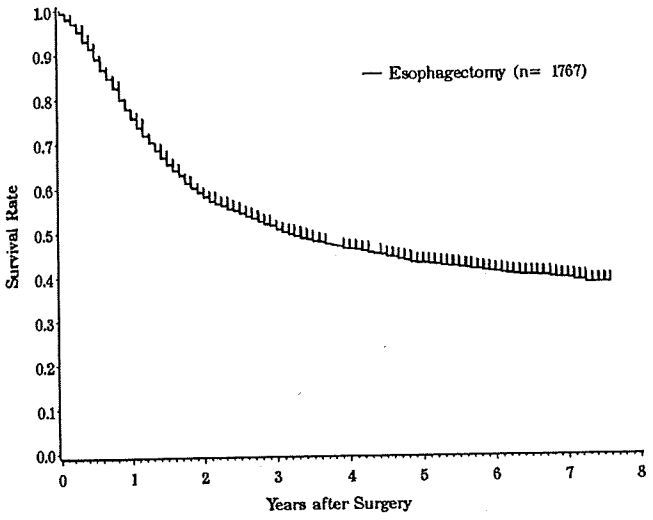
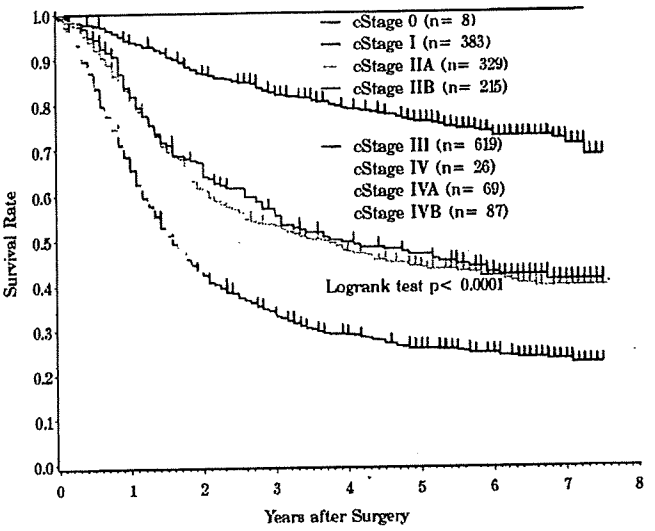


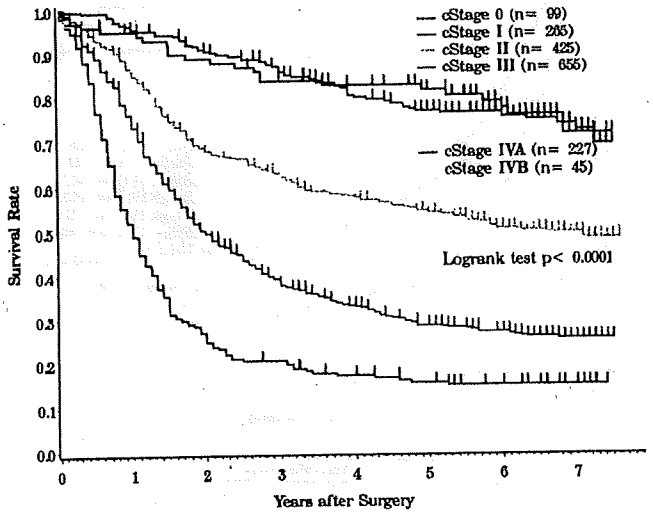
	Years after Surgery						
	1	2	3	4	5	6	7
Esophagectomy	75.8%	58.0%	51.2%	46.1%	42.6%	40.5%	39.2%

Figure 6 Survival of patients treated by esophagectomy



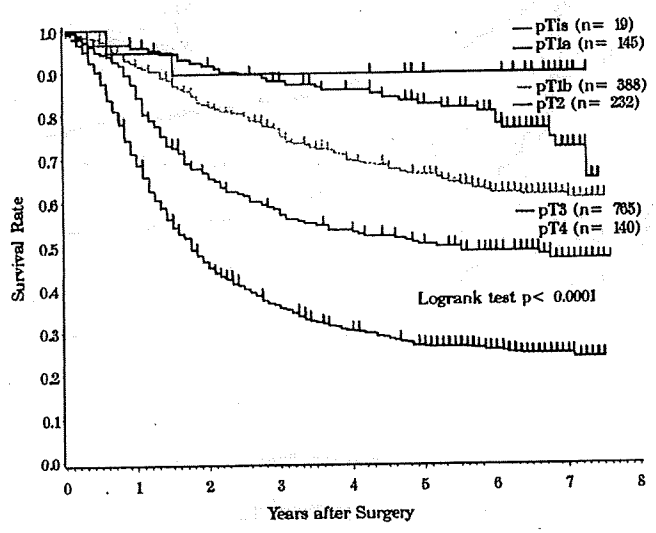
	Years after Surgery						
	1	2	3	4	5	6	7
cStage 0	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
cStage I	93.6%	86.6%	82.4%	78.9%	75.9%	72.5%	71.8%
cStage IIA	80.1%	60.9%	53.4%	47.6%	43.6%	41.6%	39.3%
cStage IIB	81.9%	64.1%	56.4%	49.5%	46.7%	42.5%	40.8%
cStage III	65.6%	42.2%	33.9%	28.9%	25.5%	24.4%	22.9%
cStage IV	34.6%	19.2%	11.5%	11.5%	11.5%	11.5%	11.5%
cStage IVA	68.9%	43.1%	40.0%	33.8%	29.0%	29.0%	29.0%
cStage IVB	56.6%	39.8%	31.2%	25.5%	19.1%	19.1%	19.1%

Figure 8 Survival of patients treated by esophagectomy in relation to clinical stage (UICC-cTNM)



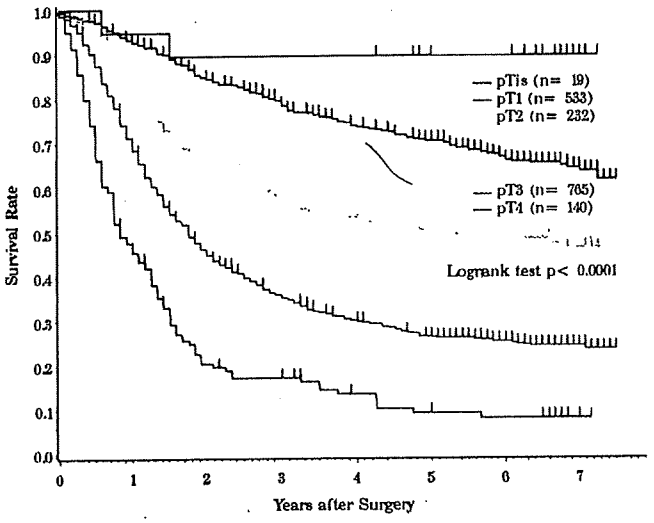
	Years after Surgery						
	1	2	3	4	5	6	7
cStage 0	94.9%	88.6%	83.4%	82.3%	81.1%	77.0%	71.3%
cStage I	95.4%	90.3%	86.3%	80.0%	76.5%	75.0%	73.4%
cStage II	84.7%	67.8%	62.7%	57.5%	54.0%	50.1%	49.2%
cStage III	73.2%	49.4%	38.7%	32.7%	28.1%	26.6%	25.0%
cStage IVA	48.9%	24.6%	20.4%	17.0%	15.3%	14.7%	14.7%
cStage IVB	23.0%	12.8%	7.7%	2.6%	-	-	-

Figure 7 Survival of patients treated by esophagectomy in relation to clinical stage



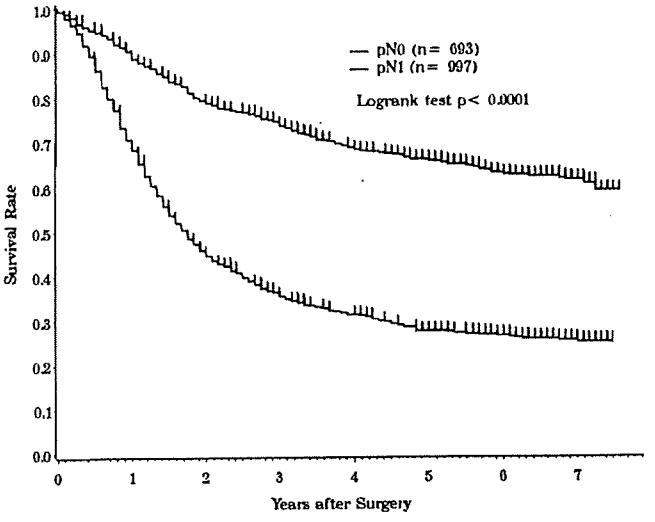
	Years after Surgery						
	1	2	3	4	5	6	7
pTis	94.7%	89.5%	89.5%	89.5%	89.5%	89.5%	89.5%
pT1a	95.8%	91.5%	87.8%	85.5%	82.2%	77.4%	72.0%
pT1b	91.4%	81.8%	76.3%	69.4%	66.1%	61.7%	61.3%
pT2	84.1%	65.2%	65.2%	53.5%	50.0%	48.4%	46.4%
pT3	68.5%	44.9%	35.9%	30.1%	26.3%	25.4%	24.4%
pT4	45.6%	20.3%	17.2%	13.4%	9.3%	8.1%	8.1%

Figure 9 Survival of patients treated by esophagectomy in relation to the depth of tumor invasion (pT)



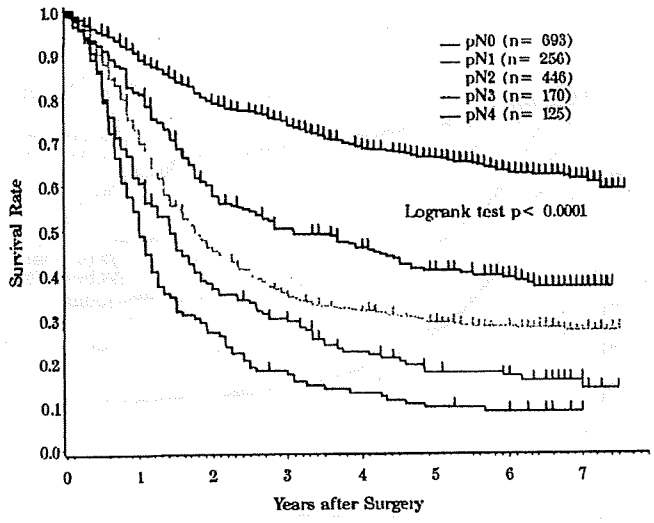
	Years after Surgery						
	1	2	3	4	5	6	7
pTis	94.7%	89.5%	89.5%	89.5%	89.5%	89.5%	89.5%
pT1	92.6%	84.4%	79.4%	73.8%	70.5%	66.0%	64.3%
pT2	84.1%	65.2%	65.2%	53.5%	50.0%	48.4%	46.4%
pT3	68.5%	44.9%	35.9%	30.1%	26.3%	25.4%	24.4%
pT4	45.6%	20.3%	17.2%	13.4%	9.1%	8.1%	8.1%

