Table 1. Patient and disease characteristics

	Type of institutions		Significance (*P*)
	A (n = 165)	B (n = 118)	
Age (years)			
Median (range)	72 (58–92)	71 (49–89)	0.2248
KPS (%)			
Median (range)	90 (70–100)	90 (50–100)	0.0002
Missing	5	3	
Pretreatment PSA level (ng/ml, %)			
Median (range)	19.0 (0.6–856.9)	23.0 (0.8–660)	
mean ± SD	47.2 ± 90.7	64.2 ± 110.9	0.5364
<4	4/160 (2.5%)	4/108 (3.7%)	
⩽4 to <10	46/160 (28.8%)	23/108 (21.3%)	
⩽10 to <20	34/160 (21.2%)	23/108 (21.3%)	0.5364
⩾20	76/160 (47.5%)	58/108 (53.7%)	
Missing	5	10	
Differentiation			
Well	33/156 (21.2%)	29/108 (26.9%)	
Moderate	57/156 (36.5%)	36/108 (33.3%)	0.6401
Poor	55/156 (35.3%)	38/108 (35.2%)	
unknown	11/156 (7.0%)	5/108 (4.6%)	
Missing	9	10	
Gleason combined score (%)			
2–6	32/70 (45.7%)	16/47 (34.0%)	
7	13/70 (18.6%)	13/47 (27.7%)	0.3624
8–10	25/70 (35.7%)	18/47 (38.3%)	
Missing	31	33	
Clinical T stage			
TX	6/162 (3.7%)	3/110 (2.7%)	
T0	0/162 (0.0%)	1/110 (0.9%)	
T1	14/162 (8.6%)	8/110 (7.3%)	
T2	58/162 (35.8%)	51/110 (46.4%)	0.5228
T3	72/162 (44.4%)	37/110 (33.6%)	
T4	8/162 (4.9%)	7/110 (6.4%)	
Unknown	4/162 (2.4%)	3/110 (2.7%)	
Missing	3	8	
Clinical N stage			
NX	1/162 (0.6%)	5/108 (4.6%)	
N0	150/162 (92.6%)	93/108 (86.1%)	
N1	9/162 (5.6%)	6/108 (5.6%)	0.0794
Unknown	2/162 (1.2%)	4/108 (3.7%)	
Missing	3	10	
*Risk group (%)			
Favorable	24/152 (15.8%)	12/96 (12.5%)	
Intermediate	50/152 (32.9%)	37/96 (38.5%)	0.5950
Unfavorable	78/152 (51.3%)	47/96 (49.0%)	
Missing	13	22	
Reason for selecting radiotherapy			
Patient preference	41/152 (27.0%)	30/116 (25.9%)	
Advanced or high-risk disease	41/152 (27.0%)	42/116 (36.2%)	
Medical contraindication	21/152 (13.8%)	15/116 (12.9%)	0.0218
Old age	27/152 (17.8%)	17/116 (14.7%)	
Others	2/152 (1.3%)	6/116 (5.2%)	
N/A or Unknown	17/152 (11.2%)	3/116 (2.6%)	
Missing	13	2	

KPS = Karnofsky performance status; PSA = prostate-specific antigen
*Favorable = meet all conditions below; Intermediate = meet 2 conditions; Unfavorable = meet only 1 or no conditions
(1) PSA ⩽ 10 (2) not poorly differentiation (3) T stage < 3
Institution types: A, academic; B, non-academic.

prostate gland, seminal vesicle and pelvic lymph nodes) was used in 26.2% of patients in A institutions and 42.4% of patients in B institutions (P = 0.0087). The median number of full-time equivalent (FTE) radiation oncologists was 2.4 in A institutions but only 0.4 in B1 institutions (P < 0.0001).

Hormonal therapy was commonly used before, during and after radiotherapy for a mean duration of 1.4 ± 1.0 years (A: 89.0%, B: 90.7%). Luteinizing hormone-releasing hormone (LH-RH) agonists and antiandrogens were frequently used as hormonal agents. In contrast, the use of chemotherapy was uncommon (A: 7.9%, B: 3.6%).

The percentages of patients with favorable, intermediate and unfavorable tumors were 15.2%, 37.0% and 47.9%, respectively. The percentages of patients with favorable, intermediate and unfavorable tumors treated with hormonal therapy were 72.2%, 93.1% and 92.0%, respectively. The use of hormonal therapy did not significantly differ between A and B institutions (Fig. 3, P = 0.12). Many patients with a favorable prognosis (A: 62.5%, B: 91.7%, P = 0.0655) received hormonal therapy, and most patients with unfavorable risk (A: 93.6%, B: 91.6%) also received hormonal therapy.

DISCUSSION

The 1999–2001 PCS revealed that more than 80% of Japanese patients treated with radical external beam radiotherapy had intermediate or unfavorable risk diseases, and that institutional type did not significantly affect disease characteristics, such as pretreatment PSA levels, Gleason combined score and T stage. In the current study, the higher rate of missing data in Gleason combined score was observed. During the period between 1999 and 2001, many Japanese physicians may consider the Gleason combined score less important for prostate cancer treatment.

Table 2. Treatment characteristics

	Type of institutions		Significance (*P*)
	A (n = 165)	B (n = 118)	
Radiotherapy			
Energy (≥10 MV) (%)			
Yes	132/156 (84.6%)	65/109 (59.6%)	<0.0001
Missing	9	9	
CT-based treatment planning (%)			
Yes	150/164 (91.5%)	91/118 (77.1%)	0.0007
Missing	1	0	
Conformal therapy (%)			
Yes	92/163 (56.4%)	28/116 (24.1%)	<0.0001
Missing	2	2	
Usage of portal films or electric portal images (%)			
Yes	146/162 (90.1%)	65/118 (55.1%)	<0.0001
Missing	3	0	
All fields treatment for each day (%)			
Yes	143/165 (86.7%)	72/118 (61.0%)	<0.0001
Pelvic irradiation (%)			
Yes	43/164 (26.2%)	50/118 (42.4%)	0.0087
Missing	1	0	
Radiation dose (cGy)			
Median (range)	6600 (1400–8200)	6900 (3000–8000)	
Mean ± SD	6610.3 ± 766.5	6592.6 ± 681.9	<0.0001
Missing	1	0	
Higher prescription dose levels (≥72 Gy) (%)			
Yes	18/164 (11.0%)	3/118 (2.5%)	0.2482
Missing	1	0	
Hormonal therapy			
Yes	146/164 (89.0%)	107/118 (90.7%)	0.6520
Missing	1	0	
Content (%)			
Orchiectomy	19/153 (12.4%)	13/97 (13.4%)	0.4382
Missing	12	21	
Estrogen agent	7/145 (4.8%)	23/98 (23.5%)	0.0008
Missing	20	20	
LH-RH agonist	121/153 (79.1%)	94/109 (86.2%)	0.4297
Missing	12	9	
Antiandrogen	104/155 (67.1%)	80/108 (74.1%)	0.2516
Missing	10	10	
Period (%)			
Before RT	131/155 (84.5%)	94/109 (86.2%)	0.6978
Missing	10	9	
During RT	122/155 (78.7%)	101/110 (91.8%)	0.0277
Missing	10	8	
After RT	115/154 (74.7%)	87/110 (79.1%)	0.0001
Missing	11	8	
Duration* (Years)			
Median (range)	0.97 (0.1–4.8)	1.27 (0.2–4.5)	
Mean ± SD	1.4 ± 1.3	1.5 ± 1.1	0.4822
Chemotherapy			
Yes	13/164 (7.9%)	4/110 (3.6%)	0.3418
Missing	1	8	

CT = computed tomography; RT = radiotherapy; LH-RH = Lutein hormone-releasing hormone.
Institution types: A, academic; B, non-academic.

