疾患であり、SRSにより優れた治療成績が報告されている[25,26]。Flickingerらによると10年局所制御率が93.2%と報告されており[26]、医学的な理由で手術困難な症例や腫瘍占拠部位により手術が困難な症例において、手術に代わる可能性が報告されている[25]。しかし、海綿静脈洞近傍の髄膜腫に対するSRSの報告では、19ヵ月の経過観察において視神経交叉の線量が8 Gyを超過した症例17例中4例で視力障害を認めている[27]。1回線量が視神経障害に関する重要な因子であるという指摘もあり[28]、視神経や脳幹などが近接する場合はSRTが検討される。

聴神経腫瘍に対してはSRSによる良好な治療成績が報告されており、長期の経過観察結果で照射後手術を受ける必要のない有効症例が98%であったと報告されている[29]。

5年後の神経機能温存率は顔面神経79%、三叉神経73%、聴力51%であった。神経のダメージには1回線量や照射される神経の長さが関係するという指摘もあり、顔面神経や三叉神経麻痺、聴力低下のリスクの軽減を目的としてSRTがさまざまな施設で検討されているが、最適な治療スケジュールは確立していない。

下垂体腺腫の放射線治療ではその占拠部位より視神経と側頭葉の有害反応が問題となる。術後早期の照射の意義は明らかでなく、予後良好と思われる症例では再燃時の照射が妥当とされている[30]。ホルモン産生腫瘍の場合は補助療法の選択肢もあり、放射線治療の適応は限られる。多くの施設では術後照射として2 Gy×25回の通常分割照射が選択されているが、われわれは視神経と側頭葉の線量低減を目的としてSRTを応用している。Mitsumoriらは48例の下垂体腺腫の治療結果をSRS（18例）とSRT（30例）で比較検討している[31]。ホルモン値の正常化に要した期間はSRS 8.5ヵ月に対し、SRT 18ヵ月とSRT群で時間を要しており、3年後の局所制御率はSRS 100%に対しSRT 85.3%であった。しかし中枢神経系の副作用のない症例を検討すると3年でSRS 72.2%に対しSRT 100%であった。SRT群で副作用が高率であったことよりSRTを推奨している。

## 5.7　転移性脳腫瘍

転移性脳腫瘍は癌による死亡の主な原因の一つであると共に、脳の圧迫による神経障害が発生するため、癌患者のQOLを著しく低下させる原因の一つとなる。転移性脳腫瘍の多くは辺縁明瞭で周囲組織への浸潤傾向が少なくCTやMRIにより比較的小さい時期に発見されることも多いため、STIのよい対象となっている。脳転移の治療は、全脳照射と手術に加え定位放射線照射の登場により、その選択の多様性と妥当性に関する検討がさまざまに行われている。RTOG（Radiation Therapy Oncology Group）では、手術適応とならない1～3個の転移性脳腫瘍に対して、全脳照射と全脳照射＋SRSの333例のランダム化比較試験を行った（RTOG9508）[32]。全体の生存期間の中央値は全脳照射5.7ヵ月 vs 全脳＋SRS 6.5ヵ月と有意差を認めなかった。しかし、1個の場合は全脳照射4.9ヵ月に対して、全脳＋SRS群が6.5ヵ月であった。6ヵ月時点でのKPS改善・維持割合も全脳照射27%に対し全脳＋SRS 43%とSRS併用群が良好であったと報告している。全脳照射は、頭蓋内の新病変出現と病巣辺縁よりの再発対策として併用されてきたが、Flickingerらは全脳照射により局所制御率は向上するが生存期間の延長はもたらさないとし[33]、Sneedらは定位放射線照射後に新病変が出現した際に全脳照射を追加することを提唱している[34,35]。定位放射線照射に全脳照射を組み合せるか否かに関しては、必要性およびその意義についての結論は出ていない。

Larsonらの分類でCategory Dに分類される転移性脳腫瘍では、分割照射によりBEDが上昇し照射線量が増大できることからSRTの有用性が考えられている。また、病巣の大きさや神経組織などリスク臓器の近接の有無、標的病変が著しい不整形の場合はSRTのよい適応となると考えられる。診断や治療方法の進歩により、脳転移と診断される症例においても数年以上の長期生存が増加しており、緩和的放射線治療の意義にも変化が認められている。従来は、短期間で1回高線量のスケジュールによる治療で、治療後早期に効果的な症状緩和が得られ最小限の急性期有害反応にとどまるShort Term Palliationが主体であった。しかし長期生存例の増加はより効果的な高い総線量によるRadical Palliationの必要性をもたらし、さらに症状出現の予防を考慮したProphylactic Palliationの検討を必要としている。SRTはRadical Palliationとして、局所制御率の向上に寄与する可能性が考えられている。転移性脳腫瘍に対する最適な照射スケジュールは明らかとなっていないが、組織型や大きさ、占拠部位を考慮した照射スケジュールの変更が必要であろう。

## 5.8　おわりに

STIの応用は、AVMや転移性脳腫瘍のみならず原発性脳腫瘍を含むさまざまな病態で検討されている。今

後適切な臨床試験の実施により治療方法の選択に関する情報の増加が期待されるが、症例の状況や推測される予後などを考慮した適切なインフォームドコンセントのもと、治療方針の選択がなされる必要がある。

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ORIGINAL PAPER

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# Primary central nervous system lymphoma in Japan 1995–1999: changes from the preceding 10 years

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**Abstract** *Purpose*: Previously, we conducted a nationwide survey of primary central nervous system lymphoma (PCNSL) treated between 1985 and 1994 in Japan. In the present study, we conducted further investigations of PCNSL patients treated between 1995 and 1999 to clarify possible changes with time in the clinical features, treatment, and outcome of this disease. *Methods*: Thirteen Japanese institutions were surveyed, and data on 101 patients with histologically-confirmed PCNSL were collected. These data were compared with those of 167 patients treated at the same institutions between 1985 and 1994. *Results*: Regarding patient and tumor characteristics, the proportion of patients with good performance status (PS) was significantly higher in the group treated during 1995–1999 than in that treated during 1985–1994, but other characteristics were not significantly different. Regarding treatment, more patients in the more recent period (66%) received systemic chemotherapy than those in the preceding period (53%, $P = 0.049$). For all patients, including those who did not complete radiotherapy, the median survival time was 17 months and 30 months in patients treated between 1985 and 1994 and those treated between 1995 and 1999, respectively, and the 5-year survival rate was 15% versus 31% ($P = 0.0003$). In both patient groups, higher age and tumor multiplicity were associated with poor prognosis in multivariate analysis. In patients treated between 1995 and 1999, those who received systemic chemotherapy showed significantly better prognosis than those who did not ($P = 0.0049$), but the difference was not significant in multivariate analysis ($P = 0.23$). *Conclusions*: The high survival rates observed in the present survey are comparable with those of recent prospective studies employing intensive chemoradiotherapy. The improvement in prognosis appeared to result, at least in part, from the increase in the proportion of patients with better PS. Since the clinical feature and treatment outcome of patients with PCNSL can thus change with the era, historical control data should not be used in comparing different treatment modalities.

**Keywords** Brain neoplasm · Lymphoma · Primary CNS lymphoma · Radiotherapy · Chemotherapy

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## Introduction

Primary central nervous system lymphoma (PCNSL) is increasing and is becoming one of the most important tumors in neuro-oncology. Radiation therapy has been the standard treatment for PCNSL until recently, but the outcome of patients treated by radiation alone has not necessarily been satisfactory (Shibamoto et al. 1990; Reni et al. 1997; Hayabuchi et al. 1998; Nelson 1999). More recently, the use of high-dose methotrexate (MTX)-containing chemotherapy before radiation appeared to have gained some success in obtaining

long-term survival (Glass et al. 1994; Blay et al. 1998; Brada et al. 1998; Abrey et al. 2000; Ferreri et al. 2000; O'Brien et al. 2000; Reni et al. 2001; Bessel et al. 2001; Caldoni & Aebi 2002; DeAngelis et al. 2002). However, there has been no randomized trial suggesting the superiority of the combined modality treatment over radiation therapy alone, and a recent study by a German group suggested a high rate of progressive disease during treatment with 6 courses of 8 g/m$^2$ of MTX (Herrlinger et al. 2002). Therefore, the benefit of high-dose MTX appears to remain uncertain. Since the clinical features of PCNSL appear to be changing with time, it may not be reasonable to consider that combined MTX-containing chemotherapy and radiation is superior to radiation alone, by comparing the results of combined treatment with the historical control data in patients treated by radiation therapy alone.

Previously, Hayabuchi et al. (Hayabuchi et al. 1998) conducted a nationwide survey of PCNSL in Japan treated between 1985 and 1994. The findings on 466 patients were previously published. Considering the increasing importance of this disease, we organized a research group consisting of 13 institutions to carry out both retrospective and prospective studies on PCNSL. As a first study of this group, we collected data on PCNSL patients treated between 1995 and 1999 at these institutions. In addition to analyzing these data on 101 patients, we compared the data with those on 167 patients from the previous survey treated between 1985 and 1994 at the same institutions, to investigate changes in the clinical feature, treatment modality, and outcome between these eras.