Figure 10 Survival of patients treated by esophagectomy in relation to the depth of tumor invasion (UICC-pTNM: pT)



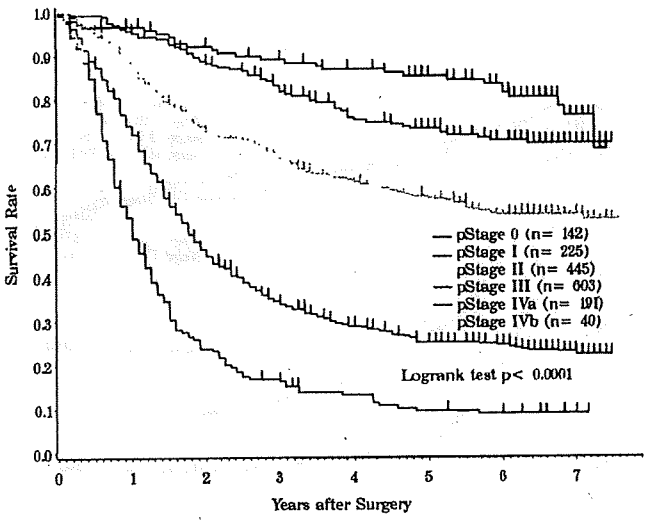
	Years after Surgery						
	1	2	3	4	5	6	7
pN0	88.8%	78.8%	74.3%	68.7%	65.8%	62.6%	61.3%
pN1	68.3%	44.8%	36.3%	31.3%	27.5%	26.4%	25.4%

Figure 12 Survival of patients treated by esophagectomy in relation to lymph node mentastasis (UICC-pTNM: pN)



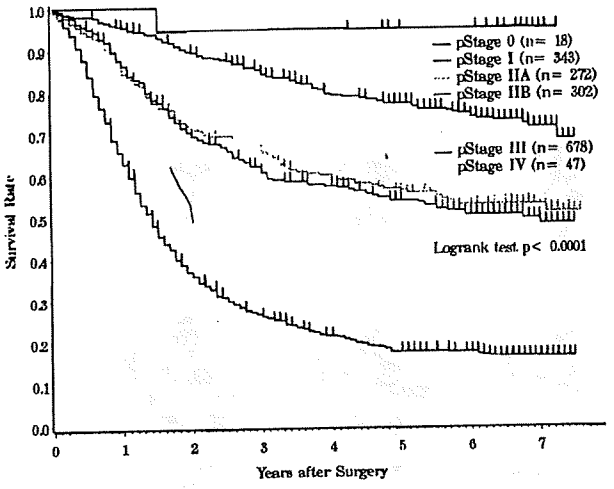
	Years after Surgery						
	1	2	3	4	5	6	7
pN0	88.8%	78.8%	74.3%	68.7%	65.8%	62.6%	61.3%
pN1	81.0%	57.6%	50.3%	45.8%	40.6%	39.1%	37.1%
pN2	69.6%	45.4%	36.0%	31.7%	29.0%	28.1%	27.2%
pN3	60.6%	36.9%	30.0%	22.3%	17.5%	16.7%	15.6%
pN4	48.8%	26.9%	18.0%	12.8%	9.4%	8.5%	8.5%

Figure 11 Survival of patients treated by esophagectomy in relation to lymph node mentastasis (pN)



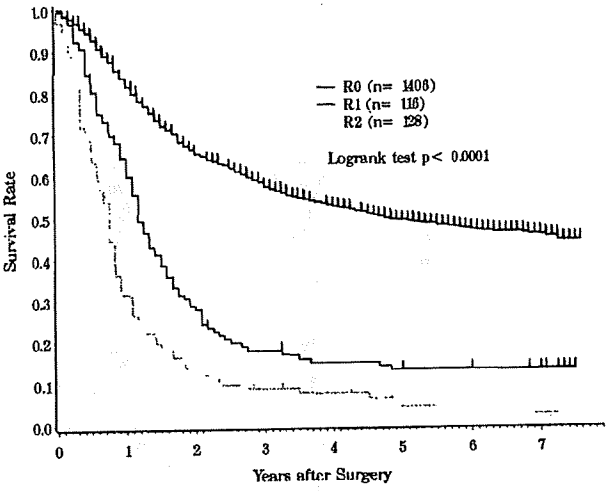
	Years after Surgery						
	1	2	3	4	5	6	7
pStage 0	96.4%	92.0%	89.0%	86.7%	85.1%	81.4%	76.0%
pStage I	95.1%	88.2%	82.6%	75.8%	73.2%	70.4%	69.7%
pStage II	86.1%	72.6%	67.7%	61.6%	57.6%	53.8%	53.8%
pStage III	71.8%	44.7%	34.6%	28.9%	25.0%	24.5%	22.8%
pStage IVa	48.6%	23.8%	16.8%	13.2%	9.4%	8.7%	8.7%
pStage IVb	23.8%	8.9%	6.0%	-	-	-	-

Figure 13 Survival of patients treated by esophagectomy in relation to pathological stage



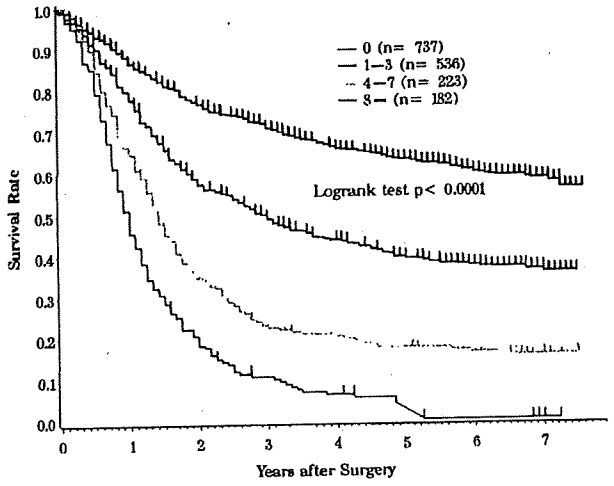
	Years after Surgery						
	1	2	3	4	5	6	7
pStage 0	100.0%	94.4%	94.4%	94.4%	94.4%	94.4%	94.4%
pStage I	95.3%	89.2%	84.6%	79.1%	76.8%	76.8%	70.8%
pStage IIA	84.4%	70.6%	66.5%	59.8%	55.9%	52.5%	52.5%
pStage IIB	86.2%	69.1%	62.0%	57.2%	53.5%	50.0%	49.1%
pStage III	62.8%	35.7%	26.3%	21.1%	17.2%	16.9%	15.8%
pStage IV	24.0%	14.4%	9.6%	4.8%	2.4%	2.4%	2.4%

Figure 14 Survival of patients treated by esophagectomy in relation to pathological stage (UICC-pTNM)



	Years after Surgery						
	1	2	3	4	5	6	7
R0	81.5%	65.2%	58.2%	52.6%	48.8%	46.6%	45.3%
R1	59.9%	27.7%	17.7%	14.7%	12.8%	12.8%	12.8%
R2	31.5%	12.0%	8.6%	7.5%	4.0%	2.0%	2.0%

Figure 16 Survival of patients treated by esophagectomy in relation to residual tumor (R)

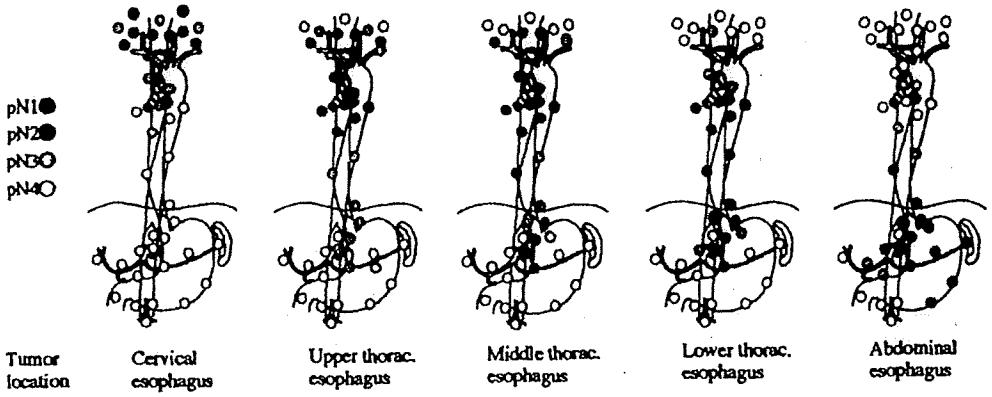


	Years after Surgery						
	1	2	3	4	5	6	7
0	86.3%	76.4%	71.4%	66.0%	63.0%	59.9%	58.3%
1-3	77.6%	57.2%	49.9%	43.8%	39.3%	37.6%	36.5%
4-7	64.5%	34.6%	22.9%	20.3%	17.5%	16.3%	15.6%
8-	45.7%	18.2%	10.6%	6.2%	3.9%	3.9%	3.9%

Figure 15 Survival of patients treated by esophagectomy in relation to number of metastatic nodes

Reference

N-category in: The Japanese Classification of Esophageal Cancer, 9th edition, Japan Esophageal Society



External-Beam Radiotherapy for Clinically Localized Prostate Cancer in Osaka, Japan, 1995–2006