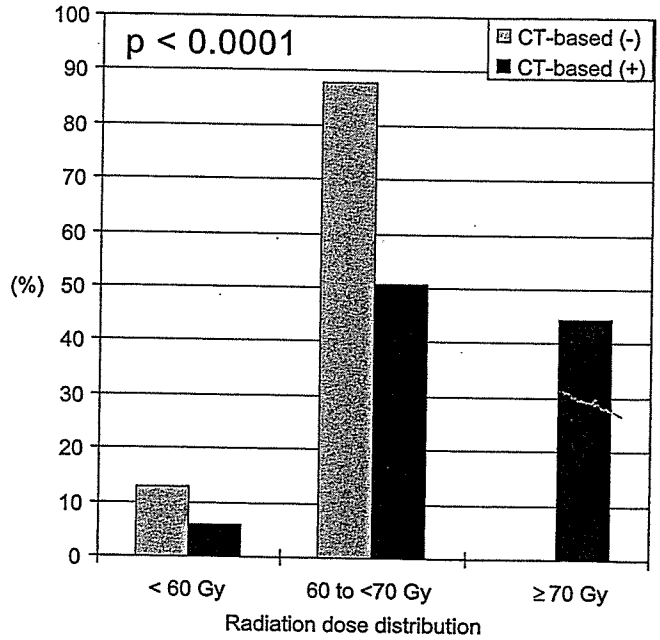

Figure 1. Radiation dose distribution for Japanese prostate cancer patients as a function of use of CT-based treatment planning.

The current study also demonstrated significant variations in radiotherapy practice patterns according to the type of institution, specifically in the beam energies utilized and in the use of a CT-based treatment planning and conformal therapy. These practice differences indicate that the quality of radiotherapy was significantly higher in academic institutions than in non-academic institutions. The lower rate of pelvic irradiation in academic institutions than in non-academic institutions may also reflect the more frequent use of CT-based treatment planning and conformal therapy in academic institutions. Similarly, two other Japanese PCS studies of esophageal cancer and cervical cancer have also identified significant differences in treatment patterns between academic and non-academic institutions (5,6).

Practice processes in non-academic institutions in Japan were closely related to structural immaturity, especially in

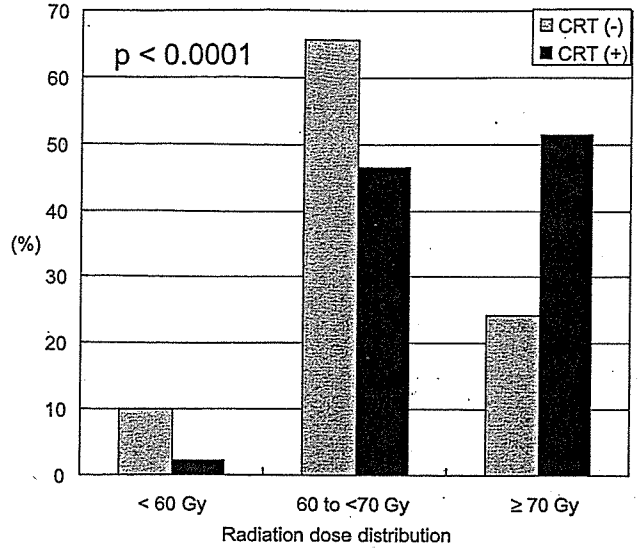

Figure 2. Radiation dose distribution for Japanese prostate cancer patients as a function of use of conformal therapy (CRT).

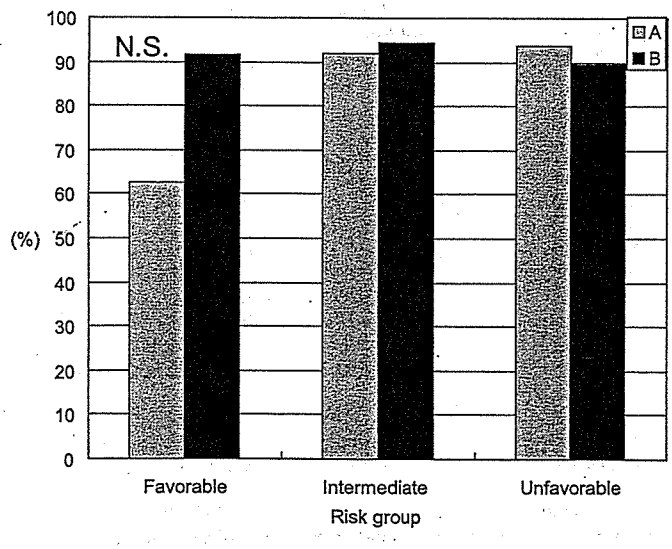

Figure 3. Hormonal therapy distribution as a function of disease risk for A (academic) and B (non-academic) institutions. Favorable meets all conditions below. Intermediate meets 2 conditions. Unfavorable meets only 1 or no conditions. (1) PSA ≤ 10 (2) not poorly differentiation (3) T stage < 3.

terms of equipment and personnel. Concerning treatment equipment and radiotherapy technique, lower rates of beam energy ≥10 MV, usage of portal films or electric portal images, and all fields treatment for each day were observed in non-academic institutions. Moreover, in non-academic institutions, only 77.1% of patients received CT-based treatment planning and 24.1% of patients received conformal therapy, compared with 91.5% and 56.4%, respectively, in academic institutions. The use of CT-based treatment planning and conformal radiotherapy significantly influenced total radiation dose. In the United States, the overall quality of radiotherapy for prostate cancer has been improving for years and has been higher than that in Japan: 95% of US patients received CT-based treatment planning and 80% received conformal therapy in the 1999 US PCS (15,17–20). On the other hand, radiotherapy for prostate cancer was still developing in Japan during the period when this national survey was conducted. Therefore, in order to provide high-quality radiotherapy in Japan, facilities need appropriate treatment planning capabilities. Modern radiotherapy requires CT-based treatment planning or conformal therapy to improve target dose distribution while reducing normal tissue dose (21).

The 1999–2001 PCS survey also revealed that the median number of FTE radiation oncologists employed by non-academic institutions to manage their many patients was lower than the median number employed by academic institutions (A: 2.4, B: 0.4, $P < 0.0001$). At the same time, the number of patients treated with radiotherapy has continually increased in every institutional type, with an overall increase of 140% over the past 10 years (22). These trends call for increasing the number of FTE radiation oncologists on duty especially in non-academic institutions.

The current study demonstrated the almost routine administration of hormonal therapy (A institutions: 89.0%, B institutions: 90.7%) to Japanese patients treated between 1999 and 2001. Moreover, the percentage of favorable risk patients receiving hormonal therapy remains high in Japan despite the results of several US studies indicating that radical radiotherapy alone can control disease in favorable risk patients. Pollack et al. (23) indicated that a total dose of 70 Gy was sufficient to control disease with a pretreatment PSA level <10 ng/mL. Hanks et al. (24) found that patients with pretreatment PSA < 10 ng/ml did not benefit from dose escalation >70 Gy. Therefore, the primary non-surgical treatment practice for US patients with favorable risk disease is radical external beam radiotherapy without hormonal therapy unlike the practice we identified in Japan. One major reason for the frequent use of hormonal therapy in Japan may be the high rate of health insurance coverage for Japanese people (25). However, in line with current treatment practice in the United States, we propose that radical external beam radiotherapy alone should also be the treatment of choice for favorable risk patients in Japan.

