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# Postoperative radiotherapy for non-small-cell lung cancer: Results of the 1999–2001 patterns of care study nationwide process survey in Japan

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KEYWORDS
Non-small-cell lung cancer;
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Patterns of care study;
Practice;
Survey;
PORT meta-analysis

**Summary** To investigate the practice process of postoperative radiation therapy for non-small-cell lung cancer (NSCLC) in Japan. Between April 2002 and March 2004, the Patterns of Care Study conducted an extramural audit survey for 76 of 556 institutions using a stratified two-stage cluster sampling. Data on treatment process of 627 patients with NSCLC who received radiation therapy were collected. Ninety-nine (16%) patients received postoperative radiation therapy between 1999 and 2001 (median age, 65 years). Pathological stage was stage I in 8%, II in 17%, IIIA in 44%, and IIIB in 20%. The median field size was 9 cm × 11 cm, and median total dose was 50 Gy. Photon energies of 6 MV or higher were used for 64 patients, whereas a cobalt-60 unit was used for five patients. Three-dimensional conformal treatment was used infrequently. Institutional stratification influenced several radiotherapy parameters such as photon energy and planning target volume. Smaller non-academic institutions provided worse quality of care. The study confirmed continuing variation in the practice of radiotherapy according to stratified institutions. Outdated equipment such as Cobalt-60 units was used, especially in non-academic institutions treating only a small number of patients per year.


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## 1. Introduction

Postoperative radiation therapy (PORT) decreases the risk of local–regional recurrence in patients with resected non-small-cell lung cancer (NSCLC) [1–3]. However, reduction in the frequency of local recurrence has not translated into a survival benefit in most studies. In 1998, the impact of PORT for NSCLC was analyzed in a meta-analysis of phase III trials [4]. After publication of the PORT meta-analysis, which emphasized deleterious effects in patients receiving PORT for completely resected N0-1 cases, much of the clinical focus on adjuvant therapy shifted to chemotherapy [5,6]. Thus, the role of PORT for patients at high risk for locoregional failure such as those with N2 disease remains unclear. Adjuvant chemotherapy trials have often permitted use of PORT as an option for patients with N2 disease [5,7]. One clinical study reported promising results for combined PORT and chemotherapy for patients with pathologic stage II or IIIA disease [8]. The results of these trials imply that PORT delivered using modern radiotherapy techniques may potentially provide a survival advantage for selected high-risk patients.

The Patterns of Care Study (PCS) is a retrospective study designed to investigate the national practice for cancer patients during a specific period [9,10]. In April 2002, the PCS started a nationwide survey for patients with NSCLC treated with radiation therapy in Japan. In the present report, we provide results of analyses focused on patients who received PORT for NSCLC during the study period. The objectives of this study were to reveal clinical practice patterns regarding PORT after publication of the PORT meta-analysis and to assess variation in clinical practice according to stratified institutions.

## 2. Materials and methods

Between April 2002 and March 2004, the PCS conducted a national survey of radiation therapy for patients with lung cancer in Japan. The Japanese PCS developed an original data format and performed an extramural audit survey for 76 of 556 institutions using a stratified two-stage cluster sampling. Data collection consisted of two steps of random sampling. Prior to random sampling, all institutions were classified into one of four groups. Criteria for stratification have been described elsewhere [10]. Briefly, the PCS stratified Japanese institutions as follows: A1, academic institutions such as university hospitals or national/regional cancer center hospitals treating $\geqq$430 patients per year; A2, academic institutions treating <430 patients; B1, non-academic institutions treating $\geqq$130 patients per year; and B2, <130 patients. The cut-off values in number of patients treated per year between A1 and A2 institutions and B1 and B2 institutions, respectively, were increased from those used in the previous PCS study because of the increase in the number of patients treated by radiation therapy in Japan [10]. Eligible patients had 1997 International Union Against Cancer (UICC) stage I–III NSCLC that was treated with PORT between 1999 and 2001, a Karnofsky Performance Status (KPS) >50 prior to start of treatment, and no evidence of other malignancies within 5 years. The current PCS collected specific information on 627 patients (A1:157, A2:117, B1:214, B2:139) who were treated with radiation therapy between 1999 and 2001. Of those, 99 (16%) patients (A1:15, A2:17, B1:45, B2:22) who received PORT constitute the subjects of the present analysis. The practice of PORT was investigated by reviewing items in each medical chart such as demographics, symptoms, history, work-up examinations, pathology, clinical stage, treatment course including radiation therapy, surgery and chemotherapy, and radiotherapy parameters. In addition, simulation films and linacgraphy of each patient were also reviewed by surveyors.

The PCS surveyors consisted of 20 board-certified radiation oncologists. For each institution, one radiation oncologist visited and surveyed data by reviewing patient charts. In order to validate the quality of collected data, the PCS utilized an internet mailing-list among all surveyors. In situ real-time check and adjustment of data input were available between each surveyor and the PCS committee. In tables, "missing" indicates that the item in the data format was left empty, whereas "unknown" means that the item in the format was completed with data "unknown". We combined "missing" and "unknown" in tables because their meanings were the same in most cases; no valid data were obtained in the given resources. Cases with missing or unknown values were included when both the percentage and significance value were calculated. Statistical significance was tested by the $\chi^2$ test. A $p$-value less than 0.05 was considered statistically significant. Overall survival was assessed from the day of surgery and was estimated by the Kaplan–Meier product limit method using the Statistical Analysis System, Version 6.12.

## 3. Results

### 3.1. Patient and tumor characteristics

Patient and clinical tumor characteristics are shown in Table 1. Of the 99 patients who received PORT, 32 were treated at academic institutions and 67 at non-academic institutions. The proportion of patients with NSCLC who received PORT was significantly higher in non-academic institutions than in academic institutions (19% versus 12%, $p=0.013$). Overall, median age was 65 years (range, 39–82), and the male to female ratio was 4:1. Ninety-three percent of patients had a KPS greater than or equal to 80%. Preoperative examinations included chest computed tomography (CT) in 97% of patients, bronchoscopy in 87%, brain CT or magnetic resonance imaging (MRI) in 75%, abdominal CT in 75%, bone scintigraphy in 83%, and mediastinoscopy in 4%. The primary tumor site was the upper lobe in 62 patients, middle lobe in 7, and lower lobe in 27. The remaining 2 patients had a primary tumor near the border of the upper and middle lobes that involved both lobes, and they were allocated to "others". Peripheral tumors were twice as common as central tumors. When tumors were analyzed by laterality, the ratio of right to left side primary site was 1.5. Clinical T- and N-classifications were T1 in 28 patients, T2 in 35, T3 in 24, T4 in 11, and N0 in 33, N1 in 19, N2 in 40, and N3 in 6, resulting in clinical stage I in 27 patients, II in 14, IIIA in 41, and IIIB in 16. The numbers less than 99 are due to missing or unknown data.

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Table 1 Patient and tumor characteristics

| | |
|---|---|
| No. of patients | 99 |
| Men | 79 |
| Women | 20 |
| Age (years) | |
| Median | 65 |
| Range | 32–89 |
| % KPS ≥ 80 | 93 |
| Preoperative work-up (%) | |
| Chest CT | 97 |
| Bronchoscopy | 87 |
| Brain CT or MRI | 75 |
| Abdominal CT | 75 |
| Bone scan | 83 |
| Mediastinoscopy | 4 |
| Primary tumor site | |
| Upper lobe | 62 |
| Middle lobe | 7 |
| Lower lobe | 27 |
| Other | 2 |
| Missing | 1 |
| Tumor location | |
| Central | 30 |
| Peripheral | 60 |
| Missing | 9 |
| Laterality | |
| Left lung | 38 |
| Right lung | 59 |
| Missing | 2 |
| Clinical T factor | |
| TX | 1 |
| T1 | 28 |
| T2 | 35 |
| T3 | 24 |
| T4 | 11 |
| Clinical N factor | |
| NX | 1 |
| N0 | 33 |
| N1 | 19 |
| N2 | 40 |
| N3 | 6 |
| Clinical stage | |
| IA | 14 |
| IB | 13 |
| IIA | 7 |
| IIB | 7 |
| IIIA | 41 |
| IIIB | 16 |
| Missing | 1 |

KPS, Karnofsky performance status score.

Table 2 Surgical procedure and tumor pathology characteristics

| | |
|---|---|
| Type of surgery | |
| Lobectomy | 78 |
| Pneumonectomy | 12 |
| Segmentectomy | 9 |
| Histopathology | |
| Squamous cell carcinoma | 47 |
| Adenocarcinoma | 43 |
| Large cell carcinoma | 7 |
| Adenosquamous carcinoma | 2 |
| Surgical margin status | |
| Negative | 55 |
| Positive | 31 |
| Missing | 13 |
| Pathological T factor | |
| T1 | 22 |
| T2 | 35 |
| T3 | 23 |
| T4 | 18 |
| Missing | 1 |
| Pathological N factor | |
| N0 | 15 |
| N1 | 19 |
| N2 | 56 |
| N3 | 4 |
| Missing | 5 |
| Pathologically involved mediastinal nodes (%)[a] | |
| No. 1 | 16 |
| No. 2 | 23 |
| No. 3 | 26 |
| No. 4 | 34 |
| No. 5 | 28 |
| No. 6 | 5 |
| No. 7 | 34 |
| No. 8 | 12 |
| Pathological stage | |
| IA | 4 |
| IB | 5 |
| IIA | 9 |
| IIB | 8 |
| IIIA | 45 |
| IIIB | 20 |
| Missing/unknown | 8 |

[a] Nearly half of the data for this item were "missing/unknown".

