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.

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Conflict of interest statement

None declared.

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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 79 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 $\geq 38^\circ$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	Pneumonitis (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	Pneumonitis (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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Ewing Sarcoma/Primitive Neuroectodermal Tumor of the Kidney in a Child

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A 6-year-old female was admitted with abdominal pain and a mass in the right abdomen. Her lactose dehydrogenase level was 1,200 IU/L, and neuron specific enolase was 120 ng/ml. Computed tomography scan confirmed a large right renal mass with necrosis. A right radical nephrectomy was performed. The tumor was completely encapsulated. Based on small round cell histology, strong MIC-2 (CD99) positive tumor cells, and EWS-FLI-1 fusion transcript, Ewing sarcoma/primitive neuroectodermal tumor of the kidney was diagnosed. Induction and follow-up with seven cycles of chemotherapy were given after surgery. She has had no evidence of recurrence 90 months from diagnosis. Pediatr Blood Cancer 2008;50:180–183. © 2006 Wiley-Liss, Inc.

Key words: electron microscopy; Ewing sarcoma/primitive neuroectodermal tumor; EWS-FLI-1; immunohistochemistry; kidney

INTRODUCTION

Ewing sarcoma/primitive neuroectodermal tumor (ES/PNET) of the kidney is a rare and highly malignant neoplasm. It affects young adults, and only a few pediatric cases (younger than 15 years) have been reported [1–9]. ES/PNET arising in the kidney act aggressively and show poor response to therapy [1]. ES/PNET of the kidney needs to be differentiated from other small round cell tumors of the kidney, because each type of tumor is treated differently. The diagnosis of this neoplasm is currently based on a combination of light microscopy, immunohistochemistry, electron microscopy, chromosomal analyses, and specific chimeric transcripts. Our patient, who was diagnosed by histochemistry and molecular biology analysis of the resected kidney and treated with chemotherapy, has remained alive more than 90 months after diagnosis.

CASE

A 6-year-old female was admitted to our hospital with abdominal pain and an abdominal mass. On physical examination, a large and firm mass was evident in the right abdomen. Laboratory evaluation showed a lactate dehydrogenase level of 1,200 IU/L (normal 218–411 IU/L), a neuron specific enolase level of 120 ng/ml (normal <10 ng/ml), and ferritin level of 160 ng/ml (normal 15–89 ng/ml). Urine catecholamine levels were within normal limits. Abdominal computed tomography (CT) scan confirmed a large right renal mass with areas of necrosis and bleeding. There was no obvious lymphadenopathy and no intra-abdominal metastasis. Bone scintigraphy and CT scan of the thorax did not detect metastasis.

A right radical nephrectomy was performed. The tumor involved a large portion of the lower part of the kidney. The tumor was completely encapsulated and was 5.0 × 4.5 × 4.5 cm. Lymph nodes were negative for malignancy. Histologic examination revealed a small round cell tumor with massive necrosis, but no rosette formations. Periodic acid-Schiff (PAS) staining revealed diastase sensitive material in the tumor cell cytoplasm. Immunohistochemistry revealed that tumor cells were strongly positive for MIC-2 (CD99) as well as vimentin. The tumor cells were negative for chromogranin A, neurofilament, and synaptophysin. Electron microscopic examination showed a high nuclear-cytoplasm ratio and aggregated glycogen granules in the cytoplasm (Fig. 1A). A higher magnification of tumor cells showed neurosecretory-type granules, microtubules, and desmosome-like structures (Fig. 1B). The expression of EWS-FLI-1 fusion transcript was demonstrated by molecular biology (Fig. 2). A single 330 base pair cDNA product was detected by ethidium bromide staining, corresponding to the EWS-FLI-1 as previously reported by Sorensen et al. [10]. Direct DNA sequencing confirmed the presence of a fusion of EWS exon 7 to the FLI-1 exon 6. Unfortunately chromosomal findings failed because proliferation of the tumor cells was poor. According to results on small round cell histology and immunohistochemical profiles, electron microscopic findings, and EWS-FLI-1 fusion transcript, the tumor was diagnosed as an ES/PNET of the kidney. Therapy was initiated with 1.5 gm/m^2 vincristine on days 1, 8, 15, 22, 29, and 36; 500 mg/m^2 cyclophosphamide on days 2, 9, 30, and 37; and 0.45 mg/m^2 dactinomycin on days 16–20 for induction and then a total of seven cycles of 4-drug chemotherapy, consisting of 1.5 gm/m^2 vincristine on days 1, 15, 22, 29, 36, and 43; 0.45 mg/m^2 dactinomycin on days 1–5; 500 mg/m^2 cyclophosphamide on days 16, 23, 30, 37, and 44; and 60 mg/m^2 doxorubicin on day 44 after surgery. She had no serious adverse effects during chemotherapy. She had no evidence of recurrence after 90 months from diagnosis and no late effects have been noted.

DISCUSSION

Though the existence of renal PNET was reported in 1975 in a review of pediatric PNETs [11], only a small number of cases have been reported. Recently, Parham et al. [12] from National Wilms Tumor Study Group Pathology Center reported that 79 of 146 cases of primary malignant neuroepithelial tumors of the kidney in adults and children were considered to be ES/PNET. Follow-up information, however, was only provided for 14 of 146 cases, and it is unclear which, if any, of those were actually ES/PNET [8]. Pediatric cases (younger than 15 years old) of ES/PNET of the kidney are extremely rare, and only ten cases have been reported previously [1–9]. Clinical characteristics, pathologic features, treatments, and outcomes of those cases are summarized in Table I.