## Materials and methods

Subjects of the present survey were patients with histologically-proven PCNSL who received radiation therapy between 1995 and 1999. Those who did not complete the planned radiotherapy were included. Clinical characteristics, treatment and prognosis of each patient shown in the Results section were asked using a detailed questionnaire. Data on 101 patients were collected from 13 institutions. For comparison, data on 167 patients treated in the preceding 10 years, i.e., between 1985 and 1994, at the same institutions were obtained from the data source of the previous nationwide survey (Hayabuchi et al. 1998) and were analyzed. Data regarding tumor size (maximum diameter at diagnosis and before radiation therapy) was asked for in the present survey, which had not been done in the previous survey. As often happens with such a survey, a number of the items were unanswered by the investigators. Various chemotherapy regimens had been used, and were categorized as follows: (A) cyclophosphamide, vincristine, and prednisolone (COP) or COP plus doxorubicin (CHOP/VEPA); (B) intravenous methotrexate (MTX) alone or MTX-containing regimens. The drugs included in regimen A had often been used in combination with MTX, and such regimens were categorized into this group; (C) cytarabine plus procarbazine; (D) nitrosourea-containing regimens. Some of the drugs in regimen A had been used in combination with nitrosoureas, and such regimens were included in this group. When MTX had been used in combination, the regimen was categorized into group B; (E) cisplatin plus etoposide; and (F) Single use or combination of miscellaneous other agents not included in the above groups. For analysis of treatment results, regimens C–F were grouped together. Differences in patient, tumor, and treatment characteristics between groups were examined by Fisher's exact test.

Survival rates were calculated from the date of starting radiotherapy using the Kaplan-Meier method, and differences in pairs of survival curves were examined by the log-rank test. Multivariate analysis of prognostic factors was carried out using the Cox proportional hazards model. In doing multivariate analysis, patients were divided into two groups, and all the parameters were entered as dichotomous variables. All statistical analyses were carried out using a computer program, Stat View Version 5 (SAS institute, Cary, NC, USA).

## Results

Table 1 shows patient, tumor, and treatment characteristics in the two groups treated between 1985 and 1994 and between 1995 and 1999. There were more patients with better WHO performance status (PS) score in the group treated between 1995 and 1999 than in the

**Table 1** Patient, tumor, and treatment characteristics

| Characteristic | | 1985–1994 | 1995–1999 | *P* |
|---|---|---|---|---|
| Gender | Male/female | 97/70 | 67/34 | 0.20 |
| Age (years) | < 60/≥ 60 | 83/84 | 53/48 | 0.71 |
| | Median (range) | 60 (15–84) | 59(15–84) | |
| Performance status | 0–2/3,4 | 69/95 | 60/41 | 0.0078 |
| Lactate dehydrogenase | Normal/high | 49/34 | 50/30 | 0.75 |
| B symptom | Yes/no | 16/133 | 11/81 | 0.83 |
| Phenotype | B/T | 75/8 | 79/6 | 0.59 |
| Tumor number | Single/multiple | 103/63 | 56/43 | 0.44 |
| Maximum tumor diameter | At diagnosis | – | 3 (1.5–9) | |
| Median (range) (cm) | Before radiation | – | 3 (0–9) | |
| Radiotherapy | Completed/not completed | 158/9 | 97/4 | 0.77 |
| Radiation field | Whole brain/partial brain | 146/21 | 92/9 | 0.43 |
| Spinal radiation | Yes/no | 15/152 | 4/97 | 0.15 |
| Total dose (Gy) | < 50/≥50 | 54/113 | 28/73 | 0.49 |
| | Median (range) | 50 (2–70) | 50 (6–80) | |
| Whole-brain dose (Gy) | < 40/≥40 | 70/97 | 42/59 | 1.0 |
| | Median (range) | 40 (0–54) | 40 (0–60) | |
| Chemotherapy | Yes / no | 78/70 | 65/34 | 0.049 |

**Table 2** Chemotherapy regimens (COP cyclophosphamide, vincristine and prednisone, CHOP/VEPA COP plus doxorubicin)

| Regimen | 1985–1994 | 1995–1999 |
|---|---|---|
| COP, CHOP/VEPA | 35 (45%) | 25 (38%) |
| Methotrexate-containing regimens | 18 (23%) | 27 (42%) |
| Cytarabine and procarbazine | 0 | 7 (11%) |
| Nitrosourea-containing regimens | 13 (17%) | 2 (3%) |
| Cisplatin and etoposide | 8 (10%) | 4 (6%) |
| Miscellaneous drugs | 4 (5%) | 0 |

group treated in the preceding 10 years, but the other patient and tumor characteristics did not differ significantly between the two groups. Radiotherapy characteristics were similar between the two groups. During both study periods, more than 85% of the patients were treated with whole-brain irradiation with or without focal boost, and the median total and whole brain doses were 50 Gy and 40 Gy, respectively. Whole spinal irradiation was employed in less than 10% of the patients. On the other hand, more patients seen between 1995 and 1999 received systemic chemotherapy than those seen between 1985 and 1994 (66% vs 53%, $P = 0.049$). Table 2 shows chemotherapy regimens used in the two groups. The use of MTX-containing regimens appeared to be increasing recently. However, a high dose of MTX ($>2$ g/m$^2$ per administration) was used in only 14 patients (14% of all patients) treated between 1995 and 1999.

Figure 1 shows overall survival curves for all patients in the two groups. Patients in the present survey had significantly better survival rates than those in the previous survey ($P = 0.0003$); median survival time was 30 vs 17 months, and the 3-year survival rate was 46% vs 24%. The 5-year survival was 31% and 15%, respectively. Table 3 summarizes survival data in the two groups according to potential prognostic factors. In both study periods, patients with ages $<60$ years, PS 0–2, or a single tumor showed significantly higher survival rates. Patients with normal lactate dehydrogenase (LDH) levels or without B symptom had better prognoses than those with high LDH level or with B symptom, respectively, in the group treated between 1995 and 1999, but not in those treated during 1985–1994.

To analyze the influence of treatment-related factors on outcome, patients who did not complete radiotherapy (and died soon) were excluded. In patients treated between 1985 and 1994, those who received partial-brain radiation, spinal radiation, or whole-brain dose $<40$ Gy showed better prognoses, but these phenomena were not observed in patients treated between 1995 and 1999. Figure 2 shows survival curves according to the treatment modality, i.e., radiation alone vs radiation plus chemotherapy. In patients treated between 1985 and 1994, the two groups showed similar prognoses. In patients treated between 1995 and 1999, however, those who received radiation plus chemotherapy showed significantly better survival than those who received radiation alone. Among these patients, 61% of the

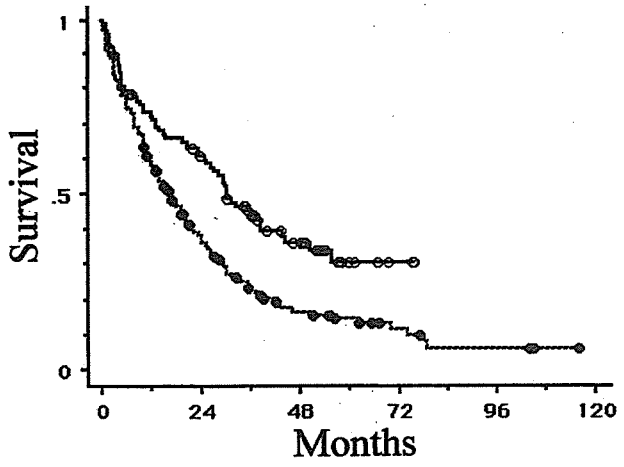


**Fig. 1** Survival curves for patients with primary central nervous system lymphoma treated between 1985 and 1994 (- - -●- - -) and for those treated between 1995 and 1999 (_____○_____). The difference was significant ($P = 0.0003$)

patients who received radiochemotherapy were younger than 60 years, but 39% of those treated with radiation alone were younger than 60 years ($P = 0.050$). Similarly, 64% of the patients who received radiochemotherapy had a PS 0–2, but 55% of those treated with radiation had a PS 0–2 ($P = 0.50$). Figure 3 shows survival curves according to the chemotherapy regimens. In patients treated between 1985 and 1994, there was no significant difference in survival curves according to the regimens. On the other hand, there was an overall difference in those treated between 1995 and 1999 ($P = 0.018$). Patients receiving MTX-containing regimens showed better survival than those treated with CHOP/VEPA or COP ($P = 0.0071$).

Multivariate analyses were performed for potential prognostic factors, which were significant in univariate analyses (Table 4). Factors concerning the radiation field and spinal radiation were not included because of the small number of patients in one of the groups. In both patient groups treated during 1985–1994 and 1995–1999, age and tumor number were suggested to be significant prognostic factors. PS and LDH level did not reach statistical significance. The radiation dose to the whole brain and chemotherapy did not prove significant in patients treated between 1985 and 1994, and in those treated between 1995 and 1999, respectively.