## 3.2. Surgery and tumor pathology characteristics (Table 2)

The primary surgical procedure was a lobectomy in 78 patients, pneumonectomy in 12, and segmentectomy in 9. Among all 99 patients, complete resection was accomplished for 55 patients. Surgical margin status was positive in 31 patients. Histopathology was squamous cell carcinoma in 47 patients, adenocarcinoma in 43, large cell carcinoma in 7, and adenosquamous carcinoma in 2. Predominantly involved mediastinal nodes confirmed pathologically to contain tumor were No. 7 (34%), No. 4 (34%), No. 5 (28%), and No. 3 (26%) according to the lymph node mapping system of the Japan Lung Cancer Society [11], although nearly half of the data for this item were "missing/unknown." The pathological T-

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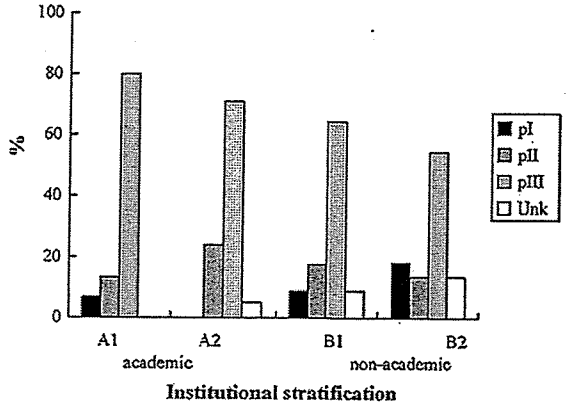


Fig. 1 Proportion of patients with pathologic stage III disease tended to be higher in large academic institutions ($p = 0.13$).

Table 3 Pathological stage in patients with complete surgery according to the stratified institution

| Pathological stage | Institutional stratification | | | | Total |
|---|---|---|---|---|---|
| | A1 | A2 | B1 | B2 | |
| I–II | 2 | 4 | 8 | 4 | 18 |
| III | 5 | 6 | 18 | 8 | 37 |
| Total | 7 | 10 | 26 | 12 | 55 |

and N-classifications were pT1 in 22 patients, pT2 in 35, pT3 in 23, and pT4 in 18, and pN0 in 15 patients, pN1 in 19, pN2 in 56, and pN3 in 4. Pathological stage was stage I in 9 patients, II in 17, IIIA in 45, and IIIB in 20, respectively. The proportion of pathological stage III patients tended to be higher in large academic institutions (Fig. 1, $p = 0.13$). Breakdown of pathological stage in 55 patients who underwent complete surgery according to the stratified institution group was shown in Table 3. As for the proportion of pathological stage III patients, no significant difference was observed between institutions.

### 3.3. Radiotherapy parameters (Table 4)

A CT-simulator was used for planning for 26 patients. Ninety-one patients were treated with opposed AP-PA fields, and field reduction during the course of radiotherapy was done for 48%. Three-dimensional treatment was used in only 2 patients. Photon energies of less than 6 MV were used for 34 patients (34%). Dose prescription by isodose line technique was performed for only 8 patients (8%). The median field size was 9 cm × 11 cm, and the median total dose was 50 Gy. The planning target volume included the ipsilateral hilus in 80%, ipsilateral mediastinum in 86%, contralateral mediastinum in 68%, contralateral hilus in 9%, ipsilateral supraclavicular region in 30%, and contralateral supraclavicular region in 22%. Institutional stratification was found to influence several radiotherapy parameters. A photon energy of 6 MV or higher was used for 73% of patients in A1, 77% in A2, and 80% in B1 institutions, whereas it was used for only 23% of patients in B2 institutions (Fig. 2, $p < 0.0001$). A Cobalt-60 unit was used only in 5 B2 institutions. The planning target volume included the contralateral mediastinum for more than 70% of patients in A1 to B1 institutions, whereas it was included in only 46% of patients treated in B2 institutions ($p = 0.011$).

Table 4 Radiotherapy parameters

| | |
|---|---|
| Simulation method | |
| CT-simulator | 26 |
| X-ray simulator | 38 |
| X-ray simulator + CT | 26 |
| Missing | 7 |
| Treatment technique | |
| AP-PA | 91 |
| Oblique | 2 |
| Three-field | 1 |
| Three-dimensional conformal | 2 |
| Other | 2 |
| Missing | 1 |
| Photon energy | |
| 60 Co | 5 |
| <6 MV | 29 |
| ≥6 MV | 64 |
| Missing | 1 |
| Dose prescription | |
| Isodose line | 8 |
| Point | 91 |
| Total dose | |
| ≤3000 cGy | 1 |
| 3001–4000 cGy | 6 |
| 4001–5000 cGy | 49 |
| 5001–6000 cGy | 37 |
| 6001–7000 cGy | 6 |
| Missing | 1 |
| Median total dose (cGy) | 5000 |
| All fields treated each day (%) | 83 |
| Median field size (cm) | |
| Left-right | 9 (range, 5–23) |
| Cranio-caudal | 11 (range, 5–20) |
| Field reduction during radiotherapy (%) | 48 |
| Field included (%) | |
| Ipsilateral hilus | 80 |
| Ipsilateral mediastinum | 86 |
| Contralateral mediastinum | 68 |
| Contralateral hilus | 9 |
| Ipsilateral supraclavicula | 30 |
| Contralateral supraclavicula | 22 |

### 3.4. Use of chemotherapy

Thirty patients (31%) received systemic chemotherapy. For 21 patients, chemotherapy and PORT were administered concurrently, mainly using a platinum-based, two-drug combination. For 9 of the 30 patients, platinum-based chemotherapy was used as induction therapy. Oral fluorouracil was used for 9 patients.

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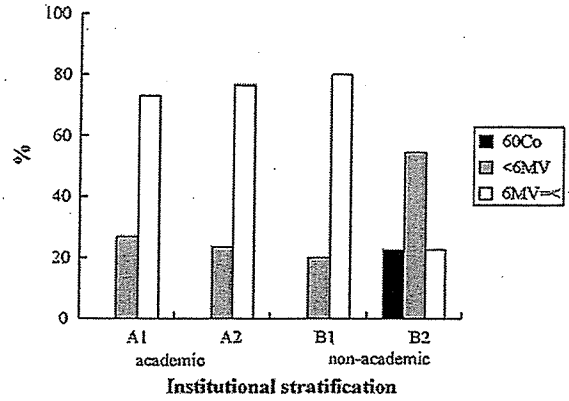


Fig. 2 A photon energy of 6 MV or higher was used for 73% of patients in A1 institutions, 77% in A2, and 80% in B1, whereas only 23% in B2 institutions ($p < 0.0001$). A Cobalt-60 unit was used only in B2 institutions.

### 3.5. Failure pattern and preliminary clinical outcome

The site of first failure was local in 6, regional in 5, and distant in 31. Of the patients who developed failure, the median time to first failure was 7 months. Although the current PCS has limitations in terms of outcome analysis due to a short follow-up period and significant variations in follow-up information according to institutional stratification [10,12], overall survival for the entire group was 88% at 1 year and 63% at 3 years, with a median follow-up period after PORT of 1.7 years.

## 4. Discussion

The results of the present PCS reflect national practices for PORT for NSCLC in Japan. However, when interpreting our data, it is important to note that they were limited to patients who received radiation therapy. We have no information about patients who did not receive radiation therapy after surgery. Thus, we have no data concerning the percentage of patients who underwent radiation therapy after surgery. Analysis of the national practice process for all patients with NSCLC in the adjuvant setting is beyond the scope of this study.

All eligible patients in this study received radiation therapy after publication of the PORT meta-analysis that emphasized deleterious effects in patients receiving PORT, especially for patients with completely resected N0-1 disease [4]. Since then, the clinical focus on adjuvant treatment has largely shifted to chemotherapy, which has become part of the postoperative standard of care for patients with NSCLC [5,6,8]. In the United States, use of PORT has substantially declined due to the lack of proven survival benefit [13]. However, PORT was still incorporated as an option in recent clinical trials that recruited patients with pathological N2 disease [5,7]. The recent analysis of Surveillance, Epidemiology, and End Results (SEER) data in the United States demonstrated that PORT was associated with improved survival for patients with N2 disease [14,15]. In addition, a recent clinical study has reported promising results for combined PORT and chemotherapy using modern radiotherapy techniques [7,8]. Thus, the current clinical question is whether adjuvant chemotherapy combined with PORT improves survival for patients at high risk for locoregional failure compared with adjuvant chemotherapy alone. Taking all of the evidence together, we conclude that PORT still plays an important role in the adjuvant setting. We believe that this PCS study provides basic data of current practice regarding PORT in Japan.