In contrast, a growing body of evidence suggests that radiotherapy with hormonal therapy is more effective than radiotherapy alone for high-risk patients. For instance, the results of various randomized trials by the Radiation Therapy Oncology Group (RTOG) and the European Organization for the Research and Treatment of Cancer (EORTC) demonstrated that combining radiotherapy with hormonal therapy was advantageous for high-risk patients with clinically localized prostate cancer (26,27). The 1999 US PCS reported that 79% of radiotherapy patients with unfavorable risk disease received hormonal therapy in the United States, reflecting the penetration and growing acceptance of clinical trial results demonstrating the efficacy of combination treatment approaches (15). In Japan, the 1999–2001 PCS also found that radiotherapy combined with hormonal therapy represents the standard care for patients with unfavorable risk disease,

with over 90% of such patients receiving combination therapy. Based upon clinical study data and the US PCS data, radiotherapy combined with hormonal therapy for Japanese patients with unfavorable risk disease appears to be a reasonable practice.

In summary, our analysis of the 1999–2001 PCS data revealed that most prostate cancer patients treated in Japan with radical external beam radiotherapy have advanced diseases and that institutional type significantly influences radiotherapy practice patterns. Differences in practice patterns must not be disregarded when they can negatively influence outcome. The impact of these practice differences on outcome should be examined in a future study. The current study also demonstrated that radiotherapy was commonly combined with hormonal therapy regardless of institution type and disease risk group. Therefore, the optimal use of hormonal therapy also needs to be addressed in future studies.

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乳腺疾患の臨床

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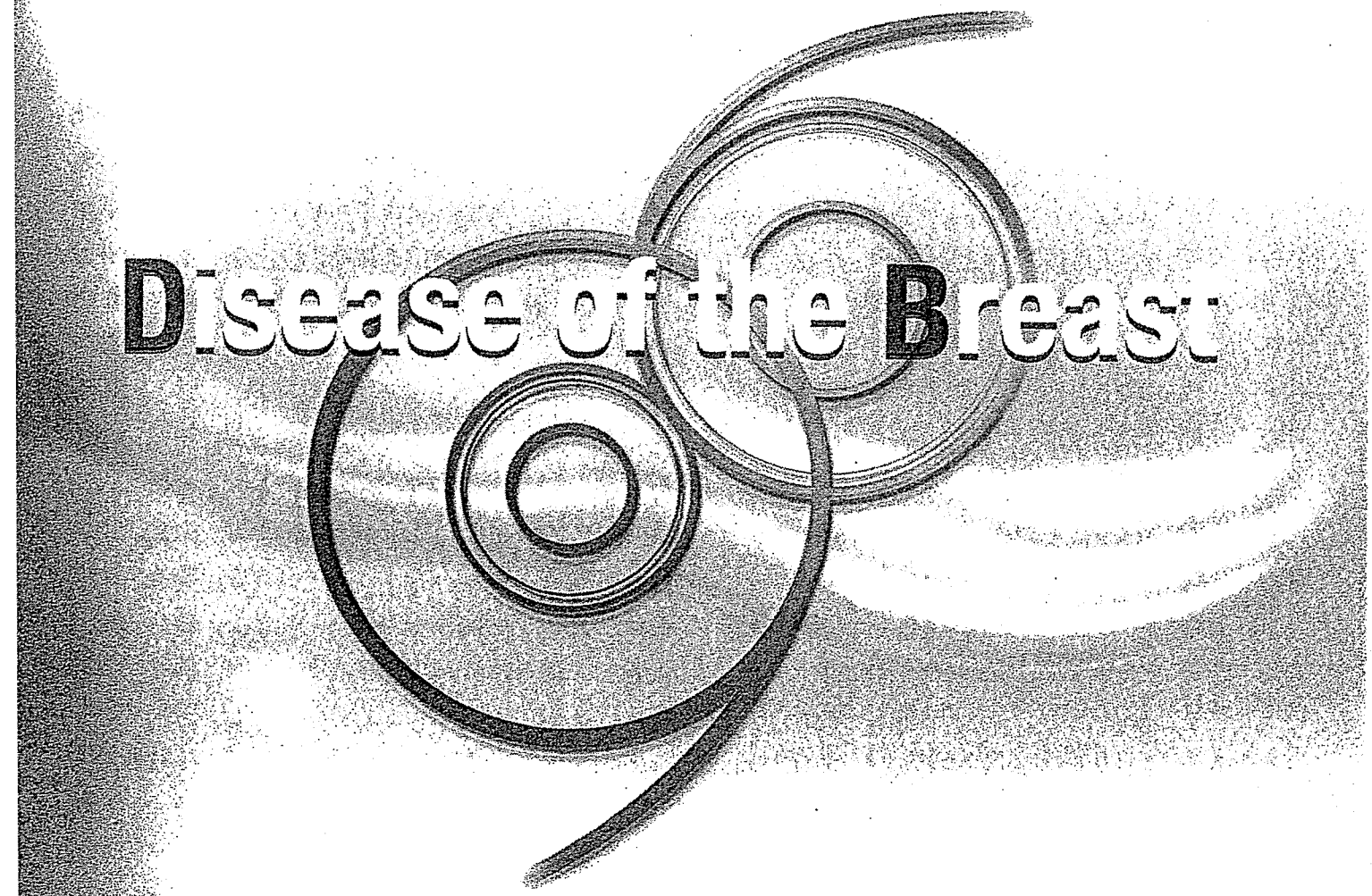

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(執筆順)

4. 骨転移・脳転移の放射線治療

はじめに　乳癌の他臓器転移において最も頻度が高いのは骨転移であり，遠隔転移の約6割を占め，肺，肝，脳転移[1]がこれに続く。放射線治療の対象となるのは主に骨および脳転移であり，放射線治療についてその目的，適応，方法を概説する。

A—骨転移に対する放射線治療

1 乳癌骨転移の特徴と放射線治療

骨転移部位は血流の多い赤色髄に多く，椎体(腰椎，胸椎，頸椎の順)，骨盤骨，肋骨，大腿骨に多く生じる。乳癌骨転移単独例の平均生存期間は28カ月との報告もあり，長期生存も期待可能である[2]。脊椎転移342症例の後ろ向き研究では，原発部位が乳癌であることは，全身状態良好，内臓転移がないことと並んで予後良好因子の一つとされており[3]，QOLの維持を目的とした放射線治療の果たす役割は大きい。

2 放射線治療の目的

骨転移に対する放射線治療の目的は，疼痛の軽減，病的骨折の予防，脊髄圧迫による麻痺の予防と改善である。有痛性骨転移は原則的に放射線治療の適応となるが，無痛性であっても臼蓋部や長管骨，脊椎などの荷重がかかり，運動障害を起こし得る部位に生じた転移に対しては放射線治療の適応がある。一般に骨転移に対する放射線治療では，50～80%に疼痛の緩和が得られ，およそ20～50%の症例には完全除痛が得られると報告されている[4][5]。