## Discussion

The most significant finding of this study appears to be that patients treated between 1995 and 1999 showed a significantly better prognosis than those treated between 1985 and 1994. Comparison of the patient and tumor characteristics revealed that there were more patients with better PS between 1995 and 1999 than between 1985 and 1994. This may be due to the earlier diagnosis of the disease in recent years and improvement in gen-

**Table 3** Survival data according to potential prognostic factors (MST median survival time in months, 5-YSR 5-year survival rate)

| Prognostic factor | | 1985–1994 | | | | 1995–1999 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *n* | MST | 5-YSR(%) | *P* | *n* | MST | 5-YSR(%) | *P* |
| Gender | Male | 97 | 15 | 8.7 | 0.13 | 67 | 32 | 31 | 0.62 |
| | Female | 70 | 22 | 23 | | 34 | 28 | 33 | |
| Age (years) | < 60 | 83 | 20 | 22 | 0.0057 | 53 | 44 | 45 | 0.0052 |
| | ≥ 60 | 84 | 13 | 6.8 | | 48 | 23 | 15 | |
| Performance status | 0–2 | 69 | 24 | 18 | 0.0015 | 60 | 37 | 32 | 0.024 |
| | 3,4 | 95 | 11 | 13 | | 41 | 12 | 30 | |
| B symptom | Yes | 16 | 10 | 7.5 | 0.30 | 11 | 14 | 18 | 0.027 |
| | No | 133 | 18 | 17 | | 81 | 36 | 35 | |
| Lactate dehyrdogenase | Normal | 49 | 22 | 31 | 0.17 | 50 | 55.5 | 43 | 0.0084 |
| | High | 34 | 21 | 5.8 | | 30 | 20.5 | (20)[b] | |
| Tumor number | Single | 103 | 22 | 19 | 0.0021 | 56 | 55.5 | 43 | 0.0083 |
| | Multiple | 63 | 11 | 7.9 | | 43 | 26 | 17 | |
| Tumor size (cm)[a] | ≤ 3 cm | – | – | – | – | 51 | 32 | 33 | 0.95 |
| | > 3 cm | – | – | – | | 41 | 37 | 31 | |
| Radiation field | Whole brain | 139 | 17 | 12 | 0.026 | 89 | 30 | 31 | 0.99 |
| | Partial brain | 19 | 35 | 38 | | 8 | 35 | (33) | |
| Spinal radiation | Yes | 15 | 31 | 37 | 0.042 | 4 | - | (50) | 0.69 |
| | No | 143 | 17 | 13 | | 93 | 30 | 30 | |
| Total dose (Gy) | < 50 | 45 | 16 | 22 | 0.79 | 24 | 29.5 | 26 | 0.16 |
| | ≥ 50 | 113 | 18 | 13 | | 73 | 36 | 32 | |
| Whole-brain dose (Gy) | < 40 | 61 | 24 | 22 | 0.025 | 38 | 32 | 26 | 0.83 |
| | ≥40 | 97 | 14 | 11 | | 59 | 30 | 32 | |
| Chemotherapy | Yes | 65 | 18 | 19 | 0.63 | 64 | 38 | 40 | 0.0049 |
| | No | 74 | 19 | 14 | | 31 | 25 | (14) | |

[a] Maximum tumor diameter before radiation
[b] Figures in parentheses are 4-year survival rate

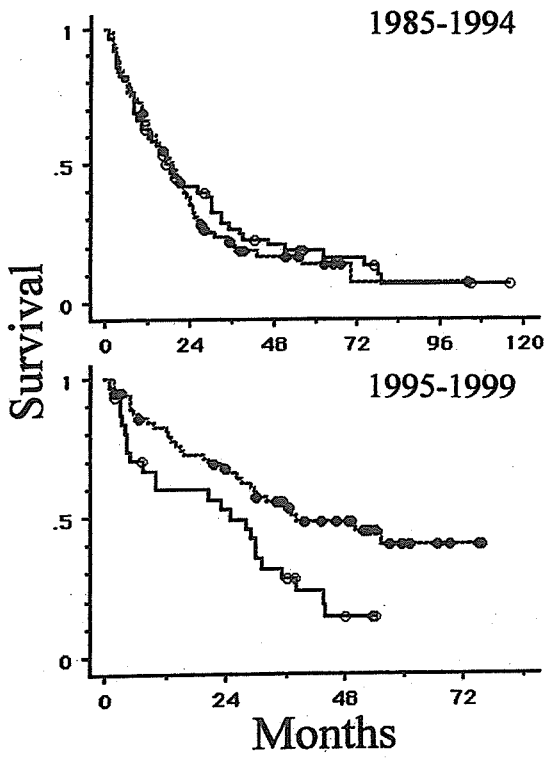


**Fig. 2** Survival curves according to the treatment modality. ____○____ : patients treated with radiation alone, - - -●- - - : patients treated with radiation and chemotherapy. The difference was significant in the group of patients treated between 1995 and 1999 (upper panel, $P = 0.63$; lower panel, $P = 0.0049$)

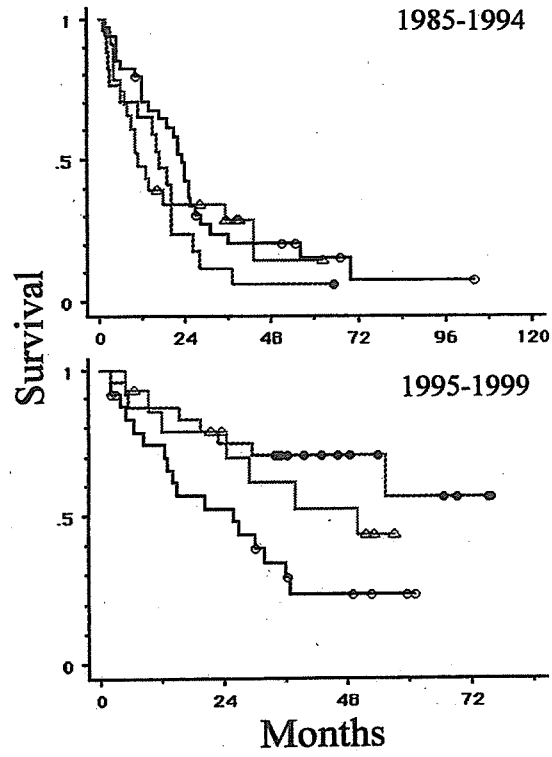


**Fig. 3** Survival curves according to chemotherapy regimens. ____○____ : cyclophosphamide, vincristine, prednisolone ± doxorubicin, - - -●- - - : methotrexate-containing regimens, - - -Δ- - - : other regimens. The difference among the curves was significant in the group of patients treated between 1995 and 1999 (upper panel, $P = 0.32$; lower panel, $P = 0.018$)

**Table 4** Multivariate anayses for potential prognostic factors that were significant in univariate analysis

| Factor | 1985–1994 ($n$= 154) | | 1995–1999 ($n$= 72) | |
|---|---|---|---|---|
| | $P$ | Relative risk | $P$ | Relative risk |
| Age (<60 vs ≥ 60 years) | 0.036 | 1.48 (1.03–2.15)[a] | 0.047 | 2.07 (1.01–4.22) |
| Performance status (0–2 vs 3,4) | 0.13 | 1.36 (0.92–2.01) | 0.13 | 1.77 (0.85–3.68) |
| Lactate dehydrogenase (normal vs high) | – | – | 0.13 | 1.70 (0.86–3.34) |
| Tumor number (single vs multiple) | 0.0093 | 1.67 (1.13–2.45) | 0.0032 | 2.82 (1.42–5.62) |
| Whole-brain dose (<40 vs ≥ 40 Gy) | 0.22 | 1.28 (0.86–1.91) | – | – |
| Chemotherapy (yes vs no) | – | – | 0.23 | 1.53 (0.32–1.31) |

[a]Figures in parentheses are 95% confidence intervals

eral care including corticosteroid therapy and less aggressive surgery. Since PS was a significant prognostic factor in univariate analysis, it is suggested that the increase in the proportion of better PS patients may, at least in part, have contributed to the improvement in prognosis in patients treated between 1995 and 1999.

Age, PS, and tumor multiplicity are well-known prognostic factors for PCNSL (Corry et al. 1998; Hayabuchi et al. 1998; O'Brien et al. 2000). The present results of univariate analyses agree with these previous observations, although the influence of PS did not reach a significant level in multivariate analysis. Patients with a high LDH level treated between 1995 and 1999 showed a poorer prognosis than those with a normal LDH level in univariate analysis. However, LDH was not a significant factor in patients treated between 1985 and 1994, as also shown in the multivariate analysis of patients treated between 1995 and 1999. The previous analysis of 466 patients in the nationwide survey suggested an association of high LDH level and poor prognosis in both univariate and multivariate analyses (Hayabuchi et al. 1998), so LDH may be a potential prognostic factor which is certainly weaker than age, PS, and tumor multiplicity. A similar finding was obtained regarding B symptom. In the newer survey, we investigated the influence of tumor size, but it did not appear to have a significant influence on patient outcome.

Regarding the method of radiation therapy, patients who were treated with a partial-brain field showed a better prognosis than those treated with a whole-brain field in the group treated between 1985 and 1994. Shibamoto et al. (Shibamoto et al. 2003) recently discussed the possible benefit of using partial-brain irradiation, especially in patients with a single lesion. Due to the retrospective nature of the present study and the small number of patients who received partial-brain irradiation, no conclusion should be drawn regarding radiation field, but avoiding whole-brain radiation may be a future topic in the treatment of PCNSL. The observation in the earlier period that patients who received spinal radiation and those who received whole-brain doses of less than 40 Gy had a better prognosis are paradoxical, and it is suggested that these observations would represent patient selection bias, which is often seen in retrospective analysis. As has been suggested by previous findings (Nelson et al. 1992; Hayabuchi et al. 1998), a higher dose of radiation did not appear to be associated with survival improvement.

