

Figure 2. Two-stage cluster sampling in the PCS. Number of institutions audited was limited to ~80 out of 700 in Japan (11).

between minimum and maximum values and help functions to indicate criteria for the definition of each of the survey items. At the PCS data center, online supporting functions such as early checking of the accuracy of data entry and image capturing was developed for the auditors that produced a dramatic improvement in the accuracy of data entry compared to that of the second PCS. During this survey period, the Individual Information Protection Act (draft) was introduced, promoting us to prepare applications for approval for the PCS from the institutional review board of each of the participating institutes before the audit was conducted. External audits of the 76 institutes were performed from July 2002 to June 2004, and two-stage cluster sampling enabled us to collect detailed and accurate data for 3396 patients with carcinoma of any of the five sites and their 13 386 images (7.03 GB). The second Japan/USA PCS workshop was held in February 2003, at the National Cancer Center, Tokyo, supported by grants from the Japanese Foundation of Aging and Health, the Japanese Society for the Promotion of Science, the Japanese Foundation of Cancer Research, Siemens Medical Ltd, Toshiba Medical Ltd and CMS Japan Ltd. In this workshop, further comparisons based on the findings of the first workshop were made, especially with regard to the best current management, the outcome for the patients with any of the five diseases surveyed in PCS and radiation doses for patients with cancer of the cervix. Leading Japanese surgical oncologists, medical oncologists and members of the Korean PCS group also participated and discussed issues from a broader viewpoint (15).

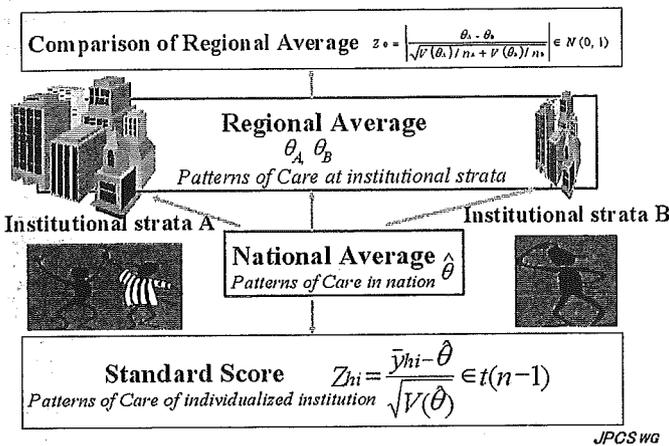


Figure 3. PCS quantitative evaluation of the quality of radiotherapy in Japan (12).

survey items could be calculated from the collected PCS data (11,12). NAs were used as a criterion for the evaluation of the quality of individual institutions as shown in Fig. 3. Computer software of PCS format was improved continually by installing new logical checking function to eliminate erroneous data obtained during audits (13). The first USA/Japan PCS workshop, supported by the National Cancer Institute and Japan Society for the Promotion of Science, was held in San Francisco in November 2001 (10,14).

THIRD PCS (PCS99-01)

In 2002, new funding for PCS (no. 14-6) enabled us to conduct the third national survey, for which we used the same study design as for the second PCS. In addition, we collected image data obtained from, for example, treatment planning simulator films and portal films by using digital camera at audit. For browsing these images, we developed a novel image database linked with the original PCS databases. In this new trial, more detailed analysis of treatment planning was possible. The PCS data format became highly sophisticated as a result of the installation of new logical checking functions based on actual data of the second PCS to determine a reasonable range

STRUCTURE OF RADIATION ONCOLOGY BY INSTITUTIONAL STRATIFICATION

PCS uses two-stage cluster sampling of institutions and patients according to institutional stratification. This is the basic mechanism that renders PCS data useful for the improvement of the nationwide structure. PCS's two-stage cluster sampling made it possible to analyse the structure in close correlation with process and outcome. Table 2 shows the structure of institutions in 2001 for which the third PCS survey was performed. Structural maturity, reflected by number of equipment and personnel, closely correlated with this stratification. In 62-78% of academic institutions such as university hospitals or cancer centers (A), 1.6-1.8 accelerators with dual energy function were installed, and computed tomography (CT) simulators and high-dose rate brachytherapy machines in nearly 70%. On the one hand, full-time equivalent (FTE) radiation oncologists and technologists in these institutions numbered ≥ 1 and ≥ 2 , respectively. On the other hand, non-academic institutions such as national, prefectural or municipal hospitals (B) showed smaller numbers of both equipment and staff. However, figures for these structures in 2001 improved by more than 20% over those in 1995, except for the number of FTE radiation oncologists in larger academic institutions (A1). The number of cancer patients/year increased markedly in all institutional strata. These findings show that this

Table 2. Structure of radiotherapy facilities in 2001 surveyed by PCS

	Stratification of institution			
	A1	A2	B1	B2
Linear accelerator (mean)	1.8	1.6	1.1	0
Dual energy machine (%)	78	62	76	38
CT simulator (%)	70	50	50	28
High-dose rate brachytherapy (%)	71	72	35	20
Radiation oncologist (FTE*, median)	2.7	1.5	0.8	0
Radiation technologist (FTE*, median)	4.0	3.0	2.0	1
Annual number of patients (mean)	630	397	264	101
Annual number patients/FTE radiation oncology	233	264	330	336

The italicized values indicate the value of each survey item in 2001 increased by more than 20%, compared with those in 1995; Dual energy machine and annual number of patients/FTE radiation oncology—there were no comparable data in 1995; A1, academic institutions like university hospital or cancer center treating ≥ 430 patients/year; A2, the same type of institutions < 430 patients/year; B1, other non-academic institutions like national, prefectural or city hospital treating ≥ 130 patients/year; B2, the same type of institutions < 130 patients/year.

*FTE, full-time equivalent (40 h/week for radiation oncology service).

stratification made appropriate differentiation of the structure possible for use in further PCS analysis.

Although the structure has been improving recently in terms of patient load, the increase in the number of radiation oncologist is still well below that of equipment.

FUTURE DEMAND FOR RADIOTHERAPY IN JAPAN

We surveyed by questionnaire the number of cancer patients in the last 13 years in the institutions audited, and the total number of patients was estimated by adjusting the number of facilities in each stratum and the number of annual patients in each institution. JASTRO has performed structure surveys every 2 years, and by combining their and our data the future demand for radiotherapy was estimated as shown in Fig. 4. It is expected that $\sim 170\,000$ patients in 2005 and $240\,000$ in 2010 will be treated with radiation. However, the dotted line in Fig. 4 shows the projected increase in 10 years, i.e. 2015, based on the assumption that half of all cancer patients will be treated with radiation as is the case in the United States. This curve is much steeper than the one for our prediction. Therefore, the number of cancer patients who require radiation is increasing rapidly in Japan.

THE USA/JAPAN PCS WORKSHOP

In the first workshop, all aspects of the similarities and differences between the two countries were compared and discussed in terms of epidemiology of esophageal, lung and uterine cervix cancer that had been surveyed with the PCSs, as well as the respective staging systems, the medical care systems and the structures of radiation oncology. It was noted that the PCS results confirmed the existence of epidemiological differences, that two-stage cluster sampling used in the PCSs functioned normally, and that the surveyed data accurately

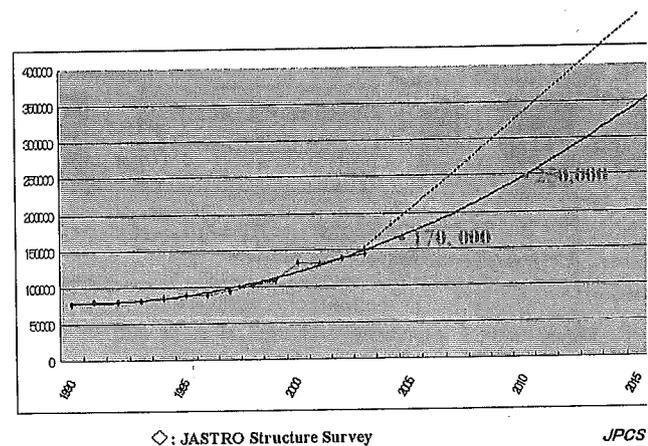


Figure 4. Estimated number of cancer patients treated with radiation in Japan based on PCS and its future demand. Dotted line shows the increase based on assumption that by 2015, a total of 50% of cancer patients will be treated with radiation as in the case in the United States.

reflected the national practice patterns. There was a significant difference in utilization of radiation between the USA and Japan, with Japan's use of radiotherapy being ~ 3.5 times lower (10,14).

