wall myocardial infarction suffered 9 years prior to this admission. However, echocardiography at this admission revealed normal heart function with an ejection fraction of 73%. One patient had stage I pulmonary emphysema with % FEV_1 predicted of 58%, but no abnormal findings on blood gas analysis. The % FEV_1 predicted in other four patients was within 98% and 116%, and was not measured in the other two patients. A median (range) PaO_2 level at the room air before treatment in the seven patients was 77.4 (66.9–87.2) Torr. A decreased creatinine clearance, 48.8 ml/min at a urine volume of 600 ml/day, was noted in one patient, while the other patients had a creatinine clearance of 78 ml/min or higher. Four and three patients had a performance status of 0 and 1, respectively, and five patients gave no history of loss of body weight. The diagnosis of small cell carcinoma was confirmed cytologically or histologically in all the patients.

The chemotherapy regimens used were cisplatin at 80 mg/m^2 on day 1 combined with etoposide at 100 mg/m^2 on days 1–3 in four patients aged between 75 and 19 years. For patients aged 80 years of older, carboplatin was dosed to a

Table 1. Patient characteristics

n	Age (yr)/ gender	Smoking history	Symptom	Weight loss (%)	Complications	Performance status	TNM stage
1	81/male	6/day × 62 yr	None	0	Type 2 DM	0	T1N2M0
2	81/female	20/day × 62 yr	None	0	OMI (inferior wall), thoracic aortic aneurysm	0	T1N1M0
3	80/female	20/day × 50 yr	Cough	11	Hypertension	1	T4N3M0
4	78/male	20/day × 46 yr	None	0	None	0	T2N2M0
5	77/male	30/day × 50 yr	Cough	7	COPD, Hypertension	1	T4N3M0
6	75/male	10/day × 55 yr	None	0	None	0	T1N2M0
7	75/male	10/day × 55 yr	Cough, Hoarseness	0	None	1	T4N2M0

COPD, Chronic obstructive pulmonary disease; OMI, old myocardial infarction; DM, diabetes mellitus.

target AUC of 5 by Calvert's formula on day 1 combined with etoposide at 80 mg/m^2 on days 1–3 in two patients and cisplatin at 25 mg/m^2 on days 1–3 combined with etoposide at 80 mg/m^2 on days 1–3 in one patient (Table 2). These regimens have been reported to be used in a JCOG phase III trial for elderly patients with extensive SCLC (10). Four cycles of chemotherapy could be completed in four patients, whereas only three cycles could be completed in two patients and only one cycle could be completed in one patient. The reason for discontinuation of the chemotherapy in these patients was prolonged myelosuppression in two patients and patient refusal for continuation of treatment in one patient. The chemotherapy dose was reduced in the subsequent cycles in four patients. The reasons for the dose reduction were grade 4 thrombocytopenia in two patients, grade 4 leukopenia in one patient and both grade 4 thrombocytopenia and leukopenia in one patient. Thoracic radiotherapy was started concurrently with the chemotherapy in five patients (early concurrent chemoradiotherapy). Treatment began with chemotherapy alone in the remaining two patients, because of a mild cytology-negative pleural effusion in one patient and too large an irradiation volume in the other patient. Two cycles of chemotherapy reduced the tumor volume successfully in both the patients and thoracic radiotherapy was then added concurrently with the third and fourth cycles of chemotherapy (late concurrent chemoradiotherapy). Thoracic radiotherapy was delivered using photon beams from a liniac or microtron accelerator with energy between 6 and 20 MV at a single dose of 2 Gy once daily up to a total dose of 50 Gy in four patients aged between 78 years or older and at a single dose of 1.5 Gy twice daily up to a total dose of 45 Gy in three patients aged between 75 and 77 years. This selection of conventional or hyperfractionated radiotherapy was determined arbitrarily. The initial irradiation field was judged as the standard in six patients and reduced in one patient. A multi-leaf collimator and conventional lead blocks were used for shaping of the irradiation field. The median irradiation area was 169 cm^2 (range, 95–278 cm^2). The projected total radiation dose was administered in all the patients, but a treatment delay of 5 days or longer was observed in three patients. The criteria of radiotherapy suspension were white blood cell count $< 1.0 \times 10^9$/L, platelet count $< 20 \times 10^9$/L, esophagitis $\geq$ grade 3, fever ≥ 38°C and performance status ≥ 3. The reason for the delay in the three patients was esophagitis, decreased platelet count and poor performance status.

