

rates is shown in Fig 3. A dose equal to or more than 60 Gy was given for 57% of focally positive margins, 86% for equal or less than 2 mm margins and 78% of 2.1-5 mm margins. This may be one reason why the patients with equal or less than 2 mm margins achieved the best IBTC rate of the three groups.

The 5 and 10 year IBTC rates according to marginal status and the doses to the tumor bed are listed in Table 4. In patients with focally positive margins, the IBTC of patients receiving radiation dose equal to or more than 60 Gy was significantly better ( $p = 0.039$ ) (Fig 4).

The 10-year IBTC rates according to age were 65.7% for those younger than 35 years and 88.0% for those equal or older than 35 years ( $p < 0.0001$ ) (Fig 5). Of IBTR patients, there were 17 (14%)

Table 4. IBTC by Tumor dose and Marginal Status

Dose	5/10 years IBTC (%)		All
	$\leq 59$ Gy	$60$ Gy $\leq$	
Positive	92.7/81.4	96.4/90.5	95.1/85.9
<2 mm	92.5/86.6	97.4/92.6	96.8/91.0
2.1-5 mm	98.1/88.7	94.3/92.0	95.2/87.0

younger than 35 years, 47 (38%) aged 35-44 years 36 (29%) aged 45-54 years, 18 (15%) aged 55-64 years, and 5 (4%) older than 65 years. The 10-year IBTC rates according to menopausal status were 91.0% for postmenopausal patients and 85.9% for

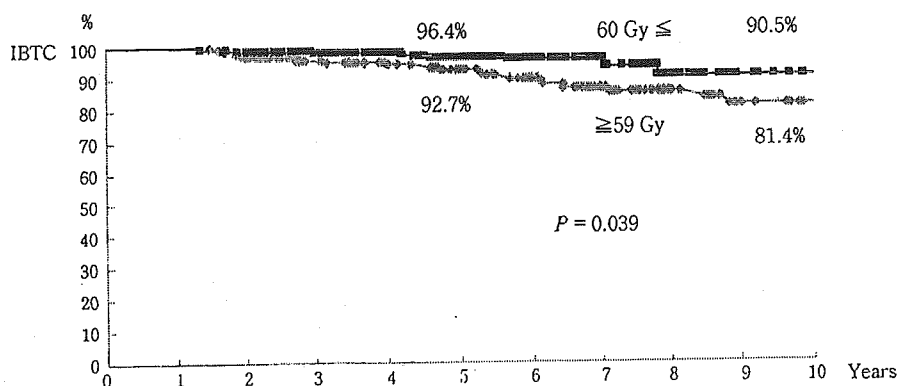


Fig 4. IBTC of margin positive patients by tumor dose. The doses to the tumor bed were less than 60 Gy in 252 (27%), 60 Gy in 456 (48%) and more than 60 Gy in 233 (25%).

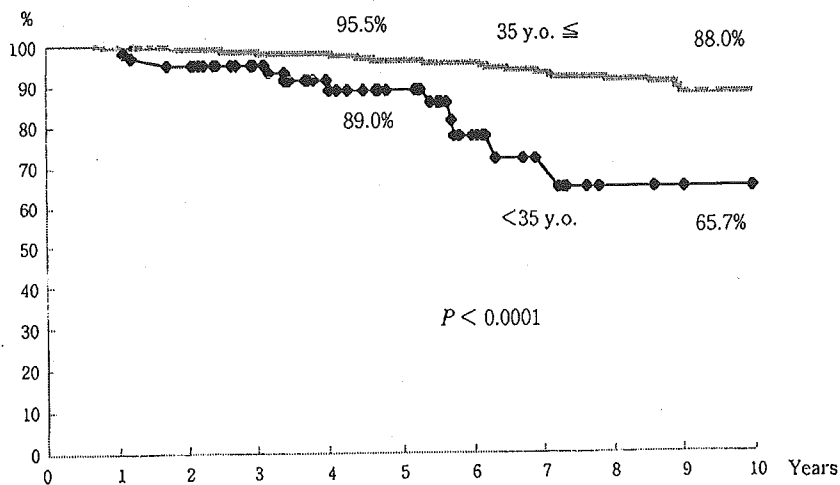


Fig 5. IBTC by age. The median age of the patients was 48 years, with a distribution of 64 (7%) in younger than 35 years.

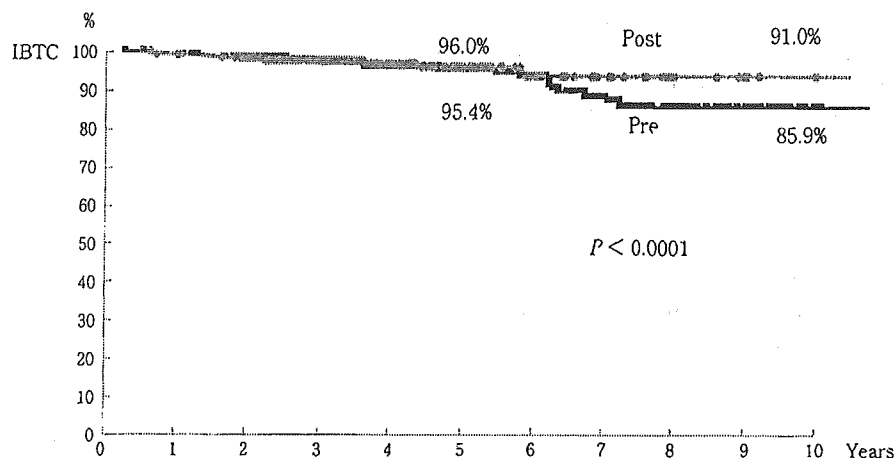


Fig 6. IBTC by menopausal status. Five hundred fourteen patients (55%) were premenopausal and 319 (34%) were postmenopausal.

Table 5. IBTC by dose and Other Factors

Dose	5/10 years IBTC (%)		All
	≤59 Gy	60 Gy ≤	
Age <35 y.o.	79.4/65.0	93.8/68.2	88.9/71.3
Premenopause	94.3/83.3	95.8/88.0	95.4/85.9
t2	91.0/76.6	95.2/89.3	92.8/84.1

n.s.  
n.s.  
 $p = 0.016$

premenopausal patients ( $p < 0.0001$ ) (Fig 6). The 10-year IBTC rates according to tumor size were 90.4% in t1 and 84.1% in t2 ( $p = 0.023$ ) patients. The other factors, such as nodal status, ER status, and use of adjuvant therapy, had no statistically significant differences in IBTC. The 5 and 10 year IBTC rates according to age, menopausal status, tumor size and radiation dose to the tumor bed are listed in Table 5. The tumor bed dose equal to or more than 60 Gy was significantly better for achieving IBTC in t2 cases ( $p = 0.016$ ). However, there was no improvement with a tumor bed dose equal or more than 60 Gy for younger age or premenopausal patients.

### Discussion

Breast conserving therapy has been recognized as a standard treatment of early stage breast cancer. Randomized trials have demonstrated that survival rates after BCT are equivalent to those

obtained after mastectomy. However, IBTR is a lifelong risk and source of anxiety for the patients. To reduce the risk of IBTR, one can remove more breast tissue at BCS, but cosmesis can be unacceptably affected by more extensive surgery. To optimize the balance between the risk of IBTR and cosmesis, the volume of residual cancer cells near the resection margin is regarded as important. Many retrospective studies have demonstrated that positive resection margins were one of the most significant factors impacting IBTR<sup>1,2</sup>. To minimize IBTR in BCT, the surgical oncologist strives for clear resection margins. Although the clinical assessment of resection margin analysis is delicate, many specific issues have been discussed. Even in patients with negative margins, IBTR occurred in more than 40% of patients without postoperative breast radiotherapy in NSABP B06<sup>3</sup>. This means that a negative margin does not equivalent no residual cancer cells in the conserved breast. In the cases with positive margins, it is nearly certain that cancer cells have been left in the breast, and IBTR is likely unavoidable without postoperative radiotherapy and/or chemohormone therapy.

It is an undeniable fact that radiotherapy reduces IBTR in negative and positive margin patients. Nevertheless, the balance between the residual cancer volume and radiation tumor control is not fully delineated. It is also not clear which patient and tumor characteristics affect IBTC in positive or close margin cases.