One of the more remarkable results of the second workshop was the identification of a significant discrepancy in radiation dose for uterine cervix cancer patients between Japan and the United States, while US medical physicists concluded, after reviewing films from Japanese institutions that there was no significant difference in dose calculation for HDR brachytherapy. Differences in dose specification method for HDR brachytherapy and anatomical dimensions such as pelvic parameters, vaginal anatomy and uterine size were suggested as causative factors and will be further explored.

The National Cancer Database (NCDB) was introduced by Dr D. P. Winchester, medical director of the NCDB and

of the American College of Surgeons. The NCDB comprises a non-population based clinical data set, which collects information from ~1600 hospital cancer registries for all cancer sites in the 50 United States. The NCDB has been used as a clinical surveillance mechanism, monitoring changes and variations in patterns of cancer care and patient outcomes. It holds information on about 70% of all newly diagnosed cases of cancer nationwide, with 850 000 cases entered every year. While the number of survey items surveyed by the NCDB is lesser (<200) than that included in the PCS, both systems have played important and complementary roles in the nationwide QA project (15). While the NCDB's mission is 'to decrease the morbidity and mortality of cancer through standard setting, education and the tracking of outcomes', PCS is more of a modality-specific study and the number of survey items is more than three or four times of that of NCDB. NCDB and PCS have been sharing information since 1999. To improve the quality of care for cancer patients in Japan, both NCDB and PCS are necessary as monitoring and evaluation mechanisms for processes and outcomes.

VARIATION OF PROCESS ACCORDING TO INSTITUTIONAL STRATIFICATION

Table 3 summarizes the evidence from the Japanese PCS that the process for the patients with breast, cervix, esophagus, lung and prostate cancer varies significantly according to institutional stratification (7,9,16–23). In general, the larger academic institutions (A) provided better quality of care for their patients than did the smaller non-academic institutions (B).

BREAST PCS

As for post-mastectomy radiotherapy for breast cancer patients more advanced and appropriate techniques, such as use of a cast or shell, simulation with CT and multileaf collimator, were used frequently in A institutions. Beam energy >6 MV, which is no longer considered suitable for breast cancer patients, was still being used in 17% of B institutions.

CERVIX PCS

A daily fraction dose ≤ 180 cGy, which is safer for elderly patients, was used more frequently in B institutions. Beam energy ≥ 10 MV, which is appropriate for deep-seated tumors, such as cancer of the uterine cervix, esophagus, lung and prostate, was used for 85% of the patients in A institutions.

PCS92–94 showed a significant difference in utilization of brachytherapy between A and B institutions, and this discrepancy in process was also observed in PCS95–97 and PCS99–01. Figure 5 shows significant differences in the utilization of brachytherapy according to stratification of institutions. In smaller institutions the utilization rate was lower, especially in B2, but PCS99–01 showed improved rates for A2, B1 and B2 institutions.

ESOPHAGUS PCS

Radiotherapy was combined with surgery more frequently in A institutions, where more surgical oncologists are working. In addition, brachytherapy was used more frequently in A than in B institutions. The rule of 'all fields treated a day', which is considered a fundamental technique in routine radiotherapy as shown in Table 1, was observed for 76–86% of patients with esophagus, lung or prostate cancer in A institutions. The rates were significantly (20–30%) lower for B institutions. Higher external radiation doses (>60 Gy) were delivered to patients in A institutions, where treatment tends to be more aggressive. There were significant differences in the use of external beam energy among strata, for example, for esophageal cancer, as shown in Fig. 6. In smaller institutions, equipment with lower energy levels was more frequently used, although a recent survey indicated that these levels have markedly improved (PCS99–01). Nevertheless, 41% of the patients in the smallest institutions (B2) were still treated with energy levels ≤ 4 MV (19). In the surgery group, the extent of lymph node dissection, indicative of the aggressiveness of procedures, was significantly different, with D3 dominant in A institutions and D2 in B institutions.

LUNG PCS

As for the small cell lung cancer (SCLC) group, field reduction during radiotherapy, which requires careful application of technical skill, was more frequently performed in A institutions. As for non-small cell lung cancer (NSCLC) group, in addition, chemotherapy and radiotherapy for contralateral mediastinum, representative of more aggressive treatment, were more frequently used. Dose prescription was determined by means of isodose line for 25% of patients at A institutions, although the rate was still lower than that of the United States.

PROSTATE PCS

For prostate cancer, advanced technologies such as CT simulator, portal image and conformal therapy were used at significantly higher rates (20–30%) at A than at B institutions. Findings also differed according to disease site. For example, adoption of CT-simulation markedly differed for breast cancer and prostate cancer. For breast cancer patients, tangential beams constitute the standard technique for whole breast irradiation, which thus does not always require a CT simulator. For prostate cancer patients, on the other hands, 3D conformal radiotherapy, which makes use of CT simulator almost a necessary, is becoming increasingly popular. Therefore, these process data must be monitored carefully for individual disease sites.

These data confirmed that the structure of radiation oncology in Japan is immature, and this influences the process for cancer patients and possibly their outcome. American PCS has proved that the variations in process significantly affected outcome (4–6). The Japanese PCS also indicated that the stratum of

Table 3. Important evidence observed by Japanese PCS that the structure significantly influenced the process of radiotherapy and surgery

Process of radiotherapy and surgery (%)	Stratification of institution		
	A	B	P-value
Breast			
PCS95-97 PMRT (16)			
Cast or shell	20.9	9.2	0.008
Simulation with CT	39.1	17.7	<0.001
Beam energy (>6 MV)	2.2	16.7	0.022
Total dose (median, range)	50 (40-61.2) Gy	50 (46-60) Gy	0.030
Multileaf collimator	27.3	2.3	0.001
Cervix			
PCS92-94 non-surgery (9)			
Daily fraction size (≤180 cGy)	30.0	52.0	<0.001
Beam energy (≥10 MV)	85.0	60.0	<0.001
Brachytherapy			
FIGO Stage I	100	100	NS
FIGO Stage II	98	92	0.037
FIGO Stage III	94	79	0.002
FIGO Stage IV	82	60	0.048
PCS95-97 non-surgery (17)	See Fig. 5		
PCS99-01 non-surgery	See Fig. 5		
PCS95-97 surgery (18)			
EBRT + ICRT	21	8	0.002
Beam energy (≥10 MV)	88	43	<0.001
Total dose			
50 Gy	29	18	<0.001
50.4 Gy	15	32	
Daily fraction size (≤180 cGy)	53	65	<0.001
Esophagus			
PCS92-94			
Surgery combined (7)	45	34	0.007
Brachytherapy combined	16	5	<0.001
All fields treated a day	75	51	<0.001
Non-surgery group			
External radiation dose (≥60 Gy) 84	84	67	<0.001
PCS95-97 non-surgery (19)	See Fig. 6		
PCS99-01 non-surgery	See Fig. 6		
PCS95-97 surgery group (20)			
Lymphatic dissection (JSED)			
D0-1	13	18	0.034
D2	31	49	
D3	49	25	
Unknown	7	8	

Table 3. Continued

Process of radiotherapy and surgery (%)	Stratification of institution		
	A	B	P-value
Dose for spinal cord			
>50 Gy	8	19	0.06
45-50 Gy	26	15	
<45 Gy	66	66	
Lung			
PCS95-97 SCLC group (21)			
Field size reduction during radiotherapy	68	52	0.01
All fields treated each day	86	69	0.01
PCI employed	3.4	0	0.01
Beam energy (≥10 MV)	80	38	<0.01
PCS95-97 NSCLC non-surgery group			
Chemotherapy	56	38	0.01
Radiotherapy contralateral mediastinum	64	55	0.01
Dose prescription isodose line	25	14	0.01
Prostate			
PCS99-01 radical Ext. RT group (22)			
CT simulator	93	77	<0.01
Portal image used	91	55	<0.01
Conformal therapy	54	24	<0.01
Beam energy (≥10 MV)	91	72	<0.01
All fields treated each day	82	56	<0.01

A, academic institutions like in A1 or A2 in Table 2; B, non-academic institution like B1 or B2 in Table 2; PMRT, post-mastectomy radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; EBRT, external beam radiotherapy; ICRT, intracavitary radiotherapy; JSED, Japanese Society for Esophageal Disease; D0, no or incomplete dissection of Group 1 lymph nodes; D1, dissection of Group 1 lymph nodes; D2, dissection of Group 2 lymph nodes, but not no or incomplete dissection of Group 3 lymph nodes; D3, dissection of Groups 1, 2 and 3 lymph nodes (bilateral cervical mediastinal and upper abdominal region); SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.