The hematological toxicities observed in the patients are summarized in Table 3. Grade 4 leukopenia, neutropenia and thrombocytopenia were noted in four, seven and three patients, respectively. Granulocyte-colony stimulating factor support was used in five patients, red blood cell transfusion was administered in two patients and platelet transfusion was administered in one patient. The non-hematological toxicities included grade 3 or more severe esophagitis, pneumonitis and neutropenic fever in one, two and three patients, respectively. One patient died of radiation pneumonitis that developed 4 months after the end of radiotherapy (Case No. 6).

Of the seven patients, complete response was achieved in six patients and partial response in one patient (Table 3). However, prophylactic cranial irradiation was given in only one patient (Case No. 6). Three patients remained alive for

Table 2. Treatment and its delivery

n	Chemotherapy				Thoracic radiotherapy			
	Regimen (mg/m^2 if not specified)	Number of cycles	Dose reduction	Duration of one cycle (days)*	Timing	Total dose (Gy)/fractions	Field size	Delay (days)
1	C (AUC = 5) d1 + E (80) ds1–3	3	Yes	30	Early Co	50/25	S	4
2	P (25) ds1–3 + E (80) ds1–3	1	NA	NA	Early Co	50/25	S	7
3	C (AUC = 5) d1 + E (80) ds1–3	4	Yes	23	Late Co	50/25	S	14
4	P (80) d1 + E (100) ds1–3	4	Yes	26	Late Co	50/25	R	1
5	P (80) d1 + E (100) ds1–3	4	No	28	Early Co	45/30	S	3
6	P (80) d1 + E (100) ds1–3	4	No	27	Early Co	45/30	S	0
7	P (80) d1 + E (100) ds1–3	3	Yes	35	Early Co	45/30	S	7

*Calculated as follows: Duration of one cycle (days) = (Day 1 of the 1st cycle – Day 1 of the last cycle)/(Number of cycles – 1).
C, carboplatin; E, etoposide; NA, not applicable; P, cisplatin; Co, concurrent; S, standard; R, reduced.

Table 3. Toxicity, tumor response and survival

n	Hematological toxicity (grade by CTC-AE v3.0)				Blood transfusion	G-CSF support	Non-hematological toxicity ≥ grade 2 (grade by CTC-AE v3.0)	Tumor response	Survival time (mo)/outcome
	WBC	Neu	Hb	Plt					
1	3	4	1	4	Platelet	None	None	CR	80.3/Alive
2	3	4	1	2	None	Used	Pneumoniti (3), esophagitis (2), anorexia (2)	CR	21.3/Dead
3	4	4	3	4	RBC	Used	Neutropenic fever (3), esophagitis (3)	CR	65.6/Alive
4	4	4	2	1	None	Used	None	CR	97.4/Alive
5	3	4	2	3	None	Used	Neutropenic fever (3), esophagitis (2), anorexia (2)	CR	13.1/Dead
6	4	4	2	1	None	None	Pneumoniti (5), neutropenic fever (3)	CR	6.4/Dead
7	4	4	4	4	RBC	Used	None	PR	24.7/Dead

WBC, white blood cell count; Neu, neutrophil count; Hb, hemoglobin; Plt, platelet count; G-CSF, granulocyte- colony stimulating factor; CTC-AE, Common Terminology Criteria for Adverse Events; CR, complete response; RBC, red blood cell; PR, partial response.

more than 5 years without recurrence. The median survival of the seven patients was 24.7 months.

DISCUSSION

The antitumor effects of the treatment regimens were reasonably good, with six complete responses and one partial response and three long-term disease-free survivors in spite of discontinuation/dose reduction of chemotherapy. This is perhaps mainly attributable to the strict selection of patients in good general condition. Thus, we believe that the standard chemoradiotherapy can be applied to LD-SCLC patients aged 75 years or older as long as they are in good general condition.