In patients treated between 1985 and 1994, those who received radiation alone and those who received radiation plus chemotherapy showed a similar prognosis. On the other hand, in patients treated between 1995 and 1999, those who received radiation plus chemotherapy had a significantly better prognosis than those who received radiation alone. However, the effect of chemotherapy was not significant in multivariate analysis. Since younger patients were more often treated with combined radiation and chemotherapy, this may be one of the reasons why the effect of chemotherapy was not supported by multivariate analysis. Analysis according to chemotherapy regimens suggested a possible advantage of MTX-containing regimens over conventional CHOP or similar regimens. Several studies have suggested the ineffectiveness of CHOP or similar regimens, especially when given before radiation (Schultz et al. 1996; O'Neill 1999; Mead et al. 2000), although post-radiation CHOP requires further investigation (Shibamoto et al. 1999). The present findings suggest that systemic chemotherapy with weak or moderate intensity may not be beneficial in PCNSL.

The findings of the present study revealed that the treatment outcome for PCNSL varies greatly with the era. Although most of the chemotherapy regimens used were of mild or moderate intensity and only 14% of the patients received high-dose-MTX-containing chemotherapy, the 5-year survival rate of 31% for all patients treated between 1995 and 1999 (including those who did not complete radiotherapy) were equal to that recently reported by the Radiation Therapy Oncology Group (DeAngelis et al. 2002) or those of other series using intensive combined modality treatment including high-dose MTX (Brada 1998; Bessell et al. 2001). Therefore, it appears to be inappropriate to discuss the usefulness of treatment modality by comparing with the historical control data. There have been no major randomized studies, except for a small one (Mead et al. 2000), regarding the benefit of combining chemotherapy with radiation, but to confirm the efficacy of chemotherapy, randomized studies appear to be necessary.

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# Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer

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**To determine the recommended phase II dose of vinorelbine in combination with cisplatin and thoracic radiotherapy (TRT) in patients with unresectable stage III non-small cell lung cancer (NSCLC), 18 patients received cisplatin (80 mg/m$^2$) on day 1 and vinorelbine (20 mg/m$^2$ in level 1, and 25 mg/m$^2$ in level 2) on days 1 and 8 every 4 weeks for 4 cycles. TRT consisted of a single dose of 2 Gy once daily for 3 weeks followed by a rest of 4 days, and then the same TRT for 3 weeks to a total dose of 60 Gy. Fifteen (83%) patients received 60 Gy of TRT and 14 (78%) patients received 4 cycles of chemotherapy. Ten (77%) of 13 patients at level 1 and all 5 patients at level 2 developed grade 3–4 neutropenia. Four (31%) patients at level 1 and 3 (60%) patients at level 2 developed grade 3–4 infection. None developed ≥grade 3 esophagitis or lung toxicity. Dose-limiting toxicity was noted in 33% of the patients in level 1 and in 60% of the patients in level 2. The overall response rate (95% confidence interval) was 83% (59–96%) with 15 partial responses. The median survival time was 30.4 months, and the 1-year, 2-year, and 3-year survival rates were 72%, 61%, and 50%, respectively. In conclusion, the recommended dose is the level 1 dose, and this regimen is feasible and promising in patients with stage III NSCLC. (Cancer Sci 2004; 95: 691–695)**

Stage III locally advanced non-small cell lung cancer (NSCLC) accounts for about 25% of all lung cancer cases.[1] Successful treatment of this disease rests on the control of both clinically apparent intrathoracic disease and occult systemic micrometastases, and therefore a combination of systemic chemotherapy and thoracic radiotherapy is indicated in many patients with good performance status and no pleural effusion.[2] Concurrent chemoradiotherapy is superior to the sequential approach, as shown by recent phase III trials in unresectable stage III NSCLC, in which the median survival time was 15.0 to 17.0 months in the concurrent arm and 13.3 to 14.6 months in the sequential arm, although acute esophagitis was more severe in the concurrent arm.[3–5] Chemotherapy regimens combined with simultaneous thoracic radiotherapy have consisted of cisplatin plus etoposide and cisplatin plus vinca alkaloids,[3,4] and a combination of cisplatin plus vindesine, with or without mitomycin, has been widely used in Japan.[5–8]

Vinorelbine, a new semisynthetic vinca alkaloid with a substitution in the catharanthine ring, interacts with tubulin and microtubule-associated proteins in a manner different from the older vinca alkaloids, and it more selectively depolymerizes microtubules in mitotic spindles.[9] Several randomized trials have shown vinorelbine to be more active against advanced or metastatic NSCLC than vindesine as a single agent or in combination with cisplatin.[10–13] Thus, incorporation of vinorelbine into concurrent chemoradiotherapy instead of vindesine is an important strategy for the treatment of locally advanced NSCLC. The objective of this study was to determine the maximum tolerated dose (MTD) and recommended dose of vinorelbine for phase II studies in combination with cisplatin, with or without mitomycin, and thoracic radiotherapy for patients with unresectable stage III NSCLC. We planned to start with the cisplatin and vinorelbine combination and then add mitomycin.

## Patients and Methods

**Patient selection.** The eligibility criteria were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease; no previous treatment; measurable disease; tumor within an estimated irradiation field no larger than half the hemithorax; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1[14]; adequate bone marrow function ($12.0\times10^9$/liter ≥white blood cell [WBC] count ≥$4.0\times10^9$/liter, neutrophil count ≥$2.0\times10^9$/liter, hemoglobin ≥10.0 g/dl, and platelet count ≥$100\times10^9$/liter), liver function (total bilirubin ≤1.5 mg/dl and transaminase ≤twice the upper limit of the normal value), and renal function (serum creatinine ≤1.5 mg/dl and creatinine clearance ≥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 pneumonia 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 or ultrasonography, and radionuclide bone scan.

**Treatment schedule.** The dose levels and doses of each anticancer agent are shown in Table 1. Cisplatin and vinorelbine were administered at dose levels 1 and 2. It was planned to give cisplatin, vinorelbine, and mitomycin at dose levels 3–5, but because the MTD was determined to be dose level 2, dose levels 3–5 were not used. Cisplatin was administered on day 1 by intravenous infusion over 60 min together with 2500 to 3000 ml of fluid for hydration. Vinorelbine diluted in 40 ml of normal saline was administered by bolus intravenous injection on days 1 and 8. All patients received prophylactic antiemetic ther-

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apy consisting of a 5HT3-antagonist and a steroid. This chemotherapy regimen was repeated every 4 weeks for 4 cycles.

Thoracic radiotherapy with photon beams from a liniac or microtron accelerator with energy between 6 and 10 MV at a single dose of 2 Gy once daily given 15 times over 3 weeks was begun on day 2 of the first cycle of cisplatin and vinorelbine chemotherapy, and followed by a short rest period of 4 days. The same radiotherapy was begun on day 1 of the second cycle of chemotherapy to a total dose of 60 Gy. The clinical target volume (CTV) was based on conventional chest X-ray and CT scans, and included the primary lesion (CTV1), involved lymph nodes whose short diameter was 1 cm or larger (CTV2), and the ipsilateral pulmonary hilum and bilateral mediastinum area (CTV3). Anterior and posterior parallel opposed fields encompassed the initial planned target volume (PTV), consisting of CTV1–3 with the superior and inferior field margins extended to 1 to 2 cm and the lateral field margins extended to 0.5 cm for respiratory variation and fixation error. The boost PTV included only CTV1–2 based on the second CT scans with the same margins. The spinal cord dose was limited to 40 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. Acute toxicity was graded according to the NCI Common Toxicity Criteria version 2.0 issued in 1998, and late toxicity associated with thoracic radiotherapy was graded according to the RTOG Late Radiation Morbidity Scoring Schema.[15] Vinorelbine administration on day 8 was omitted if any of the following toxicities was noted: WBC count $<3.0\times10^9$/liter, neutrophil count $<1.5\times10^9$/liter, platelet count $<100\times10^9$/liter, elevated hepatic transaminase level or total serum bilirubin ≥grade 2, fever ≥38°C, or performance status ≥2. Subsequent cycles of chemotherapy were delayed if any of the following toxicities was noted on day 1: WBC count $<3.0\times10^9$/liter, neutrophil count $<1.5\times10^9$/liter, platelet count $<100\times10^9$/liter, serum creatinine level ≥1.6 mg/dl, elevated hepatic transaminase level or total serum bilirubin ≥grade 2, fever ≥38°C, or performance status ≥2. The doses of cisplatin and vinorelbine were reduced by 25% in all subsequent cycles if any of the following toxicities was noted: WBC count $<1.0\times10^9$/liter, platelet count $<20\times10^9$/liter, or grade 3 or severer non-hematological toxicity, except for nausea and vomiting. The dose of cisplatin 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: WBC count $<1.0\times10^9$/liter, platelet count $<20\times10^9$/liter, esophagitis ≥grade 3, fever ≥38°C, performance status ≥3, or $PaO_2$ <70 Torr. Thoracic radiotherapy was terminated if this toxicity persisted for more than 2 weeks. Granulocyte colony-stimulating factor support was used if the neutrophil count was $<0.5\times10^9$/liter for more than 4 days, the WBC count was $<1.0\times10^9$/liter, or febrile neutropenia ≥grade 3 was noted.

**Dose-limiting toxicity, MTD, and recommended dose for phase II studies.** The dose-limiting toxicity (DLT) was defined as a neutrophil count $<0.5\times10^9$/liter lasting 4 days or longer, febrile neutropenia ≥grade 3, platelet count $<20\times10^9$/liter, grade 3 or more severe non-hematological toxicity other than nausea and vomiting, and patient's refusal to receive subsequent treatment. Doses 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 one or none of them experienced DLT, the next cohort of patients was treated at the next higher dose level. If 2 of the 6 patients experienced DLT, then 6 additional patients were enrolled at the same dose level to make a total of 12 patients. If 4 or fewer patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If 5 or more of the 12 patients experienced DLT, that level was considered to be the MTD. If 3 of the initial 6 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.