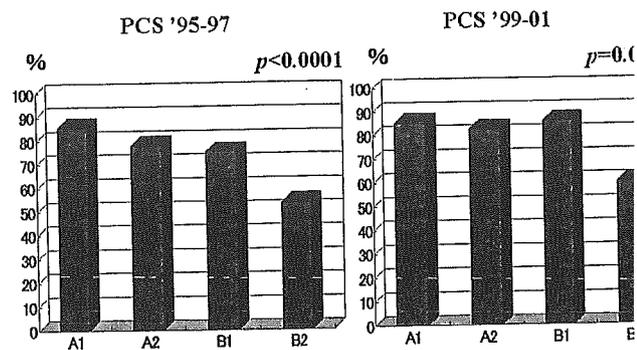


Figure 5. The utilization of brachytherapy (%) for the patients with cervix cancer by institutional stratification (9).

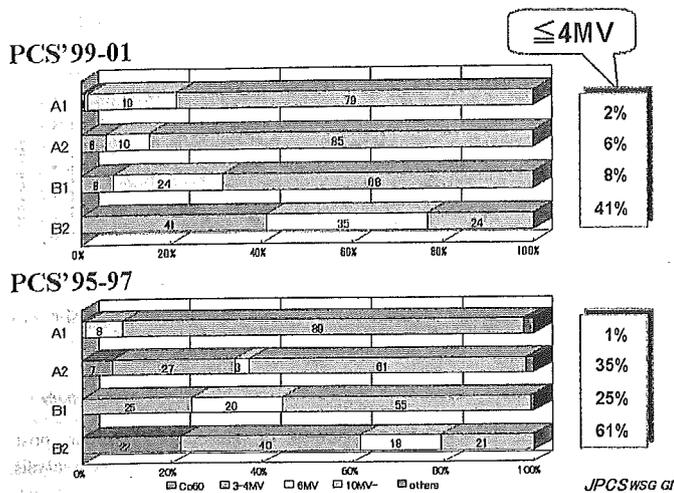


Figure 6. Proportion of external beam energy for the treatment of esophageal cancer patients by institutional stratification (19).

institution or structure affected the outcome for esophagus cancer (19,20) or uterine cervix cancer patients.

Therefore, urgent structural improvement is considered an essential component of a nationwide QA project for cancer patients. To attain the ultimate goal of improvement in patient outcomes, the basic structure of radiation oncology must be established in accordance with appropriate institutional characteristics and patient load.

AGE ANALYSIS RESULTS

PCS92-94 featured age analysis for the non-surgery group esophageal cancer. There were significant differences in the backgrounds of patients, including history of cardiovascular disease, KPS, Stage/AJCC and process-like chemotherapy, as shown in Table 4 (23). The elderly, i.e. those ≥ 75 years showed higher frequency of cardiovascular disease, lower KPS, more Stage II and less Stage III. Chemotherapy was rarely performed for these patients. However, multivariate analysis showed that age did not affect outcome, while KPS, Stage/AJCC and external dose were identified as significant prognostic factors.

The same analysis results for the SCLC group examined in PCS95-97 showed that use of chemotherapy, especially concurrent use of etoposide and cisplatin, and its cycles decreased significantly for the elderly (24). Age analysis also showed significant variations in patients' history of cardiovascular disease. Multivariate analysis using survival as the endpoint showed that age, chemotherapy and T-stage were significant prognostic factors.

PCS can provide important information to gain an understanding of actual nationwide practice, especially for the elderly, aged ≥ 75 years, which is sometimes difficult to survey because most of the elderly are generally not suitable candidates for prospective clinical studies. One important message obtained from the PCS is that radiation therapy can be used for elderly patients in almost the same manner as for younger age groups.

Table 4. Important evidence provided by Japanese PCS that the age also significantly affects the process and outcome of radiotherapy

Process of radiotherapy (%)	<65 years old	65-74 years old	≥ 75 years old	P-value
Esophagus				
PCS92-94 non-surgery group (23)				
External dose (Gy) >60	81	73	70	0.149
Chemotherapy done	50	40	19	0.001
Cardiovascular disease	15	25	42	0.001
KPS (60-70)	28	30	41	0.001
AJCC Stage III	71	62	44	0.001
Prognostic factors identified by multivariate analysis using survival as endpoint				
Age				0.220
KPS				0.001
Stage/AJCC				0.001
External dose				0.001
Lung				
PCS95-97 SCLC group (24)				
Cardiovascular disease	13	25	42	0.031
Chemotherapy	96	91	80	0.066
Concurrent with radiotherapy	44	27	25	0.029
Etoposide (%)	96	97	75	0.017
Cisplatin (%)	77	73	19	0.001
Median cycles (n)	3	3	2	0.001
Prognostic factors identified by multivariate analysis using survival as endpoint				
Age				0.032
Chemotherapy				0.030
T-stage				0.042

AJCC, American Joint Committee on Cancer; KPS, Karnofsky performance status.

BASIC STRUCTURE REQUIREMENTS FOR QA OF RADIOTHERAPY BASED ON PCS IN JAPAN

Based on the PCS data obtained during the three trials, we published guidelines for basic structure requirements for QA of radiotherapy and distributed them to all directors and chairpersons of radiotherapy facilities and medical schools throughout Japan (25).

Figure 7 shows the annual number of cancer patients treated per one external beam machine by institutional stratification. In half of the A2 and B1 institutions ≥ 250 patients were treated, and 300 or more patients in more than half of the A1 institutions. Therefore, we estimated an acceptable annual patient load as 250 on the assumption that four patients can be treated per hour and there are 7 working hours in a day. As a result, we based the guidelines for annual patient load/external

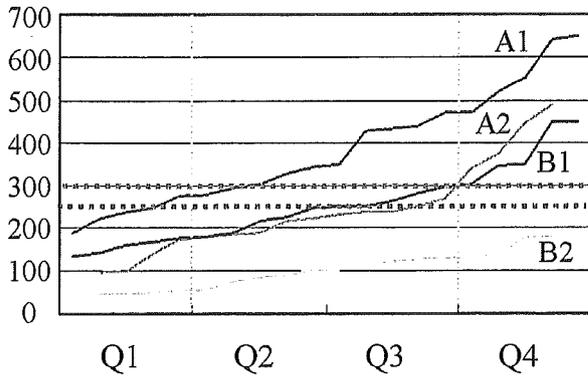


Figure 7. The distribution of annual number of cancer patients treated per one external machine by institutional stratification (25). Q1 includes four or five institutions in the lowest one-quarter (0–25%) for patient load/machine. Q2, 26–50%; Q3, 51–75%; and Q4, 76–100%.

beam machine on an annual patient load of 250–300. In more than one-quarter of the A1 institutions 450 or more patients were treated. The warning level of annual patient load/machine for institutions that urgently need structural improvement was set at 400. While the annual patient load/machine and the number of personnel in B2 institutions were below the guidelines, these institutions can be expected to play an important role in the treatment of rapidly growing numbers of cancer patients. Corresponding guidelines for annual patient load per FTE radiation oncologist and per FTE radiation technologist were set at 200 (warning level for improvement of structure: 300) and 120 (warning level: 200), respectively.