The general condition of elderly patients, however, varies widely from patient to patient. Thus, in many elderly patients 75 years of age or older, it may be better to reduce the treatment intensity, although it may be difficult to establish the standard schedule applicable to all elderly patients. There are four possible ways to modify the intensity of therapy: (1) administer chemotherapy alone; (2) change the relative timing of chemotherapy and radiotherapy; (3) decrease the drug doses and number of cycles of chemotherapy, and (4) decrease the dose and intensity of thoracic radiotherapy.

Chemotherapy alone versus chemotherapy and thoracic radiotherapy for LD-SCLC were compared in many randomized trials between the 1970s and 1980s. A meta-analysis of these trials demonstrated survival benefit of radiotherapy added to chemotherapy in younger populations of patients less than 65 years of age, but the benefit is still unclear in older patients (11). Although the findings of this meta-analysis indicated that the standard treatment in elderly patients with LD-SCLC might be chemotherapy alone, the result based on the old trials using cyclophosphamide and doxorubicin-based chemotherapy cannot be applied in the current medical setting, because chemotherapy regimens, irradiation delivery equipment and staging procedures have all evolved greatly over time.

The relative timing of chemotherapy and radiotherapy greatly influences the severity of toxicity. In late concurrent chemoradiotherapy that follows induction chemotherapy, the chemotherapy dose can be adjusted to suit each patient by evaluating the toxicity of the previous chemotherapy. In addition, the irradiation volume can be reduced by modifying the radiation treatment planning in accordance with the extent of tumor shrinkage during the induction phase. In the two patients treated by this approach in this study, the dose of the platinum drug during the concurrent chemoradiotherapy phase was reduced to 66–75% of the initial dose and that of etoposide was reduced to 50–75% of the initial dose. Sequential chemoradiotherapy consists of induction chemotherapy and subsequent radiotherapy. Because the two treatment modalities are administered separately, the treatment dose in each can be optimized for the elderly in this approach. A phase III study of concurrent versus sequential chemoradiotherapy in LD-SCLC patients younger than 75 years old revealed a 5-year survival rate of 24% in the concurrent arm and a 5-year survival rate of 18% with a lower incidence of toxicity in the sequential arm (2). The sequential schedule has not yet been evaluated in LD-SCLC patients 75 years of age or older.

A recent phase III trial showed that etoposide at 80 mg/m^2 on days 1–3 combined with either carboplatin at AUC = 5 by Carvert's formula or cisplatin at 25 mg/m^2 on days 1–3 was feasible and effective in elderly patients with extensive-disease SCLC (10). These regimens may, therefore, be applied for the treatment of LD-SCLC as well. The standard number of chemotherapy cycles administered is four. In many elderly patients, however, all four cycles cannot be completed. In two phase II studies of two cycles

of chemotherapy and concurrent thoracic radiotherapy in elderly patients with LD-SCLC, 13–25% long-term survivors were noted (12,13). Thus, the optimal number of chemotherapy cycles in the elderly should be investigated in future trials.

Thoracic radiotherapy with accelerated hyperfractionation at a total dose of 45 Gy in 30 fractions, the standard schedule for LD-SCLC, was associated with grade 3–4 esophagitis in as high as 32% of the patients and grade 4 leukopenia in 44% of the patients (2,3,5). Thus, the conventional schedule at a total dose of 45–50 Gy in 25 fractions might be preferable in the elderly (3). The severity of esophagitis is also influenced by concomitant chemotherapy, the treatment schedule and the timing of thoracic radiotherapy.

In conclusion, concurrent chemoradiotherapy promises to offer long-term benefit with acceptable toxicity in selected patients of LD-SCLC aged 75 years or older. The optimal schedule and dose of chemotherapy and thoracic radiotherapy still remains to be established in this patient population.

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Conflict of interest statement

None declared.