Results of the present study demonstrated that patients who received PORT accounted for 16% of all patients with NSCLC who received radiation therapy in Japan between 1999 and 2001. Of all 99 patients, 65 had pathological stage III disease (45, stage IIIA; 20, stage IIIB). Using a median field size of 9 cm × 11 cm, a median total dose of 50 Gy was delivered mainly through opposed AP-PA fields. Three-dimensional conformal treatment was infrequently used. Field size reduction during the course of radiotherapy was done for almost half of the patients. A dedicated CT-simulator was used for 26 patients. The PORT meta-analysis was criticized because the authors included several old studies in which a cobalt machine was used for radiotherapy. It was pointed out that suboptimal administration of PORT using outdated techniques counterbalanced the beneficial locoregional effects of PORT treatment in the meta-analysis [16]. Because of potential pulmonary/cardiac toxic effects of mediastinal radiotherapy, PORT should be delivered with modern radiotherapy techniques using CT-based three-dimensional conformal treatment planning, a technique with which target volumes and normal tissue constraints are precisely defined. Although the patients included in this PCS survey were treated between 1999 and 2001, the modern radiotherapy era, 34% of all patients were treated using photon energies <6 MV, including five patients who were treated using a cobalt machine. Institutional stratification influenced several radiotherapy parameters in PORT for NSCLC. As shown in the previous report for small-cell lung cancer in Japan [17], smaller non-academic institutions (B2) provided a lower quality of care for their patients. Planning target volume typically included the ipsilateral hilus, ipsilateral mediastinum, and contralateral mediastinum in A1 to B1 institutions, whereas the contralateral mediastinum was included for only 46% of patients treated in B2 institutions. Although there is controversy concerning prophylactic nodal irradiation in the setting of definitive radiation therapy, PORT for patients with pN2 NSCLC should include the contralateral mediastinum. Proportion of patients with pathological stage I–II who underwent complete surgery did not differ between stratified institution groups. Thus, it was considered that omission of treating the contralateral mediastinum in B2 institutions was not caused by unbalance in stage distribution. We speculate that this discrepancy in care was due mainly to the extremely small number of radiation oncologists in B2 institutions. We also found that obsolete equipment such as Cobalt-60 units were still used, especially in non-academic institutions treating only a small number of patients per year. The proportion of patients treated with 6 MV or higher photon energies was significantly higher in A1 to B1 institutions than in B2 institutions. A Cobalt-60 unit was used only in B2 institutions. The present study again confirms differences in the practice of radiotherapy according to institutional stratification status.

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We consider that the structure of radiation oncology is a domestic problem specific to each country. The results represent intrinsic problems with the structure of radiation therapy in Japan. Considering the current immaturity of the Japanese structure of radiation oncology, PCS still perform an important role in monitoring structure and process, as well as providing essential information not only to medical staff and their patients but also to administrative policy makers.

## 5. Conclusions

Through the audit survey and subsequent data analyses, the PCS established nationwide basic information on the practice of PORT for NSCLC in Japan. Even after the publication of the PORT meta-analysis, PORT was used for a considerable proportion of patients receiving radiotherapy. However, this PCS documented that outdated modalities such as cobalt-60 units were still used in small non-academic institutions during the study time frame. Thus, the current PCS confirmed the continuing existence of variation in the practice of radiotherapy according to institution stratification.

## Conflict of interest

We have no conflict of interest in connection with this paper.

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# 1. 外照射療法（3次元原体照射）
## ——特に日本の現状について——

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*4藤田保健衛生大学衛生学部診療放射線技術学科　*5大阪大学大学院医学系研究科医用物理工学

要旨：前立腺癌に対する医療実態調査研究では，全国の放射線治療施設126施設にて1996～1998年，1999～2001年に放射線治療が施行された前立腺癌症例のデータが集積された。根治的外照射例444例の解析では，88.1％に内分泌療法が併用されており，中央値66Gyの外照射が施行された。3次元原体照射は59.8％に施行されていた。5年全生存率83.6％，PSA無再発率85.3％であった。

key words　前立腺癌，放射線治療，医療実態調査研究

## はじめに

近年前立腺癌症例は急増し，それに伴い放射線治療症例も増加している。しかし，前立腺癌の放射線治療の報告はそのほとんどが欧米からであり，わが国における放射線治療の実態は不明であった。

そのような中，前立腺癌の放射線治療に関するいくつかの調査が行われた。ひとつは，厚生労働省がん研究助成金の援助を受けて行われた医療実態調査研究（Patterns of Care Study，PCS）であり，1996～1998年，1999～2001年に放射線治療が行われた前立腺癌の実態が調査された[1～4]。もうひとつは，日本放射線腫瘍学研究グループ（Japanese Radiation Oncology Study Group，JRSOG）の泌尿器腫瘍に関する部位別専門委員会にて行われた，2004年の前立腺癌放射線治療症例の実態調査である[5]。

本稿では，特にPCSにより得られた，わが国の前立腺癌の根治的放射線治療の現状について述べる。PCSとは，米国で開発された臨床的精度管理QAの手法のひとつであり，放射線治療施設を規模によって分類し（structure），治療内容を調査し（process），その治療結果など（outcome）の分析を行うもので[6]，Radiation Therapy Ocology Group（RTOG）の創設と同時に米国で立ち上げられた。わが国には1996年より本格的に導入され，施設，患者をランダムサンプリングし，放射線腫瘍医による外部調査により，食道癌，肺癌，子宮頸癌，乳癌，前立腺癌の放射線治療症例のデータが集積された[7]。ここでは，根治的放

External radiotherapy (three dimensional conformal radiotherapy): Patterns of Care Survey in Japan

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key words : prostate cancer, radiotherapy, Patterns of Care Study

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表1 Patterns of Care Studyで調査された前立腺癌症例の内訳

| 内訳 | 1996～1998年 | 1999～2001年 | 計 |
|---|---|---|---|
| 根治的外照射例 | 161 (51.8 %) | 283 (53.6 %) | 444 (52.9 %) |
| 手術併用例 | 64 (20.6 %) | 105 (19.9 %) | 169 (20.1 %) |
| 内分泌療法抵抗・再燃例 | 58 (18.6 %) | 96 (18.2 %) | 154 (18.4 %) |
| その他* | 28 ( 9.0 %) | 44 ( 8.3 %) | 72 ( 8.6 %) |
| 計 | 311 (100 %) | 528 (100 %) | 839 (100 %) |

*小線源治療例を含む

表2 根治的外照射例444例の患者背景*

| | 1996～1998年 | 1999～2001年 | p value |
|---|---|---|---|
| 年齢中央値 | 70歳 (46～89歳) | 72歳 (49～92歳) | NS |
| 組織分化度 | | | 0.0120 |
| 高分化 | 24 (16.1 %) | 62 (25.0 %) | |
| 中分化 | 79 (53.0 %) | 93 (37.5 %) | |
| 低分化 | 46 (30.9 %) | 93 (37.5 %) | |
| Gleasonスコア | | | 0.0077 |
| ≦6 | 11 (26.2 %) | 77 (45.3 %) | |
| ＝7 | 18 (42.9 %) | 35 (20.6 %) | |
| ≧8 | 13 (31.0 %) | 58 (34.1 %) | |
| T因子 | | | 0.0043 |
| T1 | 7 ( 4.5 %) | 18 ( 7.2 %) | |
| T2 | 47 (30.1 %) | 109 (43.4 %) | |
| T3 | 81 (51.9 %) | 109 (43.4 %) | |
| T4 | 21 (13.5 %) | 15 ( 6.0 %) | |
| N因子 | | | 0.0229 |
| N0 | 129 (87.8 %) | 243 (94.2 %) | |
| N1 | 18 (12.2 %) | 15 ( 5.8 %) | |
| 全治療前PSA (ng/ml) | | | NS |
| ＜10 | 41 (28.1 %) | 77 (28.7 %) | |
| 10～19.9 | 25 (17.1 %) | 57 (21.3 %) | |
| ＞20 | 80 (54.8 %) | 134 (50.0 %) | |

*不明例は除いて解析しているため，合計は必ずしも一致していない。

射線治療が施行された前立腺癌の実態，特に3次元原体照射（three dimensional conformal radiotherapy，3DCRT）の有無による治療成績等について検討した。

## I 対象と方法

日本における前立腺癌のPCSは1999年より開始され[4]，2006年現在も継続されている。今回の調査対象は，1996～1998年および1999～2001年の期間に放射線治療が施行された，遠隔転移を伴わない前立腺癌根治照射例，姑息照射例，手術併用例である。放射線腫瘍医が，全国より無作為抽出されたA施設（大学病院・がんセンター）68施設，B施設（その他の国公立病院）58施設，計126施設（全放射線治療施設の約17％）を訪問し，最大20例までをランダムに抽出し，調査し，合計839例の前立腺癌放射線治療症例の臨床データを集積した（表1）。ここでは，内分泌療法併用例を含む根治的外照射例444例を検討対象とし，年代による変化を見るために，1996～1998年（96～98PCS）および1999～2001年（99～01PCS）の期間に分けて解析した。検定には，カイ二乗検定を用いた。生存率に関しては，経過観察が2年未満の症例は除いて解析した。

## II 結果

患者背景を表2に示す。年齢の中央値は70～72歳であった。組織型では高分化腺癌がやや増加していた。臨床病期T2症例が増加しているものの，依然として，T3-4症例が半数近くを占めて