**Table 1. Dose level and the dose of each anticancer agent**

| Dose level | Cisplatin (mg/m²) | Vinorelbine (mg/m²) | Mitomycin (mg/m²) |
|---|---|---|---|
| −1 | 80 | 15 | — |
| 1 | 80 | 20 | — |
| 2 | 80 | 25 | — |
| 3 | 80 | 15 | 8 |
| 4 | 80 | 20 | 8 |
| 5 | 80 | 25 | 8 |

**Response evaluation.** Objective tumor response was evaluated according to the WHO criteria issued in 1979.[16] A complete response (CR) was defined as the disappearance of all known disease for at least 4 weeks with no new lesions appearing. A partial response (PR) was defined as an at least 50% decrease in total tumor size for at least 4 weeks without the appearance of new lesions. No change (NC) was defined as the absence of a partial or complete response with no progressive or new lesions observed for at least 4 weeks. Progressive disease was defined as a 25% or greater increase in the size of any measurable lesion or the appearance of new lesions.

**Study design, data management, and statistical considerations.** This study was designed as a phase I study at two institutions, the National Cancer Center Hospital and Kanagawa Cancer Center. The protocol and consent form were approved by the Institutional Review Board of each institution. Registration was conducted at the Registration Center. Data management, periodic monitoring, and the final analysis were performed by the Study Coordinator. A patient accrual period of 24 months and a follow-up period of 18 months were planned. Overall survival time and progression-free survival time were estimated by the Kaplan-Meier method.[17] Survival time was measured from the date of registration to the date of death due to any cause. Progression-free survival time was measured from the date of registration to the date of disease progression or death. Patients who were lost to follow-up without event were censored at the date of their last known follow-up.

## Results

**Registration and characteristics of the patients.** From October 1999 to August 2000, 13 patients were registered at dose level 1 and 5 patients at dose level 2. The detailed demographic characteristics of the patients are listed in Table 2. All patients had unresectable IIIA-N2 or IIIB disease. One of the 6 patients enrolled at dose level 1 developed bacterial meningitis during the second cycle of chemotherapy, and that case is described in detail elsewhere.[18] We did not include it in the assessment of DLT, because the bacterial meningitis was not specifically related to treatment. We registered another patient at the same dose level, and 2 cases of DLT were noted among the initial 6 patients evaluable for DLT. We added another 6 patients, and DLT was noted in 4 of the 12 patients registered at the dose level 1. Of the 5 patients registered at level 2, 3 patients developed DLT. This dose level was determined to be the MTD, and patient accrual to this study was terminated.

**Treatment delivery.** Treatment delivery was generally well maintained, and it did not differ between the two dose levels (Table 3). Full dose (60 Gy) thoracic radiotherapy was completed in 77% and 100% of the patients at dose levels 1 and 2,

**Table 2. Patients' characteristics**

| | | Median (range) | *N* (%) |
|---|---|---|---|
| Number of patients | | | 18 |
| Gender | male | | 16 (89) |
| | female | | 2 (11) |
| Age | median (range) | 59 (48–69) | |
| PS | 0 | | 4 (22) |
| | 1 | | 14 (78) |
| Body weight loss | <5% | | 12 (67) |
| | 5–9% | | 4 (22) |
| | ≥10% | | 2 (11) |
| T-factor | 1 | | 1 (6) |
| | 2 | | 6 (33) |
| | 3 | | 7 (39) |
| | 4 | | 4 (22) |
| N-factor | 2 | | 11 (61) |
| | 3 | | 7 (39) |
| Clinical stage | IIIA | | 9 (50) |
| | IIIB | | 9 (50) |
| Histology | adenocarcinoma | | 14 (78) |
| | squamous cell carcinoma | | 3 (17) |
| | adenosquamous carcinoma | | 1 (6) |

**Table 3. Treatment delivery**

| | Dose level 1 (*N*=13) | Dose level 2 (*N*=5) |
|---|---|---|
| | *N* (%) | *N* (%) |
| Initial irradiation field ($cm^2$) | | |
| median (range) | 171 (128–529) | 182 (128–248) |
| Total dose of radiotherapy (Gy) | | |
| 60 | 10 (77) | 5 (100) |
| 50–59 | 1 (8) | 0 |
| <50 | 2 (15) | 0 |
| Delay of radiotherapy (days)[1)] | | |
| <5 | 6 (60) | 3 (60) |
| 5≤ | 4 (40) | 2 (40) |
| Number of chemotherapy cycles | | |
| 4 | 10 (77) | 4 (80) |
| 3 | 0 | 1 (20) |
| 2 | 2 (15) | 0 |
| 1 | 1 (8) | 0 |
| Omission of vinorelbine administration on day 8 | | |
| 0 | 9 (69) | 2 (40) |
| 1 | 4 (31) | 2 (40) |
| 3 | 0 | 1 (20) |

*1)* Evaluated in patients who received 60 Gy radiotherapy (*N*=15).

respectively. Delays in radiotherapy evaluated in patients who completed the full course of radiotherapy amounted to less than 5 days in 60% of the patients at both levels. Full cycles (4 cycles) of chemotherapy were administered to 77% and 80% of the patients at dose levels 1 and 2, respectively, but vinorelbine administration on day 8 was more frequently omitted at dose level 2 (Table 3).

**Toxicity, MTD, and the recommended dose for phase II trials.** Acute severe toxicity was mainly hematological (Table 4). Grade 3–4 leukopenia and neutropenia were noted in 77% and 100% of the patients at dose levels 1 and 2, respectively. Grade 3 anemia was observed in 23% and 20% of the patients at dose levels 1 and 2, respectively, but no blood transfusions were required. Thrombocytopenia was mild. Grade 4 transaminase elevation was observed in 1 patient during the first cycle of chemotherapy, but no subjective manifestations associated with liver dysfunction were noted. Chemotherapy was discontinued and the transaminases quickly decreased to within their normal ranges. Transient asymptomatic grade 3 hyponatremia was noted in 1 patient. Grade 3–4 infection was noted in 7 patients. Bacterial meningitis unassociated with neutropenia developed on day 6 of the second cycle of chemotherapy in 1 patient.[18)] The other grade 3–4 infections were all associated with neutropenia. Esophagitis was mild in this study, and no grade 3–4 esophagitis was noted. No deaths occurred during or within 30 days of therapy.

DLT was noted in 4 of the 12 (33%) evaluable patients at dose level 1, and in 3 of the 5 (60%) at dose level 2. Six of these 7 DLTs were grade 3–4 infection associated with neutropenia, and the other 1 was grade 4 transaminase elevation. Thus, we determined that dose level 2 was the MTD, and dose level 1 was recommended as the dose for phase II trials.

**Table 4. Acute toxicity**

| Toxicity | Dose level 1 (*N*=13), Grade | | | | | Dose level 2 (*N*=5), Grade | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 3–4 (%) | 1 | 2 | 3 | 4 | 3–4 (%) |
| Hematological | | | | | | | | | | |
| Leukopenia | 0 | 2 | 9 | 1 | (77) | 0 | 0 | 4 | 1 | (100) |
| Neutropenia | 1 | 1 | 7 | 3 | (77) | 0 | 0 | 1 | 4 | (100) |
| Anemia | 4 | 6 | 3 | 0 | (23) | 2 | 2 | 1 | 0 | (20) |
| Thrombocytopenia | 1 | 2 | 0 | 0 | (0) | 1 | 0 | 0 | 0 | (0) |
| Non-hematological | | | | | | | | | | |
| AST | 2 | 0 | 0 | 1 | (8) | 1 | 0 | 0 | 0 | (0) |
| ALT | 7 | 0 | 0 | 1 | (8) | 0 | 1 | 0 | 0 | (0) |
| Total bilirubin | 2 | 1 | 0 | 0 | (0) | 2 | 0 | 0 | 0 | (0) |
| Creatinine | 2 | 2 | 0 | 0 | (0) | 1 | 0 | 0 | 0 | (0) |
| Hyponatremia | 6 | 0 | 1 | 0 | (8) | 1 | 0 | 0 | 0 | (0) |
| Infection | 1 | 3 | 2 | 2 | (31) | 0 | 0 | 3 | 0 | (60) |
| Nausea | 4 | 1 | 0 | 0 | (0) | 3 | 0 | 0 | 0 | (0) |
| Diarrhea | 0 | 1 | 0 | 0 | (0) | 0 | 0 | 0 | 0 | (0) |
| Stomatitis | 2 | 0 | 0 | 0 | (0) | 0 | 2 | 0 | 0 | (0) |
| Esophagitis | 6 | 1 | 0 | 0 | (0) | 4 | 0 | 0 | 0 | (0) |
| Sensory neuropathy | 2 | 0 | 0 | 0 | (0) | 0 | 0 | 0 | 0 | (0) |

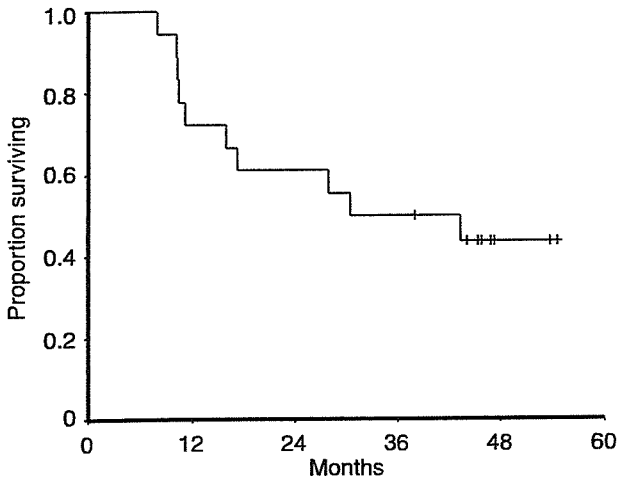


**Fig. 1.** Overall survival in 18 patients. The median (range) follow-up period of censored cases has been 35.4 (32.0–43.4) months, and the median overall survival time has not yet been reached.