3 放射線治療の方法

単純X線写真で溶骨性変化および造骨性変化の範囲，骨シンチグラフィで全身骨の転移部位の検索，CTまたはMRIで骨破壊の程度と骨外病変の範囲を把握した上で治療計画を行う。

日常臨床ではX線シミュレーターを用いて，病変の部位によって症例ごとに1門～多門の照射法を選択する。CTシミュレーターも徐々に普及し，正常臓器の線量を考慮した照射法，範囲設定を正確に把握できるようになった。骨盤骨や肋骨などは腸管や肺への照射をできるだけ避けるよう注意が必要である。

4 疼痛緩和における線量・分割方法

骨転移による疼痛緩和は，根治治療に必要とされる線量より低線量で目的を達することが示されているが，その総線量・分割方法に関して統一した見解はない。

わが国では30Gy/10回/2週が最も浸透した照射法であると思われるが，近年除痛目的として8Gy/1回照射を支持する報告が相次いでおり[6]~[8]，標準治療として広く用いられるものと思われる。Radiation Therapy Oncology Group(RTOG)9714では，長期予後が期待できる乳癌および前立腺癌からの骨転移例のみを対象として，8Gy/1回

照射と30Gy/10回の照射法をランダム化比較し，疼痛緩和率に差を認めず(65% vs 64%)，急性期有害反応の発症は1回照射法で有意に少ないことが示された[8]。

さらに初回照射後の再照射時にも疼痛緩和として1回照射法は有効で，オランダの多施設共同研究[9]では8Gy/1回の照射後に生じた疼痛の再燃に対し再照射で66%の疼痛軽減が得られた。特に乳癌では寛解率が82～89%と良好であった。また，初回に1回照射(4～8Gy)で治療された症例において疼痛の再燃がある場合にも，4Gy/1回の再照射の有用性が報告されている[10]。

5 脊髄圧迫に対する放射線治療

脊椎への転移は，ときに腫瘍の脊柱管内，神経根への浸潤や椎体の病的骨折により脊髄圧迫症状を呈することがある。麻痺の兆候を認めた場合，速やかな治療開始が必要である。可能であれば手術の施行が望ましいが，適応がない場合は放射線治療を早急に開始する。線量・分割方法に関しては遡及的研究であるが，予後不良例には8Gy/1回を，その他の症例には30Gy/10回が推奨されるとしている[11]。照射と高用量のステロイドの併用(デキサメタゾン96mg/日)が有用との報告もみられるが，大量投与による有害事象もあるので注意が必要である[12]。

6 病的骨折に対する放射線治療

CT，MRI検査で荷重のかかる長幹骨の骨皮質に50%以上の破壊がみられた場合，または病変の長軸方向の長さが2.5cm以上に及ぶ場合に病的骨折の危険が高いとされており，外科的固定術を先行した後放射線治療を検討する。線量および分割方法は疼痛緩和目的の照射に準じる。

B 脳転移に対する放射線治療

1 乳癌の脳転移と放射線治療

脳腫瘍全国統計委員会の報告(1996年)では，乳癌は脳転移の原発巣としては肺癌に次いで多い。脳転移を有する症例は基本的に予後不良であり，無治療での予後は約1～2カ月とされる。脳転移例の治療目的は主に症状の緩和となるが，後述する予後不良因子を持たない症例では手術や定位手術的照射などの積極的な治療で予後の改善が期待できる。さらに長期予後が期待できる症例では，全脳照射後の晩期有害反応が問題となる場合もあり，脳転移における放射線治療の方法と適応は，患者の予後因子を十分把握した上で計画する必要がある。

2 脳転移症例の予後因子

RTOGでは，全脳照射に関する3つのランダム化比較試験(RCT)のデータから予後因子を検討し3群に分類した。「全身状態良好(Karnofsky performance status；KPS 70以上)」，「65歳未満」，「原発巣の制御」，「頭蓋外活動性病変なし」のすべてを満たす群(class1)では生存期間の中央値は7.1カ月，全身状態不良(KPS 70未満)の群(class 3)では2.3カ月それ以外すべての症例群(class 2)では4.2カ月であった[13]。

この予後因子を用いた分類は，手術や定位手術的照射を施行する例にも有用である。予後良好群であるclass 1では，脳転移病巣の制御を目的に定位手術的照射や手術などの積極的な治療もされるが，予後が不良なclass 2，3では，まず症状の緩和を目的に全脳照射を行う。

3 全脳照射

転移性脳腫瘍に対する基本的な治療方法であり，その目的は神経症状および頭痛・嘔気など頭蓋内圧亢進による症状の緩和である。全体的な症

状の緩和は50～85%に認め，神経学的改善は約40%に認められるが，予後の著明な改善は期待できない。

a. 照射方法

頭部固定下に左右対向2門で照射する。上方は頭蓋冠より広めの照射野をとり，頭蓋底部は前・中頭蓋窩を完全に含め眼部を遮蔽する。

b. 総線量と分割方法

全脳照射の線量・分割方法は20Gy/5回から50Gy/25回までの種々の放射線照射法が報告されているが，症状の改善率に差がないことからわが国では30Gy/10回が頻用される。

c. 手術と全能照射

RCTの報告から，頭蓋外病変が制御された単発脳転移例に対して全脳照射に手術を併用する有用性が明らかとなった[14]。一方，頭蓋外活動性病変を有する場合には照射単独と比較して生存期間に差がないとする報告が多い。しかし，QOL維持の点から局所制御のもつ意味は大きく，手術可能であった症例には術後全脳照射を行うべきと考えられている。

d. 有害事象

全脳照射施行中における急性期有害事象は一過性の脳圧亢進症状があり，ステロイドやグリセオールの予防的投与を行う。

晩期有害事象としては脳萎縮，白質脳症，脳壊死，正常圧水頭症，内分泌障害などがあるが，その正確な頻度を求めることは困難である。

4 定位手術的照射

定位放射線照射は，患部の高精度固定下で病変に多方向から放射線束を集中させ，選択的に高線量を投与する放射線治療技術である。コバルト60ガンマ線を用いたガンマナイフと，直線加速器（リニアック）によるX線を用いた2つの方法があり，1回照射の場合を定位手術的照射（Stereotactic Radiosurgery；SRS）と総称する。SRSの意義は正常組織に対する影響を少なくした上で転移巣を制御することで，その効果は手術と同等とのコンセンサスが得られている[15]。さらに手術で到達できない深部の治療も可能である。

腫瘍辺縁線量で10～27Gyを投与するが，その治療成績は局所制御率で70～90%と報告されている。先の予後因子分類に従った生存期間では，class 1で16.1カ月，class 2で10.3カ月，class 3で8.7カ月との報告がある[16]。

a. 定位手術的照射の適応

転移性脳腫瘍に対する本法の適応基準は，病変の大きさが3cm以下であり，個数は3～4個以下，全身状態が良好（KPS 70以上），少なくとも3カ月以上の予後が見込まれることなどである。KPSが70未満の全身状態不良例でも，症状改善が期待できる場合には治療対象となり得る。

b. 全脳照射の併用

定位脳照射後の全脳照射の併用に関しても議論が多く，いくつかの後ろ向き研究で脳内制御率は全脳照射併用群に有意に良好であるが，生存期間には差がないと報告されている。併用の有用性を検討したRCTも進行中であり，QOLの評価を加えた今後のエビデンスの蓄積が待たれる。

c. 有害事象

SRSによる急性期有害反応は軽度であることが多く，病変の位置によっても異なるが，30%未満の症例で嘔気，頭痛，軽度のけいれん発作などが生じる。遅発性の反応は治療数カ月後に一部の症例に放射線脳壊死，脳浮腫を認めるが，その頻度は化学療法の併用で増加する可能性がある。