Time Trends, Outcome, and Risk Stratification

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Purpose: To establish an initial database of external-beam radiotherapy (EBRT) for clinically localized prostate cancer used in Osaka, Japan, and, by analyzing the results of the Osaka multicenter cooperative study, to determine time trends, outcome, and applicability of existing and the authors' original risk stratification methods.
Patients and Methods: Data of 652 patients with clinically localized prostate cancer (T1–4 N0 M0) were accrued from July to December 2007. These patients had been treated from 1995 through 2006 with consecutive definitive EBRT of ≥ 60 Gy at eleven institutions, mainly in Osaka. Altogether, 436 patients were eligible for analysis using several risk stratification methods, namely, those of D'Amico et al., the National Comprehensive Cancer Network (NCCN), and Seattle, as well as the authors' original Prostate Cancer Risk Index (PRIX).
Results: The number of patients showed a tenfold increase over 10 years, together with a rapid spread of the use of Gleason Score from 0% to > 90% of cases. The dominant RT dose fractionation was 70 Gy/35 fractions (87%). Hormone therapy had been administered to 95% of the patients and the higher PRIX corresponded to the higher rate of hormone usage. 3- and 5-year biochemical relapse-free survival (bRFS) rates were 85% and 70%, respectively. The D'Amico ($p = 0.132$), NCCN ($p = 0.138$), Seattle ($p = 0.041$) and PRIX ($p = 0.044$) classifications showed weak or no correlation with bRFS, while the own modified three-class PRIX (PRIX 0, 1–5, 6) showed a strong correlation ($p = 0.002$).
Conclusion: The use of prostate EBRT in Japan is still in its infancy, but is rapidly expanding. The short-term outcomes have been satisfactory considering the moderate RT dose. A very high rate of hormone usage may affect the outcome favorably, but also may compromise the usefulness of current risk stratification.

Key Words: Prostate cancer · Clinically localized · Risk classification · Radiation therapy · Prostate Cancer Risk Index (PRIX)

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Perkutane Strahlentherapie bei klinisch lokalisiertem Prostatakrebs in Osaka, Japan, 1995–2006. Zeitliche Entwicklung, Resultate und Risikostratifikation

Ziel: Erstellung einer ersten Datenbank zur perkutanen Strahlentherapie (EBRT) bei klinisch lokalisiertem Prostatakrebs in Osaka, Japan, und Ermittlung der zeitlichen Entwicklung, Resultate und Anwendbarkeit der existierenden und der eigenen Risikostratifikationsmethoden mittels Analyse der Ergebnisse der multizentrischen kooperativen Osaka-Studie.

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Patienten und Methodik: Daten von 652 Patienten mit klinisch lokalisiertem Prostatakrebs (T1–4 N0 M0) wurden von Juli bis Dezember 2007 erfasst. Diese Patienten waren zwischen 1995 und 2006 in elf Einrichtungen, vorwiegend in Osaka, mit konsekutiver definitiver EBRT von ≥ 60 Gy behandelt worden. Insgesamt 436 Patienten qualifizierten sich für die Analyse mittels mehrerer Risikostratifikationsmethoden, namentlich jener von D'Amico et al., National Comprehensive Cancer Network (NCCN) und Seattle sowie des eigenen Prostatakrebsrisikoindex (PRIX).

Ergebnisse: Die Anzahl der Patienten stieg binnen 10 Jahren um das Zehnfache, und gleichzeitig kam es zu einem rasch zunehmenden Einsatz des Gleason-Scores von 0% auf > 90% der Fälle. Die dominante RT-Dosisfraktionierung betrug 70 Gy/35 Fraktionen (87%). Eine Hormontherapie war 95% der Patienten verabreicht worden, und der höhere PRIX entsprach der höheren Rate des Hormoneinsatzes. Die 3- und 5-Jahres-Raten des biochemisch rezidivfreien Überlebens (bRFS) lagen bei 85% bzw. 70%. Die Klassifikationen von D'Amico et al. (p = 0,132), NCCN (p = 0,138), Seattle (p = 0,041) und PRIX (p = 0,044) zeigten eine schwache Korrelation mit dem bRFS, wogegen der eigene modifizierte Drei-Klassen-PRIX (PRIX 0, 1–5, 6) eine starke Korrrelation (p = 0,002) ergab.

Schlussfolgerung: Der Einsatz der Prostata-EBRT in Japan ist noch in der Anfangsphase begriffen, breitet sich aber rasch aus. Angesichts moderater RT-Dosen sind zufriedenstellende kurzfristige Resultate erzielt worden. Eine sehr hohe Rate von Hormonverabreichungen mag die Ergebnisse günstig beeinflussen, könnte aber auch die Nützlichkeit der gegenwärtigen Risikostratifikation gefährden.

Schlüsselwörter: Prostatakrebs · Klinisch lokalisiert · Risikostratifikation · Strahlentherapie · Prostatakrebsrisikoindex (PRIX)

Introduction

In Japan, or for that matter in many Asian countries, prostate cancer did not use to be a commonly occurring cancer or a common cause of cancer death. However, with the changes in lifestyle associated with westernization, the incidence of prostate cancer has been increasing dramatically during the past 2 decades [4, 5]. Since Japanese urologists have shown a preference for prostatectomy rather than radiation therapy (RT) for curative intervention, there are very few data on RT for prostate cancer in Japan [9, 14, 19, 21]. However, information, mainly from western countries, that RT can yield a clinical outcome comparable to that of prostatectomy, has recently become easily available not only to Japanese physicians but also to patients or the mass media via the internet. As a result, the rate of patients who wish to be and actually are treated with RT is rapidly increasing [13]. This tendency has prompted us to gather clinical evidence, especially practice-based, of the use and outcomes of prostate RT for an initial database, even though the application of this procedure in Japan is still in its infancy.

One special characteristic of prostate cancer treatment in Japan is the extremely high rate and long term of hormone therapy use. The main reason for this is likely to be the fact that there is no limit on the reimbursement by the Japanese health insurance system for the cost of hormone therapy once the patient is diagnosed with prostate cancer, regardless of any kind of accompanying therapy. In other words, one can receive hormone therapy from initial diagnosis until death, regardless of whether the therapy is administered pre- or postprostatectomy or of RT status. Moreover, medical insurance in Japan is based on a system of universal health coverage.

We recently proposed a new risk stratification method which we termed the Prostate Cancer Risk Index (PRIX), and which fully corresponds to the Partin Table [15] in terms of probability of pathologic lymph node involvement, and also corresponds to the other nomograms better than any existing risk-grouping method [20]. In this study, we accumulated as many data as possible of patients consecutively treated at main institutions in Osaka in an effort to establish an initial database for prostate external-beam radiotherapy (EBRT) in Japan, and to examine the time trends, outcome, and relative applicability of existing and our original risk stratification methods.

Patients and Methods

Collection of Data and Patient Characteristics

Between July and December 2007, eleven institutions, mainly in Osaka (eight in Osaka and one each in Kyoto, Hyogo and Aichi), Japan, participated in this study and their data were sent to Osaka University. The data thus collected were for 652 consecutive patients with clinically localized prostate cancer (T1–4 N0 M0), who had been treated with definitive EBRT of ≥ 60 Gy at one of the participating institutions from 1995 through 2006. Patients had been followed up every 3 months. No patient had received intensity-modulated radiotherapy (IMRT). Patients with postprostatectomy status were excluded. The data included age, T-classification (according to UICC 2002), pretreatment prostate-specific antigen (PSA) level, Gleason Score (GS), biochemical and clinical outcome, definition of biochemical failure, hormone therapy, EBRT dose and field, and acute and late toxicity. Data for 436 of the 652 patients were considered to meet the following criteria: T-classification was detailed as in "T2a" ("T2" was therefore ineligible) in terms of UICC 2002; all of the aforementioned data were complete except for those for clinical outcome and acute and late toxicity; the follow-up period was at least 6 months. The most frequent reason for ineligibility was omis-

Table 1. Patient characteristics stratified by PRIX. bRFS: biochemical relapse-free survival; HT: hormone therapy; PRIX: prostate cancer risk index; WPRT: whole pelvic radiation therapy.

Tabelle 1. Patientencharakteristika, stratifiziert mittels PRIX. bRFS: biochemisch rezidivfreies Überleben; HT: Hormontherapie; PRIX: Prostatakrebsrisikoindex; WPRT: Ganzbeckenbestrahlung.

PRIX	Patients (n)	Age (years)[a]	HT+ (%)	Duration of HT (months)[a]	WPRT+ (%)	Dose (Gy)[a]	Crude bRFS (%)
0	23	70 ± 5	16 (70)	30 ± 19	0 (0)	69.9 ± 0.9	100
1	47	73 ± 5	42 (89)	22 ± 15	1 (2)	69.5 ± 2.1	87
2	74	72 ± 5	67 (91)	24 ± 21	4 (5)	69.4 ± 2.2	84
3	60	72 ± 5	58 (97)	28 ± 19	6 (10)	69.6 ± 2.0	85
4	83	71 ± 6	82 (99)	28 ± 13	8 (10)	69.6 ± 2.0	87
5	81	71 ± 6	81 (100)	29 ± 18	7 (9)	69.4 ± 2.3	84
6	68	70 ± 7	68 (100)	31 ± 18	14 (21)	68.6 ± 3.6	72
Total	436	71 ± 6	414 (95)	27 ± 18	40 (9)	69.4 ± 2.4	84

[a]average ± standard deviation

Table 2. Various definitions of risk stratification for clinically localized prostate cancer. GS: Gleason Score; PSA: prostate-specific antigen.

Tabelle 2. Verschiedene Definitionen der Risikostratifikation für klinisch lokalisierten Prostatakrebs. GS: Gleason-Score; PSA: prostataspezifisches Antigen.