Late lung toxicity associated with thoracic radiotherapy was grade 3 in 1 (6%) patient, grade 2 in 4 (22%) patients, and grade 1 in 8 (44%) patients. No late esophageal toxicity was noted.

**Objective responses, relapse pattern, and survival.** All patients were included in the analyses of tumor response and survival. No CR, 15 PRs, and 1 NC were noted, and the overall response rate (95% confidence interval) was 83% (59–96%). Relapse was noted in 12 (67%) of 18 patients. Initial relapse sites were locoregional alone in 5 (28%) patients, locoregional and distant in 3 (17%) patients, and distant alone in 4 (22%) patients. Brain metastasis was detected in 5 patients, and the brain was the most frequent site of distant metastasis. The median progression-free survival time was 15.6 months, and the median overall survival time was 30.4 months. The 1-year, 2-year, and 3-year survival rates were 72%, 61%, and 50%, respectively (Fig. 1).

## Discussion

The combination of cisplatin, vindesine, and mitomycin with concurrent thoracic radiotherapy has been shown to yield an encouraging survival outcome, a median survival time of 17–19 months, and a 5-year survival rate of 16% in patients with unresectable stage III NSCLC.[5,7,8] A Japanese randomized trial revealed that replacement of vindesine by vinorelbine in combination with cisplatin and mitomycin yielded a promising response rate (57% versus 38%, $P=0.025$) and median survival time (15 months versus 11 months, $P<0.01$) in patients with stage IIIB or IV NSCLC.[13] Thus, the combination of cisplatin, vinorelbine, and mitomycin is a chemotherapy regimen with potential for combination with concurrent thoracic radiotherapy. The present study, however, showed that a DLT developed in 60% of patients who received cisplatin and vinorelbine 25 mg/m$^2$ days 1 and 8 (level 2), and since the DLTs were associated with myelosuppression, which is the major critical toxicity of mitomycin, we concluded that it would be impossible to incorporate mitomycin into this regimen.

The recommended doses of vinorelbine of 20 mg/m$^2$ on days 1 and 8 and cisplatin of 80 mg/m$^2$ on day 1 repeated every 4 weeks in this study are comparable to the doses used in the CALGB (vinorelbine 15 mg/m$^2$ on days 1 and 8 and cisplatin 80 mg/m$^2$ on day 1 repeated every 3 weeks),[19,20] and the Czech Lung Cancer Cooperative Group (vinorelbine 12.5 mg/m$^2$ on days 1, 8, and 15 and cisplatin 80 mg/m$^2$ on day 1, repeated every 4 weeks),[21] but lower than in a Mexican study (vinorelbine at 25 mg/m$^2$ on days 1 and 8 and cisplatin 100 mg/m$^2$ on day 1, repeated every 3 weeks).[22] These recommended doses are also lower than expected when compared with the recommended vinorelbine dose combined with cisplatin for metastatic NSCLC (vinorelbine 30 mg/m$^2$ on days 1 and 8 and cisplatin 80 mg/m$^2$ on day 1, repeated every 3 weeks),[23] and when compared with the results of vindesine, cisplatin, and mitomycin combined with thoracic radiotherapy, where the full doses can be administered concurrently.[8] Thus, vinorelbine can be safely administered with cisplatin and concurrent thoracic radiotherapy at a maximum dose of two-thirds the optimal dose without radiotherapy.

The results for response and survival in this study, however, were very encouraging. This may have been attributable to patient selection bias, but the percentage of patients who had stage IIIB disease in this study was similar to the percentage in the CALGB randomized phase II study.[20] In addition, 33% of the patients in this study had ≥5% body weight loss, whereas only 7% of the patients did in that study.[20] The median survival time was 30.4 months and exceeded the results of concurrent

chemoradiotherapy with old drug combinations that yielded a median survival time of 15–19 months.[3–8] Thus, it could be argued that the combination of cisplatin and vinorelbine is more active for locally advanced NSCLC than the older drug combinations, although there have not been any randomized trials comparing this regimen with old drug combinations in combination with thoracic radiotherapy in patients with stage III NSCLC. Our results also seem better than those of other trials using concurrent cisplatin, vinorelbine, and thoracic radiotherapy, in which the median survival time was 13 to 18 months.[20,22] Those trials used induction chemotherapy followed by chemoradiotherapy. Since the response rate to induction chemotherapy is no more than 40%, induction chemotherapy may be disadvantageous. This issue is being evaluated in an on-going CALGB phase III trial.

Severe esophagitis and pneumonitis have been DLTs in many trials of concurrent chemoradiotherapy, but neither was observed in this study. Nevertheless, since the occurrence of these non-hematological toxicities associated with thoracic radiotherapy is sporadic, the sample size in this study may have been too small to detect them. Thus, careful observation for these toxicities is needed in further phase II and phase III trials to definitely establish the safety profile of this regimen.

In conclusion, cisplatin and vinorelbine chemotherapy combined with concurrent full-dose thoracic radiotherapy is feasible, and the recommended dose of vinorelbine for phase II trials is 20 mg/m$^2$ on days 1 and 8 repeated every 4 weeks. This regimen was highly active in patients with stage III NSCLC.

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# 5 放射線治療の新しい展開

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Key words : Prostate Cancer, Radiation Therapy, Dose escalation, Brachytherapy

## はじめに

前立腺がんは本邦の男性悪性新生死亡の4.2%を占め（平成13年），年齢別罹患率は年齢とともに増加し，70-74歳で152，80-84歳では294となる[1]。治療方法に関しては，根治的治療として放射線治療・手術・ホルモン療法が単独あるいは集学的に応用されている。前立腺がんにはさまざまな放射線治療が応用されており，治療方法の選択にはその特徴をよく理解しインフォームドコンセントを行う必要がある。

前立腺がんに関してはさまざまなリスク分類が提唱されているが（表1），治療開始前のProstate Specific Antigen (PSA)，Gleason Score，臨床病期（T因子・N因子）による予後の差異が報告されており，治療方法選択にも応用されている[1-5]。外照射症例の予後因子解析としては，Roachらによる Radiation Therapy Oncology Group (RTOG) の臨床試験結果の解析が報告されている[5]。外照射による放射線単独の治療を受けた1,557症例の解析より，Gleason Score，T-Stage，病理学的骨盤リンパ節転移を予後因子とする4群のリスクグループを設定し，Disease-Specific Survivalを報告している。5年で96%～64%，15年では72%～27%とリスクグループにより予後には大きな差異が認められる。Sylvesterらは根治的前立腺全摘術・三次元原体放射線治療 (3D-CRT)・シードによる組織内照射およびシードと外照射の組み合わせによる治療結果を，5年PSA無再発生存率のSeattle Risk Groupによるリスク別比較を行っている[2]。Low Risk群ではいずれの治療方法でも94%～81%の5年PSA無再発生存率であるが，High Risk群では65%～28%と差があり治療方法の選択が迫られる。

## 1．前立腺がんにおける放射線治療の線量ー効果関係

欧米においては，早期前立腺がんに対する根治的放射線治療と根治的前立腺全摘術は局所制御率において同等の成績であるされている[10-12]。Cleveland Clinic FoundationとMemorial Sloan Kettering at Mercy Medical Centerで1990年より98年に治療したT1-2症例の検討で[12]，72Gy以上の外照射による放射線治療と前立腺全摘でPSA無再発生存率に有意差のないことが示されている（7年PSA無再発生存率：前立腺全摘76%，72Gy未満の外照射48%，72Gy以上の外照射81%，永久挿入密封小線源治療75%，外照射と永久挿入密封小線源治療77%）。予後因子として治療前PSA ($p<0.001$)・Gleason Score ($p<0.001$) とともに，放射線治療における総線量が指摘されている。

*Advances in radiation therapy for prostate cancer* : Minako Sumi, Division of Radiation Oncology, National Cancer Center Hospital