Many authors have suggested that a high boost

dose of radiation reduced IBTR in patients with positive resection margins. Heimann *et al.* reported 5-year a IBTC rate in patients with positive margins of 91% with a boost of >60 Gy compared to 76% with a  $\leq 60$  Gy dose<sup>9</sup>. Spivack *et al.* reported that IBTC was 8% with a boost of >60 Gy compared to 22% with a dose of  $\leq 60$  Gy<sup>9</sup>. Slotman *et al.* reported that IBTC in patients with positive or close margins was 5% with an interstitial boost of  $\geq 75$  Gy compared to 10-13% with external beam 65-70 Gy<sup>9</sup>. Schmidt-Ullrich *et al.* reported that dose escalation of the tumor bed is effective in margin positive patients. They irradiated 70 Gy in case with margin <2 mm, 65 Gy in 2-5 mm margin cases and 60 Gy in >5 mm margin cases<sup>7</sup>. Neuschatz *et al.* reported a margin radiation dose escalation trial. They irradiated a boost dose of 10 Gy in disease-free margin (DFM) cases greater than 5 mm, 14 Gy in DFM cases greater than 2-5 mm, 20 Gy in DFM cases greater than 2-0 mm or positive margin cases followed by 50-50.4 Gy irradiated of whole breast. The 5 year IBTC rate is very low, however, close or positive margins had significantly increased IBTR after 5 years. They thought that represented this a mixture of true recurrences and new primary cases<sup>9</sup>. Freedman *et al.* reported that dose escalation of the tumor bed is effective in 5 year results, but is not effective 10 years. They irradiated 66 Gy in margin positive cases, 64 Gy in cases with  $\leq 2$  mm margins and 60 Gy in cases with >5 mm margins. Systemic therapy reduced 5-year recurrence results, but not 10-year result<sup>9</sup>. These were retrospective studies and consisted of a relatively small number of patients. It is impossible to determine the effect of the radiation dose with a nonrandomized study.

The EORTC 'boost versus no boost' trial is a randomized trial for radiation dose effect. After tumorectomy followed by whole breast irradiation of 50 Gy, 5318 patients with a microscopically complete excision were randomized to no boost or a 16 Gy boost, while 251 patients with an incomplete excision were randomized to a boost dose of 10 Gy or 26 Gy. In margin negative patients, a boost dose of 16 Gy reduced the relative risk of IBTR and slight impaired cosmesis<sup>9</sup>. The results of positive margin patients are not yet reported.

Some authors reported that the extent of the positive margins influenced IBTR<sup>10-15</sup>. Gage *et al.* reported IBCR of focally positive margins was acceptably low compared with more than focally positive margins. Park *et al.* reported that the rate

of local recurrence was 7% in patients with close or negative margins, 14% in those with focally-positive margins and 27% in those with extensively positive margins<sup>10</sup>. DiBiase *et al.* reported the degree of margin positives influences IBTC<sup>13</sup>. A high dose of boost irradiation in patients with positive or close margins does not appear to confer the same risk of IBTR as patients with negative margins, however, when positive margins are focal or minimal, the impact on IBTR may be significant.

Other factors associated with IBCR were young age, premenopausal status and tumor size in our cohort. Obedian *et al.* and Tartter *et al.* reported that positive margins were significantly associated with large tumor size and young age<sup>16,17</sup>. Neuschatz *et al.* reported that patients 45 years or younger had a significantly lower rate of IBTC and that dose escalation did not fully overcome the influence of young age<sup>9</sup>. Leong *et al.* and Kini *et al.* reported that patients 35 years or younger had a significantly lower IBTC<sup>18,19</sup>. Leong *et al.* concluded that this was regardless of margin status. DiBiase *et al.* reported that stage, menopausal status and the use of chemotherapy were significant factors for IBTR<sup>20</sup>. Nixon *et al.* showed that younger patients have a higher frequency of adverse pathologic factors (including grade 3 histology, lymphatic vessel invasion, necrosis, and ER negativity) and that this was the reason for the poor prognosis compared with older patients<sup>21</sup>.

Our series was a retrospective analysis, but the number of registered patients with positive or close margins was more than one thousand and the total number of patients analyzed was 941. We think no other series has accumulated this number of patients with positive or close margins, and the number of patients is advantageous for analyzing prognostic factors. The 10-year IBTC rates were 90.8% with doses of equal to or more than 60 Gy and 84.2% in doses of less than 60 Gy in the entire cohort ( $p=0.057$ ) (Fig 3). However, in 358 patients with positive margins, the 10-year IBTC rates were 90.5% in doses of equal to or more than 60 Gy and 81.4% in doses less than 60 Gy ( $p=0.039$ ) (Fig 4). Young age and premenopausal status had the most influence on IBTC regardless of the radiation dose to the tumor bed. Pathological t-stage was significantly associated with IBTC and depended on the radiation dose.

We recommend that the tumor bed should be irradiated with at least 60 Gy in the patients with

positive margins. The median follow up time was 4.9 years at analysis, therefore further follow-up is necessary to draw final conclusions.

### Acknowledgement

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特集 手術によらない限局性前立腺癌の治療

## 放射線外部照射

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Keyword 前立腺癌, 放射線治療, 外部照射

## 要旨

近年のコンピュータ技術の発達に伴って放射線治療はめざましい進歩をとげた。外部照射では、CT 画像からターゲットの三次元的な位置情報を取得し、多分割絞りがターゲットに合わせた照射野を形成し、正確に照射を行う、いわゆる三次元原体放射線治療 (three-dimensional conformal radiotherapy ; 3DCRT) が主力となっている。3DCRT により、多くの放射線を前立腺に投与し、かつ副作用を低減化することが可能となった。放射線治療は前立腺癌の治療において今後ますます重要な役割を果たすようになっていくと思われる。

## ① はじめに

従来、わが国では、前立腺癌に対する放射線治療は、主に骨転移や内分泌療法後の再燃などに対する緩和的治療として用いられてきた。しかし、欧米では既に放射線治療は手術と匹敵する治療法と考えられており、わが国でも前立腺癌罹患率の増加とともに、前立腺癌治療における根治的治療法の一つとして認識されはじめている<sup>1,2)</sup>。特に、コンピュータ技術と機械工学のめざましい進歩によって、従来よりもさらに副作用の少ない放射線治療の実施が可能になりつつあり、前立腺癌の放射線治療症例数は年々増加している<sup>3)</sup>。

本稿では、最近の外部照射をめぐる技術の進歩を概説し、前立腺癌に対する外部照射の役割について述べる。

## ② 放射線外部照射の基本的事項

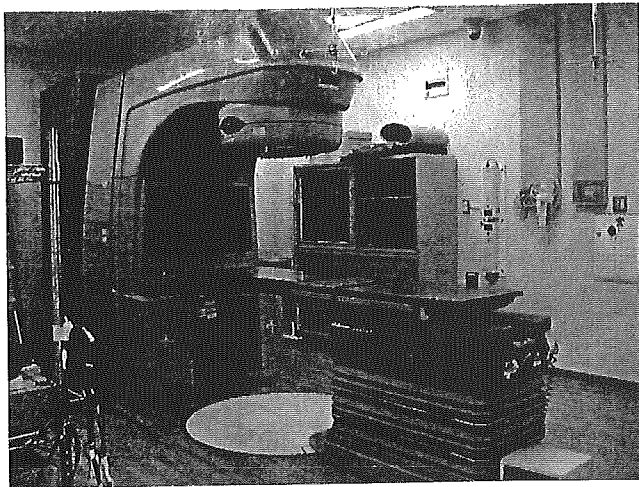
現在の外部照射の主力装置は、リニアック (直線加速器, linear accelerator) である。リニアック内部の加速管内に電子銃より電子が打ち込まれ、高周波により発生する電場で加速される。加速された電子が X 線発生用ターゲットにぶつかることにより X 線が発生し、患者に照射される。リニアックにより生み出される X 線は、診断用 X 線よりエネルギーが高く、深部臓器にも十分到達することができる。

わが国にてリニアックが医療用に初めて用いられたのは 1960 年代初頭であり、比較的古くから存在する。しかし、近年の技術の発達は、線量の安定性、出力の向上など、リニアックの性能を多に向上させた。特に重要なのが、多分割絞り (multi-leaf collimator ; MLC) の開発、改良である。

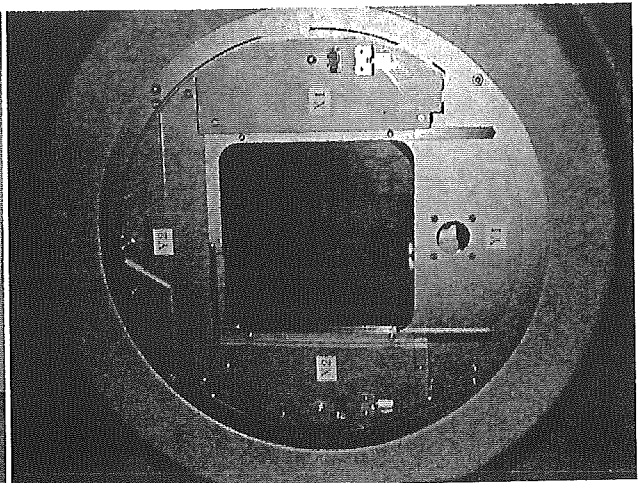
\*1) External beam radiotherapy for prostate cancer

\*2) Kazumasa Nakamura and Tomonari Sasaki : 九州大学大学院医学研究院臨床放射線科学分野 (〒812-8582 福岡市東区馬出 3-1-1)