Group or title	Definition
D'Amico et al. [6]	Low risk: T1c, T2a and PSA ≤ 10 ng/ml and GS ≤ 6 Intermediate risk: T2b or GS 7 or PSA 10–20 ng/ml High risk: T2c or PSA > 20 ng/ml or GS ≥ 8
National Comprehensive Cancer Network (NCCN) [12]	Low risk: T1–T2a and GS 2–6 and PSA < 10 ng/ml Intermediate risk: T2b–T2c or GS 7 or PSA 10–20 ng/ml High risk: T3a or GS 8–10 or PSA > 20 ng/ml Very high risk: T3b–T4 (For intermediate- and high-risk group, patients with multiple adverse factors may be shifted into the next higher risk group)
Seattle [18]	Low risk: PSA ≤ 10 ng/ml, GS < 7, and stage < T2c Intermediate risk: PSA > 10 ng/ml or GS ≥ 7 or stage ≥ T2c (one intermediate risk factor) High risk: two or more intermediate risk factors
Prostate Cancer Risk Index (PRIX) [20]	PRIX is the sum of the following three factors: PSA ≤ 10 ng/ml: 0, PSA 10–20 ng/ml: 1, PSA > 20 ng/ml: 2 GS 2–6: 0, GS 7: 1, GS 8–10: 2 T1–T2a: 0, T2b–T2c: 1, T3–4: 2

sion of GS. Since GS was initially rarely used in the field of pathology in Japan, eligible patients were all treated between 1999 and 2006 (no GS was available for any patients treated between 1995 and 1998). The patient characteristics are shown in Table 1, and will be detailed in the Results section.

Risk Stratification

In this study, we used several existing and representative risk stratification methods, namely, those of D'Amico et al. [6], the National Comprehensive Cancer Network (NCCN) [12], and Seattle [18], as well as our original risk stratification method, PRIX [20]. The definitions associated with these methods are summarized in Table 2.

In a previous publication of ours [20], we examined the correspondence between PRIX and the Partin Table (1997) [15] or the Kattan Nomogram (2000) [11]. PRIX 0 corresponded to 1–2% of pathologic lymph node involvement according to the Partin Table, PRIX 1 to 3–4%, PRIX 2 to 7–10%, PRIX 3 to 14–18%, PRIX 4 to 24–29%, PRIX 5 to 32–37%, and PRIX 6 to 42%. PRIX clearly discriminated among risks with a relatively narrow range of probability and without any overlap among different PRIXs. The D'Amico, NCCN, and Seattle classifications, on the other hand, generally produce wide ranges with overlapping, especially for intermediate- and high-risk groups. As for the Kattan Nomogram, PRIX also yielded a relatively narrow range of 60-month recurrence-free probability, whereas D'Amico, NCCN, and Seattle classifications showed wide ranges of probability, especially for high-risk groups. PRIX fully corresponded to the Partin Table in terms of pathologic lymph node involvement, and corresponded to the other nomograms better than any current risk-grouping method. We therefore hypothesized that PRIX can function as a prognostic factor or contribute to patient selection for clinically localized prostate cancer.

Endpoint and Statistical Analysis

Biochemical relapse-free survival (bRFS) was used as the only endpoint in this study. Biochemical relapse and its date were defined as identical to the clinical judgment that had been made at a given institution. All the institutions had adopted one of the following definitions of biochemical relapse: (a) American Society for Therapeutic Radiology and Oncology (ASTRO) [1], (b) Phoenix [17], or (c) start of salvage therapy.

Kaplan-Meier curves were obtained for bRFS, and the log-rank test was used to compare bRFSs. A p-value < 0.05 was deemed statistically significant.

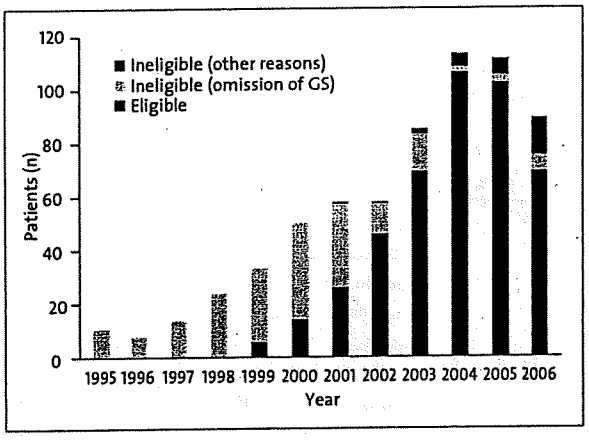
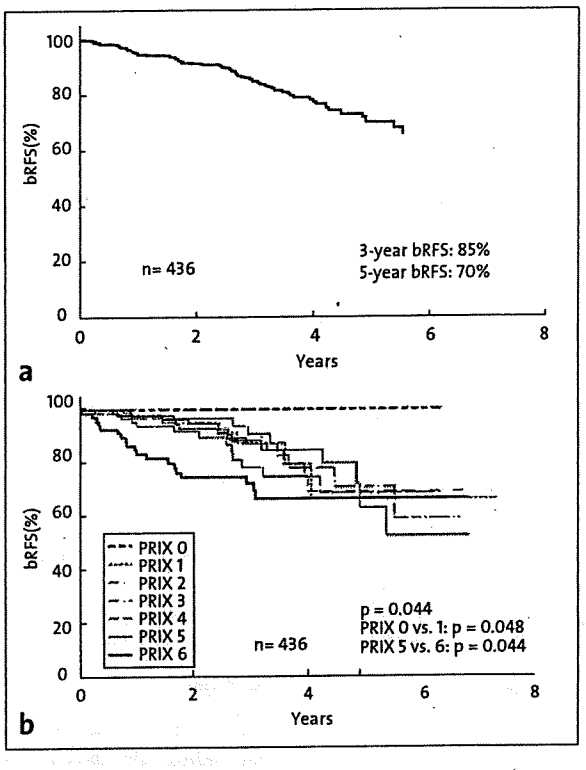


Figure 1. Time trends in the number of patients treated with definitive external-beam radiotherapy for prostate cancer at eleven institutions mainly in Osaka, Japan, 1995–2006 (n = 652).

Abbildung 1. Zeitliche Entwicklung bezüglich der Anzahl von Patienten, die sich 1995–2006 in elf Einrichtungen, hauptsächlich in Osaka, Japan, einer definitiven perkutanen Strahlenbehandlung wegen Prostatakrebs unterzogen (n = 652).



Figures 2a and 2b. Biochemical relapse-free survival (bRFS) rate for all 436 eligible, nonstratified patients (a), and for the same 436 patients stratified by Prostate Cancer Risk Index (PRIX) 0–6 (b).

Abbildungen 2a und 2b. Rate des biochemisch rezidivfreien Überlebens (bRFS) für alle 436 qualifizierten, nichtstratifizierten Patienten (a) sowie für dieselben 436 Patienten bei Stratifikation mit dem Prostatakrebsrisikoindex (PRIX) 0–6 (b).

Results

Figure 1 shows the changing trend in the number of patients who received definitive EBRT for the prostate, with a special focus on whether GS had been established. It represents all the patients (n = 652) initially enrolled in this study, including those who were subsequently considered ineligible for analysis. The number of patients showed a tenfold increase from 1995 to 2005, while, at the same time, the use of GS spread rapidly from 0% to > 90% of cases.

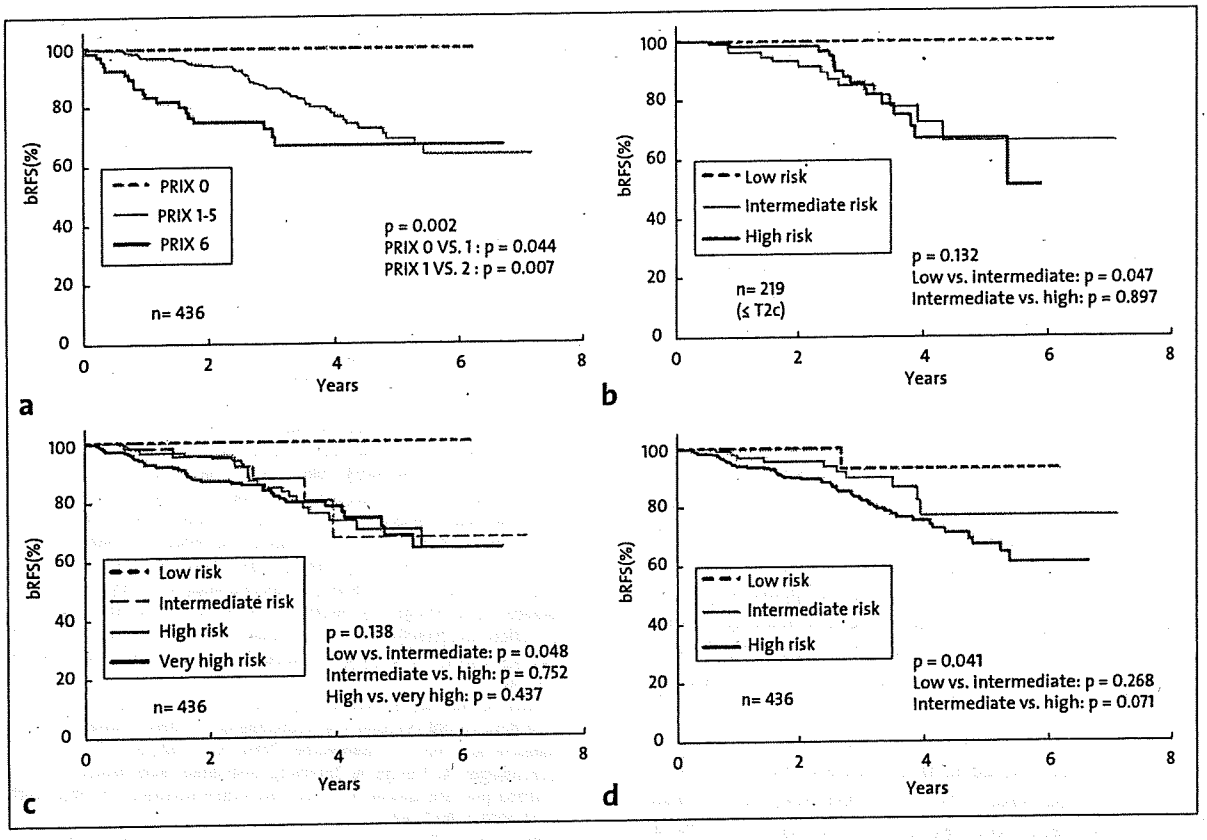
The characteristics of the patients who were eligible for analysis (n = 436) are shown in Table 1. T1 : T2 : T3 : T4 = 75 : 147 : 200 : 14, PSA ≤ 10 : 10–20 : > 20 ng/ml = 126 : 121 : 189, GS 2–6 : 7 : 8–10 = 97 : 167 : 172. Hormone therapy was administered to 95% of the patients, whereas 9% received whole pelvic RT. Nearly 90% of the patients were treated with 70 Gy in 35 fractions (60–66 Gy: 26 patients [6%]; 66–70 Gy: 15 patients [3%]; 70 Gy: 378 patients [87%]; 70–74 Gy: 17 patients [4%]).

