established as the standard therapy for cancer of the esophagus during this time period. However, according to the results of the 1996–1999 PCS for esophageal cancer patients in the United States (USPCS) (4), 89% of patients received chemotherapy in addition to RT. The author concluded that this study confirmed the use of concurrent CRT as part of the standard practice for esophageal cancer. In addition, the significant rise in the use of endoscopic ultrasound (EUS) compared to the 1992–1994 USPCS was identified in this report. It was stated that this had been caused by the revision of the American Joint Committee on Cancer (AJCC) staging system from the old 1983 version to the current 1997 version in which T-classification relies on the depth of tumor invasion.

The objectives of this study were to evaluate the 1999–2001 JPCS data for esophageal cancer patients receiving RT without surgery and also to investigate the differences in treatment process according to the depth of tumor invasion.

METHODS

On the basis of the Japanese facility master list of 1999 (5), all radiation therapy facilities, composed of more than 700 institutions, were classified as follows: A1, academic institutions (cancer centers and university hospitals) treating ≥430 patients a year; A2, <430 patients; B1, other non-academic institutions treating ≥130 patients a year; and B2, <130 patients. A stratified two-stage cluster sampling was used to select facilities and patients for review (Fig. 1). In the first stage of sampling, facilities were randomly selected for investigation. In the second stage, random sampling of patients was performed from all eligible patients of each facility. Radiation oncologists of the JPCS Working Group, who visited each selected facility and reviewed the records of the selected patients, collected data from 2002 to 2004. For this survey, 76 facilities were selected (20 from A1, 18 from A2, 20 from B1 and 18 from B2). The number of selected facilities corresponds to a little over 10% of all RT facilities in Japan. The inclusion criteria were thoracic and abdominal esophageal cancer treated with RT from 1999 to 2001, squamous cell, adenosquamous cell or adenocarcinoma histology and Karnofsky performance status (KPS) of 60 or more. Patients with distant organ metastasis or other active malignancies within 5 years prior to treatment were excluded. Cervical esophageal cancer patients were excluded because the treatment strategy and the various parameters of RT differ from thoracic and abdominal cancer patients. The clinical data of 621 esophageal cancer patients receiving RT with or without surgery were accumulated. Of these, 385 patients (62%) who received RT without surgery were analysed (106 patients from A1, 88 from A2, 142 from B1 and 49 from B2).

Statistical analyses were performed using the statistical analysis system (SAS) at the JPCS statistical center (6). Statistical significance was tested using the χ^2 test and Student's *t*-test.

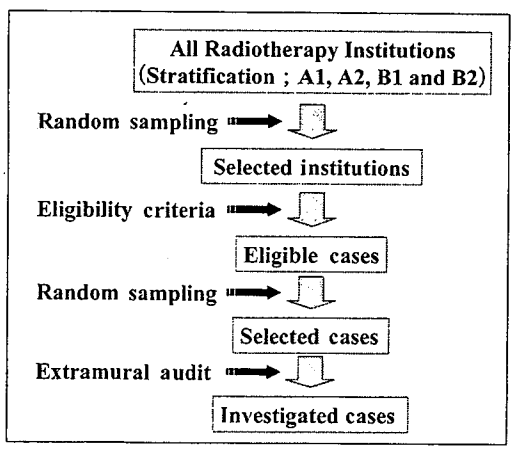

Figure 1. The method of random sampling. Patients were randomly selected by means of two-stage cluster sampling consisting of sampling of institutions from the four institutional strata in the first stage and sampling of patients from these institutions in the second stage. A1, academic institutions (cancer centers and university hospitals) treating ≥ 430 patients a year; A2, <430 patients; B1, other non-academic institutions treating ≥ 130 patients a year; and B2, <130 patients.

RESULTS

Patient and Tumor Characteristics

Patient and tumor characteristics are listed in Table 1. The median age was 71 years and 85% of patients were male. Seventy-one per cent had KPS of 80 or more. Fifty-six per cent of patients had the main lesion in the middle thoracic esophagus and 99% had squamous cell carcinoma histology. According to the 1997 International Union Against Cancer (UICC) staging system, 79 patients (21%) had T1 disease, 51 patients (13%) T2 disease, 143 patients (37%) T3 disease and 112 patients (29%) T4 disease. Among the 79 patients with T1 disease, 15 (4%) had mucosal cancer and 64 (17%) had submucosal cancer. Sixteen patients were clinical stage I, 29% were stage II, 43% were stage III and 12% were stage IVa-b. The patient characteristics according to the depth of tumor invasion were shown in Table 2. The KPS of patients with T1 disease was better than patients with T2–4 disease ($P = 0.0001$).

Pretreatment Evaluation

Procedures of pretreatment evaluation are shown in Table 3. Ninety-four per cent of patients had an esophagram, and 96% underwent endoscopy. Computed tomography (CT) scans of the chest and abdomen were obtained in 97 and 90%, respectively. There was no significant difference in the use of these procedures according to the depth of tumor invasion. EUS was used in 29%. The utilization rates of EUS for T1, T2, T3 and T4 cases were 53, 29, 21 and 21%, respectively, and T1 cases underwent

Table 1. Patient and tumor characteristics

Characteristics	No. of patients	(%)
Total no.	385	
Age (yr)		
Range	46–94	
Median	71	
Sex		
Male	328	(85)
Female	57	(15)
KPS		
60–70	94	(29)
80	137	(41)
90–100	98	(30)
Missing	56	
Tumor main location		
Upper thoracic	76	(20)
Middle thoracic	216	(56)
Lower thoracic/abdominal	92	(24)
Missing	1	
Histology		
Squamous cell	376	(99)
Adenocarcinoma	1	(0)
Adenosquamous	2	(1)
Missing	6	
T-classification		
T1 all	79	(21)
Mucosal	15	(4)
Submucosal	64	(17)
T2	51	(13)
T3	143	(37)
T4	112	(29)
Missing	0	
Clinical stage		
I	57	(16)
II	101	(29)
III	150	(43)
IVa–b	41	(12)
Missing	36	

KPS, Karnofsky performance status.

it more frequently than T2–4 cases ($P = 0.0001$). Magnetic resonance imaging (MRI) was used on 15% of patients. The performance rates for T1, T2, T3 and T4 cases were 3, 13, 12 and 26%, respectively, and this procedure was performed significantly less in T1 cases than in T2–4 cases ($P = 0.0051$).

Treatment

Treatment characteristics are shown in Table 4. Ninety-three per cent of patients were hospitalized for treatment. There was no significant difference in the ratio of hospitalization between T1 and T2–4 cases. Planned treatment was accomplished in 83% of patients. The accomplishment rates for T1, T2, T3 and T4 cases were 94, 78, 82 and 77%, respectively, and the rate for T1 cases was higher than T2–4 cases ($P = 0.0441$). Endoscopic mucosal resection (EMR) was performed in 15% of T1 cases before RT, and the performance rates for mucosal and submucosal cancer were 40 and 9%, respectively.

Treatment Strategy

Of all patients, 61% received CRT and 39% received RT alone. The utilization rates of CRT for T1, T2, T3 and T4 cases were 28, 74, 58 and 79%, respectively, and there was a significant difference in the use of CRT between T1 and T2–4 cases ($P = 0.0001$). Among patients with T1 disease, 20% with mucosal cancer and 30% with submucosal cancer received CRT.