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A



B

図 1 リニアック (A) と多分割絞り (B)  
多分割絞りにより、腫瘍に合わせたビーム形状が作られる。

従来は、X線ビームの形状は矩形であったが、リニアックの照射口に多分割絞りを取り付けることにより、腫瘍の形に合わせたビーム形状を作ることができるようになった(図1)。さらに、従来多分割絞りの幅は1~2cmであったが、最新のリニアックでは3~5mm程度のものが装備されており、それだけ膀胱、直腸などの前立腺周囲の正常組織の線量を低減することができるようになってきている。

ここで問題となってくるのが、ターゲットの位置の把握である。従来は、X線シミュレータにより、透視下のみで照射範囲を決定していた。しかし、現在では、薄くスキャンされたCT画像を用いて、ターゲット領域およびリスク臓器の三次元的な位置情報を取得し、放射線照射方向および照射野を決定する。その後、治療計画用コンピュータにて三次元的に線量分布が計算され、照射情報のすべてがオンラインでリニアックに転送され、多分割絞りがターゲットに合わせた照射野を形成し、X線が正確にターゲット領域に照射される。このような放射線治療は、三次元原体放射線治療(three-dimensional conformal radiotherapy; 3DCRT)と呼ばれ、現在の放射線治療の主力となっている。

前立腺への照射の場合には、膀胱・直腸の線量を低減し、前立腺野や精嚢へのX線の集中性を高めるため、4~6門以上の固定多門照射や回転原体

照射を行うことが多い(図2, 図3)。

実際の放射線治療では、1回の治療時間は約15分であり、身体的負担は少なく、外来で十分治療可能である。しかし、治療期間が長いことが難点であり、例えば1回2Gyにて総線量70Gyの外照射を行う場合には、合計35回、約7週間の通院が必要である。

放射線外照射に伴う有害事象は比較的軽微である。照射中は、排尿痛、軽度の下痢、肛門痛などであるが、通常照射後2~3週間で改善する。晩期有害事象の頻度も少ないが、直腸出血が問題となることがある。手術を要するような直腸出血はきわめて稀であるが、何らかの出血が認められる頻度は数%から20%程度と報告されている<sup>4)</sup>。多分割絞りを用いない通常の照射法では重篤な直腸障害を避けるには70Gy程度が限度であったが、三次元原体放射線治療が可能となったことにより、晩期有害事象の発生頻度を増加させずに70Gy以上の線量増加が可能となっている。直腸に対する線量をさらに低減し、安全に線量増加を実現するために、強度変調放射線治療(intensity-modulated radiation therapy; IMRT)が開発されているが、これに関しては別項を参照されたい。

その他の晩期有害事象として30%程度に性機能障害が認められるとされている<sup>4)</sup>。しかし、前立腺癌全摘術に比べその頻度は少なく、放射線治療に伴う性機能障害はバイアグラ<sup>®</sup>によく反応

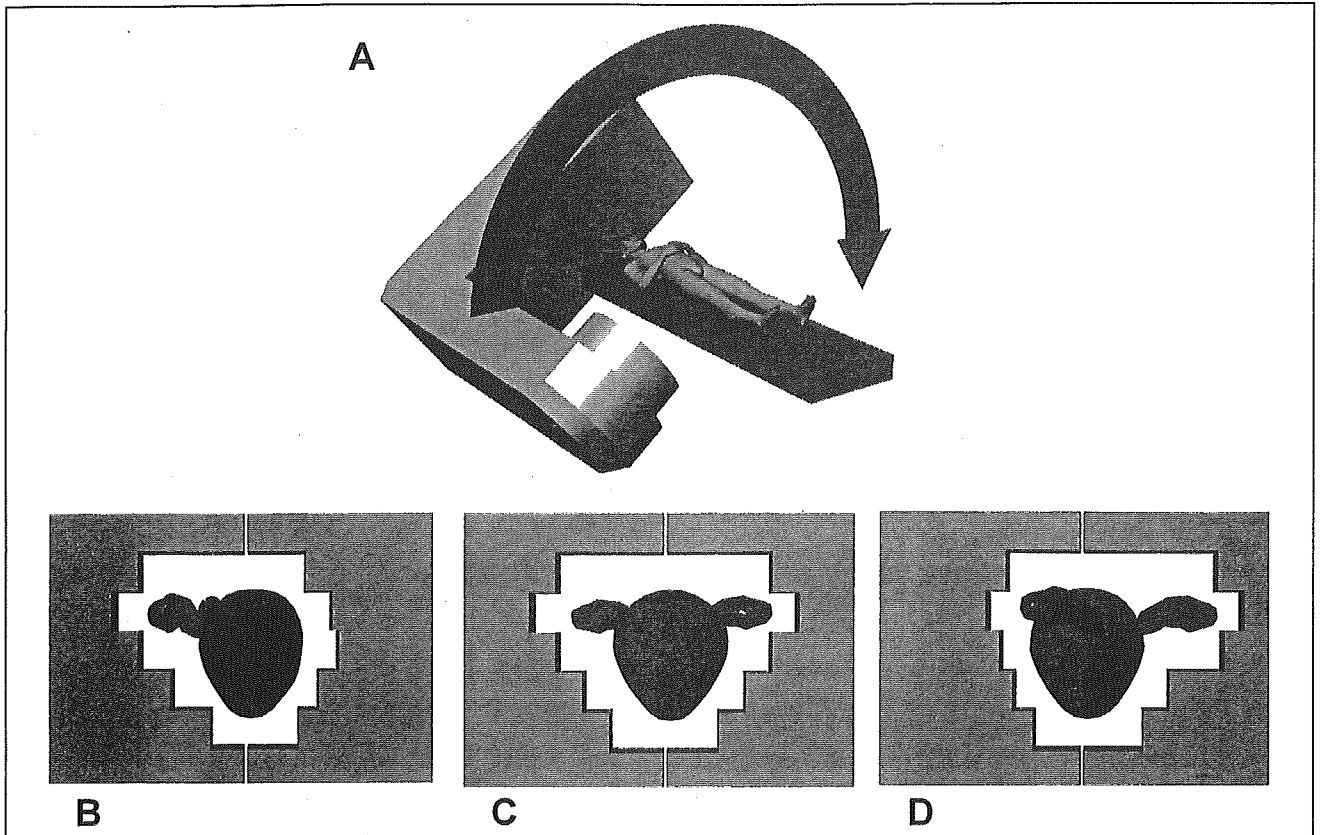


図 2 三次元原体放射線治療でのリニアック (A) および多分割絞りの動き (B~D)  
 前立腺癌に対する回転原体照射では、リニアックの回転とともに、多分割絞りが自動的にターゲットの形状に合わせて変化し、X線を集中させる。

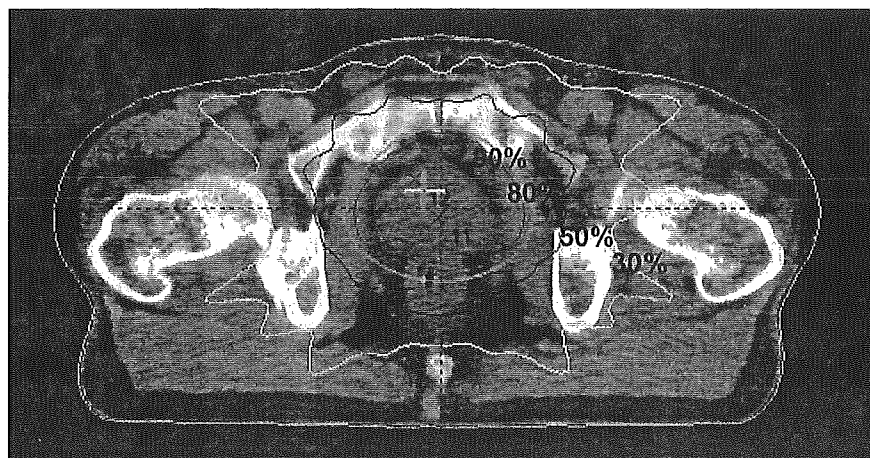


図 3 三次元原体放射線治療での線量分布  
 直腸の線量が抑えられていることがわかる。

し、また射精機能も保たれる。

### ③ 放射線外部照射の治療成績

以上に述べてきたような技術的進歩によって、前立腺癌に対する外部照射は格段の進歩をとげ、治療成績も向上している。前立腺癌の予後因子として、臨床病期、治療前 PSA (prostate specific anti-

gen) 値、Gleason score などがあるが、これらによって被膜外浸潤、リンパ節転移などの確率が予測でき、それによって異なった治療戦略が選択される。これらのリスク評価として、Partin nomogram が有名であるが<sup>5)</sup>、あくまで欧米のデータであり、日本人にそのまま当てはまるかどうかは不明である<sup>6)</sup>。しかし、現状では Partin nomogram を