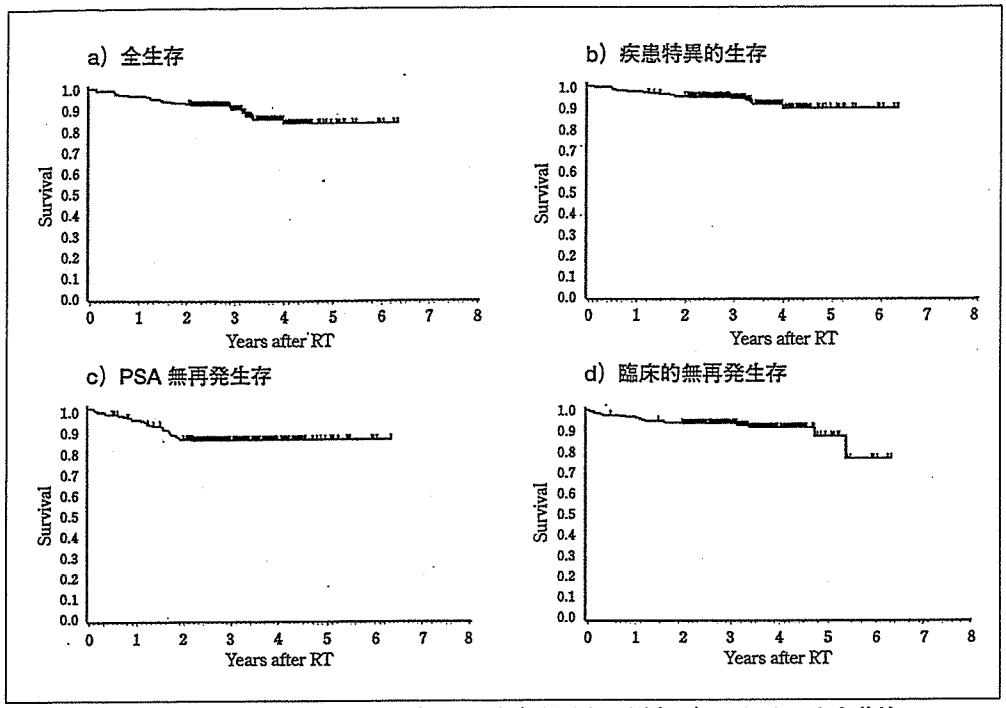


図1　2年以上経過観察例（中央値3.2年）204例（死亡例28例含む）における生存曲線

いた。N因子については，N1症例は全体の10％以下であった。また，全治療前PSA値は半数以上が20以上であった。

内分泌療法は88.1％に併用されていた。併用時期は，放射線治療前，放射線治療中，放射線治療後ともに75％以上であり，96～98PCS，99～01PCSともに大きな変化はなかった。

図1に生存曲線を示す。経過観察期間中央値3.2年にて，5年全生存率83.6％，5年疾患特異的生存率89.5％，PSA無再発率85.3％，5年臨床的無再発率76.6％であった。

前立腺局所に対する放射線照射法について，3DCRTを施行した割合は59.8％であり，この時点では，強度変調放射線治療（intensity-modulated radiotherapy，IMRT）にて治療された症例はなかった。

前立腺局所へ照射線量は，96～98PCSにて65.0Gy，99～01PCSにて68.4Gyで，照射線量は増加していた。図2に，1996～2001年に治療された全症例での3DCRTの有無による前立腺局所への線量を示す。70Gy以上照射している割合は3DCRTに多い傾向にあった。

晩期有害事象を9例に認めた。内訳は，直腸出血6例，血尿1例，尿道狭窄2例であった。このうち，3DCRT例は5.4％，通常照射例4.5％で，両者に有害事象の発生に差はなかった。

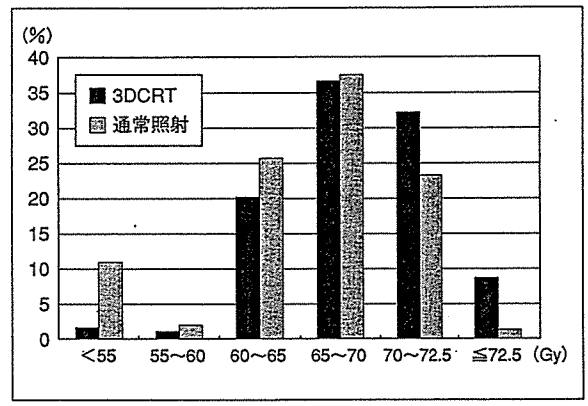


図2　前立腺への照射線量

## Ⅲ　考　察

PCSの発祥の地である米国では，1970年代より，前立腺癌の放射線治療症例の全国調査が実施されている[8,9]。投与線量は，1978年には66.0Gy，1989年には66.8Gy，1994年には68.4Gy，1999年には70.45Gyと増加している。日本はまだまだ米国よりも少なく，前立腺への投与線量は米国の1990年代初めのレベルであると言えよう。

わが国の放射線治療症例には，高率に内分泌療法が施行されている。RTOGの前立腺癌の放射線治療の臨床試験を受けた2,742人に対するメタアナリシスでは，高リスク例に関しては，長期に内分泌療法が併用されることにより，全生存率，無病生存率が改善することが示唆されている[10]。わ

が国の放射線治療症例の多くが高リスク例であることを考えれば，放射線治療と長期間の内分泌療法併用は，大部分の症例に対して，正しい治療方針であると言えるかもしれない。しかし，低リスク例では放射線治療単独で治癒する可能性が高く，内分泌療法の適応は厳格にすべきであろう。

今回の調査では，約60％に3次元原体照射が施行されていた。今回の解析では3次元原体照射の併用の有無と有害事象の発生割合に差は認められなかった。しかし，dose escalation studyにおいては明らかに3DCRTの有用性が証明されており，今後わが国でも高線量が照射されるようになれば，有用性が明らかになるものと考えられる。

日本のPCSでは，現時点では2001年のデータまでしか集積されていない。一方，JRSOG部位別専門委員会（泌尿器腫瘍）による前立腺癌の放射線治療の実態調査の結果が報告されたが，2004年に外照射にて治療された2097例のうち，半数以上が70-80 Gyの線量で治療していたとしており[5]，わが国でも急速に前立腺への投与線量は増加傾向にある。しかし，日米では，ホルモン療法併用率や社会的背景などに違いがあり，今後，米国のように変化していくかどうかは，平成18年度より始まった新しいPCSの結果を待たねばならない。

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# Postoperative Radiotherapy for Patients with Prostate Cancer in Japan; Changing Trends in National Practice between 1996–98 and 1999–2001: Patterns of Care Study for Prostate Cancer

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**Objective:** To evaluate the changing trends of standards and practices for postoperative radiotherapy (RT) for patients with prostate cancer in Japan.
**Methods:** The Japanese Patterns of Care Study (PCS) conducted a national survey in 84 institutions from 1996 to1998 (PCS96-98) and 76 institutions from 1999 to 2001 (PCS99-01). Detailed information relevant to RT was collected on a total of 169 patients (64 from 1996 to1998 and 105 from 1999 to 2001) with prostate cancer who had undergone radical prostatectomy.
**Results:** The fraction of clinical T3–4 tumours before prostatectomy decreased from 63% in the period 1996–98 to 26% in the period 1999–2001 ($P = 0.0004$). The pre-RT prostate-specific antigen level was significantly lower in 1999–2001 than in 1996–98 ($P = 0.0002$). We did not find a significant difference in the percentage of patients who received pelvic irradiation in the time periods between PCS96-98 and PCS99-01 ($P = 0.18$). Although the median radiation doses of 60 Gy were not changed between the surveys, various doses (from 20 to 74.6 Gy) were delivered to the prostatic bed. In the 1999–2001 survey, 73 of 105 patients received a median dose of 56 Gy in an adjuvant setting, while the other 32 received a median dose of 60 Gy in a salvage setting ($P = 0.0015$).
**Conclusion:** These data suggest that consensus has not been reached on the practice and management of postoperative RT for patients with prostate cancer in Japan.

*Key words: postoperative radiotherapy – prostate cancer – Patterns of Care Study*

## INTRODUCTION

The Patterns of Care Study (PCS), which was developed in the United States by the American College of Radiology and has been administered by them for over 25 years, was introduced to Japan to evaluate the current status of radiotherapy (RT) and to improve the quality of radiation oncology (1–3). The PCS in the United States has disclosed the evidences that elementary techniques contribute to improvement of outcome; for example: multiple fields' technique, dose escalation and higher energy beam selection >6 MV for prostate cancer (3). The Japanese PCS Working Group of Prostate Cancer conducted the first nationwide process survey of patients with prostate cancer who received RT between 1996 and 1998 (PCS96-98). Subsequently, a second PCS of patients treated with RT between 1999 and 2001 was conducted (PCS99-01). Nakamura et al. (4,5) presented the preliminary results of these surveys for RT in patients with prostate cancer in Japan. We present here the final analysis of PCS96-98 and PCS99-01 in order to reveal the status of national practices for postoperative RT for prostate cancer and the changing trends seen between 1996–98 and 1999–2001.