We estimate on the basis of PCS data that the respective numbers of 1400 radiation oncologists, 830 medical physicists and 1400 radiotherapy technologists will be required in 2015 (25). Recruitment and education of such personnel are essential for a nationwide QA project in the field of radiation oncology. In particular, recent advances in radiotherapy technologies such as intensity modulated radiotherapy, image-guided radiotherapy and brachytherapy require large numbers of medical physicists, who already play an important role in QA and development of new treatment equipment or techniques in most western countries. However, there are few medical physicists in Japan, while significant variations according to institutional stratification in the use of accelerators were also observed. Overutilization of equipment with insufficient personnel constitutes a potential risk of malpractice. Therefore, we need a suitable and adequate structure of equipment and personnel to provide the best quality of care for our patients. To this end, we published structural guidelines for radiation oncology (25). We also confirmed that these requirements are justified for A1–B1 institutions in terms of a reasonable reimbursement from current medical insurance systems. The break-even point for patient load/machine is estimated at ~200 patients/year (25).

IMAGE ANALYSIS

Image data were collected for the third PCS. Figure 8 shows one example of image analysis for the distribution of the lower

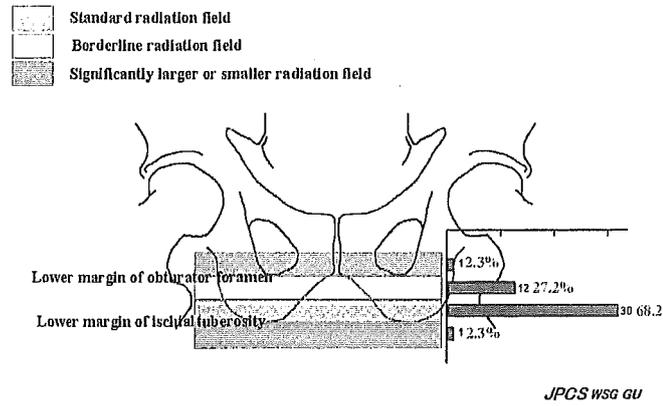


Figure 8. Distribution of lower margin of radiation field for post-prostatectomy patients with prostate cancer evaluated by PCS image analysis.

margin of the post-operative radiation field for patients with prostate cancer who underwent prostatectomy. Significant variations in radiation field patterns were observed. Nearly one-third of all patients were irradiated with inadequate (borderline field and with larger field in the craniocaudal direction.

PCS99–01 disclosed significant variations in position of the radiation field that could not be detected by text or numerical data only in the previous PCS database. For a multi-institutional prospective study, review of treatment film or condition is an essential component of the QA process. Image data of PCS can be used as criteria for the radiation field in a prospective study, while image analysis, which is part of PCS99–01, may represent a new frontier for a nationwide QA project and is both most promising and most challenging. We are currently developing an automatic image data capturing system to obtain data by means of the Radiation Therapy Oncology Group (RTOG) format or Digital Imaging and Communications in Medicine Radiation Therapy (DICOM-RT) from treatment planning computers. The feasibility of this system is now being tested.

LIMITATION OF PCS

While significant differences in patterns of care for the patients and structure were observed according to institutional stratification, there were also significant variations in follow-up rates for patients according to stratum. Figure 9 shows an example of survival curves for patients with NSCLC according to PCS and Osaka Cancer Registry (OCR) findings (26). It appears that survival curves of patients were overestimated by PCS, compared with those by OCR since follow-up rates for PCS were ~65% but those for OCR 99% or more.

Therefore, the current PCS has shown some limitations in terms of outcome analysis, because there are significant variations according to institutional stratification in the follow-up information of surveyed patients (26). This indicates an urgent need for a new data capturing mechanism using an epidemiological approach by, for example, establishing in-house c

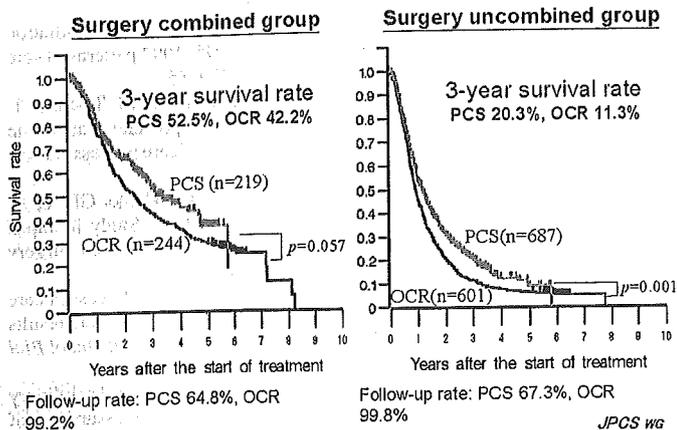


Figure 9. Survival curves for patients with NSCLC based on PCS and OCR data (26).

regional cancer registries. PCS is a labor-intensive survey that requires more than 4000 h for data collection of 3000–4000 patients. The PCS method may therefore be unique, but is not at the leading edge.

FUTURE GOALS

Considering the current immaturity of the Japanese structure of radiation oncology, PCS still can perform an important function in monitoring structure, process and outcome, as well as providing essential information not only to medical staff and their patients but also to administrative policy makers. If the structure becomes mature in Japan, a more sophisticated data capturing system similar to the NCDB in the United States through the establishment of in-house cancer registries can take over the role of PCS. We have now started the development of a prototype of the Japanese National Cancer Database based on our PCS technology.

In the meantime, however, PCS can be expected to remain useful for improving the clinical QA of radiation oncology as well as other specialties through detailed monitoring and evaluation of their structure, process and outcome.

CONCLUSIONS

The national data obtained with PCS confirmed the continuing existence of significant differences in structure of radiation oncology according to institutional stratification. PCS has been monitoring nationwide practice patterns of radiation oncology by means of external audit and reviewing medical charts of actually treated patients. PCS also confirmed that significant variations in the process remained according to stratification. PCS has thus provided overwhelming evidence of the influence of structure on the nationwide process of radiation oncology and of the existence of wide variations in both these factors.

PCS is useful for establishing the clinical QA for any of the specialties of oncology through monitoring of their structures, processes and outcomes nationwide.

‘Variation equals opportunity’ (G. E. Hanks)

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ORIGINAL ARTICLE

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Late complications after high-dose-rate interstitial brachytherapy for tongue cancer

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Abstract

Objectives. To analyze the treatment results and late complications of high-dose-rate (HDR) interstitial brachytherapy (ISBT) for early (T1N0, T2N0) mobile tongue cancer using the microSelectron-HDR.

Methods. From January 1993 through April 2001, a total of 72 patients with early squamous cell carcinomas of the mobile tongue were treated with microSelectron-HDR interstitial brachytherapy at the Department of Radiology, Osaka University Hospital. Of the patients, 18% were treated with a combination of prior external radiation and HDR-ISBT, and 82% were treated with HDR-ISBT alone. For HDR-ISBT alone, all cases were treated with a total dose of 54 Gy/9 fractions every 5 days or 60 Gy/10 fractions every 8 days. In combined therapy with an external dose of 30 to 40 Gy, HDR-ISBT was given at a total dose of 42–50 Gy. The Brinkman and alcohol indexes were used to analyze the incidence of late complications after HDR-ISBT.

Results. The 2- and 5-year local control rates were 85% and 82%, respectively. Fifteen of 72 patients (21%) treated with HDR-ISBT had late complications. Ten of 15 patients (67%) with late complications had a Brinkman index exceeding 600.

Conclusions. HDR-ISBT is useful and easily applied under local anesthesia to early or superficial lesions of the mobile tongue. However, we found an increase in late complications, such as soft-tissue ulcers and bone exposure, after irradiation of tongue cancer with 60 Gy HDR-ISBT in patients with a Brinkman index greater than 600.

Key words Brachytherapy · Tongue cancer · High dose rate · Brinkman index · Late complications

Introduction

High-dose-rate (HDR) interstitial brachytherapy (ISBT) with a microSelectron-HDR has been used to treat carcinomas of the oral cavity, such as those of the tongue and floor of the mouth. This treatment method has been available at Osaka University Hospital since 1991 as a replacement for low-dose-rate (LDR) ISBT. The advantages of and indications for HDR-ISBT are (1) easy application under local anesthesia in patients for whom ^{226}Ra needle implants or the ^{192}Ir hairpin technique are indicated, (2) elimination of radiation exposure to the medical staff, and (3) ease of treatment for elderly patients.

This report uses the Brinkman index and alcohol index to examine the incidence of late complications after HDR-ISBT for tongue cancer.