参考にすることが多く、実際の放射線治療でもリスク分類によって、内分泌療法を併用するかどうか、骨盤領域を照射するかどうか、また、総線量など、治療戦略を変えることも多い。

### 1. 線量増加

前立腺癌の局所コントロールは線量依存性があることはよく知られている<sup>7)</sup>。限局性前立腺癌に対し 60 Gy の単独照射を行い、中央値 22 年観察した報告では、69% に臨床的再発が認められ、局所再発は 36% にみられたとされている<sup>8)</sup>。すなわち、60 Gy 程度の放射線治療単独では、前立腺癌の根治は難しいといえる。Kuban らによる、T1-2 前立腺癌 4,839 例の解析では、70 Gy 以上の放射線治療単独により、低リスク群、中等度リスク群、高リスク群の 5 年 PSA 非再発率はそれぞれ 80%、70%、35% であった<sup>9)</sup>。これは D'Amico らの、手術を受けた 2,127 例の治療成績<sup>10)</sup> と遜色ないものである。70 Gy 程度の線量で低リスク群では治療成績は良好であると言えるが、中等度～高リスク群において PSA 非再発率は不良であり、内分泌療法併用などの治療戦略が必要と考えられている。

米国では、70～80 Gy 以上の線量増加研究が行われており、中等度～高リスク群においても良好な PSA 非再発率が報告されている<sup>7)</sup>。そのほかにも線量増加の有効性を示唆する報告が多数みられるが、いずれも retrospective study であり、本当に 70 Gy 以上の線量増加が有効であるかどうかは、現在米国 RTOG (Radiation Therapy Oncology Group) などで行われているランダム化比較試験の結果を待たなければならない。

### 2. 内分泌療法併用

内分泌療法は放射線治療の効果を増強することが強く示唆されている。アンドロゲン感受性のある前立腺癌由来の細胞を用いた基礎実験では、放射線照射単独の場合と比べ、アンドロゲン除去下では腫瘍制御線量がきわめて低下したと報告されている<sup>11)</sup>。注目すべきは、アンドロゲン除去により最も腫瘍が縮小したときに放射線照射をした場合が最も腫瘍制御線量が少なくすみ、腫瘍がアンドロゲン不応となり再増殖を示した後では、腫瘍制御線量は放射線単独と同程度必要であったこ

とである。また、実験腫瘍において、アンドロゲン除去下では、放射線照射によるアポトーシスが 5～10 倍増加したとの報告もみられる<sup>12)</sup>。

実際の臨床試験も内分泌療法併用放射線治療の有効性を支持している。放射線治療の約 2.5 年後に前立腺生検を行った研究では、放射線治療単独 70.2 Gy では前立腺癌細胞陽性率は約 40% であったが、81 Gy の照射では 17% まで低下したとしている<sup>7)</sup>。しかし、ネオアジュバント内分泌療法を併用した場合、治療後の陽性率は 70.2 Gy の場合にて 12%、81 Gy では 8% まで低下している。また、Bolla らによる、放射線治療単独と内分泌療法併用放射線治療のランダム化比較試験では、70 Gy の放射線治療に 3 年のアジュバント内分泌療法を併用することにより、生存率が改善したとされている<sup>13)</sup>。当施設で放射線治療を行った高リスク前立腺癌 60 例の解析においても、長期内分泌療法併用と 60～65 Gy の外照射の併用にて 3 年 PSA 非再発率 89.8% と良好であった<sup>14)</sup>。

Roach らは、RTOG で行われた前立腺癌の放射線治療に対する臨床試験のメタアナリシスの結果より、中等度リスク群ではネオアジュバント内分泌療法を、高リスク群ではネオアジュバント内分泌療法に加えて長期のアジュバント内分泌療法が必要としている<sup>15)</sup>。内分泌療法併用放射線治療の臨床試験の多くが 65～70 Gy の照射がなされているが、内分泌療法併用時の適切な線量についてはつきりとはわかっていない。

### 3. 日本における前立腺癌の放射線治療の現状

日本における放射線治療の実態を明らかにするために、放射線治療の医療実態調査研究が行われた<sup>16)</sup>。前立腺癌に関しては、1996～1998 年および 1999～2001 年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約 500 例のデータが、全国の無作為に抽出された施設よりランダムに集積された<sup>17～21)</sup>。根治的外照射例に関しては、高リスク群が多く、長期の内分泌療法がほとんどの例で併用されていた。照射線量については、1996～1998 年では中央値は 65 Gy であったが、1999～2001 年には 69 Gy と増加していた。米国での同様の調査報告では、前立腺に対して 72 Gy 以上照射されている割合は、1989 年では 3.5%、1994 年では、2.8%

であったが、1999年では44.9%と急増している<sup>22)</sup>。現在のわが国の前立腺への投与線量は米国より少ないが、社会的な背景や組織学的分化度などの患者背景が異なっており、米国のように変化していくかどうかは、今後の調査を待たねばならない。

#### 4 おわりに

めざましい技術開発に支えられて、放射線治療は日々進歩しており、治療後の生活の質を良好に保つことができる放射線治療の重要性はますます高まるものと考えられる。残念ながら日本の前立腺癌放射線治療に関するエビデンスは少ないが、今後の成果が期待される。

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## Radical External Beam Radiotherapy for Clinically Localized Prostate Cancer in Japan: Changing Trends in the Patterns of Care Process Survey Between 1996-1998 and 1999-2001

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and JAPANESE PATTERNS OF CARE STUDY  
WORKING SUBGROUP OF PROSTATE CANCER

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**Abstract.** *Background:* This report presents results of a study delineating changing trends in radical external beam radiotherapy usage for prostate cancer between the 1996-1998 and 1999-2001 Patterns of Care Study (PCS) survey periods in Japan. *Materials and Methods:* Out of the 694 patients comprising the 1996-1998 and 1999-2001 PCS surveys, the current study analyzed data for 444 patients with clinically localized prostate cancer treated with external beam radiotherapy (1996-1998 PCS: 161 patients; 1999-2001 PCS: 283 patients). *Results:* Significantly higher percentages of patients had earlier T stages (T1-T2: 48.2%) and well-differentiated tumors (23.6%) between 1999 and 2001 than between 1996 and 1998 (T1-T2: 34.6%, well-differentiated tumors: 15.1%). Although only 5.9% of patients were treated with radiotherapy by their own choice during 1996-1998, a larger proportion (26.5%) chose this treatment during 1999-2001. The median radiation dose was 65.0 Gy during 1996-1998, increasing to 68.4 Gy during 1999-2001. Moreover, the incidence of total treatment doses of  $\geq 70$  Gy was higher during 1999-2001 (38.0%) than during 1996-1998 (17.5%). On the other hand, the percentage of patients receiving conformal therapy during 1996-1998 (49.1%) was almost the

same as during 1999-2001 (50.2%). The median numbers of full-time equivalent (FTE) radiation oncologists increased in academic institutions (1.8 in 1996-1998; 2.4 in 1999-2001), while those in non-academic institutions remained low (0.5 in 1996-1998; 0.45 in 1999-2001). *Conclusion:* In Japan, fewer prostate cancer patients treated with radical external beam radiotherapy had advanced diseases. Increasing percentages of patients chose radiotherapy and received increased radiation doses, which might reflect the growing acceptance of radical external beam radiotherapy as a first-line treatment for prostate cancer in Japan.

The Patterns of Care Study (PCS) national survey is a retrospective study designed to establish the national practice process of therapies for selected malignancies over a specific time-period (1-3). In addition to documenting the practice process, the PCS is important in developing and disseminating national guidelines for cancer treatment that help promote a more uniform care process in the country. The PCS is also designed to complement the role of clinical trials in enhancing the standard of care for cancer patients (1, 4).

To improve the quality of radiation oncology, the PCS methodology was imported to Japan from the United States (5, 6). The Japanese PCS Working Group of Prostate Cancer started a nationwide process survey of patients treated with radiotherapy between 1996 and 1998 (7, 8). Subsequently, the Working Group conducted a second PCS of patients treated with radiotherapy between 1999 and 2001, and previously reported preliminary results of this second PCS for prostate cancer patients in Japan treated with radical external beam radiotherapy (9-11).

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*Key Words:* Patterns of Care Study, prostate cancer, radical external beam radiotherapy.

Table I. Patient and disease characteristics.