A higher PRIX corresponded to a higher rate of hormone therapy usage. However, even in the case of PRIX 0 patients, 70% were treated with hormone therapy (the ratio was 100% for PRIX 6). Similarly, a higher PRIX mostly corresponded to a higher rate of whole pelvic RT usage (PRIX 0: 0%, PRIX 6: 21%). The mean RT dose for PRIX 6 was slightly smaller than for PRIX 0–5 (68.6 Gy vs. 69.4–69.9 Gy), but the difference was not statistically significant. No correlation was observed between PRIX and age or duration of hormone therapy.

The median follow-up period was 33 months (range 6–88, mean 35 months). The actuarial 3- and 5-year bRFS rates were 85% and 70%, respectively, for all 436 patients (Figure 2a).

For the seven PRIX strata, 3- and 5-year bRFS rates were 100% and 100% for PRIX 0, 87% and 66% for PRIX 1, 78% and 69% for PRIX 2, 91% and 71% for PRIX 3, 88% and 68% for PRIX 4, 87% and 63% for PRIX 5, and 72% and 67% for PRIX 6, respectively (Figure 2b). Since PRIX 0 and 6 curves were obviously higher or lower than the others, while those for PRIX 1–5 did not differ from each other, we combined PRIX 1–5 into one group for the next analysis.

For the three PRIX strata (PRIX 0, 1–5, and 6), 3- and 5-year bRFS rates were 100% and 100% for PRIX 0, 86% and 69% for PRIX 1–5, and 72% and 67% for PRIX 6, respectively (Figure 3a). For comparison, when the patients were classified into three strata according to D'Amico's classification, the corresponding rates were 100% and 100% for the low-risk, 84% and 65% for the intermediate-risk, and 86% and 66% for the high-risk group (Figure 3b). For the four-stratum characterization according to NCCN's classification, the rates were 100% and 100% for the low-risk, 87% and 66% for the intermediate-risk, 84% and 69% for the high-risk, and 83% and



Figures 3a to 3d. Biochemical relapse-free survival (bRFS) rates stratified according to the Prostate Cancer Risk Index (PRIX) 0, 1–5, and 6 (a), D'Amico's classification (b), the National Comprehensive Cancer Network (NCCN) classification (c), and the Seattle classification (d).

Abbildungen 3a bis 3d. Raten des biochemisch rezidivfreien Überlebens (bRFS), stratifiziert nach dem Prostatakrebsrisikoindex (PRIX) 0, 1–5 und 6 (a) sowie den Klassifikationen von D'Amico et al. (b), National Comprehensive Cancer Network (NCCN; c) und Seattle (d).

Table 3. Univariate analysis using a log-rank test. GS: Gleason Score; PRIX: Prostate Cancer Risk Index; PSA: prostate-specific antigen; WPRT: whole pelvic radiation therapy.

Tabelle 3. Univariate Analyse unter Verwendung eines Log-Rank-Tests. GS: Gleason-Score; PRIX: Prostatakrebsrisikoindex; PSA: prostataspezifisches Antigen; WPRT: Ganzbeckenbestrahlung.

Variable	p-value
Age ≤ 70, ≥ 71 years	0.033*
< 66 Gy, ≥ 66 Gy	0.058
< 70 Gy, ≥ 70 Gy	0.367
Hormone +/–	0.746
WPRT +/–	0.982
T1–2, T3–4	0.238
PSA ≤ 10, > 10 ng/ml	0.035*
PSA ≤ 20, > 20 ng/ml	0.081
GS ≤ 6, ≥ 7	0.030*
GS ≤ 7, ≥ 8	0.097
PRIX 0, 1–6	0.033*
PRIX 0–5, 6	0.003*

*p < 0.05

67% for the very high-risk group (Figure 3c). Finally, when the patients were stratified into three groups according to Seattle's classification, the rates were 93% and 93% for the low-risk, 90% and 77% for the intermediate-risk, and 83% and 66% for the high-risk group (Figure 3d).

D'Amico's (p = 0.132), NCCN's (p = 0.138), and Seattle's (p = 0.041) classifications, as well as our seven-stratum PRIX (p = 0.044) showed weak or no correlation with bRFS, in contrast to three-stratum PRIX (PRIX 0, 1–5, 6), which showed a strong correlation (p = 0.002; Figures 2b, 3a to 3d). Each of these figures shows the p-values for paired log-rank comparison.

Univariate analysis using the log-rank test indicated that age ≤ 70 versus ≥ 71 years (p = 0.033, better for age ≥ 71), PSA ≤ 10 versus > 10 ng/ml (p = 0.035), GS ≤ 6 versus ≥ 7 (p = 0.030), PRIX 0 versus 1–6 (p = 0.033), and PRIX 0–5 versus 6 (p = 0.003) were all significant factors for bRFS (Table 3).

Discussion

Prostate cancer was not a common cancer in Japan until recently; however, its incidence and mortality are now

rapidly increasing [4, 5]. While radical prostatectomy has become widely accepted during the past 2 decades [2], the prevalence of definitive RT is still not satisfactory. Due to these circumstances, very few studies of RT for prostate cancer have been published in Japan and the data are for a relatively small number of patients treated with uncommon techniques including, for example, monotherapeutic high-dose-rate brachytherapy on 111 patients [21], carbon ion RT on 175 patients [9], and permanent brachytherapy using CT/MRI fusion method on 38 patients [19]. Even for a multiinstitutional study in conjunction with a patterns-of-care study project, only 283 patients were reported, whose data had been extracted from 66 institutions with the two-stage cluster sampling method [14].

While the data for definitive RT are thus still insufficient, the number of patients who are treated with RT or who want to be treated with RT is rapidly increasing [13]. Since establishment of treatment outcome criteria for RT in Japan has therefore become of the utmost importance, we collected clinical, practice-based data from multiple representative institutions in the Osaka district. The resultant information for 652 patients from eleven institutions represents, to the best of our knowledge, one of the largest sets of data for prostate RT in Japan.

The results of our study demonstrate that the number of patients who received definitive prostate EBRT showed a tenfold increase between 1995 and 2006, and, at the same time, use of GS evaluation has spread rapidly from 0% to > 90% of cases. Our study also showed a distinct characteristic of Japanese clinical practice, that is, a very high rate of neoadjuvant and/or adjuvant hormone therapy usage. In fact, 95% of all the patients, and even 70% of PRIX 0 or so-called low-risk patients, received hormone therapy. By contrast, data from the American College of Radiology National Patterns of Care Study show that only 51% of EBRT patients received hormone therapy [22]. A relatively low rate of whole pelvic RT administration (9%), compared to that in the USA (23%) [22], also seems to be a characteristic of Japanese clinical practice.

EBRT is becoming widely accepted during the current decade in Japan, thus following the trend in western countries. The data presented here, although still immature, are expected to enhance the current paucity of data regarding Japanese prostate EBRT, and to form the basis for a historical reference database for the coming era of three-dimensional conformal RT [7, 10] or IMRT [3, 8, 16]. At the same time, this study identified an important characteristic of Japanese prostate EBRT, that is, a very high rate of hormone therapy usage and a low rate of combining it with whole pelvic RT. The dominant dose fractionation observed in this study was 70 Gy/35 fractions. Under these circumstances, the so-called low-risk group or PRIX 0 showed obviously better bRFS than others, while the categorization of the so-called intermediate- or high-risk groups was not effective. We were able to demonstrate that PRIX 6 is clearly a prognostic factor for a worse bRFS, although the usefulness of subclassifications PRIX 1–5 remains questionable.

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RADIATION THERAPY FOR ESOPHAGEAL CANCER IN JAPAN: RESULTS OF THE PATTERNS OF CARE STUDY 1999–2001

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Purpose: To describe patient characteristics and the process of radiotherapy (RT) for patients with esophageal cancer treated between 1999 and 2001 in Japan.

Methods and Materials: The Japanese Patterns of Care Study (PCS) Working Group conducted a third nationwide survey of 76 institutions. Detailed information was accumulated on 621 patients with thoracic esophageal cancer who received RT.

Results: The median age of patients was 68 years. Eighty-eight percent were male, and 12% were female. Ninety-nine percent had squamous cell carcinoma histology. Fifty-five percent had the main lesion in the middle thoracic esophagus. Fourteen percent had clinical Stage 0–I disease, 32% had Stage IIA–IIB, 43% had Stage III, and 10% had Stage IV disease. Chemotherapy was given to 63% of patients; 39% received definitive chemoradiotherapy (CRT) without surgery and 24% pre- or postoperative CRT. Sixty-two percent of the patients aged ≥75 years were treated with RT only. Median total dose of external RT was 60 Gy for definitive CRT patients, 60 Gy for RT alone, and 40 Gy for preoperative CRT.

Conclusions: This PCS describes general aspects of RT for esophageal cancer in Japan. Squamous cell carcinoma accounted for the majority of patients. The standard total external RT dose for esophageal cancer was higher in Japan than in the United States. Chemoradiotherapy had become common for esophageal cancer treatment, but patients aged ≥75 years were more likely to be treated by RT only. © 2009 Elsevier Inc.

Patterns of Care Study, Esophageal cancer, Radiotherapy, Chemoradiation, Japan.

INTRODUCTION

The Patterns of Care Study (PCS) was established and developed in the radiation oncology field in the United States. The PCS retrospectively investigates the nationwide structure and practice of care in specific malignancies and provides useful data for improving cancer management. Patient backgrounds and standard clinical practices can be described by PCS. Penetration of clinical evidence and the compliance status of clinical guidelines can be evaluated through PCS results. The PCS also reveals the time-dependent transition of cancer treatments and provides data for international comparison. The U.S. PCS for esophageal cancer demonstrated that a majority of patients treated by radiotherapy (RT) received chemotherapy concurrently and that chemoradiotherapy (CRT) followed by surgery had become important in treatment strategies (1–4).

The PCS was introduced to Japan in the early 1990s. The Japanese PCS Group started a national survey for the major diseases in radiation oncology and has been continuously working. We previously reported PCS results for esophageal cancer for the periods 1992–1994 and 1995–1997 (5, 6).