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Phase I Study of Cisplatin Analogue Nedaplatin, Paclitaxel, and Thoracic Radiotherapy for Unresectable Stage III Non-Small Cell Lung Cancer

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Background: The standard treatment of unresectable stage III non-small cell lung cancer is concurrent chemoradiotherapy in patients in good general condition, but where the optimal chemotherapeutic regimen has not been determined.
Methods: Patients with unresectable stage III non-small cell lung cancer received nedaplatin (80 mg/m^2) and paclitaxel on day 1 every 4 weeks for 3–4 cycles and concurrent thoracic radiotherapy (60 Gy/30 fractions for 6 weeks) starting on day 1. The dose of paclitaxel was escalated from 120 mg/m^2 in level 1, 135 mg/m^2 in level 2 to 150 mg/m^2 in level 3.
Results: A total of 18 patients (14 males and 4 females, with a median age of 62.5 years) were evaluated in this study. Full cycles of chemotherapy were administered in 83% of patients in level 1, and in 50% of patients in levels 2 and 3. No more than 50% of patients developed grade 4 neutropenia. Transient grade 3 esophagitis and infection were noted in one patient, and unacceptable pneumonitis was noted in three (17%) patients, two of whom died of the toxicity. Dose-limiting toxicity (DLT), evaluated in 15 patients, noted in one of the six patients in level 1, three of the six patients in level 2 and one of the three patients in level 3. One DLT at level 2 developed later as radiation pneumonitis. Thus, the maximum tolerated dose was determined to be level 1. The overall response rate (95% confidence interval) was 67% (41–87%) with 12 partial responses.
Conclusion: The doses of paclitaxel and nedaplatin could not be escalated as a result of severe pulmonary toxicity.

Key words: non-small cell lung cancer – chemoradiotherapy – paclitaxel – nedaplatin – pneumonitis

INTRODUCTION

Locally advanced unresectable non-small cell lung cancer (NSCLC), stage IIIA disease with bulky N2 and stage IIIB disease without pleural effusion, is characterized by large primary lesions, and/or involvement of the mediastinal or supraclavicular lymph nodes, and occult systemic micrometastases (1). Concurrent chemoradiotherapy, recently shown to be superior to the sequential approach in phase III trials, is the standard medical care for this disease (2–4). Chemotherapy regimens used concurrently with thoracic radiotherapy in these randomized trials were second-generation platinum-based chemotherapy, such as combinations of cisplatin, vindesine and mitomycin, cisplatin and vinblastine, and cisplatin and etoposide. The third-generation cytotoxic agents including vinorelbine and paclitaxel, which provided a better survival rate in patients with disseminated disease than second-generation agents, must be reduced when administered concurrently with thoracic radiotherapy (5–7). Thus, the optimal chemotherapy for concurrent chemoradiotherapy has not been established.

Nedaplatin (*cis*-diammine-glycolate-O,O′-platinum II, 254-S) is a second-generation platinum derivative that has an

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antitumor activity comparable to that of cisplatin but is less toxic to the kidney as shown in preclinical experiments (8). Nedaplatin produced a promising response rate for NSCLC, especially for squamous cell lung cancer (9,10). In addition, this drug can be safely administered with full-dose thoracic radiation, as shown in patients with esophageal cancer (11). Paclitaxel is another promising drug for the treatment of stage III NSCLC, as shown by the favorable response rate and survival in phase II trials in combination with platinum and thoracic radiation (6,7).

Our previous study of the nedaplatin and paclitaxel combination in patients with systemic disease showed that the recommended dose of these drugs was 80 mg/m^2 and 180 mg/m^2, respectively, repeated every 3–4 weeks. A promising response rate of 55% was achieved in patients with squamous cell lung cancer (12). The objectives of the present study were primarily to evaluate the toxicity of nedaplatin, paclitaxel and concurrent thoracic radiotherapy and determine the recommended dose of these two drugs for a phase II trial, and secondarily to observe the antitumor effect of this regimen in patients with stage III NSCLC.

PATIENTS AND METHODS

Patient Selection

The eligibility criteria were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease indicated for curative radiotherapy; no previous treatment; measurable disease; the percentage of the normal lung volume receiving 20 Gy or more (V_{20}) (13) expected to be 30% or less; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status (14) 0 or 1; adequate bone marrow function (12.0×10^9/L $\geq$ white blood cell (WBC) count $\geq 4.0 \times 10^9$/L, neutrophil count $\geq 2.0 \times 10^9$/L, hemoglobin $\geq$ 10.0 g/dL and platelet count $\geq 100 \times 10^9$/L), liver function (total bilirubin $\leq$ 1.5 mg/dL and transaminase $\leq$ twice the upper limit of the normal value), and renal function (serum creatinine $\leq$ 1.5 mg/dL and creatinine clearance $\geq$ 60 mL/min); and a PaO_2 of 70 torr or more. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness, such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonitis or lung fibrosis identified by a chest X-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or breast-feeding. All patients gave their written informed consent.