	PCS		Significance (p)
	1996-1998 (n=161)	1999-2001 (n=283)	
Institutions	82	66	
Age (median, years)	70.4(46.5-89.8)	72.0(49.7-92.2)	0.0677
(mean±SD)	70.8±8.1	71.8±6.6	0.151
KPS (median, %)	90(40-100)	90(50-100)	0.0108
(mean+SD)	87.0±8.9	89.1±7.2	0.0252
Missing	7	8	
Pretreatment PSA level (%)			
median	21.95(0.3-900.0)	19.99(0.6-856.9)	0.9657
mean+SD	51.5±93.5	54.1±99.5	0.5341
<10	41/146(28.1%)	77/268(28.7%)	
10-19.9	25/146(17.1%)	57/268(21.3%)	
≥20	80/146(55.0%)	134/268(50.0%)	
Missing	15	15	
Differentiation			
Well	24/159(15.1%)	62/264(23.6%)	0.0209
Moderate	79/159(50.0%)	93/264(35.2%)	
Poor	46/159(28.9%)	93/264(35.2%)	
Unknown	10/159(6.3%)	16/264(6.0%)	
Missing	2	19	
Gleason combined score (%)			
2-6	11/42(26.2%)	77/171(45.0%)	0.0074
7	18/42(42.9%)	35/171(20.5%)	
8-10	13/42(31.0%)	59/171(34.5%)	
Missing	119	112	
T-stage (%)			
TX-T0	1/159(0.6%)	10/272(3.7%)	0.0022
T1	8/159(5.0%)	22/272(8.1%)	
T2	47/159(29.6%)	109/272(40.1%)	
T3-4	102/159(64.2%)	124/272(45.6%)	
Unknown	1/159(0.6%)	7/272(2.6%)	
Missing	2	11	
N-stage (%)			
NX-N0	136/157(86.6%)	249/270(92.2%)	0.0873
N1	18/157(11.5%)	15/270(5.6%)	
Unknown	3/157(1.9%)	6/270(2.2%)	
Missing	4	13	
Reason for selection of RT (%)			
Patient choice	8/136(5.9%)	71/268(26.5%)	<0.0001
Advanced or high-risk disease	43/136(31.7%)	83/268(31.0%)	
Medical contraindication	7/136(5.2%)	36/268(13.5%)	
Old age	37/136(27.2%)	44/268(16.5%)	
Others	9/136(6.6%)	8/268(3.0%)	
N/A or unknown	32/136(23.5%)	20/268(7.5%)	
Missing	25	15	

KPS=Karnofsky performance status; PSA=prostate-specific antigen; RT=radiotherapy

Over the past 10 years, remarkable changes have occurred in prostate cancer treatment policy in Japan. The number of deaths due to prostate cancer has been on a steep increase, especially in elderly patients. The proportion of prostate cancer deaths in total cancer death also showed an increase from 0.9% in 1960 to 4.2% in 2000 (12). Since entering the prostate-specific antigen (PSA) era, prostate cancers are being detected at earlier stages of disease, offering these early-stage patients a better chance of successful treatment. Moreover, the use of radical external beam radiotherapy for prostate cancer has been rapidly increasing recently, as significant new radiation treatment planning technology and methodology has become available. Therefore, to optimally treat Japanese prostate cancer patients, it is important to accurately delineate the intrinsic changes taking place in the national practice process of radiotherapy for prostate cancer in Japan. In this report, the results of our analysis of changes in the process of care for prostate cancer patients, treated with radical external beam radiotherapy between the 1996-1998 and 1999-2001 survey periods in Japan, are presented.

### Materials and Methods

The 1996-1998 PCS and the 1999-2001 PCS surveys in Japan contain detailed information about a total of 694 patients with prostate cancer treated with radiotherapy during the respective survey periods (1996-1998 PCS: 307 patients; 1999-2001PCS: 387 patients). The PCS surveys were extramural audits that utilized a stratified two-stage cluster sampling design. The Japanese PCS employed an original data format developed in collaboration with the American College of Radiology (ACR, Philadelphia, PA, USA). The PCS surveyors comprised 20 radiation oncologists from academic institutions. For each institution, one radiation oncologist collected data by reviewing patients' charts. To validate the quality of the collected data, the PCS utilized an Internet mailing list including all the surveyors. On-site real-time checks and adjustments of the data input were available to each surveyor and to the PCS committee.

Out of the 694 patients comprising the 1996-1998 and 1999-2001 PCS surveys, patients with a diagnosis of adenocarcinoma of the prostate were eligible for inclusion in the present study, unless they had one or more of the following conditions: i) hormone-refractory cancer; ii) evidence of distant metastasis; iii) concurrent or prior diagnosis of any other malignancy; iv) prior radiotherapy; v) prior prostatectomy. A total of 444 patients with clinically localized prostate cancer treated with radical external beam radiotherapy met these eligibility criteria and were selected for analysis (1996-1998 PCS: 161 patients, 82 institutions; 1999-2001 PCS: 283 patients, 66 institutions).

The criteria for both the 1996-1998 and 1999-2001 institutional stratification have been detailed elsewhere (9, 13,14). In brief, the PCS stratified Japanese institutions into: academic institutions (university hospital or cancer center) and non-academic institutions (other hospitals).

Statistical analyses were performed using the Statistical Analysis System at the PCS data center at Osaka University, Japan (15). Statistical significance was tested using the Chi-square test,

Table II. Treatment characteristics.

	PCS		Significance (p)
	1996-1998 (n=161)	1999-2001 (n=283)	
<b>Radiotherapy</b>			
Energy ( $\geq 10$ MV) (%)			
Yes	98/161(60.9%)	207/279(74.2%)	0.0035
Missing	0	4	
Were portal films or electric portal images used (%)			
Yes	-	211/280(75.3%)	
Missing	-	3	
All field treated each day (%)			
Yes	-	215/283(76.0%)	
CT-based treatment planning (%)			
Yes	130/161(80.8%)	241/282(85.5%)	0.1957
Missing	0	1	
Conformal radiotherapy (%)			
Yes	79/161(49.1%)	142/283(50.2%)	0.8223
Pelvic irradiation (%)			
Yes	69/161(42.9%)	102/283(36.0%)	0.156
Reirradiation dose (cGy)			
A+B (Total)			
Median (range)	6500(2200-7400)	6840(1400-8200)	<0.0001
(mean $\pm$ SD)	6090.9 $\pm$ 990.5	6600.8 $\pm$ 732.0	<0.0001
A			
Median (Min-Max)	6500(2200-7400)	6600(1400-8200)	<0.0001
(mean $\pm$ SD)	6250.9 $\pm$ 976.8	6610.3 $\pm$ 776.5	<0.0001
B			
Median (Min-Max)	5940(3400-7000)	6900(3000-8000)	<0.0001
(mean $\pm$ SD)	5622.4 $\pm$ 885.6	6587.5 $\pm$ 684.1	<0.0001
Hormonal therapy (%)			
Yes	138/160(86.3%)	253/282(89.7%)	0.2685
No	21/160(13.0%)	29/283(10.3%)	
Unknown	1/160(0.63%)	0/283(0%)	
Missing	1	1	
Chemotherapy			
Yes	20/159(12.6%)	17/274(6.2%)	0.0603
No	137/159(86.1%)	255/274(92.3%)	
Unknown	2/159(1.3%)	2/274(0.7%)	
Missing	2	9	

Student's *t*-test and Mann-Whitney *U*-test. A probability level of 0.05 was chosen for statistical significance.

## Results

**Patient and disease characteristics.** The patient and disease characteristics for the 1996-1998 and the 1999-2001 PCS

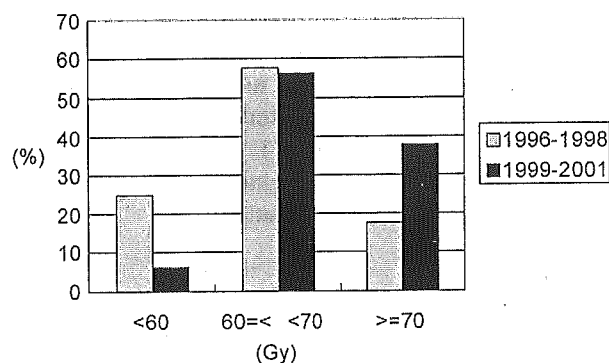


Figure 1. Distribution of external irradiation doses for prostate cancer during the 1996-1998 and 1999-2001 survey periods.

surveys are shown in Table I. Significantly higher percentages of patients had earlier T stages (T1-T2: 48.2%,  $p=0.0022$ ) and well-differentiated tumors (23.6%,  $p=0.0209$ ) between 1999 and 2001 than between 1996 and 1998 (T1-T2: 34.6%, well-differentiated tumors: 15.1%). The reasons for selecting radiotherapy during these different periods are also listed in Table I. During 1996-1998, only 5.9% (8 out of 136) of the patients received radiotherapy through their own choice, compared with the 26.5% (71 out of 268) of patients who chose radiotherapy between 1999 and 2001. This change in the rate of "patient choice" was significantly different ( $p<0.0001$ ).