表1　前立腺のリスク分類

| Risk Scoring | | | |
|---|---|---|---|
| | Seattle[2] | Mt. Sinai[3] | D'Amico[4] |
| Low | iPSA≦10<br>GS 2-6<br>StageT1a-T2b | iPSA≦10<br>GS 2-6<br>StageT1a-T2a | iPSA≦10<br>GS 2-6<br>StageT1c-T2a |
| Intermediate | iPSA>10 or<br>GS≧7 or<br>Stage≧T2c | iPSA=10.1-20 or<br>GS 7 or<br>StageT2b | iPSA=10.1-20<br>and/or<br>GS 7 and/or<br>StageT2b |
| High | 2 or 3<br>intermediate<br>risk factors | 2 or 3<br>intermediate risk<br>factors or<br>iPSA>20<br>GS 8-10 or<br>Stage≧T2c | iPSA>20 and/or<br>GS 8-10<br>StageT2c |

| 外照射によるRTOG第III相試験症例によるリスク分類[5] | | | | | | |
|---|---|---|---|---|---|---|
| Risk Group | T-Stage | Node Status | Gleason Score | Disease-Specific Survival 5-yr | 10-yr | 15-yr |
| 1 | T1-2 | Nx | 2-6 | 96% | 86% | 72% |
| 2 | T1-2 | Nx | 7 | 94% | 75% | 61% |
| | T3 | Nx | 2-6 | | | |
| | T1-3 | N+ | 2-6 | | | |
| 3 | T1-2 | Nx | 8-10 | 83% | 62% | 39% |
| | T3 | Nx | 7 | | | |
| | T1-3 | N+ | 7 | | | |
| 4 | T3 | Nx | 8-10 | 64% | 34% | 27% |
| | T1-3 | N+ | 8-10 | | | |

iPSA=initial prostate specific antigen
GS= Gleason score

表2　リスク分類と治療方法による5年PSA無再発生存率[2]

| Treatment | Seattle Risk Group | | |
|---|---|---|---|
| | Low | Intermediate | High |
| 3D-CRT; Zelefsky[6] (, 2001) | 90% | 70% | 47% |
| Seeds; Blasko[7] (Seattle, 2000) | 94% | 82% | 65% |
| Seeds+EBRT; Sylvester[8] (, 2002) | 85% | 77% | 45% |
| Radical Prostatectomy; D'Amico[4] (Univ. Pennsylvania, 2000) | 85% | 65% | 32% |
| Radical Prostatectomy; D'Amico[4] (B&W, 2000) | 83% | 50% | 28% |
| Radical Prostatectomy; Kupelian[9] (Cleveland, 1997) | 81% | 40% | — |

前立腺周囲には直腸や膀胱などリスク臓器が隣接しており，従来の放射線治療 (Conventional Radiotherapy) では腫瘍に対する高線量の投与は困難であった。そこで治療成績の向上と有害事象の軽減を目指し，さまざまな放射線治療技術が開発されてきた。本邦では高橋らにより開発された原体照射が以前より応用されており，さらに三次元原体放射線治療 (Three-dimensional conformal radiotherapy; 3D-CRT) が普及してきた。原体照射とは，森田らによれば“光子線ないし粒子線ビームを用いた二次元ないし三次元方向からの回転運動照射で，どの照射方向から見ても照射野形状がターゲット形状に一致している照射法”とされている[13]。最近ではCT-simulator，治療計画装置，照射野形状を作成するためのマルチリーフコリメーター (Multi-leaf Collimator; MLC) を搭載した治療装置とネットワークの構築によりさらに複雑な3D-CRTが可能となっている。

3D-CRTとは永田らによれば[14]，“薄い間隔で撮像された複数のCT画像に基づいて，正確なターゲット領域とリスク臓器の幾何学的配置を決定し，それらを画像処理した種々の三次元画像を用いたうえで，適切な三次元線量計算に基づく正確な放射線治療計画”とされる。従来の放射線治療が“照射方向と照射野辺縁の設定をしてからターゲット内の線量分布を確認する”のに対し，“ターゲットと関連正常臓器の輪郭を設定してから，計算された三次元画像を利用することによって，照射方向や照射門数を決定する”ように，治療計画は大きな変化を遂げた。さらに，強度変調放射線治療 (Intensity-Modulated Radiotherapy; IMRT) では“ターゲットの内部の詳細な照射線量と各種関連リスク臓器の詳細な容積線量を定義 (prescribe) した後に，治療計画装置によって最適な照射方法を決定する”こととなり，望ましい線量分布の実現が治療計画装置の進歩により可能となりつつある。治療計画の選択においては，従来治療計画を行って線量分布を計算し (forward planning),

表3　外照射による前立腺がんに対するDose Escalation Study

| Author | No. | Subset of Pt. | Dose | Local Control | p-value | Biochemical Control | p-value | Cause-specific Survival rate | p-value | Overall Survival rate | p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Kupelian[15] (Cleveland) | 1041 | All subsets | ≧72 Gy<br><72 Gy | 95%/8-yr<br>83%/8-yr | 0.026 | 87%/8-yr<br>51%/8-yr | <0.001 | | | | |
| Shipley[16] (Harvard) | 202 | T3-4, poorly diff. | 75.6 Gy<br>67.2 Gy | 84%/8-yr<br>19%/8-yr | 0.0014 | | | 67%/8-yr<br>62%/8-yr | NS | 55%/8-yr<br>51%/8-yr | NS |
| Valicenti[17] (RTOG) | 1465 | GS 8-10 | >66 Gy<br>≦66 Gy | 78%/5-yr<br>66%/5-yr | 0.076 | | | 46%/10-yr<br>31%/10-yr | <0.05 | 27%/10-yr<br>18%/10-yr | <0.05 |
| Zelefsky[18] (Memorial Sloan-Kettering C.C.) | 828 | T1-3 | 75.6 Gy<br>70.2 Gy<br><70.2 Gy | Favolable 75.6 Gy:83%/10-yr<br><70.2 Gy:57%/10-yr<br>Intermediate 75.6Gy:50%/10-yr<br><70.2 Gy:42%/10-yr<br>Unfavolable 75.6Gy:42%/10-yr<br><70.2 Gy:24%/10-yr | | | p=0.003<br>p=0.05<br>p=0.04 | | | | |
| Hanks[19] (Fox Chase C.C.) | 714 | GS 7-10 | ≧74Gy<br><74Gy | | | | | 100%/5-yr<br>89%/5-yr | 0.029 | 88%/5-yr<br>78%/5-yr | NS |
| | | T2c-T3 | ≧74Gy<br><74Gy | | | | | 95%/5-yr<br>87%/5-yr | NS | 88%/5-yr<br>73%/5-yr | 0.039 |
| Pollack[20] (M. D. Anderson C.C.) | 301 | T1-3 | 78 Gy<br>70 Gy | | | 70%/6-yr<br>64%/6-yr | p=0.03 | | | | |

その比較により最適治療計画を選択していたが，IMRTによって線量を設定したあとに治療計画を最適化するinversed planningが実現している。IMRTは総線量増加を目的とした臨床試験において，近年さかんに前立腺がんに応用されている。治療計画の比較には，線量分布図以外に容積線量ヒストグラム (Dose-Volume Histogram; DVH) が使用され，ターゲットや周囲の重要なリスク臓器の全容積中の照射線量が表示されている。TCP (tumor control probability) やNTCP (normal tissue complication probability) の計算も可能である。

前立腺がんにおいては総線量の増加により，局所制御率やPSA無再発生存率が向上することが示されている。表3に外照射によるDose escalation studyの結果を示す。Zelefskyらの Memorial Sloan-Kettering Cancer Centerにおける828症例の検討によると[18]，10年PSA無再発生存率はFavolable・Intermediate・Unfavolable riskの各々で70.2Gy未満に比較し75.6Gyで良好であった。Pollackらによる M. D. Anderson Cancer Centerの報告では[20]，T1-3症例に対する第Ⅲ相比較試験の結果，6年PSA無再発率は70Gy群で64%に対し78 Gy群で70%と有意差を認めていた (p=0.03)。特に治療前のPSAが＞10ng/mlの症例では6年PSA無再発率は70Gy群で43%に対し78Gy群では62%と良好であった (p=0.01)。6年後のGrade2以上の直腸の遅発性放射線反応は，70Gy群で12%に対し78Gy群で26%と78Gy群で有意に多く認められており注意が必要である (p= 0.001)。膀胱の遅発性放射線反応は，両群で10%であり差がなかった。現在RTOGでは3D-CRTによる72.93Gyと82.28Gyの第Ⅲ相比較試験 (RTOG P-0126) を施行中であり，結果が注目される。

## 2．粒子線治療

粒子線治療は腫瘍制御率の向上と周囲正常組織の有害反応軽減を目的として，前立腺がん治療に利用されてきた。陽子線や重粒子線は物理的特徴としてBragg peakを有し，線量のpeak-plateau ratioが高いために線量分布に優れる。この特徴を応用し周囲正常組織に対する影響を増加せずに前立腺の総線量の増加を図ることが可能となると考えられる。放射線医学総合研究所重粒子治療センターでは重粒子線の1つである炭素線を用いて，1995年より前立腺がんに対する臨床研究が開始されている。第I/II相試験の結果，その後の第II相試験では炭素線治療66GyEを行っている。

陽子線治療ではMassachusetts General Hospitalにおいて1970年代より前立腺がんに対する陽子線治療が開始された。Loma Linda大学では1991

年より局所進行前立腺がんに対して陽子線ブースト照射を用いた治療を行っている。X線照射45Gyと陽子線ブースト照射30GyEを行い5年生存率89%，5年生化学的無病生存率79%と良好な成績を報告している[21]。日本においては，筑波大学陽子線医学利用センターにおいて1985年より前立腺がんに対する陽子線治療が行われ，国立がんセンター東病院では2001年より病院設置型陽子線治療装置による前立腺がんの治療が開始されている。多施設共同臨床試験としては，アメリカでProton Radiation Oncology Group (PROG) が，早期前立腺がん (T1b-T2b, PSA ≦ 15) に対し70.2GyEと79.2GyEの第Ⅲ相比較試験を行っており，本邦でもT1b-T3bN0M0を対象とする多施設共同第Ⅱ相試験が計画されており，今後の成果が期待されている。