## SUBJECTS AND METHODS

The standard methods used in data collection for a national process survey have been described previously in detail (1,3). In brief, the PCS survey utilized a stratified two-stage cluster

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sampling design. An external audit team of radiation oncologists who were recruited from academic institutions surveyed 84 institutes from 1996 to 1998 and 76 institutes from 1999 to 2001, respectively (2). PCS96-98 and PCS99-01 stratified these institutions into either academic (university hospital or cancer centre) or non-academic institutions (other hospitals) according to a facility master list created by the Japanese Society of Therapeutic Radiation Oncology in 1997 and 2001, respectively. The following patient criteria were used in the process survey: (i) the patients had adenocarcinoma of the prostate without distant metastases; (ii) the patients were treated with RT during the period 1996–98 and 1999–2001; (iii) the patients had neither been diagnosed with any other malignancy nor treated with RT previously (4).

The PCS96-98 and PCS99-01 surveys in Japan contain detailed information on a total of 835 patients with prostate cancer treated with RT during the respective survey periods (PCS96-98: 307 patients, PCS99-01: 528 patients). A total of 169 patients who received RT after radical prostatectomy (RP) were selected for this analysis (PCS96-98: 64 patients; PCS99-01: 105 patients). In addition to the analysis of changing trends in national practice between PCS96-98 and PCS99-01, the type of RT used (adjuvant or salvage setting) was revealed in the 1999–2001 survey. Seventy-three of the 105 patients were treated with adjuvant RT and the other 32 received salvage RT.

For statistical analysis, the differences between the proportions were tested by the $\chi^2$-test. A $P$-value $< 0.05$ was considered statistically significant difference.

## RESULTS

Patients and disease characteristics in the PCS96-98 and PCS99-01 surveys are shown in Table 1. Proportion of non-academic to academic hospitals was significantly different between the two surveys (PCS96-98 and PCS99-01) ($P = 0.004$). We found a significantly lower fraction of patients with clinical T3–4 tumours (26%: $P = 0.0004$) and with positive surgical margins (56%: $P = 0.042$) between 1999 and 2001 than between 1996 and 1998 (T3–4: 63%, positive surgical margins: 78%). Although the distribution of the pre-treatment prostate-specific antigen (PSA) level was not different between the 1996–98 and 1999–2001 surveys ($P = 0.44$), the distribution of the pre-RT PSA level was significantly different between the surveys ($P = 0.0002$). In the 1999–2001 survey, 71% of the patients received RT at a <1 ng/ml level of PSA compared with 28% in the 1996–98 survey.

The treatment characteristics are shown in Table 2. The use of ≥10 MV was significantly decreased in the PCS99-01 (73%) group compared with the PCS96-98 (92%) ($P = 0.0059$) one. The frequency of conformal therapy was also significantly lower in the PCS99-01 (23%) than in the PCS96-98 (65%) ($P < 0.0001$). The percentage of pelvic irradiation was not significantly different between the two survey periods (1996–98: 52%, 1999–2001: 41%) ($P = 0.18$). The distribution of radiation doses is shown in Fig. 1. The median radiation doses during 1996–98 and 1999–2001 did not change (60 Gy).

Although the percentage of patients who received hormonal therapy was not different between the surveys (1996–98: 83% versus 1999–2001: 72%) ($P = 0.18$), a lower number of patients were treated with chemotherapy in the 1999–2001 survey (8%) than in the 1996–98 survey (27%) ($P = 0.0045$).

Table 3 shows the comparison of patient characteristics and the treatment process according to the type of RT administered (adjuvant versus salvage setting) in the PCS99-01. The fraction of patients with a pre-RT PSA < 0.4 ng/ml in the adjuvant setting was significantly higher than that in the salvage setting, and the percentage of patients with a positive surgical margin in the adjuvant setting was higher than that in the salvage setting. The fraction of patients who received pelvic irradiation was significantly higher in the adjuvant setting than in the salvage setting ($P < 0.0001$). The distribution of the total dose to the prostatic bed is shown in Fig. 2. We observed a significant difference in median doses to the prostatic fossa between the adjuvant (56 Gy) and salvage settings (60 Gy) ($P = 0.0015$). However, more than half of patients in the salvage setting received total doses of <64 Gy.

## DISCUSSION

### Patients' Characteristics

In this analysis, we revealed changes in the practice of postoperative RT for patients with prostate cancer in Japan. The fraction of patients with T3–4 tumours was significantly decreased from the PCS96-98 survey to the PCS99-01 one. This result might indicate that high-risk patients with clinical T3–4 tumours tend not to be subjected to RP. However, Ogawa et al. (6,7) documented that significantly earlier T-stages (T1–2) were found between 1999 and 2001 than between 1996 and 1998 in their analysis of the patients who received radical RT for prostate cancer. These results may indicate the recent expansion of the indications for RT in patients with prostate cancer in Japan.

The pre-RT PSA level was significantly lower in the PCS99-01 patients than in the PCS96-98 ones. This might be a reflection of the accumulating evidence that lower pre-RT PSA is associated with success in the treatment of patients with PSA failure after prostatectomy (8,9). However, in the 1996–98 survey, we did not identify whether each patient received RT in the adjuvant or salvage setting because of the lack of data. The fraction of patients who received adjuvant RT as opposed to salvage RT might differ between the surveys.

### Treatment Process

We observed significantly lower fractions of the use of ≥10 MV and conformal therapy in the PCS99-01 survey than in the PCS96-98 one. However, Ogawa et al. (6) documented that the changes in the use of ≥10 MV and conformal therapy for patients with primary prostate cancer were not significant between the PCS96-98 and PCS99-01 surveys.

Table 1. Patient background and characteristics

| | PCS | | P-value |
|---|---|---|---|
| | 1996–98 (n = 64) | 1999–2001 (n = 105) | |
| Number of institutes | 84 | 76 | |
| Number of patients | 64 | 105 | 0.004 |
| Academic | 54 | 67 | |
| Non-academic | 10 | 38 | |
| Median age (year) at RT | 67 | 67 | 0.27 |
| Range | 50–83 | 36–89 | |
| Pre-treatment PSA (ng/ml) | | | 0.44 |
| Median (range) | 12.24 (0.0–379.8) | 0.50 (15.35–268.2) | |
| <10 | 17/44 (39%) | 29/88 (33%) | |
| ≥10 to <20 | 10/44 (22%) | 21/88 (24%) | |
| ≥20 | 17/44 (39%) | 38/88 (43%) | |
| Missing | 20 | 17 | |
| Differentiation | | | 0.16 |
| Well (G1) | 11/62 (18%) | 27/99 (27%) | |
| Moderate (G2) | 23/62 (37%) | 44/99 (45%) | |
| Poor (G3–4) | 24/62 (39%) | 23/99 (23%) | |
| Unknown | 4/62 (6%) | 5/99 (5%) | |
| Missing | 2 | 6 | |
| Gleason combined score | | | 0.41 |
| 2–6 | 19/34 (56%) | 24/45 (53%) | |
| 7 | 8/34 (24%) | 8/45 (18%) | |
| 8–10 | 7/34 (20%) | 13/45 (29%) | |
| Missing | 30 | 60 | |
| Clinical T-stage | | | 0.0004 |
| T1 | 2/57 (3%) | 9/97 (9%) | |
| T2 | 14/57 (25%) | 49/97 (51%) | |
| T3 | 34/57 (60%) | 20/97 (21%) | |
| T4 | 2/57 (3%) | 5/97 (5%) | |
| Unknown | 5/57 (9%) | 14/97 (14%) | |
| Missing | 7 | 8 | |
| Clinical N-stage | | | 0.78 |
| N0 | 52/61 (85%) | 82/97 (85%) | |
| N1 | 4/61 (7%) | 4/97 (4%) | |
| Unknown | 5/61 (8%) | 11/97 (11%) | |
| Missing | 3 | 8 | |
| Pathological T-stage | | | 0.029 |
| T1 | 1/59 (1%) | 5/98 (5%) | |
| T2 | 8/59 (17%) | 27/98 (28%) | |
| T3 | 47/59 (79%) | 53/98 (54%) | |
| T4 | 1/59 (1%) | 7/98 (7%) | |
| Tx | 2/59 (2%) | 6/98 (6%) | |
| Missing | 5 | 7 | |
| Pathological N-stage | | | 0.27 |
| N0 | 45/56 (80%) | 80/99 (81%) | |
| N1 | 9/56 (16%) | 9/99 (9%) | |
| Unknown | 2/56 (4%) | 10/99 (10%) | |
| Missing | 8 | 6 | |
| Last pre-RT PSA (ng/ml) | | | 0.0002 |
| <1 | 3/11 (28%) | 60/84 (71%) | |
| ≥1 to <10 | 4/11 (36%) | 16/84 (19%) | |
| ≥10 | 4/11 (36%) | 8/84 (10%) | |
| Hormonal therapy | | | 0.18 |
| Yes | 53/64 (83%) | 76/105 (72%) | |
| Chemotherapy* | | | 0.0045 |
| Yes | 17/64 (27%) | 8/100 (8%) | |
| Extent of disease on prostatectomy | | | 0.042 |
| Confined to prostate | 4/60 (7%) | 18/103 (17%) | |
| Confined to specimen | 7/60 (12%) | 15/103 (15%) | |
| Positive surgical margin | 47/60 (78%) | 58/103 (56%) | |
| Unknown | 2/60 (3%) | 12/103 (12%) | |
| Missing | 4 | 2 | |

PCS, Patterns of Care Study; RT, radiotherapy; PSA, prostate-specific antigen.
*Including estramustine.