**Treatment characteristics.** The treatment characteristics are shown in Table II. The frequency of radiation energies  $\geq 10$  MV was significantly higher ( $p=0.0035$ ) in the 1999-2001 PCS (74.2%) compared with the 1996-1998 PCS (60.9%). On the other hand, the rates of CT-based treatment planning ( $p=0.1957$ ) and conformal radiotherapy administration ( $p=0.8223$ ) did not differ significantly between the two survey periods. For instance, the frequency of conformal therapy during 1996-1998 (49.1%) was almost the same as during 1999-2001 (50.2%). The median radiation doses during 1996-1998 and 1999-2001 were 65 Gy and 68.4 Gy, respectively. Stratifying patients by total dosage revealed that 25% of patients received total radiation doses below 60 Gy during the 1996-1998 PCS versus 6.1% during 1999-2001, whereas 38% of patients received total doses  $\geq 70$  Gy during 1999-2001 versus 17.5% during 1996-1998 (Figure 1). Increased radiation doses were predominantly administered in non-academic institutions (Table II).

During both the 1996-1998 and 1999-2001 survey periods, hormonal therapy was commonly used before, during and after radiotherapy for a mean duration of  $1.01\pm 1.04$  years and  $1.31\pm 1.03$  years, respectively (83.6% of patients in 1996-1998; 88.9% of patients in 1999-2001,  $p=0.2685$ ). In contrast, chemotherapy was infrequently administered during both periods (1996-1998: 12.6%; 1999-2001: 6.2%,  $p=0.0603$ ).

*Full-time equivalent (FTE) radiation oncologists.* In the 1996-1998 PCS, the median number of full-time equivalent (FTE) radiation oncologists was 1.8 in academic institutions and only 0.5 in non-academic institutions. In the 1999-2001 PCS, the median number of FTE radiation oncologists in academic institutions rose slightly to 2.4, but remained low at 0.45 in non-academic institutions.

## Discussion

The current study indicates that, in Japan, significantly higher percentages of patients had early primary stage disease and well-differentiated tumors during 1999-2001 than during 1996-1998. These results suggest that the likelihood of earlier-stage prostate cancer patients being treated with radiotherapy is greater than ever before in Japan. In the United States, most of the prostate cancer patients have early-stage tumors and radiotherapy has been recognized as a first-line therapy for prostate cancer (16-18). Because of the prevailing use of PSA and the increasing number of patients treated with radiotherapy in Japanese institutions (19), the opportunities for treating early-stage prostate cancer patients with radical external beam radiotherapy should increase even more in the future.

The current study also revealed a remarkable change in the selection criteria for radiotherapy in Japan between the 1996-1998 and 1999-2001 survey periods. Only 6.6% of the patients were treated with radiotherapy through their own choice in 1996-1998, whereas 26.5% of patients chose radiotherapy in 1999-2001. External beam radiotherapy did not become a popular treatment modality for prostate cancer in Japan until the end of the 1990s. A strong surgical tradition and an inadequate number of radiation oncology centers prevented earlier dissemination of this type of therapy. However, in conjunction with significant improvements in the availability of new radiation treatment planning technology and methodology, Japanese patients are becoming increasingly aware of the effectiveness of radiotherapy for prostate cancer (20). Therefore, the increasing percentage of patients choosing radiotherapy might reflect growing acceptance of radical external beam radiotherapy as a first-line therapy for prostate cancer patients in Japan.

Moreover, the radiotherapy strategy appears to have changed between the 1996-1998 and 1999-2001 survey periods. Radiation doses were higher in the 1999-2001 PCS (median, 68.4 Gy) than in the 1996-1998 PCS (65 Gy). The percentage of patients receiving radiation doses below 60 Gy dropped from 25.0% during 1996-1998 to only 6.1% during 1999-2001 (Figure 1). Conversely, the percent of patients treated with total doses of >70 Gy increased from 17.5% during 1996-1998 to 38.0% during 1999-2001, indicating that lower radiation doses were more common in the first period,

while higher doses prevailed in the second. The U.S. PCS results indicate that many prostate cancer patients have been treated with total doses of  $\geq 70$  Gy in the United States (18, 21). The use of increasing radiation doses in Japan might reflect the widespread dissemination of clinical trial results (22, 23), as well as a growing acceptance by radiation oncologists and urologists of radical external beam radiotherapy as first-line treatment for prostate cancer (24).

However, the national practice process of radiotherapy in Japan reflects structural immaturity, especially in terms of equipment and personnel. The rates of CT-based treatment planning and conformal radiotherapy administration, technology that not only improves the target volume dose distribution but also concomitantly reduces the normal tissue dose (25), did not significantly differ between the 1996-1998 and 1999-2001 survey periods. It is particularly noteworthy that the conformal therapy rates remained low (approximately 50%) during these periods. The 1999 U.S. PCS indicated that 80% of patients were treated with conformal therapy in the United States (22). With regard to personnel, the median number of FTE radiation oncologists slightly increased in academic institutions, but remained low in non-academic institutions. However, publication data documenting a progressive increase in the number of prostate cancer patients treated with radiotherapy has increased in every institution (19) demonstrates a need for Japanese institutions, both academic and non-academic, to upgrade their radiation equipment and to recruit more radiation oncologists.

By comparing the results of the 1996-1998 PCS and 1999-2001 PCS surveys, we can delineate the changes in the process of care for prostate cancer patients treated with radiotherapy in Japan. The study data indicate a trend towards less advanced diseases from 1999-2001 to 1996-1998 and suggest that radical external beam radiotherapy is gaining acceptance as first-line treatment for prostate cancer in Japan.

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## Radical External Beam Radiotherapy for Clinically Localized Prostate Cancer in Japan: Differences in the Patterns of Care between Japan and the United States

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and THE JAPANESE PATTERNS OF CARE STUDY WORKING SUBGROUP OF PROSTATE CANCER

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**Abstract.** *The current study focused on the differences in the patterns of care between Japan and the United States for clinically localized prostate cancer patients treated with radical external beam radiotherapy. Materials and Methods: Results from the 1999-2001 Japanese Patterns of Care Study (PCS) survey were compared with those of the 1999 PCS in the United States. In addition, the changing trends in the patterns of care between Japan and the United States were also analyzed. Results: Patients in Japan were found to have more advanced primary disease than patients in the United States: with higher PSA levels, advanced T stages and a Gleason combined score of 8-10. These patient characteristics in both countries have not changed from previous PCS studies. The prescribed dose of radiotherapy to the primary tumor was significantly higher in the United States and there was a rapid increase in patients treated with higher prescription dose levels ( $\geq 72$  Gy) in the United States, while only a small number of patients received these dose levels in Japan. Hormonal therapy was used more frequently in Japan than in the United States, and the percentage of patients receiving hormonal therapy has remained high for several years in Japan. Furthermore, most of the patients in the favorable risk group in Japan were treated with hormonal therapy, contrary to*

*those in the United States. Conclusion: Japanese prostate cancer patients treated with radical external beam radiotherapy were found to have more advanced disease than those in the United States and these trends have continued for the last few years. Patterns of care for prostate cancer in Japan are considerably different from those in the United States, especially in terms of the radiation dose and the use of hormonal therapy. Moreover, the changing trends in the patterns of care are also different between the two countries.*

The Patterns of Care Study (PCS) national survey is a retrospective study designed to establish national practice processes for selected malignancies over a specific time-period (1-3). In addition to documenting the practice process, the PCS is important in developing and disseminating national guidelines for cancer treatment that help promote a high-quality process of care in the country. The PCS is also designed to complement the role of clinical trials in enhancing the standard of care for cancer patients (1, 4).

To improve the quality of radiation oncology, the PCS was imported to Japan from the United States (5, 6). The Japanese PCS Working Group of Prostate Cancer started a nationwide survey for patients who underwent radiotherapy between 1996 and 1998 (7, 8). Subsequently, a second PCS of Japanese patients treated between 1999 and 2001 was conducted, for which the results concerning radical external beam radiotherapy for prostate cancer patients have been reported (9-12).

In Japan, the number of deaths due to prostate cancer has been increasing steeply, especially in elderly patients. The proportion of prostate cancer deaths in total cancer deaths also increased from 0.9% in 1960 to 4.2% in 2000 (13). Since

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**Key Words:** Patterns of care study, prostatic carcinoma, radiation therapy, hormone therapy.



entering the prostate-specific antigen (PSA) era, clinicians are detecting disease at an earlier stage, and the rates of successful treatment for early-stage patients are at historical highs. Moreover, radiotherapy has become much more common because a significant amount of new treatment planning technology and methodology has become available. Therefore, the optimal management of radiotherapy for prostate cancer patients has become a major concern in Japan. However, national practice processes have not been properly evaluated due to limited information. In July 2002, PCS audits for prostate cancer patients treated between 1999 and 2001 commenced, and data were collected for 283 patients who received radical external beam radiotherapy. Here, the results of the Japanese PCS study were compared with those of the U.S. PCS study and the differences in the patterns of care between Japan and the United States were identified. In addition, the changing trends in the patterns of radiotherapy for prostate cancer in these countries were compared.