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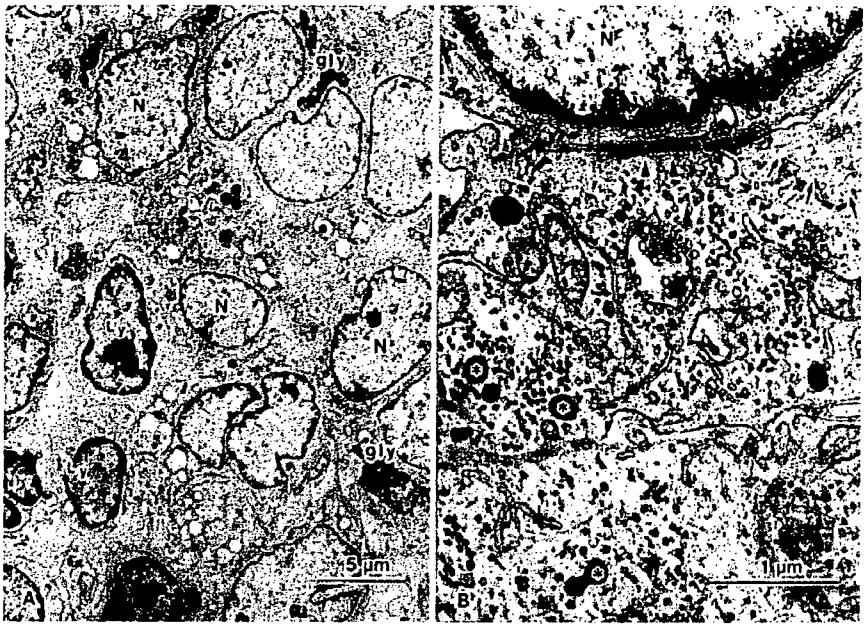

Fig. 1. Ultrastructural findings in the tumor cells. **A**: Tumor cells are oval and small (about 8–10 μm in a diameter). Nuclear-cytoplasm ratio is high. Nucleus has a few heterochromatin. Aggregated glycogen granules (gly) are observed in the cytoplasm. Ly, lymphocytes; N, nuclei. **B**: Neurosecretory granules (asterisks), microtubules (arrows), and desmosome-like structures (arrowheads) are observed in the tumor cells under higher magnification.

Several approaches can be used to arrive at a diagnosis of ES/PNET. The first approach is light microscopic examination of tumor tissue including immunohistochemistry. These tumors consist of primitive-appearing round cells with high nucleus to cytoplasmic ratios. The immunohistochemical features of ES/PNET are positive for CD99 (MIC2); however, expression of CD99 is by no means specific for ES/PNET among round cell tumors [13]. Although FLI-1 is a variable histochemical marker for ES/PNET, it is also positive in lymphoblastic lymphoma [14]. In contrast, WT-1 is a positive marker of Wilms tumor and desmoplastic round cell tumors, whereas it is a negative marker for ES/PNET, neuroblastoma and rhabdomyosarcoma. The second approach is electron microscopic examination of tumor tissue. Electron microscopic features include a specific high nuclear-cytoplasm ratio and aggregated glycogen granules in the cytoplasm. Neural differentiation appears on some cells with polar processes, which may contain microtubules or neurosecretory glands [15]. The third approach is chromosomal translocation, such as t(11;22) (q24;q12) which is positive in 88–95% of ES/PNET cases [16]. The final approach involves a molecular biologic examination. In 90–95% of cases of ES/PNET, the chimeric transcript is EWS-FLI-1; the remaining 5–10% are EWS-ERG. Other transcripts, including EWS-ETV1 and EWS-EIAF, have also been reported [16].

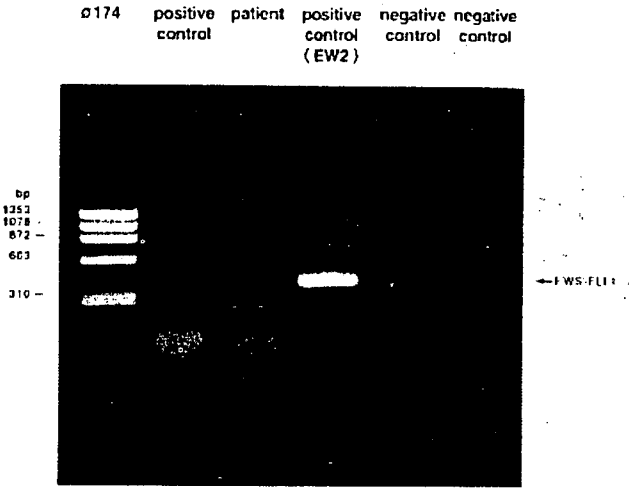

Fig. 2. A single 330 base pair transcript is detected in the patient sample following reserve transcriptase polymerase chain reactor (RT-PCR) performed on RNA extract from tumor tissue.

In terms of prognosis, the 5-year disease-free survival rate of ES/PNET is 45–55% [17], but the prognosis of ES/PNET of the kidney appears worse [1,18]. In pediatric cases (Table I), 5 of 8 patients were alive when the cases were reported; however, 1 patient (no. 6) was alive with disease, 2 patients (no. 3 and no. 5) were followed-up only for 6 and 8 months, and 1 patient was under treatment (no. 9). The follow-up duration was not described in this case. Only 2 patients (no. 8 and our case) were alive after 5 years. For 2 patients, it was not defined whether they were alive or not (Table I). Jimenez et al. [8] described that 3 of 11 patients were alive for 4–64 months, and 5 patients had local recurrence or distance metastasis then died of their disease, and 3 patients were lost to follow-up. Most of the recent therapeutic protocol for children with ES/PNET consists of vincristine, doxorubicin, cyclophsphamide, ifosphamide, and etoposide. Radiation and surgery have been used; some patients have been treated with myeloablative chemoradiotherapy followed by autologous bone marrow rescue. In spite of a lack of radiation therapy and our not using ifosphamide and etoposide for chemotherapy, our patient has survived for a relatively long period with no recurrence. Possible reasons for this good outcome might include the pathologic features of the tumor, the well-encapsulated nature of

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TABLE I. Clinical and Pathological Features of ES/PNET of the Kidney in Pediatric Cases