This discrepancy might have arisen from the significantly higher fraction of patients who had received postoperative RT in non-academic hospitals in the 1999–2001 survey than in the 1996–98 survey in our analysis ($P = 0.004$). Ogawa et al. (10) also documented in their other report that the institutional stratification significantly affected the patterns of RT, such as the beam energy and the administration of conformal therapy.

The most appropriate radiation dose in the post-prostatectomy setting is controversial, as indicated by the wide range of doses noted in previous reports (45–75 Gy) (11). The American Society for Therapeutic Radiation Oncology (ASTRO) consensus panel recommended doses of ≥64 Gy for patients with PSA failure after RP (12). On the other hand, Petrovich et al. (13) demonstrated that a median dose of 48 Gy in adjuvant RT reduced the risk of local recurrence in patients with pathological T3 prostate cancer. Our results also demonstrated that various doses were applied to the patients who had undergone RP, whether in the adjuvant or salvage setting.

Employing a conformal 3D planning system and promoting a dose escalation of >64 Gy may improve local control and biochemical relapse-free survival for patients with prostate cancer who receive postoperative RT alone (11,14). Ogawa et al. (7) showed that the radiation doses for patients with primary prostate cancer were higher in the PCS99-01 survey than in the PCS96-98 one, and discussed that the use of an increasing

**Table 2.** Treatment characteristics in RT

| | PCS | | *P*-value |
|---|---|---|---|
| | 1996–98 ($n = 64$) | 1999–2001 ($n = 105$) | |
| Energy of X-ray (local) | | | 0.0059 |
| <10 MV | 4/51 (8%) | 23/86 (27%) | |
| ⩾10 MV | 47/51 (92%) | 63/86 (73%) | |
| Missing | 13 | 19 | |
| All fields treated each day | | | – |
| Yes | – | 87/105 (83%) | |
| Pelvis irradiation | | | 0.18 |
| Yes | 33/64 (52%) | 43/105 (41%) | |
| Conformal therapy | | | <0.0001 |
| Yes | 31/48 (65%) | 24/103 (23%) | |
| Radiation dose (Gy) | | | 0.082 |
| Median | 60 | 60 | |
| Range | 40–74.6 | 20–70 | |

PCS, Patterns of Care Study.

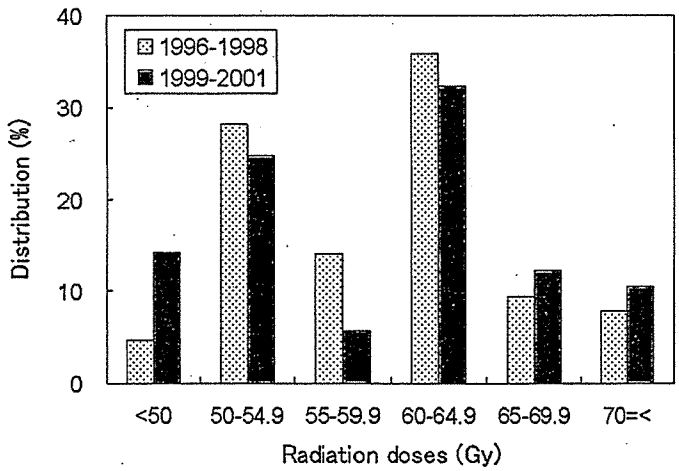


**Figure 1.** Distribution of radiation doses in patients who received RT after RP between 1996–98 and 1999–2001.

radiation dose might reflect the widespread dissemination of clinical trial results. However, our analysis revealed that the median dose for patients who received postoperative RT in Japan did not change from 1996–98 to 1999–2001. Furthermore, only half of the patients who were subjected to salvage RT in the PCS99-01 received doses of over or equal to 64 Gy, the dosage which was recommended by ASTRO (Fig. 2). Although previous reports of postoperative RT for patients with prostate cancer are rare in Japan, the next PCS may reveal the dissemination of evidence for dose escalation.

There have been no randomized trials to define the field sizes of postoperative irradiation for patients with prostate cancer, and no consensus about the best radiation therapy volume. Pelvic irradiation was performed in 40–50% of

**Table 3.** Comparison between patients in adjuvant and salvage setting in the 1999–2001 survey

| | Adjuvant ($n = 73$) | Salvage ($n = 32$) | *P*-value ($n = 32$) |
|---|---|---|---|
| Age (median) (year) at RT | 66 | 68 | 0.06 |
| Range | 36–77 | 58–89 | |
| Interval between RP and RT | | | |
| Median (range) | 1.3 (0.53–26.8) | 20.3 (0.82–61) | |
| Last pre-RT PSA (ng/ml) | | | 0.0046 |
| <0.4 | 35/56 (62%) | 8/28 (29%) | |
| ⩾0.4 to <1 | 6/56 (11%) | 11/28 (39%) | |
| ⩾1 to <10 | 11/56 (20%) | 8/28 (29%) | |
| ⩾10 | 4/56 (7%) | 1/28 (3%) | |
| Missing | 17 | 4 | |
| Extent of disease | | | <0.0001 |
| Confined to prostate | 7/68 (10%) | 11/23 (48%) | |
| Confined to specimen | 10/68 (15%) | 5/23 (22%) | |
| Positive surgical margin | 51/68 (75%) | 7/23 (30%) | |
| Missing | 5 | 9 | |
| Conformal therapy | | | 0.0041 |
| Yes | 11/73 (15%) | 13/32 (41%) | |
| Pelvic irradiation | | | <0.0001 |
| Yes | 39/73 (53%) | 4/32 (13%) | |
| Radiation dose (Gy) | | | 0.0015 |
| Median | 56 | 60 | |
| Range | 20–70 | 40–70 | |

RT, radiotherapy; RP, radical prostatectomy; PSA, prostate-specific antigen.

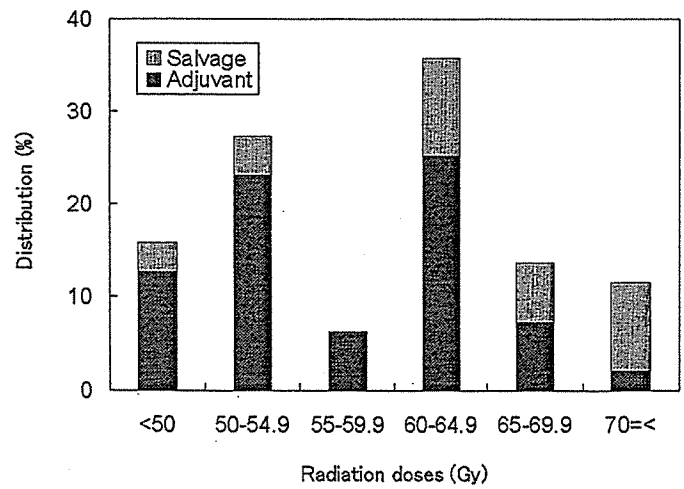


**Figure 2.** Comparison of dose distributions according to the type of RT administered in the 1999–2001 survey.

the patients, and no significant difference was found in the percentage of patients treated with pelvic irradiation between the PCS96-98 and PCS99-01 surveys. According to the previous analyses, the prostate and immediately adjacent

tissues have been considered to be a reasonable clinical target volume in the adjuvant setting (15,16). However, some previous reports documented the significant benefits of pelvic irradiation for patients in a salvage setting, showing a trend towards better PSA control in those patients with adverse pathological features (including a positive surgical margin, etc.) (17,18). However, the PCS99-01 survey revealed that a higher fraction of the patients received pelvic irradiation in the adjuvant setting than in the salvage setting in Japan.

### Adjuvant versus Salvage

The role of postoperative RT for prostate cancer has been controversial. The previous retrospective analyses showed improvement in the local control and disease-free survival of the patients with high-risk pathological features who received adjuvant RT compared with similar patients treated with RP alone (15,19,20). Recently, the first randomized study evaluating the benefits of postoperative RT in prostate cancer was reported by Bolla et al. (21), who documented a significant benefit of postoperative RT in the biochemical relapse-free survival rate and clinical locoregional failure rate in patients with high risk factors after RP by the analysis of a total of 1005 patients who were allocated to postoperative RT or observation. There is no data based on randomized trials favouring adjuvant over salvage RT. The fraction of patients in the adjuvant setting was higher than that in the salvage setting from among all patients who received postoperative RT in the PCS99-01 survey. However, this result may not reflect the actual trend towards postoperative RT in Japan, so further investigation into more cases is needed in the future.

### Conclusions

Our results revealed national trends in the treatment of prostrate cancer and changes in the practice of postoperative RT for patients in Japan with this disease. The management and strategies (including radiation field and dosages) varied, and the role of postoperative RT for patients with prostate cancer remains controversial (adjuvant RT versus salvage RT). Further evidence needs to be accumulated on postoperative RT for patients with prostate cancer in order to establish appropriate treatment strategies. In addition, continuous nationwide surveys should be performed to evaluate the dissemination of the results that have been collected.