Radiotherapy

All patients included in this study received external beam RT (ERT). The median total dose of ERT was 60 Gy and the median fraction dose was 2 Gy. There was no difference in the median total dose and the median fraction dose of ERT between T1 and T2–4 cases. Regarding irradiation fields ($\geq$40 Gy), 66% of patients received whole mediastinal irradiation. Nodal irradiation fields ($\geq$40 Gy) according to the tumor main location were shown in Table 5. Patients with upper thoracic tumors were irradiated supraclavicular region in 53%, whole mediastinal region in 70% and upper abdominal region in 3%. Patients with middle thoracic tumors were irradiated supraclavicular region in 13%, whole mediastinal region in 69% and upper abdominal region in 16%. Patients with lower thoracic tumors were irradiated supraclavicular region in 8%, whole mediastinal region in 49% and upper abdominal region in 35%. Brachytherapy (BT) was used in 10% of patients as a means of boosting the primary tumor site. Seventy-four per cent of patients who received BT were treated by high-dose-rate source and 26% by low-dose-rate source. The performance rates of BT for T1, T2, T3 and T4 cases were 20, 14, 6 and 5%, respectively, and a significant difference in its use was found between T1 and T2–4 cases ($P = 0.0018$). Among patients with T1 disease, 27% with mucosal cancer and 18% with submucosal cancer received BT.

Chemotherapy

Chemotherapy was administered in 61% of patients, as mentioned above. Of these, 73% received chemotherapy

Table 2. Patient characteristics according to depth of tumor invasion

Characteristics	T1			T2	T3	T4	Total	T1 vs. T2–4 *P* value
	m	sm	all					
Age (yr)								
Range	54–88	53–87	53–88	46–88	48–94	47–90	46–94	0.551
Median	71	72	71	73	73	66	71	
Sex (%)								
Male	73	84	82	88	85	87	85	0.772
Female	27	16	18	12	15	13	15	
KPS (%)								
60–70	18	9	11	17	35	38	28	0.0001
80	9	44	38	52	45	35	42	
90–100	73	47	51	30	20	27	30	

m, mucosal cancer; sm, submucosal cancer.

concurrently with RT, 15% before RT and 12% after RT. The most frequently used individual agents for concurrent CRT cases were 5-fluorouracil (5-FU) (97%) and cisplatin (82%). The patients who were administered the combination of cisplatin and 5-FU concomitantly were 80% of concurrent CRT cases. When the combination of cisplatin and 5-FU was used for concurrent CRT, the administration schedules were daily administration in 64%, tri-weekly/monthly administration in 19%, weekly administration in 14% and others in 4%. There was no use of paclitaxel or docetaxel in this study.

Comparison with the 1995–1997 JPCS

Comparison of work up and process for non-surgical patients between the 1995–1997 JPCS survey and this survey is shown in Table 6. Work up to including age, gender, KPS and histology was almost the same. The administration rate of chemotherapy had remarkably increased (35% versus 61%) and the performance rate of BT had decreased (17% versus 10%). Regarding ERT, the median total dose and fraction dose of ERT did not change and the ratio of whole mediastinal nodal irradiation had increased (47% versus 66%).

Table 3. The frequency of use of pretreatment diagnostic procedures (%)

Procedures	T1			T2	T3	T4	Total	T1 vs. T2–4 *P* value
	m	sm	all					
Esophagram	73	90	87	94	95	96	94	0.0637
Endoscopy	100	100	100	98	96	93	96	0.1521
Endoscopic ultrasound	60	52	53	29	21	21	29	0.0001
CT scan, chest	93	93	93	98	99	98	97	0.1079
CT scan, abdomen	83	88	87	88	90	92	90	0.4374
MRI	0	4	3	13	12	26	15	0.0051

CT, computed tomography; MRI, magnetic resonance imaging.

DISCUSSION

In this survey, we evaluated the 1999–2001 JPCS data of esophageal cancer patients receiving RT without surgery and revealed significant differences in patterns of care according to the depth of tumor invasion. Among patient characteristics, a KPS of T1 cases was better than T2–4 cases in this survey. This possibly suggests that a ratio that definitive RT/CRT was chosen for operable T1 cases increased. It is thought to be attributable that the RT/CRT has been recognized as a curable treatment for T1 tumors.

In the report of the 1996–1999 USPCS for esophageal cancer, the significant rise in the use of EUS compared to the 1992–1994 USPCS was identified (4). The performance rate of EUS in this JPCS survey was higher than in the 1996–1999 USPCS (29% versus 18%). Furthermore, more than half of T1 cases had EUS and the performance rate was significantly higher in T1 cases than in T2–4 cases. In Japan, there is an original staging system created by the Japanese Society for Esophageal Diseases (7). The particularity of the Japanese staging system is that T1 disease is subclassified into mucosal cancer as T1a and submucosal cancer as T1b. The incidences of lymph node metastasis in mucosal cancer and submucosal cancer were reported as 0–5% and 41.4–53.3%, respectively (8–11), and the survival rate for submucosal cancer is significantly worse than for mucosal cancer (12–14). From this point of view, the

Table 4. Treatment characteristics (%)

Variables	T1			T2	T3	T4	Total	T1 vs T2–4 *P* value
	m	sm	all					
Hospitalization for treatment	93	87	89	88	94	96	93	0.0637
Complete planned treatment	93	94	94	78	82	77	83	0.0441
EMR before RT	40	9	15	2	1	0	4	0.0001
Treatment strategy								
CRT	20	30	28	74	58	79	61	0.0001
RT	80	70	72	26	42	21	39	
RT details								
ERT Dose (Gy)								
Total dose – median	60	60	60	60	60	61	60	–
Total dose – range	41.4–70	30–70	30–70	18–70	12–75	4–75.6	4–75.6	
Total dose – mean	57.7 ± 9.2	59.8 ± 8.4	59.4 ± 8.5	58.4 ± 11.2	59.6 ± 10.9	57.2 ± 14.3	58.7 ± 11.7	
Fraction dose – median	2.0	2.0	2.0	2.0	2.0	2.0	2.0	–
Fraction dose – range	1.8–2.0	1.2–2.4	1.2–2.4	1.0–2.2	0.9–3.0	0.9–2.0	0.9–3.0	
Fraction dose – mean	1.93 ± 0.10	1.97 ± 0.14	1.97 ± 0.13	1.92 ± 0.20	1.91 ± 0.27	1.86 ± 0.25	1.92 ± 0.23	
ERT Field (≥40 Gy)								
Whole mediastinum	54	59	58	76	64	70	66	0.1115
BT	27	18	20	14	6	5	10	0.0018
CTx								
Sequence of CTx								
Concurrent	–	–	85	76	69	71	73	
Pre-RT	–	–	4	9	20	15	15	
Post-RT	–	–	11	13	11	14	12	
Unknown	–	–	0	2	0	0	0	
Agent for concurrent CTx								
5-fluorouracil	–	–	96	91	100	98	97	
Cisplatin	–	–	65	80	88	82	82	
Nedaplatin	–	–	9	9	6	8	7	
Carboplatin	–	–	2	6	2	1	3	
Others	–	–	2	4	2	4	3	

EMR, endoscopic mucosal resection; RT, radiotherapy; CRT, chemo-radiotherapy; ERT, external beam radiotherapy; BT, brachytherapy; CTx, chemotherapy.

diagnosis of mucosal cancer or submucosal cancer is regarded as very important. The accuracy of EUS for the diagnosis of the depth of tumor invasion for esophageal cancer has been reported to be more than 80% (15, 16). The reason why the performance rate of EUS was high in T1 cases was that EUS was thought to be the most useful procedure for the diagnosis of mucosal cancer and submucosal cancer. As a new diagnostic procedure for esophageal cancer,

Table 5. Nodal irradiation fields according to the tumor location (%)

Tumor main location	ERT field (≥ 40 Gy)		
	Supraclavicular	Whole mediastinum	Upper abdomen
Upper thoracic	53	70	3
Middle thoracic	13	69	16
Lower thoracic/abdominal	8	49	35

positron emission tomography (PET) has recently been noted. The usefulness of PET for pretreatment staging, especially for detecting lymph node metastases, has been reported (17–20). Although PET was not investigated in this survey, this procedure should be examined in a future study in order to increase its future use.