Case	Ref.	Age	Gender (yr)	Symptoms	Metastasis	Pathology (immunohistochemistries)	Chimeric transcript	Therapy	Outcome (follow-up [Mo])
1	1	4	F	Abdominal pain, fever	RPLN, liver	CD99(+),NSE(+),S-100(+), Ker(+),Act(−),Vim(−),Chro(−)	NS	IFO, CBP, VP-16 radiation	Died (1)
2	1	14	M	Bone pain, weight loss	Lung, bone, bone marrow	CD99(+),NSE(+),Vim(+),Synapto(+) (±)S-100(−),Ker(−),Act(−),Chro(−)	EWS/FLI-1(−) EWS/ERG(−)	CY, VCR, DOX,IFO,VP-16 auto BMT	Alive (under treatment)
3	2	13	NS	Abdominal pain, hematuria	No	MIC2(+),NSE(+),ker(−),Des(−), Act(−)	EWS/FLI-1(+)	Nephrectomy chemotherapy	NS
4	3	10	M	Abdominal mass	No	MIC2(+),NSE(+),Leu7(+), S-100(−),Ker(−), Des(−),Vim(−),Chro(−)	EWS/FLI-1(+)	Nephrectomy chemotherapy	Alive (6)
5	4	5	F	NS	IVC, right heart	NS	NS		NS
6	5	15	F	Abdominal pain, abdominal distention	No	MIC2(+),Vim(+),NSE(−), S-100(−)	NS	Nephrectomy CY, VCR, DOX,IFO,VP-16	Alive (8)
7	6	9	M	Abdominal pain, abdominal mass, weight loss	No	MIC2(+),NSE(−),Vim(−),Ker(−), LCA(−)	NS	Nephrectomy CY, VCR, DOX,IFO,VP-16	Alive (relapse+) (10)
8	7	9	F	Abdominal distention, abdominal mass	No	CD99(+),LCA(−),Ker(−),Act(−), NFM(−)	EWS/FLI-1(+)	Nephrectomy IFO,VP-16,CY,DOX,VCR auto BMT	Died (5)
9	8	11	M	Gross hematuria, abdominal mass	No	CD99(+)	NS	Nephrectomy VCR, DOX, VP-16, CY, DAC	Alive (64)
10	9	14	F	Abdominal pain, abdominal mass	IVC, right heart, liver	NS	NS	Chemotherapy	Died (24)
11	Present case	6	F	Abdominal pain, abdominal mass	No	MIC2(+),Vim(+)NFM(−),Chrom(−)	EWS/FLI-1(+)	Nephrectomy VCR, DAC, CY, DOX,	Alive (90)

RPLN, retroperitoneal lymphonode; IVS, inferior vena cava; NSE, neuron specific enolase; Ker, keratin; Act, actin; Vim, Vimentin; Chro, chromogrn A; MIC2, B microgloblin; Des, desmin; NFM, neurofibrofilament; Synapto, sinaptophilin; IFO, ifomide; CBD, carboplatinum; CY, cyclophosphamide; VCR, vincristine; DOX, doxrubicine; DAC, actinomycin D; BMT, bone marrow transplantation.

the tumor with no involvement beyond the capsule and the accurate diagnosis followed by prompt treatment with chemotherapy. Several approaches including cytogenetical methods are important for early, accurate diagnosis of ES/PNET.

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Cerebellar Medullomyoblastoma With Melanotic Tubular Structures

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This report describes a midline cerebellar primitive neuroectodermal tumor with muscular differentiation, that is, medullomyoblastoma with melanotic tubular structures, which developed in the cerebellar vermis in a 23-month-old male. Rhabdomyoblastic differentiation consisted both of striated muscle fibers and undifferentiated cells showing immunoreactivity for desmin and myogenic transcription factors. The presence of melanotic epithelial structures raised the issue of a teratomatous tumor. This case demonstrates the occurrence of this very rare tumor in early childhood as well as the utility of a careful search for the presence of myogenic and/or melanotic features in medulloblastomas. Pediatr Blood Cancer 2008;50:183–185. © 2006 Wiley-Liss, Inc.

Key words: brain tumors; medullomyoblastoma; pigmented medulloblastoma

INTRODUCTION

Medullomyoblastoma (MMB) is a rare variant of medulloblastoma (MB) characterized by both a primitive neuroectodermal and a striated muscle component [1], in which an additional constituent of pigmented melanocytic cells might be present [2–4]. A midline cerebellar primitive neuroectodermal tumor with muscular differentiation and melanotic tubular structures is described.

CASE

In January 2004, a 23-month-old male was hospitalized with a 4-week history of headache. General physical and neurological

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Case Report

Diffuse-type giant cell tumor/pigmented villonodular synovitis arising in the sacrum: Malignant form

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Diffuse-type giant cell tumor (GCT)/pigmented villonodular synovitis (PVNS) in the axial skeleton or spine is rare. Herein is reported a case of diffuse-type GCT/PVNS involving the sacrum and the fifth lumbar vertebra, in which the patient developed regional lymph node swelling after recurrence. The recurrent tumor was found to have atypical histological features such as spindle cell morphology, cytological atypia and high mitotic rate, which are compatible with the diagnostic criteria of secondary malignant diffuse-type GCT/PVNS. Although the nodal lesions were not sampled histologically, the clinical and histological features indicate that the current case is an example of malignant diffuse-type GCT/PVNS. This case is considered to be the first case of malignant diffuse-type GCT/PVNS in the spine, because no such lesions have been previously reported in the axial skeleton or spine. Careful surveillance should be required for diffuse-type GCT/PVNS arising at unusual site.

Key words: malignant diffuse-type giant cell tumor, metastasis, pigmented villonodular synovitis, sacrum, spine

Diffuse-type giant cell tumor (GCT), which is a synonym of pigmented villonodular synovitis (PVNS), usually arises from the joint spaces in large joints, such as knee and hip.[1] Histologically, the lesion is villous and infiltrative. Characteristically, it has a pseudoglandular or pseudoalveolar pattern.[1,2] The tumor is mainly composed of small or large histiocytic cells and giant cells. Local recurrence is common, and it often disturbs the function of the joint.

Diffuse-type GCT/PVNS rarely affects the spinal vertebra, wherein it arises from the articular facet joint.[3] Half of the lesions have been reported to occur in the cervical spine. Radiographically, it is a destructive and osteolytic lesion involving the posterior facet joint, accompanied by a soft-tissue component. The recurrence rate has been reported to be 18%.[3] Its lumbo-sacral involvement is relatively rare. Herein we report a case of PVNS that mainly involved the sacrum with a large osteolytic lesion, where the patient developed regional lymph node swelling after recurrence. The histological features of the recurrent tumor were convincing evidence of secondary malignant form of diffuse-type GCT/PVNS. To the best of our knowledge there have been no previous reports of malignant diffuse-type GCT/PVNS involving the spine and axial skeleton.