Materials and methods

Between January 1993 and April 2001, 72 patients with early-stage (T1N0, T2N0) squamous cell carcinomas of the mobile tongue were treated with HDR-ISBT using the microSelectron-HDR (Nucletron, Veenendaal, the Netherlands) at the Department of Radiology, Osaka University Hospital (Table 1). The ratio of men to women was 2.8:1, and their ages ranged from 28 to 82 years with a median of 59 years. Single-plane implants of flexible tubes are rou-

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Table 1. Case distribution of tongue cancer treated with high-dose-rate interstitial brachytherapy (HDR)

	HDR	EXT + HDR
No. of eligible cases	59	13
T-Category		
T1	22	0
T2	37	13
Age (years)		
Range	28-82	28-73
Median	60	57
Sex		
Male	44	9
Female	15	4
Brinkman index		
< 600	28	9
\geq 600	29	2
Unknown	2	2
Alcohol index		
< 60	34	10
\geq 60	23	1
Unknown	2	2
Follow-up period (months)		
Range	6-104	15-92
Median	39	36

EXT, external radiation

Table 2. Treatment methods for tongue cancer treated with HDR (T1T2N0)

EXT dose (Gy)		No. of patients	HDR dose (Gy)	
Median	Range		Median	Range
0	0	59	60	48-60
30	30-32	4	48	48
40	38-40	9 (3) ^a	48	42-50

^aNumber of patients who received chemotherapy

tinely used for HDR-ISBT implants. The implants are placed inside a target area designed to cover the lesion with a 5-mm margin. The dose prescribed is equivalent to 6 Gy in the target area. Four to eight flexible tubes are usually used for single- or double-plane implants. The volume-implant technique was used when thick tumor induration was palpated after external radiation. In patients treated only with HDR-ISBT, a total dose of 48 to 60 Gy was prescribed in the target area (Table 2). The median dose was 60 Gy. In cases of combined therapy, 4 MV X-rays were used for treatment before HDR-ISBT.

As the goal of treatment was to provide a curative brachytherapy dose that minimized acute and late damage as much as possible, the minimum effective external radiation dose was prescribed, which was usually 30 Gy over 3 weeks. However, if the lesion was too large to attain sufficient tumor regression with a 30 Gy external radiation dose before HDR-ISBT, external radiation was continued to a total dose of 40 Gy. External radiation was usually given at a dose of 2 Gy per day, 5 days a week. An ipsilateral beam was applied to the lateral border of the tongue, and either a parallel or two-to-one weighted parallel opposed beam was

used for the anterior portion of the tongue. Although the time interval between the external radiation and HDR-ISBT was usually about 3 weeks, if a dose greater than 40 Gy was delivered, a longer interval was necessary to prevent an acute mucosal reaction. The dose of HDR-ISBT administered after external radiation was basically the same interstitial radiation dose as with HDR-ISBT alone. However, if a dose greater than 30 Gy was administered, the HDR-ISBT dose was decreased by 20%-30% according to the local conditions of the lesion.

The Brinkman index¹ and alcohol index were used to analyze the incidence of late complications, such as soft-tissue ulcers and bone exposure after HDR-ISBT. Tobacco use was calculated from the number of cigarettes smoked each day and the number of years the subject had smoked. For example, if the patient had smoked ten cigarettes each day for 10 years, these two figures were multiplied together, giving a value of 100. Alcohol use was calculated in a similar manner. If the patient had three drinks each day for 20 years, the alcohol use would be 60.

Follow-up ranged from 6 to 104 months with a median of 39 months in the group with HDR alone and from 15 to 92 months with a median of 36 months in the group with combined therapy.

Local control and cause-specific survival rates were analyzed using the Kaplan-Meier method. Statistical significance was evaluated using either the χ -squared test or Mantel-Haenszel method.

Results

Local control rates and nodal metastases

For early mobile tongue cancer treated with HDR-ISBT, the 2- and 5-year local control rates for all cases were 85% and 82%, respectively. Nodal metastases after treatment occurred in 38% (27/72) of the patients. These patients received salvage surgical treatment, such as radical neck dissection or upper neck dissection. The control rate for nodal metastases was 59% (16/27).

Late complications

Table 3 shows the incidence of complications for the irradiation technique when salvage operation cases were excluded. There was no significant difference in the incidence of complications between the group receiving HDR-ISBT alone and the group receiving combined therapy ($P = 0.144$).

We examined whether patients with complications after HDR-ISBT, such as soft-tissue ulcers and bone exposure, had a Brinkman index of 600 or more. The patient characteristics according to the Brinkman index are shown in Table 4. Fifty-one percent (37/72) of the patients had a Brinkman index of less than 600, while 43% (31/72) had an index of greater than 600. Thirteen of the 37 patients (35%) who had a Brinkman index of less than 600 had a history of

Table 3. Incidence of complications from the irradiation technique, when salvage operation cases were excluded

	HDR (59)				EXT + HDR (13)			
	Single	Double	Volume	Total	Single	Double	Volume	Total
No. of cases	45	12	2		7	4	2	
Salvage operation after recurrence	6	2	0		1	2	1	
Complications								
Soft-tissue ulcers	4				1		1	
Bone exposure	1	1			2			
Soft-tissue ulcer and bone exposure	3	1	1					
Total complications	8/39	2/10	1/2	11/51 (22%)*	3/6	0/2	1/1	4/9 (44%)*

Single, single plane; Double, double plane; Volume, volume implants

* $P = 0.144$

Table 4. Patient characteristics by the Brinkman index

	Brinkman index		
	<600	≥ 600	Unknown
No. of cases	37	31	4
Sex			
Male	21	28	4
Female	16	3	0
Age (years)			
Range	28–82	47–81	32–62
Median	59	60	58
No. of patients who consumed alcohol	13 (35%)*	28 (90%)*	4
Double cancer patients	4	5	0

* $P = 0.0001$

Table 5. Complications for the two Brinkman index groups, excluding salvage operation cases

	Brinkman index		
	<600 (0–550)	≥ 600 (600–2400)	Unknown
No. of cases	37	31	4
Salvage operation after recurrence	8	3	1
Complications			
Soft-tissue ulcers	3	3	0
Bone exposure	1	3	0
Soft-tissue ulcers and bone exposure	1	4	0
Total complications	5/29 (17%)*	10/28 (36%)*	

* $P = 0.1133$

drinking. By contrast, 28 of the 31 patients (90%) with an index of 600 or greater had a history of drinking. There was a significant correlation between alcohol consumption and the Brinkman index ($P = 0.0001$).

Table 5 shows complications based on the Brinkman index. Excluding cases in which a salvage operation was done for recurrence, radiation complications (soft-tissue ulcers or bone exposure) occurred in 15 of 57 patients (26%). Only 5 of 29 patients (17%) in the group with a Brinkman index less than 600 had complications, compared with 10 of 28 patients (36%) with an index of 600 or greater, although the difference was not significant ($P = 0.1133$). However, there was a significant difference in the incidence of complications between the two Brinkman groups when

HDR-ISBT was administered alone ($P = 0.0299$, Table 6). Table 7 shows the incidence of complications according to total dose and the Brinkman index in the group receiving HDR-ISBT alone. For patients receiving 60Gy HDR-ISBT, there was a significant difference in the incidence of complications between the two Brinkman groups ($P = 0.0257$).