まとめ

骨転移に対する1回照射，脳転移に対する定位手術的照射の普及など，従来の照射手法に加え新たな知見が広まりつつある。新規治療がもつ可能性を過信し，生命予後の改善に関し科学的根拠に乏しい治療戦略が選択され，患者への負担を増や

さないよう熟慮が必要である。

（篠田充功・鹿間直人）

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CLINICAL INVESTIGATION **Lymphoma**

A PROSPECTIVE STUDY OF REDUCED-DOSE THREE-COURSE CHOP FOLLOWED BY INVOLVED-FIELD RADIOTHERAPY FOR PATIENTS 70 YEARS OLD OR MORE WITH LOCALIZED AGGRESSIVE NON-HODGKIN'S LYMPHOMA

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Purpose: We conducted a multicenter prospective study to evaluate the efficacy and safety of reduced-dose three-course CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) followed by involved-field radiotherapy for elderly patients with localized aggressive non-Hodgkin's lymphoma. The primary endpoint was compliance with the combined modality.

Methods and Materials: This study included untreated patients, ≥70 years old, with diffuse aggressive lymphoma, Stage IA or contiguous nonbulky Stage IIA. 80%-CHOP (cyclophosphamide 600 mg/m^2, doxorubicin 40 mg/m^2, vincristine 1.1 mg/m^2, and prednisolone at 80 mg/day for 5 days) was repeated every 3 weeks. After three cycles of chemotherapy, involved-field radiotherapy was performed with a radiation dose of 30–50 Gy in 15–28 fractions.

Results: Twenty-four patients with a median age of 75 years (range, 70–84 years) were enrolled. The compliance rate of the protocol study was 87.5% (95% confidence interval [CI], 67.6–97.3). Three patients received only two cycles of chemotherapy because of toxicity or second neoplasm. There were no deaths caused by severe toxicity. The 3-year progression-free and overall survival rates were 83.1% (95% CI, 75.4–90.8) and 82.9% (95% CI, 75.1–90.6), respectively.

Conclusion: Three-course 80%-CHOP followed by involved-field radiotherapy may be safe for administration to elderly patients over 70 years old. The next step is to evaluate three-course 80%-CHOP and rituximab followed by radiotherapy in elderly patients with localized disease. © 2006 Elsevier Inc.

Aggressive lymphoma, Chemotherapy, Elderly patients, Dose-intensity, Radiotherapy.

INTRODUCTION

Increased age at diagnosis is a poor prognostic indicator in aggressive non-Hodgkin's lymphoma (NHL) (1). Several factors may contribute to the differences in outcome between younger and elderly patients with NHL: (*1*) differences in disease biology, (*2*) poor compliance rate of treatment due to co-morbid illness or poor host organ tolerance, and (*3*) administration of less intensive chemotherapy (2). Some investigators reported that elderly patients with NHL, who had a good performance status and minimal co-morbid illness, can tolerate full-dose chemotherapy without increased toxicity (3–6). However, Tirelli *et al.* reported that 8 (11%) of 71 elderly patients over 70 years old (median, 77 years), who underwent aggressive treatment including combination chemotherapy regimens

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with three or more drugs or extended field radiotherapy, died as a result of treatment-related toxicity (7). Balducci and Lyman emphasized that patients over 70 years old are at high risk for neutropenic infection (8). Lyman *et al.* conducted a nationwide survey in the United States and collected data for 4522 patients with NHL from 567 oncology practices. Their results indicated that a greater proportion of elderly patients over 60 years old received a relative dose-intensity (RDI) of less than 85% during the first five cycles of chemotherapy (9). These findings suggested that physicians may modify the dose of chemotherapy according to patient's age and other clinical factors.

The Southwest Oncology Group (SWOG) conducted a prospective randomized clinical trial to assess the effectiveness of short-course CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) followed by involved-field radiotherapy in comparison with eight-course CHOP in patients with localized NHL (10). Three-cycle CHOP followed by involved-field radiotherapy is considered the standard method of care for patients with localized aggressive disease (11, 12). On the other hand, Gomez *et al.* retrospectively analyzed the outcomes of 267 consecutive elderly patients (median age, 70 years; range, 60 to 94 years) treated with CHOP. They reported that 63% of treatment-related deaths occurred after the first cycle of chemotherapy, and infection accounted for 82% of the toxicity-related deaths (4). This suggests that careful management of elderly patients should be taken into consideration, even in cases treated with short-course chemotherapy.

We conducted a multicenter prospective study to evaluate the efficacy and safety of reduced-dose short-course CHOP followed by involved-field radiotherapy in elderly patients over 70 years old with localized disease.

METHODS AND MATERIALS

Patients

Elderly patients aged 70 years old or more with localized diffuse aggressive lymphoma were recruited from December 2000. Histologic diagnoses were made according to the REAL (revised European-American classification of lymphoid neoplasms) classification or the Working Formulation (13). The localized diseases included in the present study were Stage IA or contiguous non-bulky Stage IIA. Patients with more than two extranodal diseases were excluded from the study. Eligibility criteria for inclusion in the study were as follows: good performance status (0–2) according to the Eastern Cooperative Oncology Group; elevated serum lactate dehydrogenase less than 150% of the upper limit of the institutional normal range; no co-morbidity with other serious medical conditions, including severe ischemic heart disease and cardiomyopathy. Patients were excluded from the trial if they had a history of active cancer during the previous 5 years, positive serology for human immunodeficiency virus, or the presence of hepatitis B (HB) antigen or anti-hepatitis C virus (anti-HCV) antibody, or central nervous system, testis, stomach, or spleen involvement.

No prior chemotherapy or radiotherapy was allowed before entry into the study. All patients were required to have sufficient hematologic, renal, and hepatic functions. Minimal staging procedures included clinical examination; chest radiography; gallium scintigraphy; computed tomography of the neck, chest, abdomen, and pelvis; bone marrow biopsy; and blood studies.

This study complied fully with all provisions of the Declaration of Helsinki. All participating hospitals obtained the permission of the institutional review board, and all patients gave their written informed consent before entry into the study.

Treatment

Reduced-dose chemotherapy (80%-dose CHOP) included cyclophosphamide at 600 mg/m^2 (Day 1), doxorubicin at 40 mg/m^2 (Day 1), vincristine at 1.1 mg/m^2 (Day 1), and oral prednisolone at 80 mg/day (Days 1–5). Chemotherapy was repeated at 21-day intervals. If a patient developed Grade 4 neutropenia or febrile neutropenia, all subsequent cycles were administered with granulocyte colony-stimulating factor (G-CSF) support. If febrile neutropenia developed with infection, the dose of cyclophosphamide was decreased by 150 mg/m^2 and that of doxorubicin was decreased by 10 mg/m^2 for all subsequent cycles. Chemotherapy was discontinued in cases in which Grade 4 neutropenia persisted. If a patient developed Grade 3 or 4 thrombocytopenia, the dose of cyclophosphamide was decreased by 150 mg/m^2 and that of doxorubicin was decreased by 10 mg/m^2 for all subsequent cycles. Chemotherapy was discontinued in cases in which Grade 3 or 4 thrombocytopenia persisted.