EMR is effective and the least invasive treatment method for small mucosal cancer. Its local control rate is very high and is equivalent to esophagectomy (21–23). Because of the low rate of lymph node metastasis, additional treatment is not necessary for mucosal cancer after complete resection by EMR. However, in cases with positive margin or deeper invasion identified pathologically, additional treatment should be considered. In this survey, 40% of patients with mucosal cancer and 9% with submucosal cancer received EMR before radiotherapy. Recently, positive outcomes of RT and CRT following EMR have been reported (24,25). Considering the high performance rate of EMR before RT for mucosal cancer in this survey, this combination of treatments should be examined in detail in future.

Compared with the 1995–1997 JPCS, the performance ratio of CRT has remarkably increased. There are potentially several reasons such as the facts that several reports evaluating the efficacy of CRT have been published (26–29) and that the percentage of patients who were eligible for chemotherapy has increased. In spite of the increase in the use of chemotherapy, the most common treatment regimen for T1 cases was still RT alone during this time period. Recently, positive results of CRT for T1 cases have been reported (30,31) which means we need to investigate the transition of CRT for T1 cases in the next study.

Regarding ERT, the median fraction dose and the median total dose were 2 and 60 Gy, respectively, and they were not different between T1 and T2–4 cases. This result suggests that the strength of RT was not weakened for T1 cases in the treatment of esophageal cancer. Furthermore, compared with the 1995–1997 JPCS, the median total dose did not change in spite of the remarkable increase in chemotherapy administration. This suggests that not a small number of the patients receiving CRT were treated by ERT with a dose of ≥60 Gy. According to the data of the 1996–1999 USPCS, the median total dose of ERT was 50.4 Gy (4). Additionally, the result of the phase III trial of CRT with high dose (64.8 Gy) versus standard dose (50.4 Gy) for esophageal cancer was published in 2002 (32). In this report it is concluded that the higher radiation dose did not increase survival or local/regional control and the standard radiation dose for patients treated with concurrent CRT was 50.4 Gy. The patients in our study were treated in 1999–2001, so we need to compare with the result of the next PCS in order to evaluate the change of irradiation dose after this report. However, when we look at the clinical situation, the result of this trial seems not to be accepted at this moment in Japan.

With the comparison of the ratio of whole mediastinal irradiation between this survey and the 1995–1997 JPCS, irradiation fields became wider. However, from the results of the analysis of irradiation fields according to the tumor main location, it is suggested that the three-field (supraclavicular, whole mediastinal and upper abdominal region) nodal irradiation was rarely used and the localized fields were used at a constant rate. Cardiopulmonary toxicities after CRT have become a topic of interest since the paper by Ishikura et al. (33). These toxicities may be attributable to the usage of chemotherapy and extremely large field such as the so-called 'super-long-T field'. As it is anticipated that long-term survivors after CRT for esophageal cancer will increase hereafter, investigations of late toxicities including cardiovascular toxicities, the optimum ERT dose and the optimum ERT fields need to be carried out.

The performance ratio of BT was 10% and patients with T1 disease had BT significantly more frequently than those with T2–4 disease. This result suggested that in Japan BT was often used to boost irradiation following ERT for T1 disease rather than for advanced cancer. Compared with the 1995–1997 JPCS, the performance ratio of BT has decreased (17% versus 10%). As a result of the introduction of CRT and use of the 3D-treatment technique, it is thought that there may be a change of direction in the use of BT for esophageal cancer in the future.

Table 6. Comparison of process for non-surgical esophageal cancer patients between the 1995–1997 JPCS and the 1999–2001 JPCS

	1995–1997	1999–2001
Work up		
Age (median, years)	70	71
Male/Female (%)	85/15	85/15
KPS ≥80 (%)	72	71
Squamous cell carcinoma (%)	100	99
Treatment		
ERT – total dose (median, Gy)	60	60
– fraction dose (median, Gy)	2.0	2.0
Whole mediastinal irradiation (≥40 Gy, %)	47	66
Use of BT (%)	17	10
Administration of CTx (%)	35	61
Concurrent administration of CTx (%)	72	73

JPCS, Japanese Patterns of Care Study.

Regarding the sequence of chemotherapy administration, concurrent use with RT was the most common for any depth of tumor invasion. Cisplatin and 5-fluorouracil were the most frequently used agents in concurrent CRT. Evidence of the effectiveness of the combination of cisplatin and 5-fluorouracil has been shown for cancer of the esophagus (26–29), and it is thought that this has affected the choice of agents. However, as for the dosage method, daily low-dose administration was used most commonly without enough evidence. The evaluation of this method is entrusted to the future. Although the use of taxane has remarkably increased recently in the USA (4), this agent was not used at all during the time period in this survey. However, as docetaxel was covered by health insurance for esophageal cancer from 2004 in Japan, it is predicted that its use will increase in future.

CONCLUSIONS

We evaluated the 1999–2001 JPCS data for non-surgical esophageal cancer patients. The performance rate of CRT had remarkably increased compared with the 1995–1997 JPCS survey. However the common treatment for T1 cases was still RT alone. The standard dose of ERT was 60 Gy in spite of the remarkable increase in chemotherapy administration. Moreover, this survey showed significant differences in many parameters of work up and treatment process between T1 and T2–4 cases.

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Conflict of interest statement
None declared.