Discussion

In Japan, ISBT is a major treatment modality for carcinomas of the oral cavity, including the tongue, floor of the

Table 6. Incidence of complications according to the Brinkman index in the group receiving HDR alone

	Brinkman index		
	<600 (0-550)	≥600(600-2400)	Unknown
No. of cases	28	29	2
Salvage operation after recurrence	5	3	0
Complications			
Soft-tissue ulcers	1	3	0
Bone exposure	0	2	0
Soft-tissue ulcer and bone exposure	1	4	0
Total complications	2/23 (9%)*	9/26 (35%)*	

* $P = 0.0299$.**Table 7.** Incidence of complications according to total dose and the Brinkman index in the group receiving HDR alone

	HDR (54 Gy)		HDR (60 Gy)		
	Brinkman index		Brinkman index		
	<600	≥600	<600	≥600	Unknown
No. of cases	5	8	21	21	2
Salvage operation after recurrence	1	1	4	2	0
Regional lymph node metastases	2	6	7	8	1
Complications (excluding recurrent cases)					
Soft-tissue ulcers	1	0	0	3	0
Bone exposure	0	0	0	2	0
Soft-tissue ulcer and bone exposure	0	2	1	2	0
Total complications	1/4	2/7	1/17 (6%)*	7/19 (37%)*	0/2

* $P = 0.0257$.

mouth, and oropharynx. The microSelectron-HDR is often used for brachytherapy of carcinomas of the oral cavity.²⁻⁴ This apparatus has been used at the Osaka University Hospital since 1991 as a replacement for LDR-ISBT. Inoue et al.⁵ reported that the 5-year local control rates for LDR-ISBT and HDR-ISBT were 84% and 87%, respectively, and the 7-year local control rates for these two groups were 77% and 87%. They concluded that HDR-ISBT is a good alternative to traditional LDR-ISBT for early tongue cancer. Inoue et al.⁶ reported that hyperfractionated high-dose-rate interstitial brachytherapy has been established as a monotherapy for early mobile tongue cancer at the Osaka University Hospital and concluded that the treatment results obtained with hyperfractionated HDR-ISBT of 60 Gy/10 fractions per week for mobile tongue cancer were the same as or better than those for continuous LDR-ISBT of 70 Gy/week.

We found that the 2-, 5-, and 7-year local control rates of HDR-ISBT for early mobile tongue carcinomas were 85%, 82%, and 82%, respectively.

The implant technique was performed under local anesthesia in all patients, and there were no postoperative problems, such as severe bleeding, pain, or discomfort. We also used HDR-ISBT on patients with recurrent or residual tumors, on elderly patients in poor general health, and on patients who rejected surgical treatment. We used the HDR-ISBT technique of inserting applicators from the

submandibular region into the dorsal surface of the tongue. There have been concerns that this approach may cause nodal metastases or occult metastases owing to tumor dissemination. However, we found no occult metastases in the patients we treated with the submandibular approach with the HDR-ISBT technique. Nodal metastases occurred in 27 of 72 patients (38%) that we treated. The nodal control rate for these metastases was 59% (16/27). The treatment policy for nodal metastases is not discussed here because prophylactic lymph node irradiation is not done at Osaka University Hospital. According to our policy, surgical treatment is the first choice for nodal metastases.

As a late effect of brachytherapy for tongue cancer Yoshioka et al.⁷ reported a tendency for problems such as speech or swallowing dysfunction, pain or contracted feeling, or general dissatisfaction to increase with the tongue hemiatrophy grade, and they demonstrated that the frequency of T2 and nonsuperficial-type tumors also tended to increase with the same grading system.

Kakimoto et al.⁸ reported that in the LDR group, 3 of 6 patients experienced soft-tissue ulcers and 12 of 61 patients experienced bone exposure or radiation osteomyelitis; by contrast, in the HDR group, 3 of 14 patients experienced soft-tissue ulcers and no patients experienced bone exposure or radiation osteomyelitis. There were no significant differences in the incidences of soft-tissue ulcers and bone

exposure between the LDR and HDR groups for T3 mobile tongue cancer.

In this series, soft-tissue ulcers or bone exposure occurred in 15 of 57 patients (26%). Cases requiring a salvage operation were not included in this calculation. For the group that received HDR-ISBT alone, there was a significant difference in the incidence of these complications between the two Brinkman groups ($P = 0.0299$). In addition, we found an increase in late complications, such as soft-tissue ulcers or bone exposure, after irradiation of 60 Gy HDR-ISBT for tongue cancer in the patients with a Brinkman index greater than 600 ($P = 0.0257$). These results indicate that the Brinkman index is a very important prognostic factor in the incidence of complications after HDR-ISBT for early mobile tongue cancer.

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Radiotherapy for Uterine Cervical Cancer: Results of the 1995-1997 Patterns of Care Process Survey in Japan

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Objective: The aim of this study is to establish Japanese national practice patterns for uterine cervical cancer patients who received radiotherapy without surgery.

Methods: The Japanese Patterns of Care Study (JPCS) conducted a national survey of 73 institutions using two-stage cluster sampling, and collected specific information on 591 patients with uterine cervical cancer treated by radiotherapy without planned surgery between 1995 and 1997.

Results: The median age of the patients was 70 years. Karnofsky performance status (KPS) was ≥ 90 for 37%. Most patients (95%) had histology of squamous cell carcinoma. Ten percent were stage I, 29% stage II, 48% stage III and 13% stage IVA. Photon beams of 10-14 MV were the most used for external beam radiotherapy (EBRT). The beam energy utilized varied significantly by institution strata. Midline block was used in $\sim 70\%$ of institutions. Intracavitary brachytherapy (ICBT) was performed in 77%. Institution strata correlated significantly with the ICBT application. The majority of patients (89%) were treated with high-dose-rate (HDR) ICBT. The median single point A dose of HDR-ICBT was 600 cGy. The median summated point A dose from EBRT and HDR-ICBT was 5800 cGy (range: 1196-8600). The median overall treatment time including ICBT was 49 days. Twenty-four percent of the patients received chemotherapy. Concurrent chemoradiation was performed in 5%.

Conclusions: The JPCS established the Japanese national practice patterns of care for uterine cervical cancer patients treated with radiotherapy without planned surgery between 1995 and 1997. This survey demonstrated that the institutional strata significantly affected several practice patterns.

Key words: cervical neoplasms - radiotherapy - Patterns of Care Study

INTRODUCTION

Radiotherapy has long played an important role in the treatment of uterine cervical cancer. The method has developed with the advance of technology and a large amount of clinical experience. Hence, cervical cancer has become one of the diseases in which patterns of radiotherapy practice are well standardized.

The Patterns of Care Study (PCS) has established the national average of process of care for several malignancies including cervical cancer in the USA (1). The Japanese Patterns of Care Study (JPCS) conducted the first nationwide survey for uterine cervical cancer from 1996 to 1997. The first JPCS survey demonstrated the practice patterns for cervical cancer patients treated with radiotherapy between 1992 and 1994 in Japan (2).

In September 1998, the JPCS started the second national survey of patients with uterine cervical cancer treated with radiotherapy during 1995-1997. Although its institution stratification and patient eligibility were almost the same as the first survey, the data format was newly developed. The national

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practice patterns of post-operative radiotherapy during 1995–1997 have already been published elsewhere (3). The purpose of this study is to establish national patterns of practice for uterine cervical cancer patients who received radiation therapy without planned surgical treatments during the period 1995–1997. The influence of institutional stratification on process of care was also analyzed.

PATIENTS AND METHODS

The JPCS conducted a national survey of patients with uterine cervical cancer treated with radiotherapy during 1995–1997. The survey was performed from September 1998 to March 2001. The JPCS developed an original data format for patients with uterine cervical cancer with reference to the fifth PCS format of the American College of Radiology (ACR). Seventy-three out of 556 institutions were selected for the survey by using a stratified two-staged cluster sampling method. The data collection method consisted of two steps of random sampling. Prior to the random sampling, all the institutions were classified into four groups. The criteria for stratification of the institutions have been described elsewhere (2,3). Briefly, institutional stratification of JPCS was as follows: A1, academic institutions treating ≥ 300 patients a year; A2, academic institutions treating < 300 patients a year; B1, non-academic institutions treating ≥ 120 patients a year; and B2, non-academic institutions treating < 120 patients a year. Academic institutions include cancer center hospitals and university hospitals. Non-academic institutions consist of other facilities such as national, prefectural, municipal and private hospitals.

The first step was to randomly select institutions from each group. The second step was to randomly select eligible patients from each of the sampled institutions. To be eligible for this study, patients had to meet several criteria: carcinoma, treated from 1995 to 1997, without distant metastases, without prior or concurrent malignancies, without gross para-aortic lymph node metastases and no previous pelvic radiotherapy. The JPCS surveyors consisted of 20 radiation oncologists from 10 academic institutions. One radiation oncologist visited and surveyed the data by reviewing patients' charts for each of the institutions. Data collection included patient characteristics (e.g. patient history, age, performance status, laboratory data, pathology, staging), extent of work-up for lymph node status, details of treatment (e.g. radiotherapy, chemotherapy, surgery) and treatment outcomes. The JPCS collected clinical data on 1065 patients with uterine cervical cancer who were treated with radiotherapy. In this study, 591 patients treated by radiotherapy without planned surgery were analyzed. These include 207 patients from A1 institutions, 145 patients from A2 institutions, 179 patients from B1 institutions and 60 patients from B2 institutions.