Involved-field radiotherapy was performed after three cycles of chemotherapy. The involved-field was defined as the regional area including the primary lesion and involved nodes determined by prechemotherapy evaluations and adjacent uninvolved nodes. The radiation dose was 30–30.6 Gy given in 15–20 fractions over 3–4 weeks for patients who achieved complete remission (CR), and 40–50 Gy in 20–28 fractions over 4–6 weeks for those who did not achieve CR. Response was assessed using the standard criteria (14).

No central pathologic review was performed in this study.

Follow-up

Response to chemotherapy was evaluated after three cycles of CHOP, or after discontinuation of the planned treatment. Thereafter, clinical examination was performed every 6 months for the first 5 years, and then at the discretion of the attending physician. A neck, chest, and abdominal computed tomographic scan was performed after 6 months, and then every 6 months during the first 5 years.

Outcome measures

The primary endpoint was compliance with the combined modality therapy. Completion of the study protocol was defined as completion of three cycles of chemotherapy and planned radiation therapy. The events were defined as going off-protocol, a 5-week delay of administration of chemotherapy, disease progression or relapse, or death due to any cause. Calculation of compliance with the protocol was performed among all registered patients. The secondary endpoints included progression-free survival, overall survival, and toxicity. Progression-free survival was calculated using disease progression or death due to any cause as an event, and overall survival was calculated using death due to any cause as an event. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria grading system version 2.0. Tumor responses were classified as CR, CRu (CR unconfirmed), partial

remission, stable disease, or progressive disease according to the proposed International Workshop criteria (14).

Statistical analysis

Sample size was calculated on the basis of the primary endpoint. Based on various results obtained in previous studies with CHOP chemotherapy in this patient population, compliance with this protocol was assumed conservatively to be 90%, and the lower limit of compliance was assumed to be 70% (7, 12, 15–17). To confirm the rate of compliance with this protocol, it was calculated that 30 patients recruited over the 3 years of the study would be required to provide 80% power at the overall 5% (alpha = 0.05, 2 sides) significance level.

The progression-free survival and overall survival rate were calculated using the Kaplan-Meier method. Analyses of efficacy and safety included all patients. Statistical analyses were performed with JMP software version 5.0.1 (SAS Institute Inc., Cary, NC) by our trial office.

RESULTS

Compliance with the study protocol

The median follow-up period was 38 months (range, 2–55 months). The compliance rate with the study protocol was 87.5% (95% CI [confidence interval], 67.6–97.3). The lower limit of 95% CI was slightly below 70%, which was the threshold value defined before the study. The study protocol was not completed in 3 patients who received only two cycles of chemotherapy. The physician stopped treatment using the protocol in 1 patient, and another patient refused administration of the third round of chemotherapy. In addition, they received radiotherapy after going off-protocol. Another 1 patient developed pancreatic cancer during chemotherapy, and the protocol was stopped. In 6 patients, the administration of chemotherapy was delayed owing to hematologic toxicity, and the median interruption of chemotherapy was 2 days (range, 1–14 days). The dose of chemotherapy was reduced because of hematologic toxicity in 1 patient who was 84 years old and had Stage II disease.

Patient characteristics and response to treatment

The number of patients enrolled in the study did not increase after permission was granted for administration of rituximab (Rituxan; Roche, Basel, Switzerland) in Japan in September 2003. We stopped this protocol in February 2004. Twenty-four patients were enrolled from eight Japanese institutions between December 2000 and February 2004. The initial characteristics of all 24 patients are summarized in Table 1. The median age was 75 years (range, 70–84 years), and 4 patients (16%) were over 80 years old. Response rates after chemotherapy were 50% (12 patients) for CR, 25% (6 patients) for CRu, and 20% (5 patients) for partial remission or stable disease. Treatment response was not evaluated in 1 patient (4%) who developed pancreatic cancer during chemotherapy and died before evaluation of his response. Response rates after combined treatment were 67% (16 patients) for CR, 21% (5 patients) for CRu, and 8% (2 patients) for partial remission.

Table 1. Patient characteristics

Characteristics	No. of patients (%)
Age, years	
Median	75
Range	70–84
70–75	15 (62)
≥76	9 (38)
Gender	
Male	13 (54)
Female	11 (46)
Performance status (ECOG)	
0	18 (75)
1	6 (25)
Location	
Waldeyer's ring	11 (46)
Neck node	6 (25)
Maxillary sinus	3 (13)
Thyroid	2 (8)
Parotid gland	1 (4)
Paravertebral area	1 (4)
Stage	
I	16 (67)
II	8 (33)
Lactate dehydrogenase	
≤ULN	20 (83)
>ULN, <1.5 × ULN	4 (17)
Stage-modified International Prognostic Index*	
1	14 (59)
2	8 (33)
3	2 (8)
Tumor size	
<6 cm	19 (79)
6 cm <10 cm	4 (17)
≥10 cm	1 (4)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ULN = upper limit of the institutional normal range.

* Stage-modified International Prognostic Index; Age (≤60 vs. >60), stage (I vs. II), serum lactate dehydrogenase (normal vs. increased), performance status (0–1 vs. 2).

Progression-free and overall survival rates

The 3-year progression-free and overall survival rates were 83.1% (95% CI, 75.4–90.8) and 82.9% (95% CI, 75.1–90.6), respectively (Fig. 1). The 3-year progression-free and overall survival rates according to stage-modified International Prognostic Index score were 78.7% and 77.9% for score 1, 87.5% and 87.5% for score 2, and 100% and 100% for score 3, respectively. To date, no recurrence in the radiation field has been found. Four patients developed relapse at distant sites: lung, bone marrow, liver, kidney, heart, adrenal gland, and abdominal lymph nodes.

Toxicity

During chemotherapy, severe hematologic toxicity (Grade 3–4) occurred in 23 patients, and severe nonhematologic toxicity (Grade 3–4) occurred in 3 (diabetes mellitus in 2

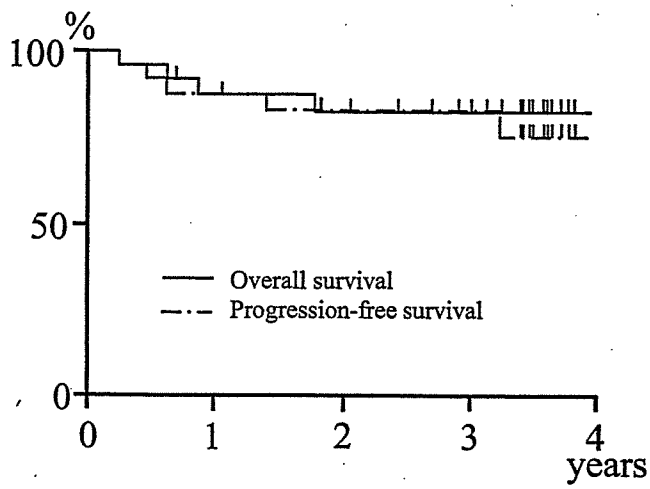

Fig. 1. Overall and progression-free survival curves of all 24 patients.

patients, pneumonia in 1) (Table 2). Only 1 patient experienced severe hematologic toxicity (Grade 4), and no patients developed symptoms of heart failure. During radiotherapy, severe hematologic toxicity (Grade 3) occurred in 1 patient, and nonhematologic severe toxicity (Grade 3) occurred in 1 (mucositis). In 2 patients, radiotherapy was interrupted for 10 and 11 days, respectively, because of radiation-induced mucositis. None of the patients died as a result of treatment-related toxicity.