## 3．組織内照射

前立腺がんに対する組織内照射には$^{125}$Iや$^{103}$Pd等の核種を密封したシード線源による永久挿入密封小線源治療や低線量率$^{192}$Ir線源による一時装着法，高線量率$^{192}$Ir線源による高線量率組織内照射がある（表4）。永久挿入密封小線源治療は限局性の前立腺がんの中，特にLow Risk群で以前より欧米では広く応用されてきた。古くは1914年に$^{226}$Raを用いた報告があるが[31]，1980年代より経直腸的超音波ガイドによるアプローチにより発展を遂げリアルタイムに三次元的表示が可能となった。アメリカでは標準的治療の一環として1998年には23,000件が施行され，症例の増加により年間50,000件以上の実施が想定されている。表3に$^{125}$Iや$^{103}$Pdでの永久挿入密封小線源治療単独治療および外照射との併用による治療成績を示す。

日本では，厚生労働省の定める「診療用放射線照射器具を永久的に挿入された患者の退出について」平成15年3月3日医薬安第0313001号通知および「患者に永久的に挿入された診療用放射線照射器具（ヨウ素125シード，金198グレイン）の取扱いについて」平成15年7月15日医政指発第0715002号が出され，$^{125}$Iシード線源の供給が開始されたことにより永久挿入密封小線源治療は標準治療の選択肢の一つとして普及することが予想される。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では「シード線源による前立腺永久挿入密封小線源治療の安全管理に関するガイドライン」を作成し，安全性の確保と放射線治療の質の向上を目指している。$^{125}$Iシードは，軌道電子捕獲により崩壊し平均エネルギーは28.5keVと低く，半減期は59.4日であり周囲への正常組織への影響を低く抑えることが可能である。

American Brachytherapy Society (ABS) は1999年に発表した前立腺永久挿入密封小線源治療に関する勧告のなかで[32]，単独治療の場合は①T1-T2aで，②Gleason sum 2-6かつ，③PSA＜10ng/mlという選択基準を示している。また，外照射に加え追加治療として行うべき症例としては，①T2b, T2cまたは，②Gleason sum 8-10または，③PSA＞20ng/mlという選択基準を示している。会陰浸潤例や生検で陽性多数である場合，両葉で陽性であった症例およびMRI上被膜浸潤が陽性の症例では外照射のboostとしての前立腺永久挿入密封小線源治療の選択を勧めている。さらに，前立腺体積が60cc以上の症例ではホルモン療法による体積の減少後に検討されるべきである。臨床的除外基準としては，期待寿命5年未満の症例やTURPによる大きな，または治癒前の欠損のある症例，施術に関する危険の高い症例および遠隔転移症例を挙げている。また合併症のリスクの高い症例として，大きな中葉，骨盤既照射例，AUA Scoreの高い症例，骨盤内手術の回数が多い症例および重症糖尿病症例が指摘されている。また，TURPの既往，前立腺体積が60cc以上の症例，大きな中葉，精嚢が生検陽性の症例で技術的に十分な照射が困難であると述べている。1995年にAmerican

表4　前立腺永久挿入密封小線源治療症例のPSA

| | No. | Treatment | T Stage | Definition | Follow-up | PSA Outcome by Pretreatment PSA | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 0～4 | 4～10 | 10～20 | 20～ |
| Beyer (1997)[22] | 489 | I-125 | T1-2 | ≧4:0 | 5 yr | 93 % | 72 % | 42 % | 38 % |
| Blasko (2000)[7] | 230 | Pd-103 | T1-2 | 2 rises | 9 yr | 90 % | 87 % | 80 % | 67 % |
| Critz (1998)[23] | 689 | I-125+EBRT | T1-2 | ≧0.5 | 5 yr | 94 % | 93 % | 74 % | 69 % |
| Dattoli (2003)[24] | 102 | Pd-103+EBRT | T2a-T3 | ≧1.0 | 4 yr | 82 % | | 85 % | 75 % |
| Grado (1998)[25] | 490 | I-125/ Pd-103±EBRT | T1-3 | 2 rises | 5 yr | 88 % | | 72 % | 57 % |
| Grimm (2001)[26] | 125 | I-125 | T1-2b | 2 rises | 10 yr | 97 % | 78 % | 86 % | 55 % |
| Ragde (2000)[27] | 147 | I-125/ Pd-103 | T1-3 | 3 rises | 12 yr | | | 66 % | |
| | 82 | I-125/ Pd-103+EBRT | | 3 rises | 12 yr | | | 79 % | |
| Stock (1997)[28] | 258 | I-125/ Pd-103 | T1-2 | 2 rises | 4 yr | 75 % | | 74 % | 34 % |
| Sharkey (2000)[29] | 65 | Pd-103 | | ≧1.5 | 4 yr | 90 % | 75 % | 57 % | — |
| Zelefsky (2000)[30] | 248 | I-125 | T1c-2b | 3 rises | 5 yr | 96 % | 84 % | 62 % | |

Association of Physics and Medicine (AAPM) の Task Group No. 43 (TG-43) により線量計算アルゴリズムの変更が勧告されており[33]，$^{125}$Iシードによる前立腺永久挿入密封小線源治療に関するABSによる処方線量のガイドラインも単独治療で160Gyより144Gyへ変更された。40-50Gyの外照射を併用する場合は110～120Gyより100～110Gyへ変更されている。挿入後の線量評価の実施も勧告されているが最適な時期は明らかでなく，挿入後4週間頃のCT実施が報告されている。記載すべき線量としては①処方線量，②前立腺体積を100%含む線量である$D_{100}$，③前立腺体積を90%含む線量である$D_{90}$，④処方線量を照射される前立腺体積の比率$V_{100}$が勧告されている。

高線量率$^{192}$Ir線源による高線量率組織内照射は，本邦では永久挿入密封小線源が使用できなかった為，前立腺がんに応用されてきた。従来の報告の多数は欧米での放射線物理学的・生物学的利点を利用した検討であり，ほとんどが外照射との併用である。

## 4．前立腺全摘術後のPSA再発

根治的前立腺全摘術後25-35%に再発を生じるとされ[34-35]，局所再発例には放射線治療，遠隔転移例には内分泌療法が施行されている。再発形式のひとつとして，術後の経過観察中に局所再発が画像上は明らかでないもののPSAの上昇を認めるPSA再発がある。表5に根治的前立腺全摘術後のPSA再発に対する放射線治療成績を示す。PSA倍加時間が短いほど，早期に臨床的再発が生じることが指摘されており[46]，局所再発か遠隔転移かを予測する因子としては，術後PSA再発までの期間が2年以内，PSA倍加時間が6ヵ月未満，Gleason scoreが8以上のものが遠隔転移と相関する因子とする報告がある[47]。根治的前立腺全摘術後のPSA再発に対する標準的治療法は確立されていないが，1997年ASTRO (American Society for Therapeutic Radiology and Oncology) Consensus Panelにおいて根治的前立腺摘出後PSA上昇に対する放射線治療の解析がおこなわれ，1999年にConsensus Panel Statementとして報告された[48]。Massachusetts General Hospital (Zietman)・Washington University (Hudson)・Mayo Clinic (Schild)・Wayne State University (Forman) のデータの解析より総線量64Gy以上で通常分割照射（1回線量1.8～2.0Gy）が推奨された。治療のタイミングについては，Parkerらの分析より早期の放射線治療の有効性が示されつつある[49]。

## おわりに

前立腺がんの放射線治療の選択肢は，外照射や永久挿入密封小線源治療および粒子線治療な

表5　根治的前立腺全摘術後のPSA failureに対する放射線治療

| Author | No. | Median pre-RT PSA | Gleason score 8-10 | Seminal Vesicle+ or LN+ | Dose Median | Follow-up Median | Biochemical Control |
|---|---|---|---|---|---|---|---|
| Leventis[45] | 49 | 2.1 | 7% | 27% | 66Gy | 29 mos | 24%/5-yr |
| Catton[46] | 43 | | 15% | 35% | 60Gy | 43 mos | 20%/5-yr |
| Pisansky[47] | 166 | 0.9 | 16% | 31% | 64Gy | 52 mos | 46%/ 5-yr |
| Anscher[48] | 89 | 1.4 | 26% | 34% | 66Gy | 48 mos | 50%/ 4-yr |
| Nudell[49] | 69 | 0.1-29.3 | 22% | 10% | 60-74Gy | 37 mos | 47%/4-yr |
| Cadeddu[50] | 82 | 2.8(mean) | 15% | 15% | 64Gy (mean) | 8.3 years (mean) | 10%/ 5-yr |
| Garg[51] | 78 | 1.2 | 35% | 38% | 66Gy | 25 mos | 57/78 |
| Do[52] | 60 | | 17% | 37% | 64.8Gy | 36 mos (mean) | 30/60 |
| Morris[53] | 48 | 1.7 | 34% | 25% | 60-64Gy | 32 mos (mean) | 47%/3-yr |
| Crane[54] | 41 | 2.7 | 35% | 29% | 60Gy | 55 mos | 8/41 |

ど多岐にわたり，その最適な選択については今後の検討課題となっている。外照射は3D-CRTやIMRTの応用により，永久挿入密封小線源治療および粒子線治療はその物理学および生物学的特性により，正常組織の線量軽減による有害事象の制御と総線量の増加による治療効果の向上を目指している。治療の選択にあたっては，臨床病期や治療前PSA，Gleason Scoreおよび前立腺の容積や形態，合併症の有無などの総合的な検討が必要である。

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