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診療
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前立腺癌根治的放射線治療における日米の相違点
医療実態調査研究（PCS）による検討

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はじめに

近年，人口の高齢化や生活習慣の欧米化，さらにはprostate-specific antigen（PSA）の導入により日本における前立腺癌患者は増加の一途をたどっている。さらに，放射線治療機器の高精度化や患者本人の希望により，前立腺癌に対して放射線治療が施行される機会も急激に増加している。しかしながら，日本における前立腺癌に対する放射線治療の現状についての報告は少ない。今回我々は，日本における前立腺癌に対する外部照射療法の実態を明らかにするために医療実態調査研究（patterns of care study：PCS）の調査結果を検討し，米国の外部照射療法におけるPCSの調査結果との比較検討を行った。

1．対象と方法

日本におけるPCSは，わが国における放射線治療の実態を明らかにするために，1996年から子宮頸癌，食道癌について，1998年からは乳癌，子宮頸癌，食道癌，肺癌，前立腺癌の5疾患について行われている。PCSにおける調査データは2段階クラスタサンプリングにより抽出された施設への訪問調査を行うことにより収集した[1]。

今回の検討では，日本において1999～2001年に前立腺癌に対して根治照射が施行されたPCS症例（無作為抽出された283例）の患者背景，治療様式について，1999年に米国で治療されたPCS調査症例（392例）との比較を行った。さらに，日米における患者背景，治療様式の経時的変化についても検討を行った[2]。日本における経時的変化の検討には，1996～1998 PCS，1999～2001 PCSの調査結果と現在調査中の2003～2005 PCSの調査結果を使用した。また，米国における経時的変化の検討には，1994 PCSと1999 PCSの調査結果を使用した[3]。

2．結　果

1）患者背景における日米の違い（表1）

患者背景においては，対象症例の年齢はほぼ同じであったが，日本のほうが米国と比較して進行症例（PSA＞20 ng/ml，T3～4，グリソンスコア8～10）が多かった。それに対して米国においては，大部分の症例がPSA＜20 ng/ml，T1～2，グリソンスコア2～6であった。日本において放射線治療を選択した理由では，「進行症例」が32%と一番多く，次に多かっ

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表1　日本（1999～2001 PCS）と米国（1999 PCS）における患者背景

	日本 1999～2001 PCS（n＝283）	米国 1999 PCS（n＝392）
年齢（歳）	72	71
（中央値，範囲）	（49～92）	（49～86）
治療前 PSA 値（ng/ml）		
＜10	29%	61%
10～19.9	21%	23%
>=20	50%	16%
グリソン指数		
2～6	45%	55%
7	21%	26%
8～10	34%	19%
T 分類		
TX～T0	4%	8%
T1	8%	44%
T2	40%	34%
T3～4	46%	7%
Unknown	2%	7%
放射線治療を選択した理由		
患者の希望	27%	—
進行症例	32%	—
全身状態不良	14%	—
高齢	17%	—
その他	3%	—
不明	7%	—

PSA＝prostate-specific antigen

たのは「患者の希望」であり27%であった。

患者背景の経時的変化における日米の違いにおいては，米国では進行症例（PSA＞20 ng/ml，T3～4，グリソンスコア 8～10）の頻度は少なく，その傾向は以前のPCSでも同様であった（図1A）。それに対して，日本における経時的変化では進行症例の頻度が高い状況が続いていた（図1B）。しかしながら，次第に進行症例が減ってきており，日本でも米国のように早期癌が多い状態に近づいてきていることが明らかとなった。

2）治療法における日米の違い（表2）

外部照射法においては，10 MV 以上のエネルギーを使用した比率は日米ともに73～74%と同等であったが，米国のほうがCT治療計画，3次元原体照射法（3DCRT）が行われている割合が高かった。また，米国では日本よりも高線量（72 Gy 以上）が高頻度で使用されていた。それに対してホルモン療法は日本において高頻度で使用されていた。

これらの治療法（CT治療計画，ホルモン療法，高線量）は米国では前回PCSと比較して急激に頻度が増加していた（図2A）。それに対して，日本ではCT治療計画，ホルモン療法の頻度におけるPCSごとの変化は少なかった。しかしながら，高線量の比率については日本でもPCSごとに次第に上昇していた（図2B）。日本における総線量の経時的変化においては，1996～1998 PCSでは60 Gy 未満の比率が多く，70 Gy 以上の比率が少なかったが，2003～2005 PCSにおいては60 Gy 未満の線量がなくなり，逆に70 Gy 以上の比率が半数を超えるようになっていた（図3）。以上の結果から，日本における前立

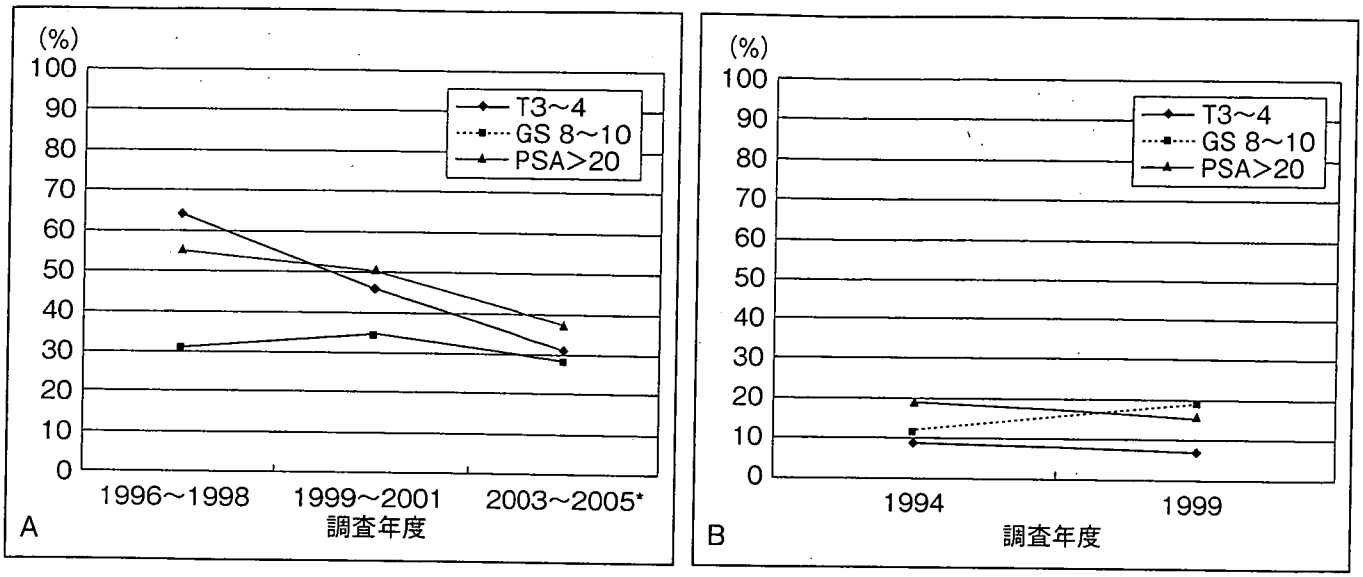

図1　米国と日本における患者背景の変化

A　米国では進行症例（T3～4，グリソンスコア，PSA＞20 ng/ml）の割合は1994～1999年の間で20%以下にとどまっていた。

B　それに対して日本では進行症例の割合は米国と比べて高かったが経時的にその割合が減ってきている。*調査中。

表2　日本（1999～2001 PCS）と米国（1999 PCS）における治療背景

	日本 1999～2001 PCS（n＝283）	米国 1999 PCS（n＝392）
放射線治療		
エネルギー（＞10 MV）		
Yes	74%	73%
CT治療計画		
Yes	86%	95%
原体照射法		
Yes	50%	80%
高線量（＞72 Gy）		
Yes	8%	43%
ホルモン療法		
Yes	89%	51%

腺癌における総線量は次第に増加していることが明らかとなった。

3. 考　察

今回のPCSの検討により，日本における前立腺癌に対する外部照射療法の実態が明らかになった。患者背景においては，日本における前立腺癌患者は進行症例が多いが，早期症例の割合が徐々に増えており，米国の状況に近づいてきていることが示唆された。