**Materials and Methods**

The 1999-2001 Japanese PCS consisted of an extramural audit survey of 66 institutions using stratified 2-stage cluster sampling (2). Data were collected for 528 patients with prostate cancer who received radiotherapy. The PCS group developed an original data format in collaboration with the American College of Radiology (ACR, Philadelphia, PA, USA). The following patient eligibility criteria were used: prostatic adenocarcinoma without evidence of distant metastasis; radiotherapy between 1999 and 2001 with no prior radiotherapy; no concurrent or prior diagnosis of another malignancy. Patients who had prior prostatectomy and patients with hormone-refractory cancer were excluded from the analysis. The PCS surveyors were 20 radiation oncologists from academic institutions. For each institution surveyed, one radiation oncologist visited and surveyed data by reviewing the patients' charts. In order to validate data quality, the PCS utilized an internet mailing list including all the surveyors. On-site real-time checks and adjustments of the data input were available to each surveyor and to the PCS committee. Among the 528 patients identified, 283 patients who received radical external beam radiotherapy were selected for analysis, and the results for these patients are reported.

In the current study, the results of the PCS in Japan (1999-2001) were compared with those of the PCS in the United States (1999). Regarding risk, the 1999 U.S. PCS identified the following as adverse features: PSA >10 ng/mL; Gleason combined score >6; and T stage ≥3. On this basis, the U.S. PCS categorized patients into the following risk groups: favorable – zero adverse features; intermediate – one adverse feature; unfavorable – 2 or more adverse features (14). Because data for the Gleason combined score were missing for 40% (112/283) of our study patients, we substituted tumor differentiation for the Gleason combined score as one of the adverse features. Thus, the set of adverse features for Japanese patients was the following: PSA >10 ng/mL; poorly-differentiated disease; T stage ≥3. Japanese patients were then categorized into the following risk groups: favorable – zero adverse features; intermediate – one adverse feature; unfavorable – 2 or more adverse features.

Table I. Patient and disease characteristics: comparison of PCS results between Japan and the United States

	Japan/1999-2001	United States/1999*
No. of institutions	76	58
No. of patients	283	392
<b>Patient characteristics</b>		
Age (years)		
Median (Min-Max)	72 (49-92)	71.0 (49-86)
Mean	71.8±6.6	70.8
Pretreatment PSA level (ng/ml)		
Med (Min-Max)	20.0 (0.3-856.9)	-
mean±SD	90.0±7.1	-
<10	77/268 (28.7%)	60.5%
10-20	57/268 (21.3%)	23%
≥20	134/268 (50.0%)	15.50%
Missing	15	1%
Gleason combined score		
2-6	77/171 (45.0%)	54.3%
7	35/171 (20.5%)	25.8%
8-10	59/171 (34.5%)	18.8%
Missing	112	1.1%
T stage		
TX-T0	10/272 (3.7%)	7.8%
T1	22/272 (8.1%)	43.9%
T2	109/272 (40.1%)	33.7%
T3-4	124/272 (45.6%)	6.8%
Unknown	7/272 (2.6%)	7.8%
Missing	11	-
Risk group (%)		
Favorable	36/248 (14.5%)**	38.3%***
Intermediate	87/248 (35.1%)**	37.7%***
Unfavorable	125/248 (50.4%)**	24.0%***
Missing	35	-
<b>Treatment characteristics</b>		
Energy (>10 MV) (%)		
Yes	197/265 (74.3%)	73.0%
Missing	18	-
CT-based treatment planning		
Yes	241/282 (85.5%)	95.0%
Missing	1	-
Conformal therapy		
Yes	120/279 (43.0%)	80.0%
Missing	4	-
Radiation dose (cGy)		
Median (Min-Max)	6840 (1400-8200)	-
mean±SD	6602.9 + 731.1	-
Missing	1	-
Higher prescription dose levels (≥72 Gy)		
Yes	21/282 (7.5%)	43.0%
Missing	1	-
Administration of pelvic irradiation		
Yes	93/282 (33.0%)	23.2%
Missing	1	-
Hormonal therapy		
Yes	253/282 (89.7%)	51.3%
Missing	1.0	-

\*Zelevsky *et al*: Int J Radiat Oncol Biol Phys 59: 1053-1106, 2004. PSA = prostate-specific antigen. \*\*Favorable = zero adverse feature; Intermediate = one adverse feature; Unfavorable = 2 or more adverse features. Adverse features: PSA >10 ng/mL; Gleason combined score >6; and T stage ≥3. \*\*\*Favorable = zero adverse features; Intermediate = one adverse feature; Unfavorable = 2 or more adverse features. Adverse features: PSA >10 ng/mL; poorly-differentiated; and T stage ≥3.

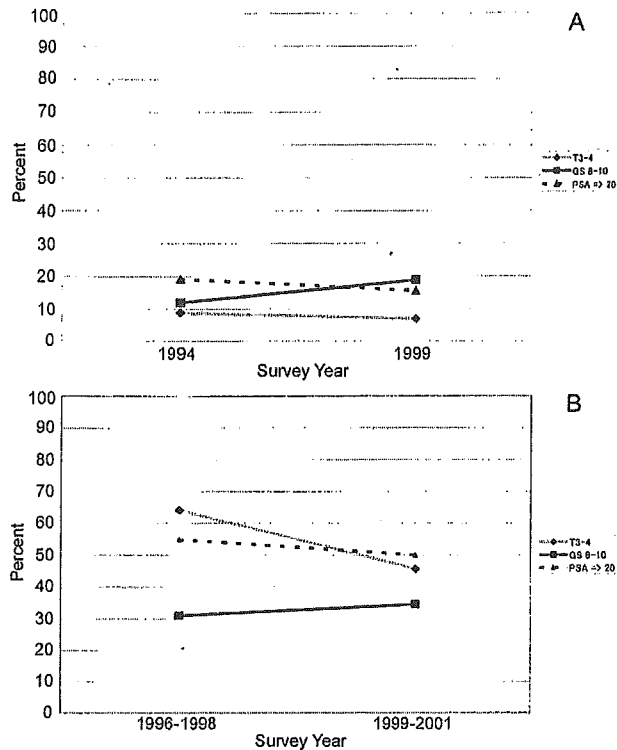


Figure 1. Changing trend in disease characteristics in Japan and the United States. In the United States, the proportions of T3-4, Gleason score of 8-10, and PSA  $\geq 20$  ng/mL were all below 20% in the periods 1994 and 1999 (Figure 1A). On the other hand, in Japan, the proportions of these adverse factors were all over 30% in the periods 1996-1998 and 1999-2001 (Figure 1B).

The differences in the changing trends in the patterns of care between Japan and the United States were also analyzed. Results of the 1996-1998 PCS in Japan (7) and the 1994 PCS in the United States (14, 15) were used as a baseline for the patterns of care.

Statistical analyses were performed using the Statistical Analysis System at the PCS data center at Osaka University, Japan (16). Statistical significance was tested using the Chi-square test and the Student's *t*-test. A *p* value  $< 0.05$  was considered statistically significant.

## Results

**Comparison of patient characteristics between Japan and the United States.** Comparisons of patient characteristics between Japan (1999-2001) and the United States (1999) are shown in Table I. The patients in Japan were found to have more advanced primary disease than those in the United States with higher PSA levels ( $\geq 20$  ng/mL), advanced T stages (T3-4) and a Gleason combined score of 8-10. Regarding the risk groups, the percentage of Japanese patients with favorable, intermediate and unfavorable tumors were 14.5%, 35.1% and 50.4%, respectively, compared to 38.3%, 37.7% and 24.0%, respectively, in the United States.

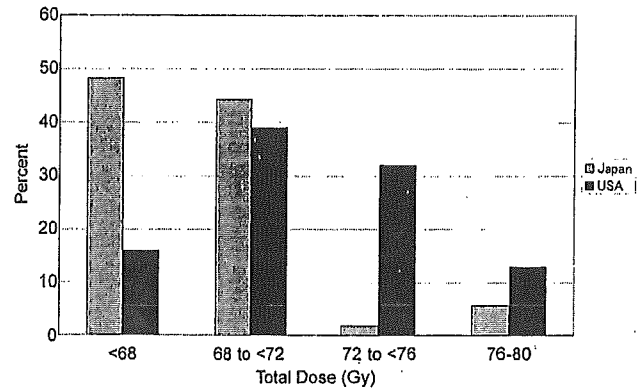


Figure 2. Radiation dose distribution in Japan and the United States. The distributions of total dose to the prostate in the United States were significantly higher ( $p < 0.00001$ ) than those in Japan.

By comparing the results from the previous PCS (1996-1998 Japan PCS and 1994 U.S. PCS), Japanese patients have continued to exhibit advanced disease for several years, while the proportion of U.S. patients with advanced disease has remained low from 1994 to 1999 (Figure 1A and 1B).