Pretreatment Evaluation

The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest X-rays, chest computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan, and radionuclide bone scan.

Treatment Schedule

Paclitaxel and nedaplatin were administered as previously described (12). Briefly, paclitaxel diluted in 500 ml of 5% glucose was administered as a 3-h intravenous infusion with premedication consisting of dexamethasone, ranitidine and diphenhydramine. Nedaplatin diluted in 250 ml of normal saline was administered in a 1-h intravenous infusion. This treatment was repeated every 4 weeks for 3–4 cycles. The dose of paclitaxel was escalated as follows: 120 mg/m^2 (level 1), 135 mg/m^2 (level 2), and 150 mg/m^2 (level 2). The dose of nedaplatin was 80 mg/m^2 through the levels 1–3.

Thoracic radiation therapy was given with photon beams from a liniac or microtron accelerator with energy between 6 and 10 MV. The total dose of 60 Gy was delivered at a single dose of 2 Gy once daily Monday through Friday for 6 weeks without interruption beginning on day 1 of the chemotherapy. Three-dimensional conformal radiotherapy technique was used in all patients. The gross target volume (GTV) included the primary lesion (GTV1) and involved lymph nodes whose short diameter was 1 cm or larger (GTV2) based on conventional chest X-ray and CT scans. The clinical target volume (CTV) consisted of CTV1 and CTV2, identical to GTV1 and GTV2, respectively, and CTV3, the ipsilateral hilum and bilateral mediastinum area. The contralateral hilum was excluded from the CTV. The supraclavicular fossa was also excluded unless it was involved. The planning target volume (PTV) for the initial dose up to 40 Gy consisted of CTV1-3 with the superior and inferior field margins extended to 1–2 cm and the lateral field margins extended to 0.5 cm for respiratory variation and fixation error. The PTV for the boost 20 Gy included only CTV1-2 based on the second CT scans with the same margins. The spinal cord dose was limited to 44 Gy by using oblique parallel opposed fields.

Toxicity Assessment and Treatment Modification

Complete blood cell counts and differential counts, routine chemistry determinations and a chest X-ray were performed once a week during the course of treatment. Toxicity was graded according to the NCI Common Toxicity Criteria version 2.0. Subsequent cycles of chemotherapy were delayed if any of the following toxicities was noted on day 1: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, serum creatinine level $\geq$1.6 mg/dL, infection $\geq$ grade 2, elevated hepatic transaminase level or total serum bilirubin $\geq$ grade 2, pneumonitis $\geq$ grade 2, peripheral neuropathy, musculoskeletal pain $\geq$ grade 3, fever $\geq$ 38°C, or performance status $\geq$ 2. Chemotherapy was terminated if the toxicities did not

recover within 2 weeks. The doses of nedaplatin and paclitaxel were reduced by 25% in all subsequent cycles if any of the dose-limiting toxicities (DLTs) defined below were noted. The dose of nedaplatin was reduced by 25% in all subsequent cycles if the serum creatinine level was elevated to 2.0 mg/dl or higher. Thoracic radiotherapy was suspended if any of the following toxicities was noted: fever $\geq 38^{\circ}$C, infection $\geq$ grade 2, esophagitis of grade 3, performance status ≥ 3, or radiation pneumonitis was suspected. Thoracic radiotherapy was terminated if radiation pneumonitis that required corticosteroid administration was noted, or radiotherapy was not completed within 60 days. Both chemotherapy and thoracic radiotherapy were terminated if any of the following was noted: disease progression, any of the grade 4 non-hematological toxicities except abnormal electrolytes, performance status of 4, patient refusal to receive subsequent treatment, protocol violation, or patient death of any cause. Granulocyte colony-stimulating factor and antibiotics were administered if febrile neutropenia was noted.