DISCUSSION

Cyclophosphamide, doxorubicin, vincristine, and prednisolone is the standard regimen for treatment of patients with aggressive NHL (2, 18). Kouroukis *et al.* conducted a systematic review with regard to chemotherapy in elderly patients with advanced-stage aggressive NHL. This systematic review demonstrated that anthracycline-containing regimens, such as CHOP or CTVP (cyclophosphamide, pirarubicin, vincristine, and prednisolone), improved overall survival as compared with other regimens without anthracycline (2). Tirelli *et al.* performed a randomized trial to compare the efficacy of the CHOP regimen with that of VMP (etoposide, mitoxantrone, and prednimustine) for elderly patients over 70 years old, and showed that the overall survival rate was 30% with VMP vs. 65% with CHOP ($p = 0.004$) (18). The Dutch-Belgian Hemato-Oncology Cooperative Group conducted a randomized trial to evaluate the use of G-CSF for elderly patients over 65 years old (17). This study demonstrated that the addition of G-CSF improved the RDI of chemotherapy, but had no effect on overall survival. The rate of protocol completion of CHOP or G-CSF was approximately 70%, and patients older than 80 years completed significantly fewer treatments as compared with younger patients as a result of toxicity, refusal, or death (43% vs. 80%; $p < 0.001$). In addition, G-CSF did not prevent serious infections. Compared with this result, the rate of protocol completion in the present study was not unsatisfactory. Recently, the addition of rituximab, which is a chimeric human/murine immunoglobulin G1 monoclonal antibody that binds specifically to the B-cell-surface antigen CD20, to the full-course CHOP regimen was shown to improve treatment outcome in patients with advanced disease (19, 20). However, the role of rituximab has not been clarified in patients with localized disease. The present study was conducted before permission for use of rituximab for diffuse large B-cell lymphoma was granted in Japan, and we applied the CHOP regimen in the present study. In comparison with Western series, patients with nodal disease were less frequent in this study. However, these observations agreed well with our previous nationwide survey among Japanese radiation oncologists (15).

Recent prospective studies demonstrated the safety of the three-weekly full-dose CHOP regimen and two-weekly CHOP regimen for elderly patients older than 60 years (19, 21). However, there is controversy regarding

Table 2. Toxicity in the chemotherapy phase and radiotherapy phase

	Chemotherapy ($n = 24$)					Radiotherapy ($n = 21$)*				
	Grade					Grade				
	0	1	2	3	4	0	1	2	3	4
White blood cell	0	1	0	22	1	15	4	1	1	0
Hemoglobin	7	14	3	0	0	12	9	0	0	0
Platelet	17	6	0	1	0	19	2	0	0	0
Emesis	16	8	0	0	0	18	3	0	0	0
Mucositis	22	1	1	0	0	2	13	5	1	0
Pnuemonitis	22	0	1	1	0	20	1	0	0	0
Fever	21	1	1	1	0	—	—	—	—	—
Liver dysfunction	22	2	0	0	0	—	—	—	—	—
Renal dysfunction	24	0	0	0	0	—	—	—	—	—
Peripheral neuropathy	17	7	0	0	0	20	1	0	0	0
Diabetes mellitus	21	0	1	2	0	—	—	—	—	—

* Three patients were off-protocol.

the standard care for elderly patients over 75 years of age. Epelbaum *et al.* reported a 5-year survival rate of 80% in patients treated with ≥70% RDI of CHOP in their first cycle of chemotherapy and a 5-year survival rate of only 32% in those receiving ≤70% ($p = 0.0001$) (22). Kwak *et al.* retrospectively analyzed 115 patients treated with CHOP or other anthracycline-containing regimens, and emphasized the actual RDI of doxorubicin ≥75% as the single most important predictor of survival (23). Lee *et al.* reported that elderly patients who received doxorubicin at doses of ≥10 mg/m^2 per week had treatment outcomes that were comparable to those of young patients, and showed that in elderly patients the dose intensity of doxorubicin was a more important prognostic factor than the mean RDI of each agent (6).

The Eastern Cooperative Oncology Group conducted a randomized trial to compare low-dose (30 Gy) radiotherapy with observations in patients with localized disease achieving CR after eight-cycle CHOP (24). This study demonstrated that for patients in CR after CHOP, low-dose radiotherapy prolonged disease-free survival and provided local control, but no survival benefit was observed. Thirty-one percent of the patients in this study had bulky disease, and it was not possible to evaluate the role of radiotherapy for patients with localized disease. The Groupe d'Etude des Lymphomes de l'Adulte (GELA) conducted a prospective randomized trial to evaluate the role of consolidated radiotherapy for elderly patients over 60 years old who were treated with four-cycle CHOP (25). Bulky disease was observed in 9% of patients, and extranodal disease in 57%. The event-free survival and overall survival were not significantly different between the chemotherapy alone and the combination therapy groups. The criticism of this trial was that for patients with bulky disease four cycles of CHOP were not only effective at eliminating microscopic sites of disease (26). Therefore, we could not reach definitive conclusions regarding the role of radiotherapy for localized disease.

The clinical outcome after short-course CHOP followed by involved-field radiotherapy is excellent for patients with localized disease and no adverse factors (10). However, this combined therapy is not satisfactory for patients with poor prognostic factors, such as bulky tumors or advanced age. We should establish more effective combined therapy for patients with localized disease and poor prognostic factors. The addition of rituximab improved the treatment outcome for elderly patients with aggressive disease with CD20, but did not increase the toxicity (19, 20). A GELA study, which included Stage II–IV disease, demonstrated that rituximab was more effective for patients at low risk than for those at high risk (19). However, it has not yet been established whether the addition of rituximab produces survival benefit for patients with localized disease. A phase II study (SWOG 0014) was conducted to evaluate the efficacy and safety of four-course rituximab plus three-course CHOP followed by radiotherapy for patients with localized disease (27). The treatment outcome was excellent, and 2-year overall and progression-free survival rates were 95% and 94%, respectively. A prospective randomized trial is currently in progress to compare short-course CHOP followed by radiotherapy with this combined therapy with rituximab.

Combined modality therapy with reduced-dose CHOP and involved-field radiotherapy may be safe for administration to elderly patients aged 70 years old or more, with good performance status and minimal co-morbid illness, with Stage I or nonbulky Stage II disease. The next step is to evaluate combined therapy, including reduced-dose CHOP and radiotherapy plus rituximab for elderly patients 70 years of age or more.