米国のほうが日本と比較して早期症例が多い理由としては，米国のほうがスクリーニングとしてのPSA検査がより広く行われているため日本と比較して早期例がより多く発見される可能性が考えられる。しかしながら，同じ米国でもAfrican-AmericanやHispanicにおける人種ではCaucasianと比較して進行症例が多いことも明らかとなっている[4]。両国の患者間による癌の生物学的な違いによる可能性もあり，今後の検討が必要であると考えられる。また，患者の希望により放射線治療が選択された割合が多かったことも明らかと

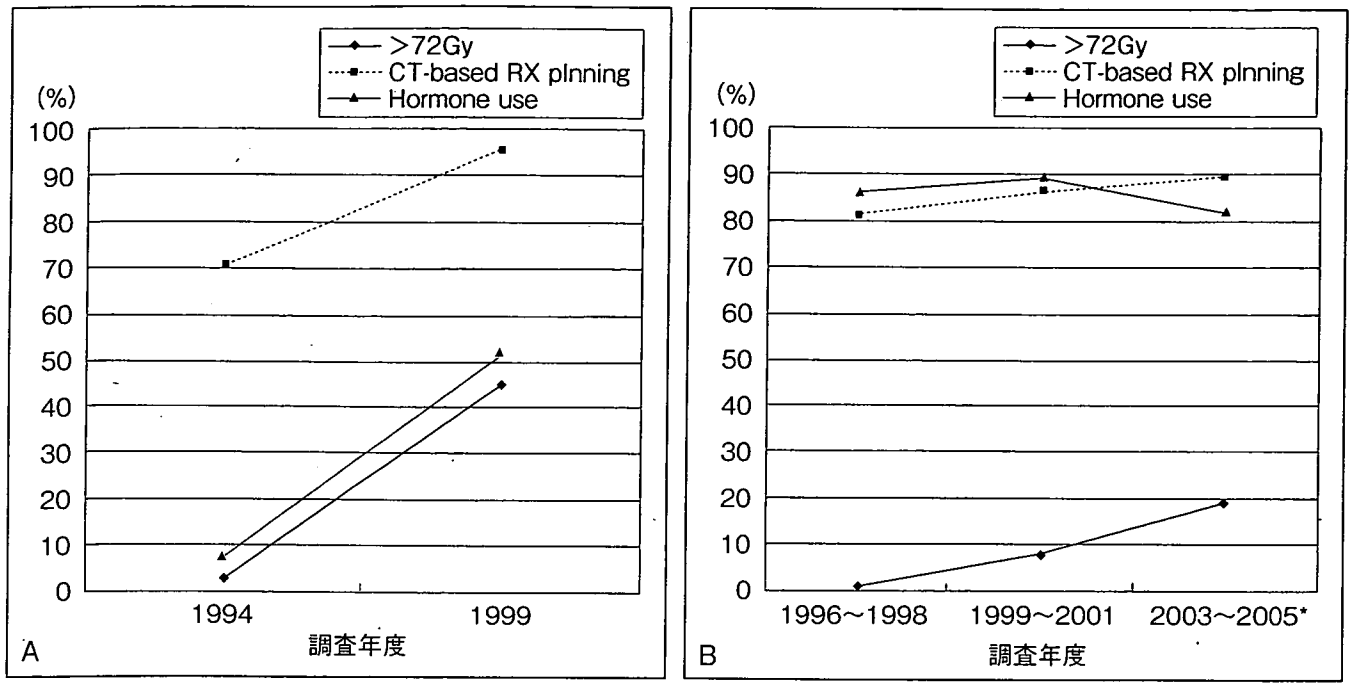

図2　米国と日本における治療法の変化
A　米国では治療法（高線量（72 Gy 以上），CT 治療計画，ホルモン療法）の割合は 1994 ～ 1999 年の間で急激に上昇していた。
B　それに対して日本では上記の治療法の比率における経時的変化は緩やかであった。* 調査中。

なった。

これらの結果は，日本でも PSA 検査の普及が急速に進んできていることや報道やインターネットの普及等により患者自身がより多くの情報を国内外から取り入れることが可能になっていることなどが理由としてあげられる。以上より，今後日本においても前立腺癌に対する放射線治療はより重要なものになっていくことが示唆された。

放射線治療法においては，日本における外部照射法では，照射線量の増加傾向が認められ，特に 60 Gy 未満という不十分な照射線量の比率が減り，逆に 70 Gy 以上の比率が増えていた。照射線量の増加については，日本でも外部照射療法が根治的治療であることが認識されてきた結果であると考えられる[5]。しかしながら，日本では CT 治療計画や 3DCRT の頻度が米国と比較して少なく，さらには米国よりも高線量を使用する頻度が少なかった。日本において高線量を使用した頻度が米国と比較して少ない理由としては，現時点では高線量を安全に投与できる施設が日本では少ないためであると考えられる。今後日本においても 3DCRT，さらには IMRT（intensity modulated radiotherapy）のような高精度治療が安全に

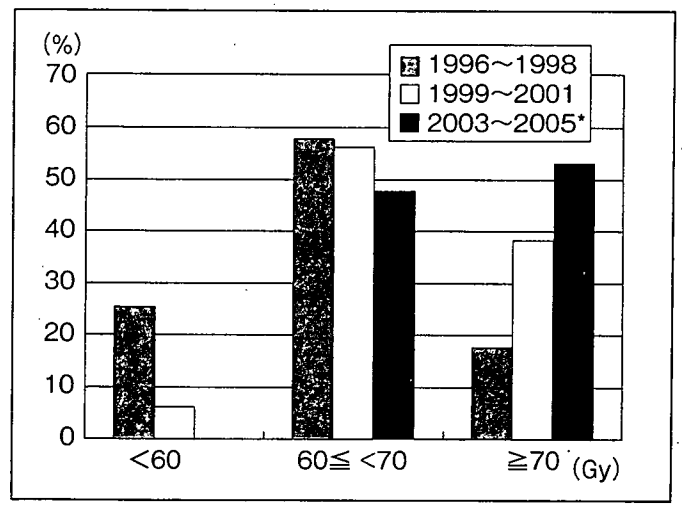

図3　1996 ～ 1998 PCS，1999-2001 PCS と現在調査中の 2003 ～ 2005 PCS における照射線量の分布
* 調査中。

行われるような施設が全国規模で浸透していくことが望まれる。

一方，ホルモン療法については米国と比較して日本では高頻度で併用され続けていることが明らかとなった。その理由として日本では米国と比較して進行癌が多いことがあげられる。また，患者の性的活動性が欧米と比較して一般的に低い傾向があるために，ホルモン療法の副作用であるerectile dysfunction（ED）を社会的に容認する傾向にあることもその一因かもしれない[6]。さらには高価なLH-RHアナログ剤や抗アンドロゲン剤を長期間使用することが現在の日本の保険制度では可能であることも，ホルモン療法が多用されてきた要因の一つであると考えられる[7]。しかしながら米国における前立腺癌による死亡者数はほぼ横ばいで推移しているのに対して日本における前立腺癌による死亡者数は急激に増加している[8]。ホルモン療法の多用のみでは治療成績の向上に寄与していない可能性もあり，今後日本人に対する適切なホルモン療法の使用法について明らかにしていく必要があると考えられた。