DLT, Maximum Tolerated Dose (MTD), and Recommended Dose For Phase II Trials

The DLT was defined as a grade 4 leukopenia, grade 4 neutropenia lasting 7 days or longer, febrile neutropenia, platelet count $<20 \times 10^9$/L, grade 3 or a more severe non-hematological toxicity other than nausea, vomiting and transient electrolyte abnormality, and treatment termination before two cycles of chemotherapy and thoracic radiotherapy were completed. Dose levels were escalated according to the frequency of DLT evaluated during the first and second cycles of chemotherapy and thoracic radiation. Six patients were initially enrolled at each dose level. If none to two of the six patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If three or more of the six patients experienced DLT, that level was considered to be the MTD. The recommended dose for phase II trials was defined as the dose preceding the MTD.

Response Evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (15).

Study Design, Data Management and Statistical Analyses

This study was designed as a phase I study at the National Cancer Center Hospital. The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center. Registration was conducted at the Registration Center. Data management, periodic monitoring, and the final analysis were performed by the Study Coordinator. A patient accrual period of 2 years and a follow-up period of 3 years were planned. Overall survival time and progression-free survival time were estimated by the Kaplan–Meier method (16). Overall survival time was measured from the date of registration to the date of death from any cause or last follow-up. Progression-free survival time was measured from the date of registration to the date of disease progression or death from any cause or last follow-up. Patients who were lost to follow-up without event were censored at the date of their most known follow-up. A confidence interval for the response rate was calculated using methods for exact binomial confidence intervals. Response rates among patients with squamous cell carcinoma and those with non-squamous carcinoma were assessed with the χ^2 test. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for statistical analyses.

RESULTS

Registration and Characteristics of The Patients

From October 2003 to July 2004, six patients were registered at dose level 1, eight patients at dose level 2 and five patients at dose level 3. Two patients at dose level 2 were excluded from the DLT evaluation, because they discontinued receiving the treatment early because of disease progression and anaphylactic shock, respectively. Initially, DLT was noted in only two of the six patients at dose level 2, and therefore, patient registration at dose level 3 was started. However, severe radiation pneumonitis developed 5 weeks after the end of radiotherapy in another patient at dose level 2 and this pneumonitis was counted as DLT. Thus, because DLT was finally noted in three of the six patients at dose level 2, patient registration at dose level 3 was stopped. One patient at dose level 3 was found to be ineligible because the radiation treatment planning showed that the V_{20} exceeded 30%. The patient did not receive the current treatment and was excluded from the analysis. Thus, a total of 18 patients were subjects of this study and their detailed demographic characteristics are listed in Table 1.

Treatment Delivery

The planned three to four cycles of chemotherapy were administered in 83% of patients in level 1 and in 50% of patients in levels 2 and 3. Radiation delivery was generally well maintained and it did not differ among the three dose levels (Table 2).

Toxicity, DLT and MTD

Hematological toxicity was generally mild. No more than 50% of patients developed grade 4 neutropenia, and no one developed grade 2 or higher thrombocytopenia (Table 3). Non-hematological toxicity other than lung toxicity was also well tolerated. One patient developed transient grade 3 esophagitis and grade 3 infection not associated with neutropenia, which were considered DLTs. Another patient developed grade 4 anaphylactic shock 1 min after the second cycle infusion of paclitaxel, but soon recovered with fluid

Table 1. Patient characteristics

	n	(%)
Number of patients	18	
Gender		
male	14	(78)
female	4	(22)
Age		
median (range), years	62.5	(46–69)
PS		
0	11	(61)
1	7	(39)
Body weight loss		
< 5%	15	(83)
5–9%	2	(11)
≥ 10%	1	(6)
Clinical stage		
IIIA	10	(56)
IIIB	8	(44)
Histology		
adenocarcinoma	8	(44)
squamous cell carcinoma	6	(33)
non-small cell, not specified	4	(22)

PS, performance status.

replacement and oxygen therapy. This patient was excluded from DLT evaluation. One patient in level 1 and another patient in level 2 developed grade 4 pneumonitis after completion of two cycles of chemotherapy and thoracic radiotherapy and they died of the pneumonitis. The V_{20} and mean lung dose (MLD) of these patients were 23% and 30%, and 1341 cGy and 1675 cGy, respectively.