The objectives of this study were (*1*) to summarize the structure and process of RT for patients with esophageal cancer treated between 1999 and 2001 and show comparable data from the U.S. PCS study; and (2) to compare patient characteristics and treatment strategies with regard to patient age.

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Table 1. Investigated institutions and patients with esophageal cancer in the Japanese Patterns of Care Study (1999–2001)

Institutions	No. of Institutions	Patients	Age group		
			<65 y	65–74 y	≥75 y
Total institutions	76	621	244	213	164
Academic (A)	38	358 (57.6)	164 (67.2)	126 (59.2)	68 (41.5)
Treat ≥430/y (A1)	20	196 (31.6)	89 (36.5)	69 (32.4)	38 (23.2)
Treat <430/y (A2)	18	162 (26.1)	75 (30.7)	57 (26.8)	30 (18.3)
Nonacademic (B)	38	263 (42.4)	80 (32.8)	87 (40.8)	96 (58.5)
Treat ≥130/y (B1)	20	186 (30.0)	52 (21.3)	62 (29.1)	72 (43.9)
Treat <130/y (B2)	18	77 (12.4)	28 (11.5)	25 (11.7)	24 (14.6)

Values in parentheses are percentages.

METHODS AND MATERIALS

Between July 2002 and June 2004, the Japanese PCS Group conducted a third national survey for esophageal cancer. Eligibility criteria were as follows: (*1*) thoracic esophageal cancer, (2) squamous cell carcinoma (SCC), adenocarcinoma, or adenosquamous cell carcinoma, (*3*) no distant metastasis, (*4*) no prior or concurrent malignancies within 5 years, (*5*) Karnofsky performance score (KPS) >50, and (6) RT started between January 1999 and December 2001. Seventy-six of approximately 700 institutions were selected for the survey by use of a stratified two-stage cluster sampling method. Before the random sampling, all RT institutions were classified into four groups according to type and number of patients who received RT. The criteria for stratification have been detailed elsewhere (7). In brief, Japanese RT institutions were stratified as follows: A1, academic institutions including university hospitals and cancer centers treating ≥430 newly diagnosed patients by RT per year; A2, <430 patients; B1 nonacademic institutions including national, prefectural, municipal, or private hospitals treating ≥130 patients per year; B2, <130 patients.

The Japanese PCS surveyors, who were active radiation oncologists, performed on-site review at each participating facility. They used an originally developed database format for esophageal cancer and investigated patient charts, radiotherapy records, and image films. Data collection included patient characteristics (*e.g.*, history, age, KPS, clinical examination results, laboratory data, diagnostic procedures, histology, and stage), details of therapeutic information (*e.g.*, RT, chemotherapy, surgery, and combinations thereof), and treatment outcomes. The Japanese PCS collected detailed clinical data on 621 patients who met the eligibility criteria for this study. Table 1 lists the number of the investigated institutions and the patients in this study. Three hundred fifty-five patients (57.6%) were from 38 academic institutions, and 263 (42.4%) were from 38 nonacademic institutions. Two hundred forty-four patients (39.3%) were aged <65 years (younger age group), 213 patients (34.3%) were aged 65–74 years (middle age group), and 164 patients (26.4%) were aged ≥75 years (older age group).

Statistical significance was tested using the χ^2 test. Ratios were calculated including unknown data but excluding missing data.

RESULTS

Median age of the patients was 68 years. Median height and body weight were 162 cm and 52.5 kg, respectively. Regarding comorbid diseases, hypertension was seen in 25% of patients, ischemic heart disease in 7%, cerebrovascular disease in 16%, chronic hepatitis in 13%, diabetes in 13%, and chronic nephritis or renal failure in 4%. Fifteen percent of esophageal cancers were detected by mass screening or medical checkup for other disease. Swallowing function at diagnosis was evaluable in 588 patients: 20% had no symptoms related to swallowing function, 33% could eat a normal diet with some symptoms, 32% could eat soft food only, 12% could drink liquids but could not eat solid food, and 3% could take nothing by mouth. Patient and tumor characteristics are shown in Table 2. Eighty-seven percent were male, and 13% were female. The female ratio in the older age group was 21% and was higher than in the other age groups ($p = 0.001$). Median KPS score was 80; 76% of patients had a score of ≥80. Patients with a good KPS score of 90–100 were fewer in the older age group than in the other groups (25% vs. 39%; $p = 0.001$). Six-hundred six (99%) of the evaluable 612 patients had SCC histology. Adenocarcinoma and adenosquamous cell carcinoma accounted for <1%. Fifty-five percent had the main lesion in the middle thoracic esophagus, 27% in the lower esophagus, and 19% in the upper esophagus. The ratio of tumor histology and main tumor location were not different among age groups. Fourteen percent had clinical Stage 0 or I disease, 32% had Stage IIA or IIB, 43% had Stage III, and 10% had Stage IV disease. The ratio clinical of Stage 0 to IIb was different among age groups (41% in the younger age group, 40% in the middle age group, and 59% in older age group).

Major treatment combinations are shown in Table 3. All patients except 8 who were treated by brachytherapy alone received external-beam RT. Chemotherapy was given to 63% of the patients; 39% received definitive CRT without surgery, and 24% received surgery in combination with RT or CRT. Fifty patients (8%) who were treated by RT and surgery did not receive chemotherapy. Twenty-seven percent of the all patients were treated by RT alone without chemotherapy or surgery. In the older age group, 62% were treated by RT alone, 35% by chemotherapy, and only 4% received surgery. Utilization ratios of chemotherapy and surgery in the older age group were significantly lower than in the younger and middle age groups ($p < 0.01$). Combinations of surgery and CRT were more frequently used in academic institutions than in nonacademic institutions (31% vs. 14%; $p < 0.01$); RT alone was applied to 33% of patients in nonacademic institutions.

Regarding drugs used for chemotherapy, 5-fluorouracil was used by 98% of patients who received CRT, cisplatin

Table 2. Characteristics of esophageal cancer patients according to age groups

Characteristic	Age group <65 y (n = 244)	65–74 y (n = 213)	≥75 y (n = 164)	Total (n = 621)	p
Gender					0.014
Male	219 (90)	191 (90)	129 (79)	539 (87)	
Female	25 (10)	22 (10)	35 (21)	82 (13)	
KPS					0.001
60–70	42 (20)	33 (18)	49 (36)	124 (24)	
80	85 (41)	79 (43)	54 (39)	218 (41)	
90–100	81 (39)	70 (39)	34 (25)	185 (35)	
Missing	36	31	27	94	
Histology					0.547
SCC	238 (99)	209 (99)	159 (100)	606 (99)	
Adeno.	1 (0)	2 (1)	0	3 (0)	
Adenosq.	2 (1)	1 (1)	0	3 (0)	
Missing	3	1	5	9	
Site of lesion					0.8422
Upper	42 (18)	43 (20)	31 (18)	116 (19)	
Middle	132 (55)	114 (54)	89 (62)	335 (55)	
Lower	65 (27)	56 (26)	42 (20)	163 (27)	
Missing	5	—	2	7	
Longitudinal tumor size by endoscopy (cm)					0.595
≤5.0	75 (52)	63 (49)	67 (59)	205 (53)	
5.1–10.0	56 (39)	54 (42)	40 (35)	150 (39)	
10.1–15.0	12 (8)	10 (8)	6 (5)	28 (7)	
≥15.1	2 (1)	3 (2)	0	5 (1)	
Missing	99	83	51	233	
Median (cm)	5	6	5	5	
Clinical stage*					0.001
0, I	21 (10)	28 (15)	26 (18)	75 (14)	
IIa, IIb	68 (31)	48 (25)	59 (41)	175 (32)	
IIII	96 (44)	94 (49)	47 (33)	237 (43)	
V	30 (14)	30 (10)	7 (5)	57 (10)	
Unknown	4 (2)	3 (2)	5 (4)	12 (2)	
Missing	25	20	20	65	

Abbreviations: KPS = Karnofsky performance status; SCC = squamous cell carcinoma; Adeno. = adenocarcinoma; Adenosq. = adenosquamous cell carcinoma.

Values are number (percentage) except where noted.

* Staging system by the International Union Against Cancer, 1997.

by 85%, and nedaplatin by 98%. Only 1 patient used a taxane.

Thirty-eight patients (6%) received brachytherapy. High-dose-rate iridium or cobalt therapy was used for 28 patients, and low-dose-rate therapy was given to 10 patients. Five hundred fifty-six patients (90%) were admitted to hospitals during RT. Fifteen patients (3%) were treated on investigational approved protocols.

Details about external RT given to 412 patients who did not receive surgery but were treated by definitive CRT or RT alone are shown in Table 4. The median total dose of external RT was 60 Gy and did not differ among age groups. The median fractionation dose was 2 Gy.

Hyperfractionation was used for 16% of patients. The median initial longitudinal field size was 17 cm. Significant differences in field size among age groups were observed (mean value: 20 cm, 17 cm, and 15 cm in the younger, middle, and older age groups, respectively).

Mediastinal nodal RT for apparent or subclinical lymph node metastases was given to 82% of patients, whereas supraclavicular or upper abdominal area irradiation was given to 33% and 22%, respectively.

Table 5 shows patient backgrounds and RT parameters for definitive CRT, RT alone, and preoperative CRT. Median age of the preoperative CRT patients was 63 years and was younger than for definitive CRT and RT-alone patients. The preoperative CRT group contains 71% of the patients with Stage III–IV disease, and the ratio was higher than in the definitive CRT and RT-alone groups (62% and 58%, respectively). Median total dose was 60 Gy in definitive CRT and RT-alone patients and 40 Gy for preoperative CRT patients. Median initial longitudinal field size was 18 cm for definitive CRT patients and was longer than in RT-alone patients.