Statistical significance was tested by the χ^2 test. Cases with unknown values were included, but cases with missing values were not included in calculations of percentage and significance.

RESULTS

PATIENTS AND TUMOR CHARACTERISTICS (TABLE 1)

Data on height and weight were collected in 384 (65%) and 429 (73%) patients, respectively. The median height was 150 cm (range 119–168) whilst the median weight was 50 kg (range 26–97). Age data were collected for all 591 patients. Seventy-four patients (13%) were younger than 50 years, and 194 patients (33%) were older than 74 years. Patients over 74 years were frequently seen in A2 (37%) and B2 (50%) compared with in A1 (28%) and B1 (29%) institutions. The Karnofsky performance status (KPS) was 90–100 in 37%, and was < 80 in 23%. The KPS distribution varied significantly by the institution strata ($P = 0.002$). Although approximately half of the patients in the A1 stratum had a favorable KPS (90–100), this was only the case for 20% of B2 institutions. Data on the pre-treatment hemoglobin value were obtained for 489 cases (83%). There was a significant difference in hemoglobin value among the groups of institutions ($P < 0.0001$). Patients of A1 and B1 institutions had higher hemoglobin values than those of A2 and B2 institutions. Most patients (95%) had histology of squamous cell carcinoma. No significant difference in histology was observed among each stratum. Patients with stage III were seen most frequently. Information of hydronephrosis/non-functioning kidney was noted for 267 of 280 stage III patients (95%), and 72 of 75 stage IVA patients (96%). Sixty patients (22%) with stage III and 41 patients (57%) with stage IVA had hydronephrosis/non-functioning kidney. Institutional strata did not significantly affect this distribution.

For the assessment of pelvic nodal status, lymphangiography (four out of 495 patients; 1%) and surgical exploration (17 out of 505 patients; 3%) were rarely performed. Data on the nodal status were recorded using computed tomography (CT) in 369 out of 547 patients (67%) and magnetic resonance imaging (MRI) in 320 out of 540 patients (59%). However, data with an 'unknown' value were frequent for these items (CT, 146; MRI, 128). There was no significant difference among each institutional stratum for these variables on pelvic nodal evaluation.

TREATMENT

Only 12 (2%) of 519 patients for whom information was available entered an investigational protocol.

External beam radiotherapy

Treatment parameters of external beam radiotherapy (EBRT) according to the stratified institutions are listed in Table 2. Photon beams of 10–14 MV were the most popular category used for EBRT. Beam energies utilized varied significantly by institution strata ($P < 0.0001$). A beam energy of ≥ 10 MV was used for 93% in A1, 68% in A2, 55% in B1 and 18% in B2. For most patients, EBRT was given in daily fraction doses of 1.0 or 2.0 Gy. Treatment volume included only the pelvic region for almost all patients. Extended field prophylactic radiotherapy including the para-aortic region was rarely performed. Th

Table 1. Patient and tumor characteristics

Characteristics	Stratification of institutions				P-value	Total
	A1	A2	B1	B2		
No. of patients	207	145	179	60		591
Age, years						
Range	28-91	33-90	33-94	33-94		28-94
Median	69	71	69	75		70
KPS					0.002	
≤70	35 (17%)	42 (29%)	39 (22%)	17 (28%)		133 (23%)
80	68 (34%)	51 (36%)	82 (46%)	31 (52%)		232 (40%)
90	83 (41%)	39 (28%)	55 (31%)	12 (20%)		189 (32%)
100	16 (8%)	10 (7%)	2	0		28 (5%)
Missing	5	3	1	0		9
Hemoglobin (g/dl)					<0.0001	
<10	39 (21%)	39 (29%)	46 (26%)	23 (38%)		147 (26%)
10-12	61 (33%)	49 (36%)	54 (31%)	24 (40%)		188 (34%)
>12	67 (36%)	28 (20%)	51 (29%)	8 (14%)		154 (28%)
Unknown	17 (9%)	21 (15%)	25 (14%)	5 (8%)		68 (12%)
Missing	23	8	3	0		34
Histology					0.244	
Squamous cell carcinoma	188 (92%)	137 (95%)	173 (98%)	56 (95%)		554 (95%)
Adenocarcinoma	14 (7%)	4 (3%)	3	2		23 (4%)
Adenosquamous cell carcinoma	1	2	0	1		4
Other	2	1	1	0		4
Missing	2	1	2	1		6
FIGO stage					0.01	
I	9 (4%)	26 (18%)	16 (9%)	6 (10%)		57 (10%)
II	62 (30%)	38 (27%)	56 (32%)	15 (25%)		171 (29%)
III	115 (56%)	57 (40%)	75 (42%)	33 (55%)		280 (48%)
IVA	17 (8%)	22 (15%)	30 (17%)	6 (10%)		75 (13%)
Other (CIS, IVB)	4 (2%)	0	1	0		5
Missing	0	2	1	0		3

majority of the patients were treated with anterior and posterior opposed fields. The four-box technique was rarely used. Approximately 70% of the patients had a midline block (MLB) for a portion of their treatment course. Use of an MLB varied significantly among each stratum ($P < 0.0001$). An MLB was used more frequently in A1 compared with other strata.

Brachytherapy

Only one patient (B2 institution) was treated with interstitial brachytherapy. Table 3 shows details of intracavitary brachytherapy (ICBT). ICBT was performed for approximately three-quarters of patients. Institution strata correlated significantly with the application of ICBT. ICBT was administered to 85%

of patients in A1, 78% in A2, 75% in B1 and 53% in B2 ($P < 0.0001$). Performance of ICBT correlated well with the use of an MLB for EBRT. However, a discrepancy was observed between these two in A2 institutions. Further analysis of MLB utilization for patients treated with ICBT revealed that the MLB utilization rate was lower in A2 (74%) than other strata (A1, 93%; B1, 92%; B2, 88%). Use of ICBT according to the FIGO stage was noted for 584 patients. Forty-three patients with stage I received ICBT (75%), 144 patients with stage II (85%), 220 patients with stage III (79%) and 42 patients with stage IVA (55%). The majority of patients were treated with high-dose-rate (HDR) ICBT. Low-dose-rate (LDR) was used slightly more frequently in A1 institutions (14%) compared with other strata (2-7%). The most popular radionuclide used for brachytherapy sources was cobalt-60 (Co-60), followed by

Table 2. Treatment parameters of external beam radiotherapy

Parameters	Stratification of institutions				P-value	Total
	A1	A2	B1	B2		
Beam energy					<0.0001	
Co-60	1	7 (5%)	0	9 (15%)		17 (3%)
3-5 MV	1	23 (16%)	44 (25%)	11 (18%)		79 (14%)
6-9 MV	12 (6%)	6 (4%)	35 (20%)	29 (48%)		82 (14%)
10-14 MV	145 (74%)	87 (62%)	95 (55%)	11 (18%)		338 (59%)
≥15 MV	37 (19%)	8 (6%)	0	0		45 (8%)
Other/unknown	1	9 (7%)	0	0		10 (2%)
Missing	10	5	5	0		20
Treatment volume					NS	
Pelvis only	197 (97%)	138 (98%)	170 (98%)	60 (100%)		571 (98%)
Pelvis + PAN	5	3	2	0		5
Other	1	0	2	0		2
Missing	4	4	5	0		13
Technique					NS	
AP-PA	195 (99%)	136 (96%)	169 (97%)	60 (100%)		560 (98%)
4-field box	2	4 (3%)	5 (3%)	0		11 (2%)
Other	0	1	0	0		1
Missing	10	4	5	0		19
Midline block					<0.0001	
Yes	156 (81%)	82 (59%)	120 (71%)	28 (47%)		386 (69%)
No	36 (19%)	56 (40%)	47 (28%)	32 (53%)		171 (30%)
Unknown	1	2	1	0		4
Missing	14	5	11	0		30
Daily fraction size					0.0094	
<180 cGy	2 (1%)	8 (6%)	2 (1%)	1 (1%)		13 (2%)
180 cGy	74 (37%)	72 (51%)	85 (49%)	28 (47%)		259 (45%)
181-199 cGy	0	0	0	0		0
200 cGy	124 (61%)	58 (41%)	86 (50%)	31 (52%)		299 (52%)
>200 cGy	1	2 (1%)	0	0		3
Unknown	1	1	0	0		2
Missing	5	4	6	0		15

PAN, para-aortic lymph nodes.

iridium-192 (Ir-192). Ir-192 was used more frequently in A1 institutions than in A2 and B1. Adequate sedation was rarely performed at the time of ICBT applicator insertion. Over half of the patients were treated without any sedation. Patients in B1 institutions tended to be treated more with sedation than other institution strata. The most frequently used method was the use of non-steroidal anti-inflammatory drugs (NSAIDs) delivered orally or rectally in all strata. ICBT was done using various methods. A combination of tandem and ovoid applicator was most frequently used regardless of institution strata.