Table 2. Treatment delivery

Dose level	Level 1	Level 2	Level 3
	(*n* = 6)	(*n* = 8)	(*n* = 4)
Number of chemotherapy cycles			
3–4	5	4	2
2	1	3	1
1	0	1	1
Total radiation dose (Gy)			
60	6	7	3
50–59	0	1	0
NE	0	0	1
Radiotherapy delay (days)			
0–4	5	7	2
5–9	1	0	1
NE	0	1	1

NE, not evaluable.

Table 3. Toxicity in all patients

Dose level	Level 1 (*n* = 6)			Level 2 (*n* = 8)			Level 3 (*n* = 4)		
Toxicity grade	2	3	4	2	3	4	2	3	4
Leukopenia	2	3	0	3	3	0	1	2	1
Neutropenia	0	4	1	2	3	1	0	2	2
Anemia	0	0	0	2	0	0	2	0	0
GPT elevation	1	0	0	2	0	0	0	0	0
Total bilirubin elevation	1	0	0	1	0	0	1	0	0
Infection	0	0	0	1	1	0	0	0	0
Allergic reaction	1	0	0	2	0	1	0	0	0
Anorexia	1	0	0	2	0	0	0	0	0
Nausea	0	0	0	1	0	0	0	0	0
Constipation	0	0	0	2	0	0	0	0	0
Esophagitis	1	0	0	2	1	0	0	0	0
Pneumonitis	0	0	1*	1	0	1*	0	0	0
Musculoskeletal pain	1	0	0	1	0	0	1	0	0
Alopecia	4	0	0	4	0	0	0	0	0

GPT, glutamic pyruvic transaminase.
*Pneumonitis was fatal in these patients.

Both patients were former heavy smokers with a smoking index of 520 and 1680, respectively. The chest CT scan of the former patient disclosed mild emphysematous, but no interstitial changes. A spirometry analysis showed a vital capacity (VC) of 3480 ml (104% of predicted), and a forced expiratory volume one second percent (FEV1.0%) of 82%. The lung diffusing capacity measurement using carbon monoxide (DL_{CO}) was not done in this patient. The PaO_2 was 93.3 torr. The serum LDH level before treatment was 241 IU/l (the upper limit of the normal value was 229 IU/l). The chest CT scan of the latter patient disclosed slight changes in the dorsal portion of the both lungs, which were considered the gravitation effect, or fibrotic changes. The VC was 3810 ml (107% of predicted), % DL_{CO} was 111%, and PaO_2 was 99.7 torr. The serum LDH level before treatment was 147 IU/l. Another patient in level 2, whose V_{20} and MLD were 15% and 822 cGy, respectively, developed grade 2 pneumonitis when he received 52 Gy of radiotherapy and the subsequent protocol treatment was stopped. The chest CT scan of this patient before treatment showed no abnormal findings except for lung cancer. Pulmonary function test values were all within normal limits. The serum LDH level before treatment was 178 IU/l. Thus, in total three (17%) of 18 patients developed unacceptable severe pneumonitis induced by the current treatment, which was counted as DLT.

To sum up, DLT was noted in one of six patients in level 1, three of six patients in level 2, and one of three patients in level 3. The DLTs were pneumonitis in three patients, grade 4 leukopenia in one patient, and grade 3 esophagitis and grade 3 infection in one patient. Thus, the MTD was determined to be level 1.

Objective Response and Survival

All patients were included in the analyses of tumor response and survival. No CR, 12 PRs, and 3 SD were noted among the 18 patients and the overall response rate (95% confidence interval) was 67% (41–87%). The response rate in patients having squamous cell carcinoma was 100%, while that for non-squamous histology was 58%. The median progression-free survival time was 9.7 months. The median overall survival time has not yet been reached and the 1-year survival rate was 78%.