米国では，CT治療計画，ホルモン療法，高線量などが前回PCSと比較して急激に頻度が増加していた。その理由としては，これらの変化が国内外エビデンス（EBM）のNational practiceへの浸透率に関わっていたことが考えられる[9]。1990年代後半には，前立腺癌に対して線量の増加により治療成績が向上すること，原体照射法の使用により晩発性合併症が減らせること，進行症例においてはホルモン療法併用により治療成績が向上することが報告されており[10-12]，米国ではこれらの臨床試験等のデータが治療方法に反映されやすい状況にあったと考えられる。それに対して日本ではCT治療計画，ホルモン療法，高線量については緩やかな増加にとどまっている。このことは，EBMの知見がそのまま反映される形にはなっていなかったことを意味する。その理由として，現状では日本発の臨床試験のデータが少なく，放射線治療の効果が日本では広く認められていなかったためであると考えられた。したがって，今後の日本においては，欧米からの臨床試験データを取り入れながら，日本人に合わせた放射線治療法を広めていく必要があると考えられた。

ま と め

前立腺癌根治的放射線治療について，日米両国間の患者背景，照射法，ホルモン療法併用法における違いが明らかとなった。さらに，治療様式の経時的変化における両国の違いも認められた。がん対策基本法の制定によって，今後の日本においてはどの施設でも根治的放射線療法を安全に施行できることが望まれている。今後は本研究のような医療実態調査研究を有効利用することによって，日本の放射線治療の現状を明らかにして放射線治療の質を向上させることが期待される。外部照射療法に関しては，現状では日本からの放射線治療成績の報告は少なく，欧米の治療方法を日本人の患者にそのまま当てはめてよいかどうかは，はっきりとしていない。したがって，日本人を対象とした前立腺癌治療に対するエビデンスの構築が早急に必要である。

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Summary

Radical external beam radiotherapy for prostate cancer in Japan；differences in the patterns of care between Japan and the United States

This study focused on the differences in the patterns of care for prostate cancer patients treated with radical external beam radiotherapy between Japan and the United States. Results from the 1999-2001 Japanese Patterns of Care Study (PCS) survey were compared with those of the 1999 PCS in the United States. In addition, the changing trends in the patterns of care between Japan and the United States were also analyzed. Patients in Japan were found to have more advanced primary disease than those in the United States, but the proportions of advanced disease have gradually decreased in Japan. The distributions of CT-based treatment planning, conformal therapy and higher doses were higher in the United States, and a drastic change in these parameters occurred in the United States, while only moderate changes occurred in Japan. These results indicate that patterns of care for prostate cancer in Japan are considerably different from those in the United States, and the changing trends in the patterns of care are also different between the two countries.

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REVIEW

Radical external beam radiotherapy for prostate cancer in Japan: differences in the patterns of care among Japan, Germany, and the United States

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Abstract Optimal management of radiotherapy for prostate cancer patients has become a major concern for physicians in Japan. We reviewed published reports identifying the differences in the patterns of care for prostate cancer patients treated with radical external beam radiotherapy in Japan, Germany, and the United States. The reports indicate that Japanese patients have more advanced primary disease than patients in Germany or the United States. These patient characteristics for Japan and the United States have been almost unchanged for several years. Regarding radiotherapy, conformal radiotherapy was less frequently administered to patients in Japan than patients in Germany or the United States, and the total radiation dose was higher in Germany and the United States than in Japan. Concerning changes in trends in the patterns of radiotherapy, the percentage of patients treated with higher dose levels in the United States has rapidly increased, whereas the percentage of patients receiving these dose levels in Japan has remained extremely low. On the other hand, hormonal therapy has been used more frequently in Japan than in Germany or the United States. These findings indicate that patient characteristics and patterns of care for prostate cancer in Japan are considerably different from those in Germany or the United States.

Key words Patterns of Care Study · Prostate cancer · Type of institution · Radiation therapy · Hormone therapy

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I ntroduction

In Japan, the number of deaths due to prostate cancer has been steeply increasing, especially among elderly patients. The proportion of prostate cancer deaths among total cancer deaths also increased from 0.9% in 1960 to 4.2% in 2000.[1] Since entering the prostate-specific antigen (PSA) era, clinicians are detecting

disease at an earlier stage, and the rates of successful treatment for early-stage patients are at historical highs. Moreover, radiotherapy has become much more common because of significant advances in treatment planning technology and methodology. Therefore, the optimal management of radiotherapy for prostate cancer patients has become a major concern in Japan. However, we have not been able to evaluate national practice processes properly owing to the limited information available.

The Patterns of Care Study (PCS) national survey is a retrospective study designed to establish national practice processes for selected malignancies over a specific time period.[2–4] In addition to documenting the practice process, the PCS is important for developing and disseminating national guidelines for cancer treatment that help promote a high-quality process of care in the country. To improve the quality of radiation oncology, PCS methodology was introduced to Japan from the United States.[5,6] The Japanese PCS Working Group of Prostate Cancer started a nationwide survey for patients who underwent radiotherapy between 1996 and 1998.[7,8] Subsequently, a second PCS of Japanese patients treated between 1999 and 2001 was conducted, and we have previously reported the results of the first and the second PCS regarding radical external beam radiotherapy for prostate cancer patients.[9–13]

In the current study, we reviewed the published reports of the Japanese 1999–2001 PCS study,[11] the German 1998–2000 PCS study,[14] and the 1999 United States PCS study,[15] focusing on differences in the patterns of care between Japan, Germany, and the United States during approximately the same time periods. In addition, we reviewed the changes in trends in the patterns of radiotherapy for prostate cancer patients in Japan and the United States by comparing their most recent PCS results.[10] Although the PCS results of Germany were derived from only a few institutions, we believe these results should at least roughly represent the German national averages in the patterns of care for prostate cancer.

Comparison of patient characteristics among Japan, Germany, and the United States

Ogawa et al. previously indicated that during the period of 1999–2001, most prostate cancer patients in Japan treated with radical external beam radiotherapy had advanced disease, with more than 80% of patients having intermediate or unfavorable risk diseases[11] (Table 1). In contrast, Zelefsky et al. showed that in the United States many prostate cancer patients had early-stage disease during 1999.[15] A comparison of patients in Japan with those in the United States found that the Japanese patients had more advanced disease than their U.S. counterparts.[12] The current study compared patients in Japan with those in Germany, as reported by Vordermark et al.,[14] and found that Japanese patients once again had more advanced disease than their German counterparts. Compared with their German and U.S. counterparts, Japanese patients had higher pretreatment PSA levels, more advanced T stage, and a higher proportion of Gleason scores of 8–10. The median PSA level in Japan was 20.0 ng/ml versus 11.3 ng/ml in Germany and <10 ng/ml in the United States. The median Gleason combined score and the percentage of Gleason combined scores of 8–10 were 7 and 34.5% in Japan, respectively, whereas the median Gleason combined score was 6 in Germany and the percentage of Gleason combined score of 8–10 was 18.8% in the Unites States. The percentage of T3-4 tumors was 45.6% in Japan versus 32.0% and 6.8% in Germany and in the United States, respectively. Moreover, comparing risk groups between Japan and the United States, the proportion of Japanese patients in the unfavorable risk group was 50.4% versus 24.0% in the United States. These results indicate that higher proportions of patients with advanced disease were treated with radical external beam radiotherapy in Japan than in Germany or the United States. Whether these differences among patients in Japan, Germany, and the United States resulted from differences in access to medical care or from biological differences between the tumors themselves remains unknown. Further investigation of potential differences in disease characteristics between individuals in these countries would be informative.