CLINICAL SUMMARY

A 53-year-old woman complained of a 5 month history of numbness and pain from the left buttock to the lower leg. Muscle weakness of the lower extremities was not apparent. Laboratory data showed no remarkable changes. Plain radiography showed an irregular osteolytic lesion with cortical destruction in the left side of the sacrum. CT revealed an osteolytic lesion in the lateral vertebra and facet of S1, associated with a posterior soft-tissue mass, which measured 5 × 4 cm (Fig. 1a). Magnetic resonance imaging (MRI) demonstrated a mass on T1-weighted imaging (WI) of low intensity (Fig. 1b) and on T2-WI of intermediate intensity. The mass involved the S1 and L5 vertebral body, and was extending toward the posterior elements of the vertebra and posterior soft tissue. The tumor also involved the facet joint between S1 and L5. Bone scintigraphy showed no abnormal uptake, except for the lumbo-sacral area. After open biopsy,

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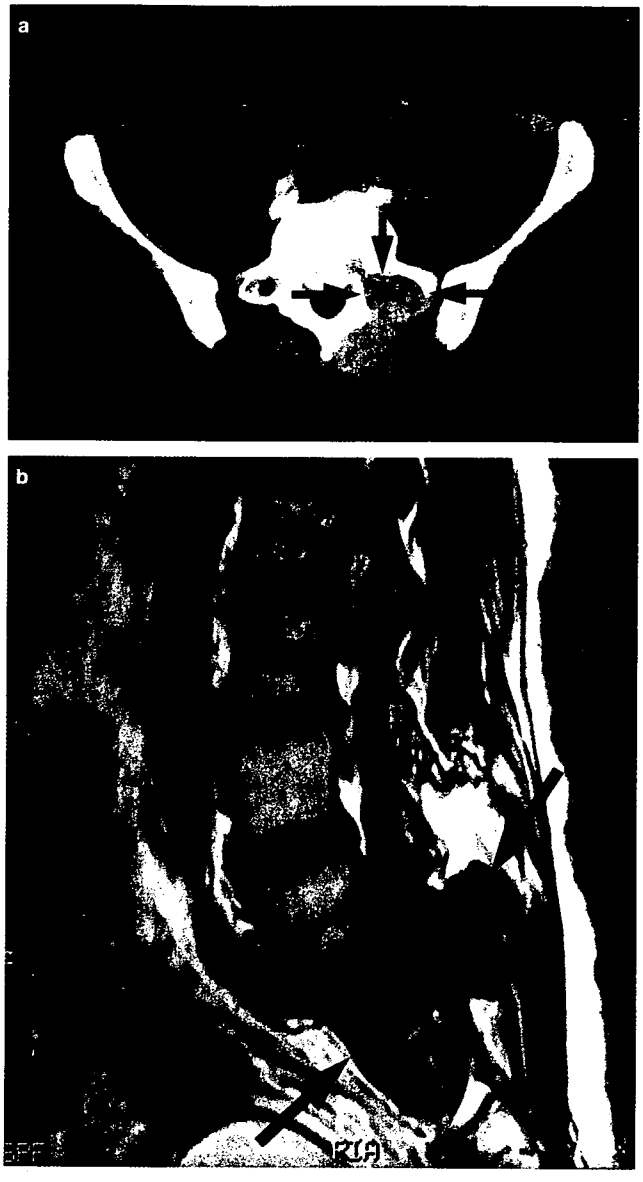

Figure 1 (**a**) CT of an osteolytic lesion in the lamina and facet joint with a posterior soft-tissue mass (arrows). (**b**) Magnetic resonance T1-weighted image of a mass lesion in the vertebral body and posterior elements of S1 and L5 (arrows).

tumor resection and curettage followed by auto-bone graft were performed. Ten months after the surgery, local recurrence was detected on MRI and en bloc resection was performed for the recurrent tumor. Follow-up MRI demonstrated a second recurrence and swelling in the left inguinal (Fig. 2a) and para-aortic (Fig. 2b) lymph nodes, 7 months after the second surgery. However, these nodal lesions were not sampled histologically. The patient underwent chemotherapy (high-dose ifosphamide, cyclophosphamide, adriamycin, vincristine) for both the recurrence and the possibility of the nodal metastatic lesions.

PATHOLOGICAL FINDINGS

Grossly, the fragmentally resected initial surgical specimen was a brownish color with focal whitish or yellowish areas. Microscopically, biopsy and resected specimens indicated essentially the same findings. Although a typical villous pattern was not evident, a pseudoglandular pattern was seen on low-power view (Fig. 3a). The tumor was mainly composed of histiocytic cells with eosinophilic cytoplasm, accompanied by hemosiderin deposits in their cytoplasm (Fig. 3b). Osteoclast-like multinucleated giant cells were scattered throughout the lesion (Fig. 3c). Aggregates of xanthoma cells (Fig. 3d) and chronic inflammatory infiltrate were also prominent throughout the tumor. Mitotic figures were occasionally seen (0–1/10 high-power fields (HPF)), but abnormal ones were never detected. The recurrent tumor had a nodular and infiltrative growth pattern (Fig. 4a). The tumor was mainly composed of a cellular proliferation of rounded or oval cells with deeply eosinophilic cytoplasm and mild nuclear pleomorphism (Fig. 4b), accompanied by scattered osteoclast-like multinucleated giant cells. Focally, short spindle-shaped cells were arranged in fascicles (Fig. 4c). Mitotic figures were frequently seen (38/10 HPF). No tumor necrosis was detected in any part of the tumor. Immunohistochemically, mononuclear cells and osteoclast-like multinucleated giant cells of the primary tumor were positive for CD68 (KP-1; 1:300; Dako Cytomation, Glostrup, Denmark). Mononuclear histiocytic cells had no immunoreactivity for desmin (D33; 1:100; Dako Cytomation) or S-100 protein (polyclonal; 1:400; Dako Cytomation). A total of 5.6% of the mononuclear cells of the primary tumor were positive for Ki-67 (MIB-1; 1:100; Dako Cytomation). Only small numbers of mononuclear cells in the recurrent tumor were positive for CD68, while multinucleated giant cells were constantly positive for CD68. A total of 21.25% of the mononuclear cells were positive for Ki-67 in the recurrent tumor (Fig. 4d). No tumor cells in the primary or recurrent tumor were immunoreactive for p53 (PAb 1801; 1:100; Oncogene Research Products, San Diego, CA).