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# Influence of Age on the Pattern and Outcome of External Beam Radiotherapy for Clinically Localized Prostate Cancer

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**Abstract.** *Background: The influence of age on the patterns and outcomes of external beam radiotherapy for clinically localized prostate cancer patients was examined. Materials and Methods: The Japanese Patterns of Care Study surveys were used to compare the processes and outcomes of radical external beam radiotherapy in 140 elderly patients (>75 years old) and 304 younger patients (<75 years old). Results: Although the Karnofsky performance status was significantly different between elderly and younger patients, there were no significant differences in disease characteristics such as pretreatment PSA level, differentiation, Gleason combined score and clinical T stage. There were also no significant differences in the treatment characteristics such as CT-based treatment planning, conformal therapy, total radiation doses (both a median of 66.0 Gy) and hormonal therapy usage. Moreover, no significant differences in overall survival, biochemical relapse-free survival and late toxicity rates were observed between elderly and younger patients. Conclusion: Age did not influence the disease characteristics, patterns of external beam radiotherapy, survival and late toxicities for clinically localized prostate cancer patients. Therefore, radiotherapy could represent an important treatment modality for elderly patients as well as for younger ones.*

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*Key Words:* Patterns of care study, prostatic carcinoma, age, elderly patients, radiation therapy.

Although treatment decision making in clinically localized prostate cancer is complex, most physicians consider age when deciding on treatment between the principal options of radiotherapy, surgery, hormonal therapy or observation (1-3). Surgery is often not offered to patients ≥70 years of age, while observation or hormonal therapy is frequently considered for patients ≥75 years of age. Radiotherapy also has been the treatment of choice for elderly patients, including those 75 years or older.

Life expectancy has increased steadily in industrialized countries during the past 100 years, and there is a growing demand to treat elderly prostate cancer patients (4, 5). At the beginning of the 1990s, the survival rates reported in several series of untreated patients (6, 7) created a consensus that elderly patients die with and not due to prostate cancer, but more recent studies are challenging this commonly held opinion. According to these new data, patients with adverse prognostic features and/or a life expectancy of more than 5 years, even patients aged 75 years or over, showed high mortality rates from prostate cancer (8-10). These assertions seem to justify the fact that elderly patients with prostate cancer undergo radical radiotherapy because the typical life expectancy in Japan is 10 years for 75-year-old men and 8 years for 80-year-old men (11). However, the role of radiotherapy for elderly patients, including those 75 years or older, has not been fully described.

Since 1996, the Japanese Patterns of Care Study (PCS) Working Group of Prostate Cancer has conducted a nationwide process survey for prostate cancer patients who underwent radiotherapy in Japan (12-18). Here, the PCS results were examined to answer specific questions about the process and outcome of external beam radiotherapy for elderly patients with prostate cancer (≥75 years) as compared to younger patients (<75 years).

0250-7005/2006 $2.00+.40

## Materials and Methods

The PCS national survey is a retrospective study designed to establish national practice for selected malignancies over a specific time-period (19, 20). In addition to documenting the practice, the PCS is important in developing and spreading national guidelines for cancer treatment. This helps to promote a higher quality care in the country (19-21). The PCS was imported to Japan from the United States in order to improve the quality of radiation oncology nationwide in Japan.

The PCS methodology has been described previously (19-21). In brief, the PCS surveys were extramural audits that utilized a stratified two-stage cluster sampling design. The PCS surveyors consisted of 20 radiation oncologists from academic institutions, with one radiation oncologist compiling data by reviewing the patients' charts for each institution. The following patient eligibility criteria were used: prostatic adenocarcinoma without evidence of distant metastasis; radiotherapy between 1996 and 1998 or between 1999 and 2001 with no prior radiotherapy; and no concurrent or prior diagnosis of another malignancy. Patients who had had prior prostatectomy and patients with hormone-refractory cancer were excluded from the analysis.

The PCS data used in the current study are the results of two Japanese national surveys conducted to evaluate prostate cancer patients treated with radical external beam radiotherapy in the 1996-1998 and 1999-2001 PCS. Because of appropriate random sampling, the results of these studies represent true Japanese national averages (19-21). Out of the 694 patients comprising the 1996-1998 and 1999-2001 PCS surveys, a total of 444 patients with clinically localized prostate cancer treated with radical external beam radiotherapy met the eligibility criteria and were selected for analysis (1996-1998 PCS: 161 patients, 38 institutions; 1999-2001 PCS: 283 patients, 66 institutions). The patients were categorized into two age groups: ≥75 years (140 patients) and <75 years (304 patients), and the comparison data were used to examine the influences of age on patient and disease characteristics, treatment characteristics, overall and biochemical relapse-free survival and late toxicities.

The median follow-up of all patients was 2.0 years (range, 0.1-6.3 years). Biochemical relapse-free survival was defined by the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus definition (22). Statistical analyses were performed using the Statistical Analysis System at the PCS statistical center (23). Statistical significance was tested using the Chi-square test, Mann-Whitney *U*-test and the Kaplan-Meier method (24). A probability level of 0.05 was chosen for statistical significance. The Radiation Therapy Oncology Group (RTOG) late toxicity scales (25) were used to assess late toxicity.

## Results

The patient and disease characteristics according to age group are shown in Table I. With regard to patient characteristics, the Karnofsky performance status (KPS) in elderly patients was significantly lower than that of younger patients ($p=0.0040$). On the other hand, there were no significant differences in disease characteristics such as pretreatment PSA level ($p=0.3290$), differentiation ($p=0.1030$), Gleason combined score ($p=0.1413$) and clinical T stage ($p=0.6836$).

Table II indicates the treatment characteristics according to age group. There were no significant differences in the patterns of radiotherapy; such as CT-based treatment planning ($p=0.5987$), conformal therapy ($p=0.0759$), total radiation doses (both: median 66 Gy, $p=0.1446$) and hormonal therapy usage ($p=0.6758$).

At a median follow-up of 2.0 years, 17 patients had died of prostate cancer, 6 of intercurrent diseases, 3 of another cancer and 2 of unknown causes. The 2- and 5-year actuarial overall survival rates were 93.4% and 88.8% in elderly patients, and 95.5% and 84.3% in younger patients (Figure 1). There were no significant differences in overall survival between these groups ($p=0.8524$). Biochemical failure was noted in 54 patients. The 2- and 5-year actuarial biochemical relapse-free survival rates were 90.8% and 90.8% in elderly patients, and 84.3% and 83.5% in younger patients (Figure 2). In addition, there were no significant differences in biochemical relapse-free survival between the elderly and younger patients ($p=0.1362$).

Table III indicates the incidence of late toxicities (≥Grade 2) in elderly and younger patients. Twenty out of 140 older patients (14.3%) and 37 out of 304 younger patients (12.2%) suffered late toxicities. There was one patient with grade 3 gastrointestinal toxicity in the younger age group. There were no significant differences in the incidence of late toxicities between elderly patients and younger patients (gastrointestinal: $p=0.9599$, genitourinary: $p=0.0597$).

Among the elderly patients, the median total radiation dose was 66.0 Gy (range, 60-82 Gy) for patients treated with conformal therapy and 63.0 Gy (range, 30.6-80 Gy) for patients treated without conformal therapy ($p<0.0001$). Moreover, 41% of patients with conformal therapy were treated with total doses of 70 Gy or more, while only 17.1% of patients without conformal therapy were treated with these dose levels ($p<0.0001$). Although significantly higher total doses were delivered to patients with conformal therapy than those without conformal therapy, there were no significant differences ($p=0.1152$) in the incidence of late toxicities between patients with conformal therapy (15.4%) and those without conformal therapy (9.8%).

## Discussion

The results of the current study indicated that age did not influence the disease characteristics for clinically localized prostate cancer patients who underwent external beam radiotherapy. Because of appropriate random sampling of the PCS surveys, the results of these studies represent true Japanese national averages. Several authors also compared elderly patients with younger patients and found no differences in the patient characteristics (5, 26, 27). Suzuki *et al.* indicated that elderly patients ≥80 years old presented