Changing trend in patient characteristics for Japan and the United States

Ogawa et al. compared the changes in patient characteristics for Japan and the United States, comparing their most recent PCS (1999–2001 Japan PCS and 1999 U.S. PCS) with their previous PCS (1996–1998 Japan PCS and 1994 U.S. PCS). They found that the patient characteristics in for both countries had remained almost unchanged between the study periods[12] (Table 2). Although the incidence of the patients with T3-4 diseases significantly decreased at 1999–2001, Japanese patients treated with radical radiotherapy continued to exhibit advanced disease (PSA >20 ng/ml and Gleason combined scores of 8–10). On the other hand, the proportion of U.S. patients with advanced disease remained low from 1994 to 1999. These results thus demonstrate persistence of the trend for Japanese patients to have more advanced

Table 1. Patient and treatment characteristics: comparison of PCS results among Japan, Germany, and the United States

Parameter	Japan/1999–2001[a]	Germany/1998–2000[b]	United States/1999[c]
No. of institutions	76	6	58
No. of patients investigated	283	148	392
Patient characteristics			
Age (years)			
Median	72	—	71
Mean	71.8	69	70.8
Pretreatment PSA level (ng/ml)			
Median	20.0	11.3	<10[d]
Mean	90.0	32.1	—
<10	28.7%	—	60.5%
≥10 but <20	21.3%	—	23.0%
≥20	50.0%	—	15.5%
Unknown	—	—	1.0%
Gleason combined score			
Median	7	9	≤6[e]
Mean	6.5	5.8	—
2–6	45.0%	—	54.3%
7	20.5%	—	25.8%
8–10	34.5%	—	18.8%
Unknown	—	—	1.1%
T stage			
TX-T0	0%	0%	7.8%
T1	8.1%	33.0%	43.9%
T2	40.1%	26.0%	33.7%
T3–4	45.6%	32.0%	6.8%
Unknown	2.6%	9.0%	7.8%
N stage			
N0	83.10%	87.0%	—
N1	6.40%	13.0%	—
Nx	9.40%	—	—
Risk group (%)			
Favorable	14.5%[g]	—	38.3%[f]
Intermediate	35.1%[g]	—	37.7%[f]
Unfavorable	50.4%[g]	—	24.0%[f]
Radiotherapy			
Energy (> 10 MV) (%)			
Yes	74.3%	—	73.0%
CT-based treatment planning			
Yes	85.5%	—	95.0%
Conformal therapy			
Yes	43.0%	100%	80.0%
Radiation dose (Gy)			
Median	68.4	—	—
Mean	66.0	69.1	—
Higher dose levels (≥ 72 Gy)			
Yes	7.5%	—	43.0%
Administration of pelvic irradiation			
Yes	33.0%	28.5%	23.2%
Hormonal therapy			
Yes	89.7%	70.5%	51.3%

PCS, patterns of care study; PSA, prostate-specific antigen; CT, computed tomography

[a] Ogawa et al.[11]

[b] Vordermark et al.[14]

[c] Zelefsky et al.[15]

[d] Because 60.5% of patients had PSA values <10 ng/ml, the median should be <10 ng/ml

[e] Because 54.3% of patients had Gleason combined score of 2–6, the median should be ≤6

[f] Favorable, zero adverse features; intermediate, one adverse features; unfavorable, two or more adverse features. Adverse features: PSA >10 ng/ml; Gleason combined score >6; T stage ≥3

[g] Favorable, zero adverse features; intermediate, one adverse features; unfavorable, two or more adverse features. Adverse features: PSA >10 ng/ml; poor differentiation; T stage ≥3

Table 2. Changes in trends in patient and treatment characteristics for Japan and the United States

Parameter	Japan			U.S.		
	1996–1998[a]	1999–2001[b]	Trends	1994[c]	1999[d]	Trends
Patient characteristics						
T stage >3	64%	46%	↓	9%	7%	→
PSA ≥20 ng/ml	55%	50%	→	12%	19%	→
GS ≥8	31%	35%	→	19%	15%	→
Treatment characteristics						
High dose (≥ 72 Gy)	2%	8%	→	3%	45%	↑
CT-based RT planning	81%	86%	→	71%	96%	↑
Hormone therapy usage	86%	90%	→	8%	51%	↑

GS, Glascow Score; RT, radiotherapy
[a] Ogawa et al.[10]
[b] Ogawa et al.[11]
[c] Zietman et al.[24]
[d] Zelefsky et al.[15]

Table 3. Radiation dose and hormone therapy usage distribution in Japan and the United States

Parameter	Japan (%)		United States (%)
	1996–1998[a]	1999–2001[b]	1999[c]
Radiation dose (Gy)			
<68	76.3	47.5	16.0
68 to <72	22.5	45.0	39.0
72 to <76	1.3	7.5	32.0
76–80	0	0	13.0
Hormone therapy usage			
Favorable	76.5	72.0	31.0
Intermediate	85.4	91.8	54.0
Unfavorable	87.1	91.1	79.0

[a] Data reanalyzed from the 1996–1998 Japan PCS results
[b] Ogawa et al.[13]
[c] Zelefsky et al.[15]

disease than their U.S. counterparts during approximately the period of 1990s.

Comparison of patterns of treatment among Japan, Germany and the United States

A previous comparison study by Ogawa et al. identified considerable differences in the patterns of care for prostate cancer between Japan and the United States[12] (Table 1). The current study also identified many differences in the patterns of radiotherapy not only between Japan and the United States but also between Japan and Germany. With regard to equipment, conformal radiotherapy was administered to only 43% of the patients in Japan versus 80% of patients in the United States and 100% in Germany. With regard to radiation doses, the mean total radiation dose for Germany was 69.1 Gy versus 66.0 Gy in Japan. Radiation doses employed in the United States were significantly higher than those used in Japan (Table 3), with almost half (45%) of the U.S. patients receiving prescribed dose levels of ≥72 Gy. The administration of higher radiation doses in Germany and the United States probably reflects the penetration into clinical practice of various reports published during the 1990s indicating that higher radiation doses were associated with a statistically significant improvement in outcome.[16,17] On the other hand, only a small number of patients in Japan (7.5%) received the higher doses (≥72 Gy) during 1999–2001. One reason for this difference may be the lower incidence of conformal radiotherapy in Japan. As mentioned above, conformal radiotherapy was administered to 85% and 100% of patients in the United States and Germany, respectively, but to only 43% of patients in Japan. Previous PCS results indicated that treatment processes in Japanese institutions were closely related to structural immaturity in terms of equipment.[4,9,11] Therefore, to provide high-quality radiotherapy in Japan,

facilities need appropriate treatment planning capability. Modern radiotherapy requires computed tomography (CT)-based treatment planning and conformal radiotherapy to improve the target dose distribution while concomitantly reducing the dose to normal tissues.[18] Another reason for the radiation dose difference may be the high incidence of hormonal therapy in Japan. At present, it is possible that many Japanese radiation oncologists consider the higher dose levels (≥72 Gy) unnecessary for prostate cancer patients when combined with long-term hormonal therapy.