DISCUSSION

The occurrence of diffuse-type GCT/PVNS in the spine is rare. The vast majority of the cases affect the cervical and lumbar regions (41%).[3] The current case occurred mainly in the sacrum, but also involved the fifth lumbar vertebra. According to Giannini *et al.* only three cases involved the L5–S1 region.[3–5] Previously reported cases of spinal diffuse-type GCT/PVNS frequently involved the facet joint, therefore spinal diffuse-type GCT/PVNS is considered to originate from the synovial membranes that line the diarthrodial joints of the vertebral arches. The left facet joint between L5 and S1 was also affected in the present case. The symptoms and signs of

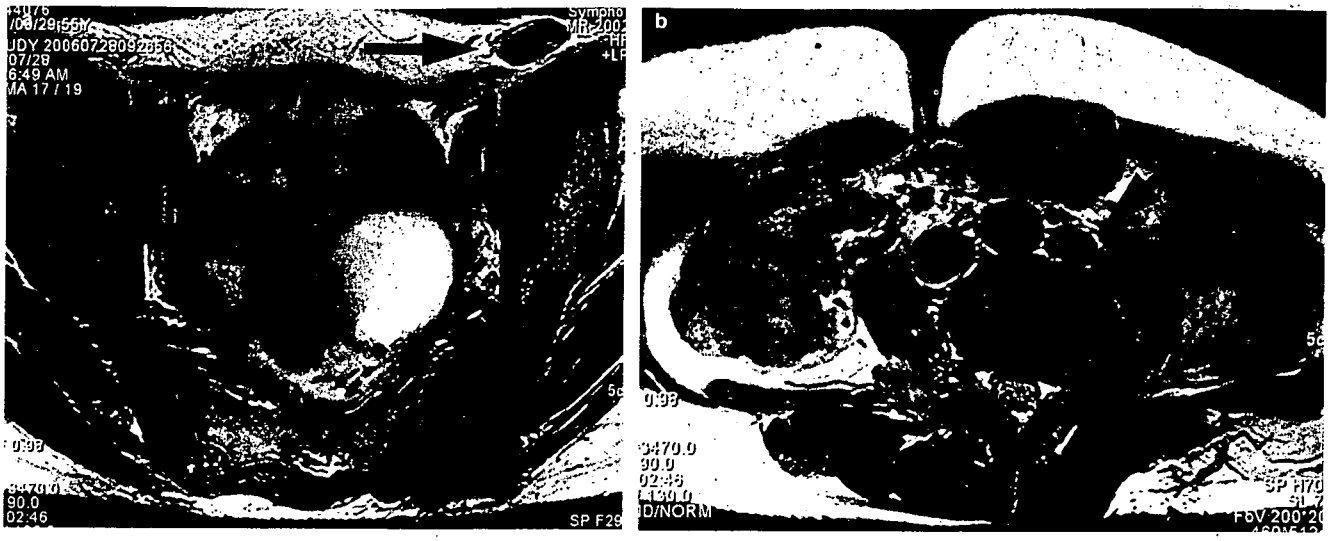

Figure 2 Magnetic resonance imaging of multi-nodular swelling of the (**a**) left inguinal (arrow) and (**b**) para-aortic (arrow) lymph nodes, indicating lymph node metastases.

spinal diffuse-type GCT/PVNS were similar to those of other spinal epidural tumoral masses, according to their location. The present case mainly presented sciatica. Concerning the clinical outcome, Giannini *et al.* reported that although the local recurrence rate was relatively high, repeated surgical excision appeared to be curative.[3]

Anatomically, the present case had an osteolytic lesion without mineralization mainly in the sacrum. Therefore, considering the histological features, the differential diagnosis of the current primary lesion are giant cell-containing osteolytic lesions, including GCT, aneurysmal bone cyst (ABC), chondroblastoma, chondromyxoid fibroma, giant cell reparative granuloma, brown tumor and osteoclast-rich osteosarcoma. The sacrum is the most common primary site in the axial skeleton of GCT. GCT frequently contains aggregates of foamy cells as seen in diffuse-type GCT/PVNS. However, GCT usually involves the vertebral body and its multicentric occurrence is very rare.

Malignant diffuse-type GCT/PVNS or malignant giant cell tumor of tendon sheath (GCTTS) is an extremely rare condition[6–11] and its definition is given as a benign GCTTS or diffuse-type GCT/PVNS, which coexists with frankly malignant areas, or given as the original lesion is typically benign GCTTS or diffuse-type GCT/PVNS with a recurrent lesion that appears to be malignant.[2,9] According to Bertoni *et al.* 75% of cases occur in the knee joint.[9] Half the patients with malignant diffuse-type GCT/PVNS develop distant metastasis and die of the disease, thus making it a very aggressive malignant tumor. Based on pathological features and clinical presentation, there is a possibility that the present case is an example of the latter condition because of the regional lymph node swelling and malignant histology in the recurrent lesion. Most cases of malignant diffuse-type GCT/PVNS have been reported to occur in large joints in the extremities such as the knee, ankle or foot.[9] The present case affected mainly the sacrum and the fifth lumbar vertebrae. There have been no case reports of malignant diffuse-type GCT/PVNS arising in the axial skeleton or spine.