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Patterns of Care Study for Postmastectomy Radiotherapy in Japan: Its Role in Monitoring the Patterns of Changes in Practice

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Background: Three prospective randomized clinical trials (RCT) in the 1990s demonstrated the survival benefit of postmastectomy radiotherapy (PMRT) for patients with locally advanced breast cancer. The present study was performed to evaluate whether the Patterns of Care Study (PCS) fulfills a role in monitoring the patterns of changes in clinical practices in Japan.
Methods: The first survey (JPCS-1) involved 79 Japanese facilities by two-stage cluster sampling of facilities and patients, and was carried out during 1998–2000. JPCS-1 included 1124 patients with breast cancer who were treated between 1995 and 1997. The second survey (JPCS-2) was carried out during 2001–2003, involving 827 patients who were treated between 1999 and 2001 in 76 facilities.
Results: Patients with adverse risk factors, including pathologically axillary positive nodes (≥4) and/or advanced primary disease (pT3–4) accounted for 57% of the patients who received PMRT in JPCS-1 and 72% of those in JPCS-2 ($P = 0.039$). The multiple radiotherapy target volume including the chest wall and regional lymph nodes was applied in 18% of the patients in JPCS-1 and 44% of those in JPCS-2 ($P < 0.001$). However, the dose distribution was calculated in only 42% of the patients in both surveys ($P = 0.467$).
Conclusions: The eligibility and the target volume for PMRT were influenced by the outcome of RCT, but the quality of radiotherapy did not improve sufficiently. The PCS survey is useful to monitor the changes in patterns of clinical practice and can clarify some problems with radiotherapy techniques.

Key words: breast cancer – mastectomy – patterns of care – radiotherapy

INTRODUCTION

Over the last two decades, prospective randomized clinical trials (RCT) and meta-analysis demonstrated that postmastectomy radiotherapy (PMRT) improved the loco-regional control of patients with locally advanced breast cancer, but failed to improve overall survival (1–3). Any reduction in breast cancer mortality has been offset by mortality from late adverse effects of radiotherapy, including heart disease (1). In the late 1990s, three prospective RCT demonstrated that PMRT improved not only loco-regional control but also overall survival of patients with locally advanced breast cancer (3–6). Recent meta-analysis demonstrated that PMRT with an optimal dose and optimal radiotherapy target volume was significantly associated with improved survival for up to 10 years (7). The adequate radiotherapy technique of PMRT should be established to provide the effectiveness of PMRT without increases in lethal toxicity. The recent development of three-dimensional radiotherapy planning and quality assurance of radiotherapy technique has facilitated the reduction of severe radiation-induced toxicity. In 2001, the American Society of Clinical Oncology (ASCO) proposed the clinical guidelines for PMRT to improve the level of clinical practice (8).

The Patterns of Care Study in the United States (USPCS) sponsored by the American College of Radiology has made significant contributions to improvements in the care of patients with breast cancer and with other types of cancer (9,10). The Japanese Patterns of Care Study (JPCS) Working

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Group collaborated with USPCS to evaluate each radiotherapy practice pattern and improved the research method (11–13). We conducted two national surveys to evaluate the clinical practice of radiotherapy in Japan. The first goal of this study was to evaluate whether PCS surveys fulfill the role of monitoring changes in practice patterns in Japan after three prospective randomized trials, which demonstrated the efficacy of PMRT in the late 1990s (3,5,6). In addition, the second goal of this study was to clarify whether the radiotherapy technique has been improved sufficiently to provide effectiveness of PMRT.

METHODS

We developed a data format system, which we installed on portable computers. The extramural audits of facilities were conducted by the JPCS Working Group. The audits were performed by member physicians of the working group. The audits reviewed the patients' clinical records and input the data into the portable computer on-site. The method of data collection and the JPCS data format have been reported in detail previously (14).

In 1995, according to the Japanese facility master list, a total of 556 facilities nationwide were stratified into four classifications according to the category of facility type and the number of patients, and 79 facilities were sampled at random. The first survey (JPCS-1) was carried out during 1998-2000, and collected data of 1124 patients with breast cancer treated with radiotherapy between 1995 and 1997 using two-stage cluster sampling of facilities and patients (15). In 1999, a total of 641 facilities nationwide were stratified using the same method, and 76 facilities were sampled at random. The second survey (JPCS-2) was carried out in 2001–2003, and involved 827 patients who were treated between 1999 and 2001. We could not keep the same number of facilities in the two surveys because of difficulties in gaining approval for an extramural audit from the institutional review board (14). The eligibility criteria for these surveys were as follows: (1) absence of distant metastases, (2) no bilateral lesions, (3) females, (4) no gross multiple tumors, (5) no diffuse-micro-calcification on pretreatment mammography, (6) absence of prior or concurrent malignancies, (7) absence of prior history of radiotherapy for beast cancer and (8) absence of collagen vascular disease other than rheumatoid arthritis. These eligibility criteria for the patients who received breast conservative therapy were the same as those for patients who underwent PMRT. The study office sampled the patients at random from the patient list regardless of the treatment procedures, including breast conservative therapy and PMRT.

The clinical and pathological stages were classified according to the Fifth Classification of the International Union against Cancer (UICC) (16). Academic facilities were defined as university hospitals or cancer centers and non-academic facilities were defined as other hospitals. Differences in proportion were evaluated by chi-squared test.

RESULTS

JPCS-1 included 866 patients treated with breast conservative therapy and 258 patients treated with mastectomy and PMRT. JPCS-2 included 746 patients treated with breast conservative therapy and 81 patients treated with mastectomy followed by PMRT. The patient characteristics are shown in Table 1. The proportion of patients who received PMRT among those who received postoperative radiotherapy decreased from 22.9% to 9.7% ($P < 0.001$). Among the patients who received PMRT, the proportions of those with adverse risk factors, including four or more axillary positive nodes and/or advanced primary disease (pT3-4), were 57% in JPCS-1 and 72% in JPCS-2 ($P = 0.039$).

The radiotherapy target volume included the chest wall in 31% and in 63% of the patients in JPCS-1 and in JPCS-2, respectively ($P < 0.001$). The radiotherapy target volume included the regional lymph node area, such as the supraclavicular fossa and/or internal mammary lymph nodes in 87% of the patients in JPCS-1 and in 79% of those in JPCS-2 ($P = 0.083$). The radiotherapy target volume included both chest wall and regional lymph node area in 18% of the patients in JPCS-1 and 44% of those in JPCS-2 ($P < 0.001$) (Fig. 1). The majority of the patients in JPCS-1 received irradiation of the regional lymph node area alone. In the academic facilities, the proportions of patients who received both chest wall irradiation and regional lymph node irradiation were 28% of the patients in JPCS-1 and 58% of those in JPCS-2 ($P = 0.001$). In the non-academic facilities, the proportions of patients receiving both treatments were 10% in JPCS-1 and 36% in JPCS-2 ($P < 0.001$).

The dose distribution at the iso-center plane was calculated in only 42% of the patients both in JPCS-1 and in JPCS-2 ($P = 0.467$). In the academic facilities, the dose distribution was calculated in only 46% of the patients in JPCS-1 and 52% of those in JPCS-2 ($P = 0.120$). In the non-academic facilities, the dose distribution was calculated in only 39% and in 36% of the patients in both surveys, respectively ($P = 0.894$). Among all facilities, the multiple-plane dose distribution was calculated in 4% of the patients in JPCS-1 and 15% of those in JPCS-2 ($P < 0.001$).

The immobilization cast was used in 14 and in 35% of the patients in JPCS-1 and in JPCS-2, respectively ($P < 0.001$). In the academic facilities, the immobilization cast was used in 21% of the patients in JPCS-1 and 58% of those in JPCS-2 ($P < 0.001$). In the non-academic facilities, the immobilization cast was used in 9% of the patients in JPCS-1 and 20% of those in JPCS-2 ($P = 0.018$).

No marked differences were found between the two surveys regarding the daily fraction size, total irradiation dose or photon beam energy (Table 2).

DISCUSSION

The effectiveness and the safety of breast conservative therapy have been confirmed by many randomized trials and pooled-