Table I. *Patient and disease characteristics.*

| | Age group | | Significance (*p*) |
|---|---|---|---|
| | <75 (n=304) | ≥75 (n=140) | |
| Patient characteristics | | | |
| Age (years) | | | |
| Median (Min-Max) | 69.3 (46-74) | 78.0 (75-92) | <0.001 |
| KPS (%) | | | |
| ≤80 | 68/291 (22.7) | 47/130 (36.2) | 0.004 |
| 90-100 | 231/299 (77.3) | 83/130 (63.8) | |
| Missing | 5 | 10 | |
| Hypertension | | | |
| Yes | 95/295 (32.2%) | 39/137 (28.5%) | 0.5502 |
| Unknown | 17/295 (5.8%) | 11/137 (8.0%) | |
| Missing | 9 | 3 | |
| Angina | | | |
| Yes | 30/295 (10.2%) | 18/137 (13.1%) | 0.598 |
| Unknown | 23/295 (7.8%) | 12/137 (8.8%) | |
| Missing | 9 | 3 | |
| Myocardical infraction | | | |
| Yes | 13/295 (4.4%) | 11/137 (8.0%) | 0.3101 |
| Unknown | 22/295 (7.5%) | 10/137 (7.3%) | |
| Missing | 9 | 3 | |
| Hepatitis | | | |
| Yes | 27/297 (9.1%) | 7/137 (5.1%) | 0.2922 |
| Unknown | 20/297 (6.7%) | 12/137 (8.8%) | |
| Missing | 7 | 3 | |
| Liver cirrhosis | | | |
| Yes | 4/294 (1.4%) | 0/137 (0%) | 0.225 |
| Unknown | 21/294 (7.1%) | 14/137 (10.2%) | |
| Missing | 10 | 3 | |
| Diabetes | | | |
| Yes | 34/296 (11.5%) | 12/137 (8.8%) | |
| No | 244/296 (82.4%) | 112/137 (81.8%) | 0.3362 |
| Unknown | 18/296 (6.1%) | 13/137 (9.5%) | |
| Missing | 8 | 3 | |
| Disease characteristics | | | |
| Pretreatment PSA level (ng/ml, %) | | | |
| Median (Min-Max) | 20.55 (0.8-900) | 22.58 (0.3-856.9) | |
| <4 | 14/282 (5.0%) | 11/132 (8.3%) | |
| 4≤ <10 | 69/282 (24.4%) | 24/132 (18.2%) | |
| 10≤ <20 | 56/282 (19.9%) | 26/132 (19.7%) | 0.329 |
| ≥20 | 143/282 (50.8%) | 71/132 (53.8%) | |
| Missing | 22 | 8 | |
| Differenatiation | | | |
| Well | 66/284 (23.2%) | 20/139 (14.4%) | |
| Moderate | 117/284 (41.2%) | 55/139 (39.6%) | 0.1030 |
| Poor | 84/284 (29.6%) | 55/136 (39.6%) | |
| Unknown | 15/284 (5.3%) | 9/139 (6.5%) | |
| Other | 2/284 (0.7%) | 0 | |
| Missing | 20 | 1 | |
| Gleason combined score (%) | | | |
| 2-6 | 62/147 (42.2%) | 26/47 (39.4%) | |
| 7 | 41/147 (27.9%) | 12/66 (18.2%) | 0.1413 |
| 8-10 | 44/147 (30.0%) | 28/66 (42.4%) | |
| Missing | 157 | 74 | |
| Clinical T stage | | | |
| TX | 7/294 (2.4%) | 3/137 (2.2%) | |
| T0 | 1/294 (0.7%) | 0 | |
| T1 | 18/294 (6.1%) | 12/137 (8.8%) | |
| T2 | 110/294 (37.4%) | 46/137 (33.6%) | 0.6836 |
| T3 | 125/294 (42.5%) | 65/137 (47.4%) | |
| T4 | 26/294 (8.8%) | 10/137 (7.3%) | |
| Unknown | 7/294 (2.4%) | 1/137 (0.7%) | |
| Missing | 10 | 3 | |
| Clinical N stage | | | |
| NX | 11/292 (3.8%) | 2/135 (1.5%) | |
| N0 | 246/292 (84.2%) | 126/135 (93.3%) | |
| N1 | 27/292 (9.2%) | 6/135 (4.4%) | 0.0731 |
| Unknown | 8/292 (2.7%) | 1/135 (0.7%) | |
| Missing | 12 | 5 | |

KPS=Karnofsky performance status; PSA=prostate-specific antigen.

with similar histological grade and disease stage as younger patients (26). Geinitz *et al.* indicated that there were no significant differences in disease characteristics between patients of ≥75 years and <75 years (5). These results suggest that elderly patients present with similar disease characteristics as younger patients.

The results of the current study also indicated that age did not influence the patterns of external beam radiotherapy for clinically localized prostate cancer patients. Although the KPS of elderly patients was significantly lower than that of younger patients, treatment characteristics, such as CT-based treatment planning, conformal therapy, total radiation doses and hormonal therapy usage, were not significantly different. Several authors also compared elderly patients with younger patients and found no differences in the patterns of external beam radiotherapy (5, 26, 27). Geinitz *et al.* found that 3D conformal radiotherapy for prostate cancer with doses of 70 Gy was well tolerated in patients aged 75 years or older as well as in younger patients (5). Hanks *et al.* found that radiotherapy could be given to prostate cancer patients without age bias (27). These results suggest that elderly patients can tolerate standard external beam radiotherapy in the same way as younger patients.

In spite of the short median follow-up period, the results of the current study indicated that age did not influence the overall survival and biochemical relapse-free survival rates and incidence of late toxicities for clinically localized prostate cancer patients. Although intercurrent death would result in a poorer overall survival for patients 75 years or older, the overall survivals were similar between patients of

Table II. *Treatment characteristics.*

| | Age group | | Significance (*p*) |
|---|---|---|---|
| | <75 (n=304) | ≥75 (n=140) | |
| Radiotherapy | | | |
| Energy (≥10 MV) (%) | | | |
| Yes | 210/301 (70.0%) | 95/139 (68.4%) | 0.7636 |
| Missing | 3 | 1 | |
| CT-based treatment planning (%) | | | |
| Yes | 249/304 (81.9%) | 114/139 (82.0%) | 0.5987 |
| Unknown | 6/304 (2.0%) | 1/139 (0.7%) | |
| Missing | 0 | 1 | |
| Conformal therapy (%) | | | |
| Yes | 143/256 (55.9%) | 78/119 (65.6%) | 0.0759 |
| Missing | 48 | 21 | |
| All fields treated each day (%) | | | |
| Yes | 146/196 (74.5%) | 69/87 (79.3%) | 0.3811 |
| Missing | 108 | 53 | |
| Pelvic irradiation (%) | | | |
| Yes | 119/304 (39.1%) | 52/140 (37.1%) | 0.6781 |
| Radiation dose (cGy) | | | |
| Median (Min-Max) | 6600 (1400-7600) | 6600 (3000-8200) | 0.1446 |
| Missing | 0 | 1 | |
| Hormonal therapy | | | |
| Yes | 266/303 (87.8%) | 125/139 (89.9%) | 0.6758 |
| Unknown | 1/303 (0.3%) | 0 | |
| Missing | 1 | 1 | |
| Content (%) | | | |
| Orchiectomy | 34/274 (12.4%) | 15/127 (11.8%) | 0.8368 |
| Unknown | 4/274 (1.5%) | 1/127 (0.8%) | |
| Missing | 30 | 13 | |
| Estrogen agent | 35/263 (13.3%) | 13/123 (10.6%) | 0.7609 |
| Unknown | 10/263 (3.8%) | 7/123 (5.7%) | |
| Missing | 41 | 17 | |
| LH-RH agonist | 226/281 (80.4%) | 101/132 (76.5%) | 0.0880 |
| Unknown | 9/281 (3.2%) | 9/132 (6.8%) | |
| Missing | 23 | 8 | |
| Antiandrogen | 190/282 (67.4%) | 80/130 (61.5%) | 0.6352 |
| Unknown | 15/282 (5.3%) | 10/130 (7.7%) | |
| Missing | 22 | 10 | |
| Period (%) | | | |
| Before RT (77.3%) | 243/285 (84.5%) | 102/132 (77.3%) | 0.0887 |
| Unknown | 1/285 (0.4%) | 0 | |
| Missing | 19 | 8 | |
| During RT (78.9%) | 230/284 (81.0%) | 105/133 (78.9%) | 0.6693 |
| Unknown | 6/284 (2.1%) | 3/133 (2.3%) | |
| Missing | 20 | 7 | |
| After RT | 216/282 (76.6%) | 95/133 (71.4%) | 0.4092 |
| Unknown | 26/282 (9.2%) | 13/133 (9.8%) | |
| Missing | 22 | 7 | |
| Duration* (Years) | | | |
| Median (Min-Max) | 0.96 (0.0-4.8) | 1.01 (0.0-4.5) | 0.4822 |
| Chemotherapy | | | |
| Yes | 30/298 (10.1%) | 7/135 (5.2%) | |
| No | 264/298 (88.6%) | 128/135 (94.8%) | 0.0907 |
| Unknown | 4/298 (1.3%) | 0 | |
| Missing | 6 | 5 | |

CT=computed tomography; RT=radiotherapy; LH-RH=Lutein hormone-releasing hormone.

Table III. *Late toxicities.*

| | Age group | | Significance (*p*) |
|---|---|---|---|
| | <75 (n=304) | ≥75 (n=140) | |
| Gastrointestinal (≥Grade 2) | | | |
| Yes | 34/298 (11.4%) | 15/135 (11.1%) | |
| No | 261/298 (87.6%) | 119/135 (88.1%) | N.S. (0.9599) |
| Unknown | 3/298 (3.0%) | 1/135 (0.7%) | |
| Missing | 6 | 5 | |
| Genitourinary (≥Grade 2) | | | |
| Yes | 3/193 (1.6%) | 5/87 (5.7%) | |
| No | 180/193 (93.2%) | 74/87 (85.1%) | N.S. (0.0597) |
| Unknown | 10/193 (5.2%) | 8/87 (9.2%) | |
| Missing | 111 | 53 | |

N.S.=Not significant.

≥75 years and those of 75< years. Perhaps patients older than 75 who are selected for radiotherapy may be in better health than the average person in that age group. Previously, several authors also reported the favorable results of external beam radiotherapy for elderly patients. Villa *et al.* reviewed 183 elderly patients >70 years of age with localized prostate cancer, treated with radical external beam radiotherapy, and found that elderly patients with clinically localized prostate cancer can fare well when treated with radical irradiation, with very limited acute and late toxicity (28). Alibhai *et al.* indicated that potentially curative therapy, such as radiotherapy, results in significantly improved life expectancy and quality-adjusted