Radiation dose and treatment duration

For the following analyses regarding dose of ICBT, 361 patients (HDR, 327 patients; LDR, 34 patients) treated with a combination of tandem and vaginal applicator or tandem only were analyzed. Total dosage of radiotherapy in 327 patients treated with HDR-ICBT according to the institution strata is shown in Table 4. The median single point A dose of ICBT was 600 cGy for HDR, and 1412 cGy for LDR. The most frequent category of single dose of HDR-ICBT was 600-699 cGy, followed by 500-599 and 700-799 cGy.

Table 3. Details of intracavitary brachytherapy (ICBT)

Parameters	Stratification of institutions				P-value	Total
	A1	A2	B1	B2		
ICBT					<0.0001	
Yes	177 (85%)	111 (78%)	134 (75%)	32 (53%)		454 (77%)
No	30 (15%)	32 (22%)	42 (24%)	28 (47%)		132 (23%)
Unknown/other	0	0	3	0		3
Missing	0	2	0	0		2
Dose rate					0.011	
HDR	147 (84%)	104 (98%)	107 (88%)	28 (90%)		386 (89%)
LDR	25 (14%)	2 (2%)	9 (7%)	1 (3%)		37 (9%)
MDR	1	0	1	0		2
Mix*	1	0	1	0		2
N/A	1	0	3 (3%)	2 (7%)		6 (1%)
Missing	2	5	13	1		21
Source					0.0001	
Co-60	80 (46%)	83 (78%)	89 (67%)	17 (55%)		269 (60%)
Ir-192	69 (39%)	19 (18%)	12 (9%)	13 (42%)		113 (25%)
Cs-137	27 (15%)	4 (4%)	1	1 (3%)		33 (7%)
Ra-226	0	0	9 (7%)	0		9 (2%)
Unknown	0	1	21 (16%)	0		22 (5%)
Missing	1	4	2	1		8
Sedation					<0.0001	
None	100 (61%)	56 (62%)	30 (26%)	13 (57%)		199 (51%)
General/spinal anesthesia	0	2 (2%)	0	0		2
NSAID (orally/rectally)	28 (17%)	21 (23%)	50 (44%)	8 (35%)		107 (28%)
Conscious sedation	19 (12%)	0	10 (9%)	0		29 (7%)
Unknown	16 (10%)	11 (12%)	24 (21%)	1		52 (13%)
Missing	14	21	20	10		65
Method of ICBT					0.0075	
Tandem + vaginal applicator	146 (82%)	86 (83%)	96 (73%)	24 (77%)		352 (79%)
Tandem only	24 (14%)	4 (4%)	2 (1%)	0		30 (7%)
Vaginal applicator	7 (4%)	11 (10%)	4 (3%)	0		22 (5%)
Unknown	0	3 (3%)	30 (23%)	7 (23%)		40 (9%)
Missing	0	7	2	1		10

*Patients treated with a combination of HDR-ICBT and LDR-ICBT.

HDR, high-dose-rate; ICBT, intracavitary brachytherapy; LDR, low-dose-rate; MDR, medium-dose-rate; N/A, not applicable; NSAID, non-steroidal anti-inflammatory drug.

A single dose ≥ 800 cGy was rarely applied. Single dose HDR-ICBT use was significantly lower in A2 than those of other strata.

The median total dose of EBRT delivered to the central pelvis (point A) and the lateral pelvis (point B) was 3220 and 5000 cGy, respectively. The median total dose of ICBT at point A was 2400 cGy for HDR and 2850 cGy for LDR. Consequently, the median summated point A dose from EBRT and ICBT was 5800 cGy (range 1196–8820) for HDR, and 6974 cGy (range 4464–9160) for LDR.

Table 5 shows the total radiotherapy doses in patients treated with HDR-ICBT according to the FIGO stage. FIGO stage significantly affected the EBRT doses to the central pelvis (point A). In contrast, total point A dose from HDR-ICBT was not affected by stage. The cumulative point A dose of EBRT and HDR-ICBT increased significantly with increasing FIGO stage. The total dose to the lateral pelvis (point B) from EBRT also varied significantly by FIGO stage, although those median values were almost the same. Some patients with stage III/IV received a total point B dose of >6000 cGy.

Table 4. Dosage* of radiotherapy according to the stratification of institutions

Dose (cGy)	Stratification of institutions				P-value	Total
	A1	A2	B1	B2		
EBRT						
Total point A dose					0.0021	
0-1999	8 (6%)	8 (10%)	2 (3%)	5 (24%)		23 (8%)
2000-2999	12 (9%)	17 (21%)	11 (16%)	2 (10%)		42 (14%)
3000-3999	56 (41%)	23 (29%)	33 (47%)	7 (33%)		119 (38%)
4000-4999	32 (23%)	18 (23%)	3 (4%)	4 (19%)		57 (18%)
5000+	30 (21%)	14 (17%)	22 (30%)	3 (14%)		69 (22%)
Missing	5	8	4	0		17
Median	3240	3960	3060	3060		3220
Total point B dose					<0.0001	
0-1999	0	0	0	0		0
2000-2999	0	1	1	2 (11%)		4 (1%)
3000-3999	1	4 (5%)	2 (3%)	0		7 (2%)
4000-4999	27 (20%)	22 (28%)	5 (7%)	5 (26%)		59 (19%)
5000-5999	109 (79%)	46 (60%)	61 (87%)	11 (58%)		227 (74%)
6000+	1	5 (6%)	1	1		8 (3%)
Missing	5	10	5	2		22
Median	5000	5000	5000	5000		5000
HDR-ICBT						
Single point A dose					<0.0001	
0-499	6 (4%)	9 (11%)	1 (2%)	0		16 (5%)
500-599	42 (30%)	37 (43%)	11 (18%)	10 (48%)		100 (33%)
600-699	73 (52%)	32 (38%)	29 (48%)	11 (52%)		145 (47%)
700-799	19 (14%)	5 (6%)	19 (32%)	0		43 (14%)
800+	0	2 (2%)	0	0		2 (1%)
Missing	3	3	15	0		21
Median	600	575	600	600		600
Total point A dose					0.02	
0-999	2 (1%)	2 (3%)	0	0		4 (1%)
1000-1999	46 (33%)	18 (23%)	10 (17%)	6 (29%)		80 (26%)
2000-2999	53 (38%)	52 (59%)	29 (48%)	11 (52%)		145 (48%)
3000-3999	39 (28%)	13 (15%)	21 (35%)	4 (19%)		77 (25%)
4000+	0	0	0	0		0
Missing	3	3	15	0		21
Median	2400	2400	2400	2045		2400
EBRT + HDR-ICBT						
Total point A dose					0.0022	
0-3999	6 (4%)	7 (8%)	4 (7%)	4 (19%)		21 (7%)
4000-4999	21 (16%)	11 (14%)	3 (5%)	4 (19%)		39 (13%)
5000-5999	47 (35%)	25 (31%)	20 (34%)	6 (29%)		98 (33%)
6000-6999	33 (24%)	28 (35%)	17 (29%)	4 (19%)		82 (28%)
7000+	29 (21%)	10 (12%)	15 (25%)	3 (14%)		57 (19%)
Missing	7	7	16	0		30
Median	5800	5730	6000	5200		5800

A total of 327 patients were treated with HDR-ICBT with a combination of tandem and vaginal applicator, or tandem only.

*Dose at left side.

HDR-ICBT, high-dose-rate intracavitary brachytherapy; EBRT, external beam radiotherapy.