**Comparison of patterns of radiotherapy.** With regard to technique, conformal radiotherapy was administered to 43% of the patients in Japan and to 80% of the patients in the United States (Table I). The distributions of total radiation dose to the prostate in the United States were significantly higher ( $p < 0.00001$ ) than those in Japan (Figure 2). In the United States, there was a rapid increase in patients treated with higher prescription dose levels ( $\geq 72$  Gy) compared to the 1994 PCS results and almost half (44.5%) of patients were treated with these higher doses in 1999 (Figure 3A). In contrast, only a small number of patients (7.5%) received these dose levels in Japan between 1996-1998 and 1999-2001 (Figure 3B). Whole pelvic radiation therapy (WRT) was less frequently performed in both countries (33% of the patients in Japan and 23.2% of the patients in the United States).

The analysis of changing trends in the higher prescribed radiation doses and radiation field (use of WRT) indicates that a marked change in these parameters occurred in the United States between 1994 to 1999, while only moderate or minor changes occurred in Japan between 1996-1998 and 1999-2001 (Figure 3A and 3B).

**Comparison of patterns of hormonal therapy.** With regard to hormonal therapy, 89.7% of the patients in Japan and 51.3% in the United States received hormonal therapy. The mean duration of hormonal therapy in Japan was  $1.4 \pm 1.0$  years. The percentages of patients with favorable, intermediate and unfavorable tumors treated with hormonal therapy in Japan were 72.0%, 91.8% and 91.1%, respectively, compared to

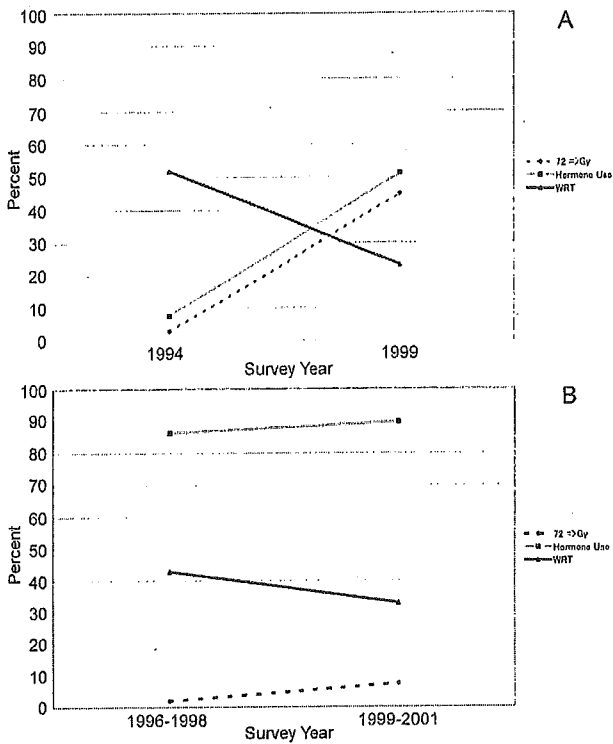


Figure 3. Changing trends in the treatment characteristics in Japan and the United States. There were marked changes concerning the percentage of higher prescribed radiation doses ( $\geq 72$  Gy), whole pelvic radiation therapy (WRT) and hormone use in the United States from 1994 to 1999 (Figure 3A). In contrast, only moderate or minor changes in the proportions of patients undergoing these treatments were observed in Japan between 1996-1998 and 1999-2001 (Figure 3B).

31%, 54% and 79%, respectively, in the United States (Figure 4). Most of the patients (72.0%) in the favorable risk group in Japan were treated with hormonal therapy, while only 31% of these patients received hormonal therapy in the United States. On the other hand, 80-90% of patients in the unfavorable risk group were treated with radiotherapy in conjunction with hormonal therapy in both Japan (91.1%) and the United States (79%).

The analysis of changing trends in the use of hormone therapy indicated that a rapid increase was observed in the United States from 1994 to 1999, while only minor changes in the proportion of patients receiving hormonal treatment were observed in Japan between 1996-1998 and 1999-2001 (Figure 3A and 3B).

### Discussion

The results of the current study indicate that patients in Japan had more advanced diseases compared to patients in

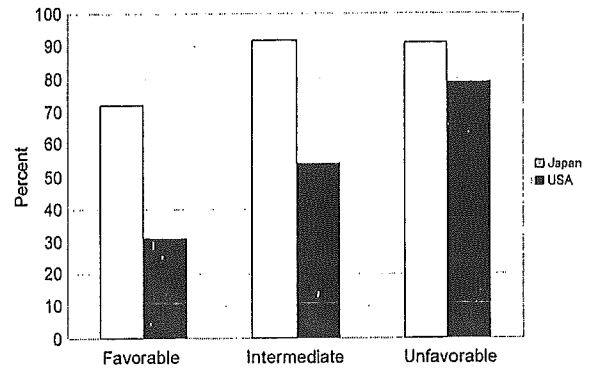


Figure 4. Hormonal therapy distribution according to the risk groups for prostate cancer patients in Japan and in the United States.

the United States. Japanese patients had higher pretreatment PSA levels, advanced T stage and a Gleason score of 8-10 such that the proportion of Japanese patients in the unfavorable risk group was 50.4% compared to 24% in the United States. Moreover, these trends for more advanced disease in Japan compared to the United States continued for several years (Figure 1A and 1B). These results indicate that higher proportions of patients with advanced disease were treated with radical external beam radiotherapy in Japan than in the United States. However, it is not known whether these differences between patients in Japan and the United States resulted from differences in access to medical care or to biological differences within the tumors themselves. Further investigation of the different disease characteristics between individuals in the two countries would be informative.

The current study also indicates that there were many differences in the patterns of radiotherapy between Japan and the United States. The radiation doses employed in the United States were significantly higher than those used in Japan, with almost half (44.5%) of the patients in the United States being treated with higher prescription dose levels ( $\geq 72$  Gy). This practice in the United States probably reflects the penetration into clinical practice of various reports published in the 1990's indicating that higher radiation doses were associated with a statistically significant improvement in outcome (17, 18). On the other hand, a minority of patients in Japan were treated with higher doses ( $\geq 72$  Gy), with only 7.5% receiving these higher doses in the period 1999-2001. One reason for this may be the lower incidence of conformal therapy. Conformal radiotherapy was administered to 85% of patients in the United States while only 43% of the Japanese patients received this treatment. The processes in Japanese institutions were closely related to structural

immaturity in terms of equipment (9-12). Therefore, in order to provide good quality radiotherapy in Japan, facilities need appropriate treatment planning capability. Modern radiotherapy requires CT-based treatment planning and conformal therapy in order to improve the target dose distribution, while concomitantly reducing the dose to normal tissues (19). Another reason may be the high incidence of hormonal therapy in Japan. At present, many Japanese radiation oncologists may consider the higher dose levels ( $\geq 72$  Gy) unnecessary for prostate cancer patients when combined with long-term hormonal therapy.

With regard to the patterns of hormonal therapy, the combination of radiotherapy with hormonal therapy was almost routinely (89.7% of the patients surveyed) administered to Japanese patients treated between 1999 and 2001 compared to 51.3% in the United States in 1999. The percentage of patients receiving hormonal therapy remained high in Japan in the periods 1996-1998 and 1999-2001, while there was a rapid increase in the use of hormonal therapy in the United States from 1994 to 1999.

Furthermore, the administration of hormonal therapy to favorable risk patients was considerably different in Japan compared to the United States as only 30% of these patients in the United States, were treated with hormonal therapy (Figure 1). Several studies from the United States have indicated that radical radiotherapy alone could control the disease in patients with a favorable risk status. Zietman *et al.* indicated that a total dose of 70 Gy was sufficient to control the disease when the pretreatment PSA level was less than 10 ng/mL (20). Hanks *et al.* found that prostate cancer patients with a pretreatment PSA level  $< 10$  ng/ml did not benefit from a dose escalation above 70 Gy (21). Therefore, radical external beam radiotherapy without hormonal therapy has been the primary treatment for patients in the United States with favorable risk diseases. On the other hand, 72% of the patients in the favorable risk group in Japan were treated with long-term hormonal therapy (Figure 1). The high rate of health insurance coverage may explain the frequent administration of hormonal therapy in Japan (22). However, hormonal therapy was found to be unnecessary for favorable risk patients in the United States (20, 21). Therefore, radical external beam radiotherapy without hormonal therapy should also be the treatment of choice for favorable risk patients in Japan.

In conclusion, a comparison of the Japanese and U.S. PCS results revealed several differences in the patterns of care between these two countries. Higher proportions of patients with advanced disease were treated with radical external beam radiotherapy in Japan compared to the United States, and this trend has continued for the last few years. The patterns of care for prostate cancer in Japan are significantly different from those in the United States,

especially in terms of radiation dose and the use of hormonal therapy. Moreover, the changing trends in the patterns of care are also different between these countries. In the United States, radiotherapy for prostate cancer has become widely applied as an established treatment, while it was still developing in Japan during the period of the national survey. Repeat surveys and point-by-point comparisons with results from other countries, such as the United States, will demonstrate how external beam radiotherapy for prostate cancer has been developed and optimized for patients in Japan.

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