With regard to hormonal therapy, differing patterns of care in hormonal therapy were found among Japan, Germany, and the United States. Most of the patients in Japan (89.7%) received hormonal therapy in conjunction with radiotherapy, whereas this combined therapy was administered less frequently in Germany (70.5%) and the United States (51.3%). Regarding the frequency of hormonal therapy for the various risk groups, the administration of hormonal therapy to favorable-risk patients was different in Japan than in the United States (Table 3). Most of the patients (72.0%) in the favorable-risk group in Japan during 1999–2001 were treated with hormonal therapy, whereas only 31% of favorable-risk patients received hormonal therapy in the United States. Several studies from the United States have indicated that radical radiotherapy alone could control prostate cancer in patients with a favorable-risk status. Zietman indicated that a total dose of 70 Gy was sufficient to control the disease when the pretreatment PSA level was <10 ng/ml.[19] Hanks et al. found that prostate cancer patients with a pretreatment PSA level of <10 ng/ml did not benefit from a dose above 70 Gy.[20] Therefore, radical external beam radiotherapy without hormonal therapy has been the primary treatment for patients in the United States with favorable-risk disease. On the other hand, 72% of the patients in the favorable-risk group in Japan were treated with long-term hormonal therapy. The high rate of health insurance coverage for Japanese people may explain the frequent administration of hormonal therapy in Japan.[21] However, because hormonal therapy has been found to be unnecessary for favorable-risk patients in the United States,[19,20] radical external beam radiotherapy without hormonal therapy may also be the treatment of choice for favorable-risk patients in Japan.

Changing trends in the patterns of treatment between Japan and the United States

Ogawa et al. compared the changes in trends in the patterns of care, and these changes were found to be quite different between Japan and the United States[12] (Table 2). Concerning radiotherapy, the United States has seen a rapid increase in CT-based treatment planning and in the percentage of patients treated with a higher dose levels (≥72 Gy) compared to the 1994 PCS results, with almost half (44.5%) of patients being treated with these higher doses in 1999 compared with 3% in 1994. In contrast, the percentage of patients receiving higher dose levels in Japan has remained below 10%, not only for 1996–1998 but also for 1999–2001. These changing trends in higher prescribed radiation doses and CT-based radiotherapy planning in the United States between 1994 and 1999 demonstrate a drastic change in these parameters over that 5-year period, whereas only minor changes, except the significant decrease of patients treated with <68 Gy (Table 3), occurred in Japan between 1996–1998 and 1999–2001.

Concerning hormone therapy, the percentage of patients receiving hormonal therapy remained high in Japan for the periods 1996–1998 and 1999–2001, whereas the use of hormonal therapy in the United States showed a rapid increase from 1994 to 1999. The significantly increased use of hormonal therapy for high-risk patients in the United States reflects the penetration and growing acceptance of clinical trial results that have demonstrated the efficacy of these treatment approaches.[22] The randomized trial RTOG 8610 demonstrated an increase in disease-free survival for locally advanced prostate cancer patients treated with neoadjuvant total androgen blockade plus radiotherapy compared with radiotherapy alone.[23] PCS results in the United States indicate a rapid increase in the use of hormonal therapy from 1994 to 1999, whereas PCS results in Japan indicate that the use of hormonal therapy in patients with unfavorable-risk disease has remained high (>90%) (Table 3). Therefore, radiotherapy in conjunction with hormonal therapy appears to be an accepted approach for the unfavorable-risk group in both Japan and the United States.

Conclusions

Comparisons of Japanese, German, and U.S. PCS results revealed several differences in the patterns of care among these countries. Higher proportions of patients treated with radical external beam radiotherapy in Japan had advanced disease compared with those in Germany and the United States. A specific comparison between Japan and the United States shows that this trend has continued over the past several years. Patterns of care for prostate cancer in Japan significantly differ from those in Germany and the United States, especially with respect to radiation dose and the use of hormonal therapy.

Moreover, changes in trends in the patterns of care also show differences between Japan and the United States. These results suggest that in Germany and the United States, radiotherapy for prostate cancer has become widely applied as an established treatment, whereas its use in Japan was still immature and developing during the period when this national survey was conducted.

We now are analyzing 2003–2005 Japan PCS data. Repeat surveys and point-by-point comparisons with results from other countries, such as Germany and the United States, should demonstrate how external beam radiotherapy for prostate cancer is being developed and optimized for patients in Japan.

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HEPATOLOGY

Radiotherapy for lymph node metastases in patients with hepatocellular carcinoma: Retrospective study

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Abstract

Aim: This study was conducted to evaluate the effect of external radiation therapy on lymph node metastases from hepatocellular carcinoma (HCC).

Methods: A total 28 patients with cytopathologically proven HCC were subjected to radiation therapy over a 5-year period, and treatment was continued in all cases. All patients underwent irradiation with a total dose ranging between 46 and 60 Gy in daily 2.0-Gy fractions, five times a week.

Results: Among the metastatic lesions treated, 18 (64%) and five (18%) patients achieved partial responses and complete responses, respectively. The 1- and 2-year overall survival rates and the median survival time were 53% and 33%, respectively, and 13 months in patients given external beam radiation therapy (EBRT) for a non-palliative, near-cure intent ($n = 21$).

Conclusions: Although lymph node metastasis from HCC is sensitive to EBRT, the intent of EBRT should be limited to palliation. For palliative purposes, it is useful in treatment with 50 Gy in 25 fractions for these patients.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in Japan, with a mortality of 28.6 per 100 000 in 2001. During recent years, because of the progress achieved in treatment methods, the likelihood of improving local control and the survival rate in HCC has increased. However, prolongation of life might also result in the increased development of metastatic lesions. Liver, lung, bone, lymph node, adrenal, brain and elsewhere are known as the metastatic regions of HCC. Above all, lymph node metastasis (LNM) is likely to accompany systematic metastases, and a treatment method has not yet been established. As external beam radiation therapy (EBRT) has long been used in cancer therapy, we felt that it might be of benefit in the treatment of metastatic HCC lesions.

In our institution EBRT has been used in HCC patients with LNM since 1994. Because the role and efficacy of EBRT for LNM from HCC has not been determined, a retrospective study was conducted of our experience over the past 5 years to evaluate the objective response of LN lesions from HCC and side-effects of EBRT. This study constitutes a preliminary report on the results for 28 HCC patients with LNM who received EBRT.

Method

EBRT was performed on 28 HCC patients diagnosed with LNM until July 2005 (Table 1). All 28 patients had HCC confirmed by hepatoma resection or liver biopsy. Patients with cholangiocarcinoma or mixed HCC and cholangiocarcinoma were excluded from this study. EBRT was not the initial treatment in all patients (Table 2). After resection, transcatheter arterial embolization (TAE), radiofrequency ablation (RFA), or percutaneous ethanol injection therapy (PEIT) of the primary tumor, the regular follow-up consisted of monthly liver function tests plus serum alpha-fetoprotein (AFP). Also, enhanced computed tomography (CT) scans were performed every 6 months on all patients. Diagnosis of LNM was made by the enhanced CT scans during the clinical follow-up studies (Table 3).

The lymph nodes were not the only site of recurrences in all patients. Characteristics of intrahepatic tumors at the time of positive LNs are shown in Table 2. Information regarding other metastasis at the same time is listed in Table 3.

In this paper, the locoregional abdominal lymph node metastasis from HCC was grossly classified to hepatic portal, peripancreatic and para-aortic nodes on the basis of the increase