Bertoni *et al.* documented eight cases of malignant diffuse-type GCT/PVNS and stated that the important histological features of malignancy were (i) a nodular or solid infiltrative pattern; (ii) large, plump, round or oval cells with deep eosinophilic cytoplasm and indistinct borders; (iii) large nuclei with prominent nucleoli; and (iv) necrotic areas.[9] Although the present recurrent tumor had no necrotic areas, a nodular and infiltrative growth pattern, and cellular proliferation of rounded or oval cells were both evident. In addition, mitotic figures were frequently seen (maximum: 38/10 HPF) and cellular fascicles of spindle-shaped cells were noted in part. Somerhausen and Fletcher reviewed 50 cases of extra-articular diffuse-type GCT/PVNS and found seven cases of malignant/atypical histological features and/or malignant behavior.[10] Among them, two patients developed distant metastases. One patient had spindle cell morphology with high mitotic activity (up to 25/10 HPF) at the primary site, whereas the other patient had the usual benign morphology, even at the metastatic site. Somerhausen and Fletcher stated that atypical features such as increased mitotic activity, necrosis, spindle morphology and cytological atypia are not indicative of malignancy when present individually. The highest mitotic count was 26/10 HPF in their series. In the present case, there was an invasion into the medullary cavity of the sacrum in the primary tumor. Moreover, the present case also had combined histological atypical features com-

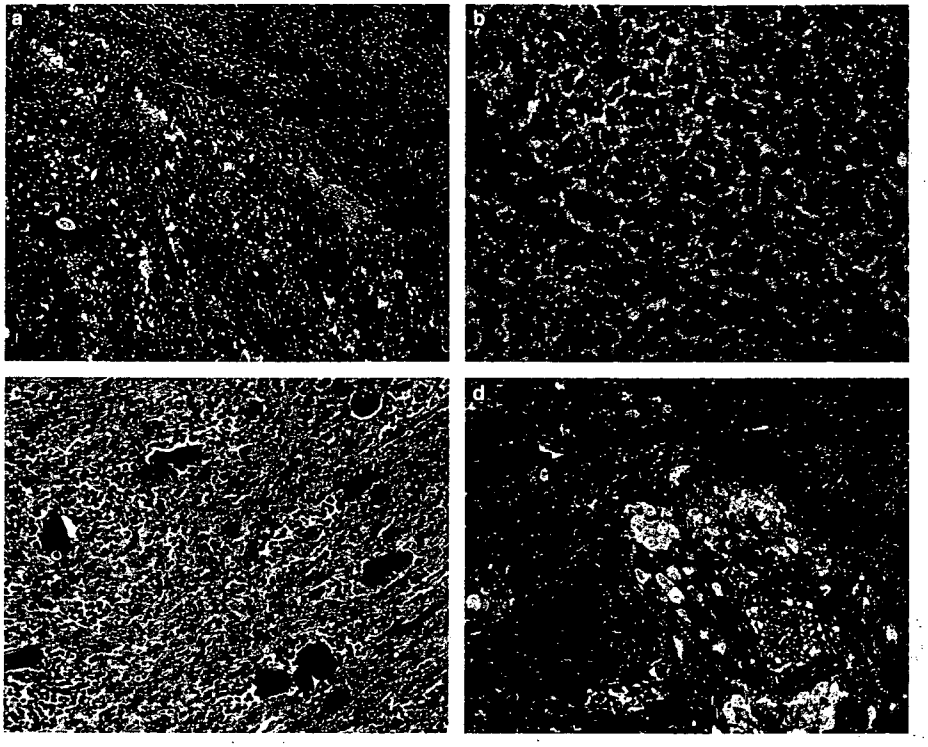

Figure 3 (**a**) Pseudoglandular pattern of the primary benign diffuse-type giant cell tumor/pigmented villonodular synovitis on low-power view. (**b**) Rounded or polygonal mononuclear cells with eosinophilic cytoplasm and intracytoplasmic hemosiderin. (**c**) Scattered osteoclast-like multinucleated giant cells. (**d**) Aggregates of xanthoma cells intermixed with rounded cells.

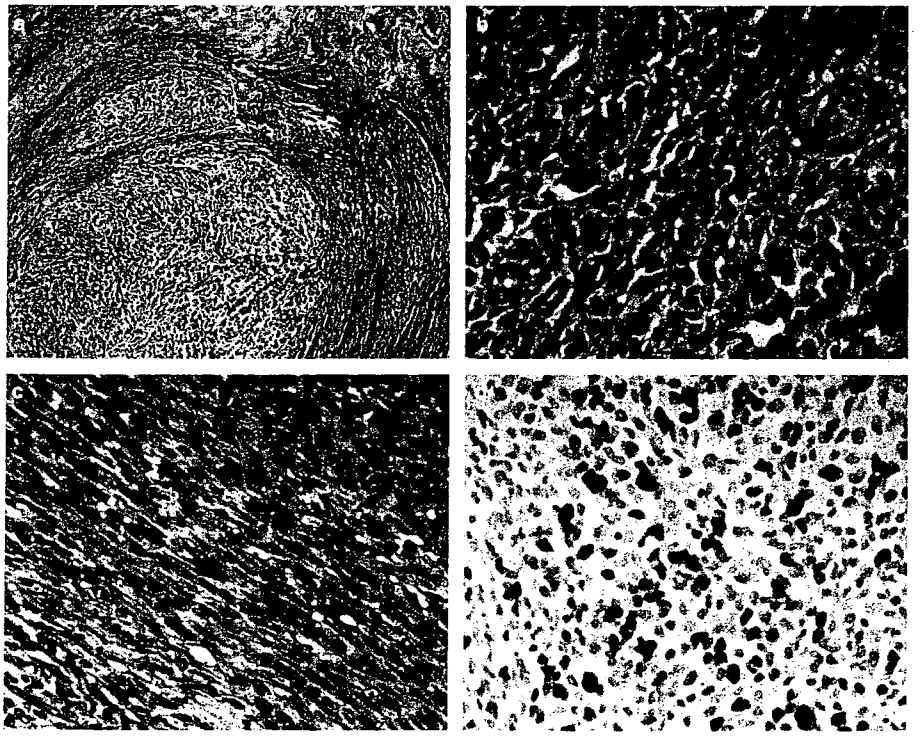

Figure 4 (**a**) Nodular or infiltrative growth pattern of the recurrent tumor in the fibro-collagenous tissue. (**b**) Rounded mononuclear cells with deeply eosinophilic cytoplasm showing mild nuclear pleomorphism. (**c**) Cellular proliferation of ovoid or short spindle-shaped cells in a fascicular arrangement. Note the frequent mitotic figures in these cells. (**d**) High proliferating activities as shown by frequent Ki-67-positive cells (21%).

prising spindle cell morphology, cytological atypia and a very high mitotic rate in the recurrent tumor. Therefore, the clinical and histological features of the current case confirm that this is an example of malignant diffuse-type GCT/PNVS.