DISCUSSION

In the United States two PCSs for esophageal cancer were conducted for the periods 1992–1994 and 1996–1999 (1–4). They established the national and international benchmarks of esophageal cancer treatments and showed the role of RT

Table 3. Treatment combinations according to age groups

Treatment combination	Total	Age group			Institutions	
		<65 y (n = 144)	65–74 y (n = 141)	≥75 y (n = 164)	Academic (n = 358)	Nonacademic (n = 263)
RT with chemotherapy						
Total	393 (63)	180 (74)	155 (73)	58 (34)	240 (67)	153 (58)
Definitively	244 (39)	87 (36)	101 (47)	56 (34)	128 (36)	116 (44)
With surgery	148 (24)	92 (38)	54 (25)	2 (1)	111 (31)	37 (14)
Unknown	1	1	0	0	1	0
RT without chemotherapy						
Total	219 (35)	59 (24)	56 (26)	104 (63)	111 (31)	108 (41)
Definitively	169 (27)	26 (11)	42 (20)	101 (62)	83 (23)	86 (33)
With surgery	50 (8)	33 (14)	14 (7)	3 (2)	28 (8)	22 (8)
Unknown	0	0	0	0	0	0
Unknown about chemotherapy						
Total	9 (1)	5 (2)	2 (1)	2 (1)	7 (2)	2 (1)
Definitively	2	1	1	0	2 (1)	0
With surgery	6 (1)	3 (1)	1	2 (1)	4 (1)	2 (1)
Unknown	1	1	0	0	1	0

Abbreviation: RT = radiotherapy.
Values are number (percentage).

in multidisciplinary management of this disease. The Japanese PCS group conducted two large surveys in the 1990s and reported patient backgrounds and RT practices for esophageal cancer (5, 6). A summary of patient backgrounds and treatments from three Japanese PCSs and two U.S. PCSs is shown in Table 6.

The incidence of adenocarcinoma of the esophagus has rapidly increased in the United States since the 1970s and has accounted for approximately half of esophageal cancers in recent years (8, 9). The U.S. PCS for 1996–1999 reported the ratio of adenocarcinoma and SCC as 48.7% and 49.6%, respectively (3). Some reports from European countries also showed an increasing incidence of adenocarcinoma (10). On the other hand, this trend is not observed in Asian countries. A recent report based on the cancer registry in Japan showed the ratio of SCC to adenocarcinoma to be 26:1 (11). Preliminary results of the Korean PCS reported that 96% of investigated patients had SCC histology (12). Consistent with the previous two Japanese PCSs, 99% of patients in this study had SCC. Although adenocarcinoma mainly arises in the lower esophagus near the esophagogastric junction, the most common location of the main lesion for SCC is the midthoracic esophagus. More than half of patients had the main lesion in the midthoracic esophagus in this study. Differences in tumor histology and main tumor location may have an influence on treatment strategies and results (*i.e.* type of surgery, setting of target volume of RT, and adverse effects of the treatments).

The discrepancy between the United States and Japan was also identified in the pretherapy evaluations. Both endoscopy and esophagram were the standard evaluation methods for esophageal cancer in Japan, but approximately one third of patients did not receive an esophagram in the United States. Barium study is the traditional and relatively easy method for evaluating the gastrointestinal tract and is used for mass screening for gastric cancer in Japan. Because most gastroenterologists are skilled in doing esophagrams in Japan, it was routinely used for evaluation of esophageal cancer. Endoscopic ultrasound is the most accurate method to define both T and N staging of esophageal carcinoma in the current staging system (13). The current International Union Against Cancer staging system adopted depth of tumor invasion for T staging, which increased use of endoscopic ultrasound in each country.

Since the Intergroup study reported by Cooper *et al.* (14) showed the superiority of CRT over RT alone for esophageal cancer, the application of CRT has increased in the United States (3, 4). The ratio of using chemotherapy in combination with RT in Japan has also increased, from 40% in PCS 1995–1997 to 63% in PCS 1999–2001. Most of the CRT patients in Japan used cisplatin and 5-fluorouracil for chemotherapy. One reason is that taxanes had not been approved for esophageal cancer in Japan until 2003. The other reason was that not enough evidence was shown regarding the use of taxanes in CRT for esophageal cancer in the 1990s.

In the U.S. PCS, median total external RT dose was 50.4 Gy (1, 3). However, our data showed the median total external dose in Japan to be 60 Gy, and it was same for RT-only patients and definitive CRT patients. Not many clinical trials have investigated the total dose in CRT for esophageal cancer. The standard dose used in the United States is considered to be based on the results of a Phase III trial (INT 0123) showing no benefit of higher radiation on survival or locoregional control (15). After publication of the results of INT 0123, clinical studies investigating total RT dose in esophageal cancer in the United States seem to have been stopped. On the other hand, some Phase II studies conducted in Japan in the 1990s testing the efficacy of CRT for esophageal cancer used a total dose of 60 Gy, and preliminary results showed excellent outcomes (16, 17). Ohtsu *et al.* (16) studied 44 patients

Table 4. External RT parameters in nonsurgery patients

Characteristic	Age group <65 y (n = 244)	65–74 y (n = 213)	≥75 y (n = 164)	Total (n = 621)	p
Total external RT dose (Gy)					—
<30	4 (4)	7 (5)	6 (4)	17 (4)	
30.1–40	14 (12)	13 (9)	9 (6)	36 (9)	
40.1–50	7 (6)	12 (9)	13 (8)	32 (8)	
50.1–60	40 (35)	40 (28)	47 (30)	127 (31)	
60.1–70	40 (35)	66 (47)	77 (49)	183 (44)	
>70	9 (8)	3 (2)	4 (3)	16 (4)	
Missing	—	—	1	1	
Median (Gy)	60.0	60.0	60.0	60.0	
Hyperfractionation					0.500
Done	14 (12)	25 (18)	25 (16)	64 (16)	
Not done	100 (88)	116 (82)	132 (84)	348 (84)	
Missing	—	—	—	—	
Initial longitudinal field size (cm)					0.001
≤10.0	3 (3)	14 (10)	25 (16)	42 (10)	
10.1–15.0	21 (19)	39 (28)	53 (34)	113 (28)	
15.1–20	35 (31)	48 (34)	47 (30)	130 (32)	
20.1–25	34 (30)	26 (19)	18 (12)	78 (19)	
≥25.1	19 (17)	13 (9)	12 (8)	44 (11)	
Missing	2	1	2	5	
Mean (cm)	20	17	15	17	
Mediastinal nodal area irradiation					0.063
Done	96 (86)	110 (79)	116 (74)	322 (79)	
Not done	16 (14)	29 (21)	41 (26)	86 (21)	
Unknown	—	—	—	—	
Missing	2	2	—	4	
Supraclavicular nodal area irradiation					
Done	41 (37)	31 (22)	27 (17)	99 (24)	0.003
Not done	70 (63)	108 (78)	129 (82)	307 (75)	
Unknown	—	—	1 (1)	1	
Missing	3	2	—	5	
Upper abdominal nodal area irradiation					0.050
Done	32 (29)	33 (24)	25 (16)	90 (22)	
Not done	79 (71)	106 (76)	130 (83)	315 (77)	
Unknown	—	—	2 (1)	2 (1)	
Missing	3	2	—	5	
Field reduction					0.517
Done	87 (78)	104 (74)	111 (71)	302 (74)	
Not done	24 (21)	35 (25)	45 (29)	104 (25)	
Unknown	1 (1)	1 (1)	1 (1)	3 (1)	
Missing	2	1	—	3	

Abbreviation: RT = radiotherapy.
Values are number (percentage).

with T4 and/or M1 by lymph node treated with 60 Gy of external RT and concurrently administered cisplatin and 5-fluorouracil. Three-year overall survival was 23%. This result, published in 1999, may have impacted clinical practice during this study period. Supported by the results of this study, a total dose of 60 Gy in CRT might become standard practice in Japan. Ishikura *et al.* (18) reported substantial late pulmonary and cardiac toxicities by 60 Gy of thoracic CRT with a conventional opposed two-beam technique. Additional investigation regarding the optimal total dose of CRT for esophageal cancer with modern RT techniques is warranted.

Patients aged ≥75 years account for 26% of all patients in this study. Some characteristics of patient backgrounds and differences of treatment for elderly patients are apparent from this study. More early-stage patients and more low-KPS patients were included in the elderly group than in the middle or younger age groups. Elderly patients were not frequently treated by multimodality treatments in combination with surgery and chemotherapy but rather by RT alone. Although surgery in combination with CRT or chemotherapy is the standard treatment for operable esophageal cancer, patients with a low performance status or with comorbid disease were medically unfit for surgery. Radiotherapy alone might be frequently chosen as the most noninvasive treatment for elderly esophageal cancer patients. Meanwhile, 34% of elderly patients received

Table 5. Backgrounds and radiotherapy parameters of patients who received definitive CRT, RT alone, or preoperative CRT

Parameter	Definitive CRT (n = 241)	RT alone* (n = 146)	Preoperative CRT (n = 86)
Male/female	89/11	80/20	86/14
Age (y), median	68	78	63
KPS >90	29	34	36
Main tumor lesion, upper	21	18	20
Stage 0–IIb	36	34	29
Stage III–IV	62	58	71
Total external RT dose (Gy)			
≤30	4	5	35
30.1–40	11	4	33
40.1–50	7	10	12
50.1–60	32	31	12
60.1–70	43	45	10
≥70.1	4	4	
Median (Gy)	60	60	40
Initial longitudinal† field size (cm)			
≤10	5	17	3
10.1–15.0	23	36	27
15.1–20.0	36	26	37

Abbreviations: CRT = chemoradiotherapy; RT = radiotherapy.
Values are percentages except where noted.
* RT without chemotherapy.
† Craniocaudal direction.

definitive CRT. There are not enough data available regarding the efficacy of chemoradiation in elderly or low-KPS patients (19), and criteria for reducing RT dose and chemotherapy dose for these patients have not been established. The intensity of chemotherapy used for CRT was not clearly investigated in this study, but regarding RT field, a narrow field excluding the supraclavicular area was generally preferred for elderly patients. Further clinical investigations evaluating the role of CRT and RT in elderly esophageal cancer patients are needed.