DISCUSSION

The feasible doses of anticancer agents in this study were paclitaxel 120 mg/m^2 and nedaplatin 80 mg/m^2 every 4 weeks. These figures are lower than those in a randomized phase II trial for stage III NSCLC conducted in the USA, where paclitaxel 135 mg/m^2 and cisplatin 80 mg/m^2 were administered every 3 weeks concurrently with thoracic radiotherapy (6). The occurrence of severe pneumonitis hampered the dose escalation of the anticancer agents in this study. A Japanese phase I/II study of weekly paclitaxel, nedaplatin and concurrent thoracic radiotherapy for stage III NSCLC showed that the DLT was also pneumonitis and that the response rate was 75% and progression-free survival was 5.6 months, similar to the outcome of this study (17). The reasons for the frequent pneumonitis in this study remain unknown. Paclitaxel was the most frequently used anticancer agent together with thoracic radiotherapy in patients with NSCLC outside Japan. A randomized phase II study of induction chemotherapy followed by concurrent chemoradiation therapy in patients with stage III NSCLC (CALGB study 9431) showed that grade 3–4 pneumonitis during chemoradiation was noted in 14% of patients treated with gemcitabine and cisplatin, 20% of patients treated with paclitaxel and cisplatin, and 20% of patients treated with vinorelbine and cisplatin. One patient died of pneumonitis in the vinorelbine and cisplatin arm (6). Thus, incidence of pneumonitis in patients receiving paclitaxel was reported to be the same as that for other agents in this setting. Nedaplatin was a new agent but one of the platinum that has been repeatedly shown to be safely administered with radiation (1). A case series of 24 esophageal cancer patients treated with radiation therapy (60–70 Gy) combined with Nedaplatin (80–120 mg) and 5-fluorouracil (500–1000 mg for 5 days) showed that toxicity was mainly hematological and no grade 3 or higher non-hematological toxicity was observed (18). Treatment-related pneumonitis may be more readily developed among Japanese patients, because gefitinib-induced pneumonitis is more common in Japan than in other countries (19–21). Similarly, a relatively high incidence of drug-induced pneumonitis was noted among Japanese patients in association with the use of weekly docetaxel (20) and leflunomide, a newly developed disease-modifying antirheumatic drug that exhibits anti-inflammatory, antiproliferative and immunosuppressive effects (22). Further studies are needed to define ethnic or geographic variation of treatment-related pneumonitis.

Recent dose–volume histogram studies showed that the volume–dose parameters such as the V20 and MLD were significantly associated with development of severe radiation pneumonitis (23). The V_{20} and MLD in the three patients who developed unacceptable pneumonitis in this study (15–30% and 822–1675 cGy, respectively) were not so large, and therefore, the severe pneumonitis in these patients could not be fully explained by their irradiation volume alone. Patient characteristics such as age, sex, smoking habit, location of the primary tumor and pre-existing lung diseases may be associated with the development of radiation pneumonitis, but their contribution was inconclusive (24).

Radiation pneumonitis is the most common dose-limiting complication of thoracic radiation. Its incidence varies greatly from one report to another: the incidence of grade 2 radiation pneumonitis was between 2% and 33% and that of grade 3 was between 0% and 20% (25). This inconsistency among reports can be explained by the different radiation pneumonitis scoring system and follow-up duration in each study. No scoring system for radiation pneumonitis is perfect. The distinction between grade 2 and grade 3 toxicity is highly subjective. In addition, these scoring systems do not account for intercurrent symptoms from tumor, infection and chronic lung illnesses such as chronic obstructive pulmonary diseases (25).

For future trials, it is an important strategy to reduce the lung volume receiving radiation without an increase in the local recurrence rate. Elective nodal regions with potential subclinical micrometastases (CTV3 in this study) have been included in the standard irradiation volume. The advent of three-dimensional conformal treatment techniques, however, has allowed for a more precise definition of target volume and may allow the possibility of reduced toxicity and increased radiation dose delivery by the omission of elective nodal irradiation (26). We are conducting a phase I study of high-dose thoracic three-dimensional conformal radiotherapy without elective nodal irradiation concurrently combined with cisplatin and vinorelbine in patients with inoperable stage III non-small cell lung cancer.

In conclusion, the doses of paclitaxel and nedaplatin combined with thoracic radiotherapy could not be escalated owing to severe pulmonary toxicity. We do not recommend a phase II study of this chemoradiotherapy regimen.