In conclusion, we describe a case of PVNS arising in the sacrum, with malignant histology after local recurrence. It was difficult to predict its aggressive biological behavior when reviewing the histological findings of the primary

tumor, therefore careful surveillance is required for histologically typical diffuse-type GCT/PVNS arising at an unusual site.

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症例報告

ホジキンリンパ腫の治療後に発症した二次がんの2例

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Two Cases of Hodgkin's Lymphoma Developed Second Malignancy after Completion of the Treatment

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Abstract Case 1 is a 34-year-old woman who developed Hodgkin's lymphoma (HL) of stage III at 16 years of age and received chemoradiotherapy. The disease relapsed at 19 years of age and underwent second-line chemotherapy in combination with splenectomy and radiotherapy. At 33 years of age, 13 years after completion of the treatment of HL, she developed an undifferentiated sarcoma. Therefore, she received chemotherapy and surgery and remained in complete remission (CR) for more than 52 months. Case 2 is a 20-year-old man who developed HL of stage III at 4 years of age and received chemotherapy without radiotherapy, concerning the risk of late adverse effect. At 20 years of age, 14 years after completion of the treatment of HL, he developed a non-Hodgkin's lymphoma (NHL) of gastric mucosa for which chemo- and radiotherapy were administered, resulting in CR for 13 months. In Western countries, the reported incidence of second malignancy after the treatment of HL is so high that 20% of HL patients died of second malignancy. On the other hand, only a few patients with second malignancy after HL were reported in Japan. Because of low incidence of HL compared to Western countries, the long-term follow-up system is not yet established in Japan. Therefore, the number of second malignancy among survivors of HL would increase in the future when a nationwide follow-up system is organized.

要 旨 症例1は34歳の女性．16歳時にホジキンリンパ腫（HL）を発症し，化学療法と放射線治療を受けた．19歳時に再発し化学療法，放射線治療と脾臓摘出術を受けた．13年後の33歳時にundifferentiated sarcomaを発症し，化学療法と手術を受け，52カ月間寛解を維持している．症例2は20歳の男性．4歳時にHLを発症し，化学療法を受けた．14年後の20歳時に非ホジキンリンパ腫（NHL）を発症し，化学療法と放射線治療を受け，13カ月間寛解を維持している．欧米ではHL後の二次がんの発症率は高いが，本邦ではまれである．しかし本邦における全国規模でのフォローアップ体制が確立されていないことや，本邦からの多数例の報告においても観察期間が短いことを考慮すると，HL治療後の二次がん発症の実態を明らかにするために，長期にわたる経過観察の必要性が示唆された．

Key words: Hodgkin's lymphoma, second malignancy, undifferentiated sarcoma, post radiation sarcoma, second non-Hodgkin's lymphoma

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I. はじめに

小児ホジキンリンパ腫（Hodgkin's lymphoma: HL）はわが国では非常にまれな疾患であり，その発症頻度は全小児がんの4%を占める欧米と比較すると，約1/10程度と推測されている[1-3]．欧米においては，従来標準的治療

とされてきた放射線照射と化学療法の併用で高い長期生存率が得られるようになったが，晩期合併症，とりわけ二次がんを高率に発症することが知られている[4-9]．一方，わが国の HL 157 例の後方視的検討によれば，二次性腫瘍の発症は 1 例のみであった[10]．今回われわれは，HL の治療終了 13 年後と 14 年後に，それぞれ右背部の undifferentiated sarcoma と非ホジキンリンパ腫（non-Hodgkin's lymphoma: NHL）を発症した 2 症例を経験したので報告する．

II. 症　　例

1. 症 例 1

患者：34 歳，女性．

主訴：右背部腫瘤．

既往歴：16 歳 1 カ月時に HL（結節硬化型，stage III（頸部，腹部））を発症し，COPP 療法（サイクロフォスファマイド，ビンクリスチン，プレドニゾロン，プロカルバジン）6 コースと放射線照射 30Gy（全腹部照射＋マントル型照射）を受けた．19 歳 11 カ月時に HL の再発（肝，大動脈周囲リンパ節，脾）が認められ，脾臓摘出術と ABVD 療法（ドキソルビシン，ブレオマイシン，ビンブラスチン，ダカルバジン）を 7 コース，局所照射 35Gy を施行された．今回の背部腫瘤はこの照射野に含まれていた．

家族歴：特記事項なし．

現病歴：33 歳 2 カ月時に右背部の腫瘤に気づき，MRI で L2 から L4 レベルの右傍脊柱筋内に T2WI で high intensity を呈する腫瘍が認められた．切開生検で診断に至らず，広範切除術を施行され malignant giant cell tumor と診断された．その後外来で経過観察されていたが，34 歳 11 カ月時に MRI で局所再発が認められ，生検の結果，骨肉腫類似の組織像を呈する post radiation sarcoma と診断された．

治療経過：イフォスファミドとビンクリスチン，ドキソルビシンとサイクロフォスファマイドからなる化学療法を 2 コースずつ施行したが，種々の合併症により化学療法の継続が困難となったため，腫瘍広範切除術を施行し治療終了とした．その後 52 カ月間再発を認めていない．

2. 症 例 2

患者：20 歳，男性．

主訴：嘔吐，体重減少．

既往歴：4 歳 10 カ月時に HL（混合細胞型，stage III（頸部，腹部））を発症し，COPP 療法を 12 コース施行された．晩期障害を考慮して放射線治療は行わなかった．

幼少時より肺炎を繰り返しており，7 歳時に IgG 4 サブクラス欠損症と診断された．

家族歴：特記事項なし．

現病歴：19 歳 6 カ月時に心窩部痛，嘔吐，体重減少が出現した．胃内視鏡検査と病理組織検査で胃炎（*Helicobacter pylori* 陽性）と診断され，プロトンポンプインヒビターの投与で症状は軽快した．20 歳 7 カ月時，経過観察のための内視鏡検査で胃角部に潰瘍を認め，病理組織検査で NHL と診断された．