In conclusion, this PCS describes patient backgrounds and general patterns of RT practice for esophageal cancer

Table 6. Comparison of patient backgrounds and treatment combinations among three Japanese PCSs and U.S. PCSs

Parameter	PCS 1992–1994 (n = 561)	PCS 1995–1997 (n = 776)	PCS 1999–2001 (n = 621)	U.S. PCS 1992–1994 (n = 400)	U.S. PCS 1996–1999 (n = 414)
Academic/nonacademic	46/54	62/38	58/42	51/49	NA
Median age (y)	66	67	68	66.7	64
Male/female	86/14	85/14	87/13	76.5/23.5	77/23
KPS ≥90	33	27	35	47	56
Esophagram done	NA	92	93	69	64
Endoscopy done	NA	91	96	94	96
Endoscopic ultrasound done	NA	21	27	4	18
Clinical Stage I by AJCC, 1983 version	15	19	20	15	16
Squamous cell carcinoma	99	100	99	61.5	49
Main tumor location, middle thorax	NA	62	55	NA	NA
External RT done	99	99	99	Nearly all	100
External beam energy >6 MV	85	78	92	>76	NA
Median fraction external RT dose (Gy)	2.0	2.0	2.0	1.8	1.8
Median total external RT dose (Gy)	60.0	60.0	60.0	50.4	50.4
Brachytherapy done	10	12	6	8.5	6
Chemotherapy done	35	40	63	75	89
Preoperative RT + CT followed by surgery	16	9	16	14.5	27
Surgery followed by RT + CT	22	19	18	11	6
Definitive CRT	22	25	39 5	4	56
RT alone without surgery or CT	34	44	27	20	10

Abbreviations: PCS = Patterns of Care Study; NA = not applicable; KPS = Karnofsky performance status; AJCC = American Joint Committee on Cancer; RT = radiotherapy; CT = chemotherapy; CRT = chemoradiotherapy.
Values are percentages except where noted.

in Japan. Tumor histology and standard RT dose were different between the United States and Japan. Care should be taken when comparing data from these two countries. This study also revealed the treatment characteristics for elderly esophageal cancer patients. Repeated surveys will demonstrate the trends for esophageal cancer treatment in Japan and will provide useful data for international comparison.

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5TH JUCTS AND THE 5TH S.TAKAHASHI MEMORIAL INTERNATIONAL JOINT SYMPOSIUM

A PRELIMINARY STUDY OF IN-HOUSE MONTE CARLO SIMULATIONS: AN INTEGRATED MONTE CARLO VERIFICATION SYSTEM

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Purpose: To develop an infrastructure for the integrated Monte Carlo verification system (MCVS) to verify the accuracy of conventional dose calculations, which often fail to accurately predict dose distributions, mainly due to inhomogeneities in the patient's anatomy, for example, in lung and bone.

Methods and Materials: The MCVS consists of the graphical user interface (GUI) based on a computational environment for radiotherapy research (CERR) with MATLAB language. The MCVS GUI acts as an interface between the MCVS and a commercial treatment planning system to import the treatment plan, create MC input files, and analyze MC output dose files. The MCVS consists of the EGSnrc MC codes, which include EGSnrc/BEAMnrc to simulate the treatment head and EGSnrc/DOSXYZnrc to calculate the dose distributions in the patient/phantom. In order to improve computation time without approximations, an in-house cluster system was constructed.

Results: The phase-space data of a 6-MV photon beam from a Varian Clinac unit was developed and used to establish several benchmarks under homogeneous conditions. The MC results agreed with the ionization chamber measurements to within 1%. The MCVS GUI could import and display the radiotherapy treatment plan created by the MC method and various treatment planning systems, such as RTOG and DICOM-RT formats. Dose distributions could be analyzed by using dose profiles and dose volume histograms and compared on the same platform. With the cluster system, calculation time was improved in line with the increase in the number of central processing units (CPUs) at a computation efficiency of more than 98%.

Conclusions: Development of the MCVS was successful for performing MC simulations and analyzing dose distributions. © 2009 Elsevier Inc.

Monte Carlo simulations, Verification, Photon beam, High precision radiotherapy.

INTRODUCTION

Improvements in dose delivery techniques have rendered it possible to point the dose exactly to the tumor volume and spare the surrounding normal tissues. However, beam delivery in radiotherapy has become increasingly complex since the advent of three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and stereotactic body radiotherapy (SBRT). Especially with these high-precision radiation therapies, accurate dose calculations are essential for radiotherapy planning. To meet this need, comparatively accurate dose calculation algorithms, such as the convolution/superposition method, have come into use for commercial treatment planning systems (1-3). However, these algorithms often fail to predict accurate dose distributions, mainly due to inhomogeneities in the patient's anatomy, for example, in lung and bone, and to several multileaf collimator (MLC)-specific effects, which include leakage of radiation, the tongue-and-groove effect, and beam hardening (4-10). For example, some conventional algorithms in widespread use for commercial treatment planning systems cause systematic errors exceeding 10% in the thoracic area (11). Although the accuracy required for dose computation is generally between 1% and 2%, major errors in the doses calculated by conventional dose algorithms

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reportedly exceeded that criterion (5, 12-15). These uncertainties concerning dose distributions may cause unintended geographic misses of the target or an overdosage to normal tissues due to the incorrect prediction of isodose coverage and may thus negatively affect the clinical outcome (16).

Monte Carlo (MC) simulation is the most accurate dose calculation method currently available, since it can accurately calculate realistic radiation transport through the accelerator treatment head, the MLC, and the patient's internal anatomy. Moreover, the MC method uses the only algorithm that considers all aspects of photon and electron transport within a heterogeneous situation. The most widely used MC code is EGSnrc, which includes EGSnrc/BEAMnrc and EGSnrc/DOSXYZnrc (17, 18). BEAMnrc is an MC user code for modeling the linear accelerator, and DOSXYZnrc is its counterpart for 3D absorbed dose calculations.

The purpose of this study was to develop an integrated MC dose calculation system, which we called the MC verification system (MCVS). In this paper, we describe in detail the key features of the MCVS and the results of dose calculation accuracy benchmarks.

METHODS AND MATERIALS

Overview of the MCVS

Figure 1 shows a schematic diagram of the usual calculation flow for plan verification. The MCVS consists of two MC codes, that is, EGSnrc/BEAMnrc, which simulates radiation transport through the complex geometry of the linear accelerator treatment head, and EGSnrc/DOSXYZnrc, which calculates the patient's heterogeneous internal anatomy. The MCVS has an interface with a commercial treatment planning systems (Eclipse, Varian Medical Systems, Palo Alto, CA) and reads the information needed for the MC simulation transferred in the DICOM-RT format. With the graphical user interface (GUI), the MC input files are auto-created, and the output files are then processed for display and/or analysis.

Linear accelerator head simulation

For this study, a 6-MV photon beam from a Varian Clinac 23EX unit was simulated with the EGSnrc/BEAMnrc code. The following modeled linear accelerator head components were used: target/backing, primary collimator, vacuum window, flattening filter, mirror, and jaws on the X and Y coordinates. The monitor ion chamber could be omitted from modeling since it had only a minor attenuating effect on the photon beam (19). Figure 2 shows the schema of the simulated geometry. The phase-space data (PSD) file was scored at a plane immediately behind the lower jaws. The mean electron beam energy incident on the target and the full width half maximum (FWHM) of the radial intensity distribution were set to 5.95 MeV and 0.8 mm, respectively. The FWHM of energy distribution was consistently 3% of the mean energy. The distributions of the energy and intensity were assumed to be Gaussian in shape.

For MC simulation, 4.0×10^7 electron histories were simulated. The photon and electron cutoff energies, PCUT and ECUT, of 0.010 MeV and 0.700 MeV were used for all simulations. The variance reduction technique directional bremsstrahlung splitting was used during head simulation with a splitting number of 500 while the electron was also split. The PSD file contained approximately 8.5×10^6 to 3.4×10^7 photons which corresponded to the 270 MB to 1.0 GB file size for 10×10, 20×20, and 30×30 cm^2 open fields.

Dose calculations for a water phantom

The EGSnrc/DOSXYZnrc was used to calculate doses for a phantom. The $50 \times 50 \times 50$ cm^3 simulated water phantom was divided

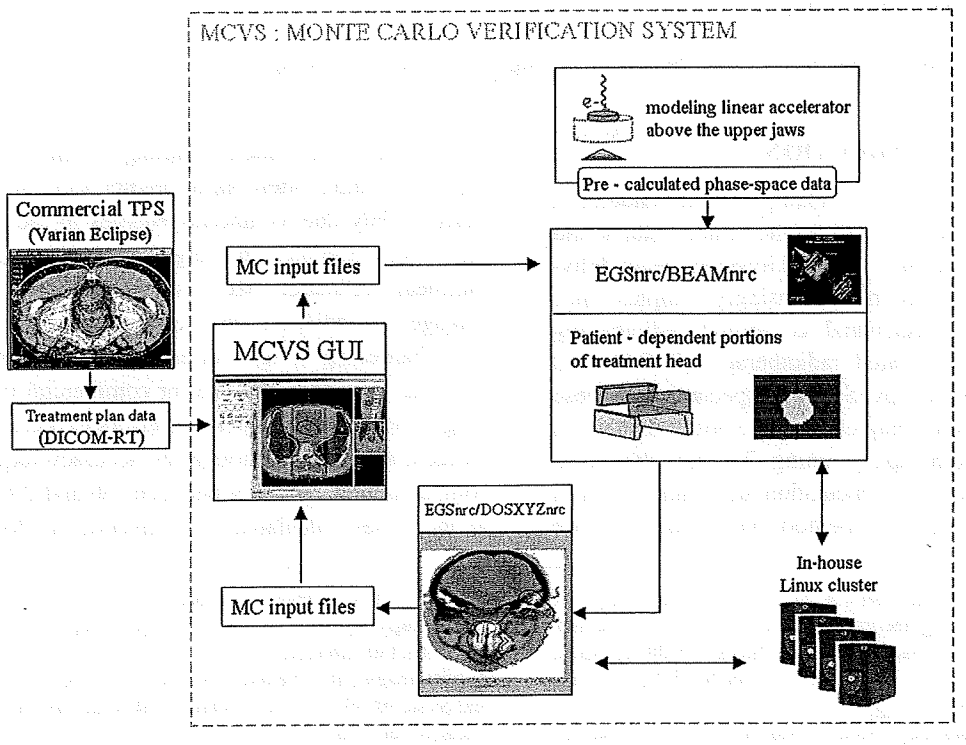

Fig. 1. Schematic diagram of the MCVS GUI showing the EGSnrc MC dose calculations in relation to an Eclipse treatment planning system. The MCVS GUI acts as an interface between EGSnrc and commercial treatment planning systems to read the radiotherapy planning data, create the patient phantom data, and analyze the output dose files calculated by EGSnrc.