入院時現症：体重 45.0 kg，身長 156.1 cm．心音，呼吸音ともに異常なし．腹部は軟，肝脾腫を認めず，表在リンパ節を触知しなかった．

入院時検査所見：末梢血液検査，生化学検査では異常を認めなかったが，sIL-2R は著明に上昇（1993U/*l*）していた．骨髄所見は正常であった．

画像所見：診断時の胃内視鏡写真（Fig. 1）では胃角部から前庭部大彎後壁に潰瘍性病変を認めた．胃十二指腸造影検査では胃角から前庭部に不整な陥凹性病変を認めるが筋層浸潤はなく，CT と Ga シンチで他病変を認めなかった．

病理組織所見（Fig. 2）：大型で好塩基性の強い細胞質をもった異型リンパ球をびまん性に認め，免疫染色は CD20，CD30，CD79a，LCA が陽性であり，diffuse large B-cell lymphoma と診断された．ホジキン細胞や Reed Sternberg 細胞は認めなかった．

治療経過：胃原発の diffuse large B-cell lymphoma stage I として，CHOP 療法（サイクロフォスファマイド，ビンクリスチン，プレドニゾロン，ドキソルビシン）を 3 コース施行し，組織学的に寛解を確認した．その後，放射線を全胃に 30Gy 照射した．原発巣には 10.5Gy 追加照射し，治療を終了した．その後 13 カ月間寛解を維持している．

III. 考　　察

小児 HL の治療は，放射線療法から始まったが，1970 年代に多剤併用化学療法の有効性が示され，欧米において放射線療法と化学療法とを併用することで，長期生存率は 90%を超えるようになった．一方で，二次がん，性腺障害，成長障害や心・肺合併症などの重篤な晩期障害が報告されるようになり[11,12]，その中でも二次がんの累積発症率（15～30 年）は 7～26.3%と高率であり[4-8]，相対危険度は 7～18.5 であった[9,13]．二次がんはおもに固形癌，急性白血病，NHL であり，これらの報告の中では放射線治療歴，照射線量，照射と化学療法の併用，アルキル化剤投与歴，化学療法の積算量；診断時年齢，摘

Fig. 1 Endoscopic examination of case 2 showed the ulcerative lesions (arrow) on the posterior wall in the corpus of the stomach

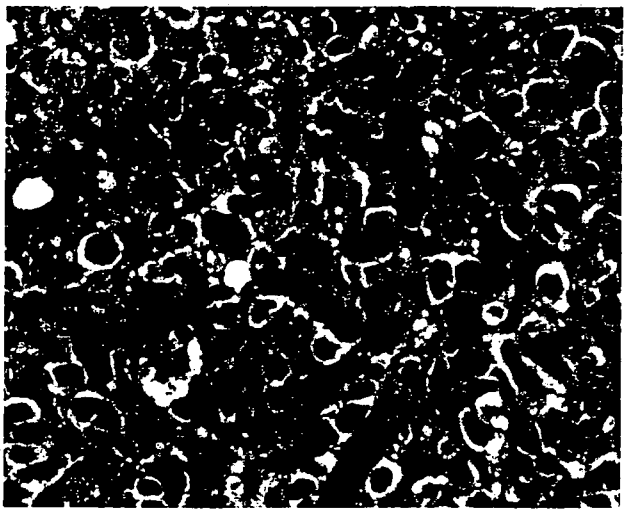

Fig. 2 Histopathological image of the biopsied specimen of the gastric mucosa of case 2
The section showed patchy and diffuse infiltration of large atypical lymphocytes with pale cytoplasms. No typical Hodgkin's cells or R-S cells were detected.

脾などがリスク因子として報告されている[4-9]．このため近年では，化学療法のコース数を減じたり，アルキル化剤を省略したりするようになってきており[14,15]，さらに，限局期だけでなく進行期においても，化学療法後に完全寛解となった場合に放射線療法を省略できるかどうかについて，多くのランダマイズ試験で検討されている[16-18]．一方，本邦ではHLの発症率が非常に低いために標準的治療が確立されておらず，施設により異なる治療がなされてきた．日本小児白血病/リンパ腫研究グループによるHL 157例の後方視的検討によれば[10]，わが国の治療はCOPP＋ABVDのレジメンが一般的で非照射例が半数を占めていたが，全体の成績は欧米と同等であり二次性腫瘍の報告はデスモイド腫瘍の1例のみで発症率は0.6%であった．しかし，HLに対するフォローアップ体制が確立されていないことや，観察期間が約5年と短いことを考慮すると，二次がんの発症が少ないことが，非照射例が多いことに起因しているかどうかは現時点では不明であると思われる．Bhatiaらの小児HL 1,380例の報告によると，アルキル化剤を含む化学療法が二次性の白血病とNHLのリスク因子で，発症の中央値はHLの治療終了から14年であった[4]．自験例の症例1は照射野からの発症であるが，症例2では幼児期にHLを発症したため，晩期障害のリスクを考慮して放射線治療を行わなかったので，二次性NHLのリスク因子となったのはアルキル化剤（サイクロフォスファマイド，プロカルバジン）と考えられる．上述した本邦の調査では，非照射レジメンで治療された症例の割合は多かったが，化学療法のコース数は多い傾向があり，また観察期間も短いため，今後二次がんを発症する症例の増加が予想される．今回報告した2症例の治療の比較を示した（Table 1）．当施設では過去に17例のHLを治療しており，そのうち2症例に二次がんが発症したことは，本邦におけるHL治

Table 1 Treatment summaries in two patients with HL

	Case 1	Case 2
Cumulative dose of chemotherapy (mg/m^2)		
COPP		
Cyclophosphamide	3,724	5,375
Vincristine	17	30
Procarbazine	11,200	16,800
Prednisolone	3,360	6,720
ABVD		
Doxorubicin	350	0
Bleomycin	140	0
Vinblastine	84	0
Dacarbazine	5,250	0
Cumulative dose of radiotherapy (Gy)		
Whole abdomen	30	0
Mantle field	30	0
Local	35	0
Surgery	Splenectomy	(−)