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
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 breast 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 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 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-
For the last two decades, breast conservative therapy has become more frequently performed in Japan. The national survey conducted by the Japanese Breast Cancer Society indicated that 40% of patients with breast cancer received breast conservative therapy in 2000, and that nowadays more than half of the patients receive such treatment (21). However, three prospective randomized trials indicated that PMRT improved the overall survival of pre-menopausal and post-menopausal patients with locally advanced breast cancer who had pathologically four or more axillary positive nodes, and that PMRT has been used widely in the United States and in the other Western countries (2–5). Fowble reviewed a large number of reports regarding chest wall recurrence after mastectomy, and reported that 8–36% of patients with four or more pathologically positive nodes underwent treatment with mastectomy and adjuvant systemic chemotherapy (2). However, in Japan PMRT has been used infrequently in patients with adverse risk factors, because many Japanese surgeons consider that chest wall recurrence is infrequent after mastectomy and systemic therapy alone (22). However, the evidence-based guidelines for clinical practice conducted by the Japanese Breast Cancer Society recommended that PMRT should be applied in patients with pathologically four or more axillary positive nodes. These clinical guidelines may have affected the increment in a number of patients receiving PMRT in Japan. The dissemination of high-quality evidence that does not result in the progress of practical techniques would expose patients to severe adverse effects. We should monitor clinical practice to evaluate whether appropriate radiotherapy for PMRT is being performed.

PMRT has been recommended for patients with four or more pathologically proven axillary positive nodes and/or advanced primary disease (8). The clinical benefit of PMRT for patients without adverse risk factors is controversial (23,24). Smith
Table 2. Radiotherapy technique in two surveys

<table>
<thead>
<tr>
<th></th>
<th>JPCS-1 (n = 258)</th>
<th>JPCS-2 (n = 81)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total radiation dose (Gy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(median, range)</td>
<td>49 (10–60)</td>
<td>49 (18–60)</td>
<td>0.738</td>
</tr>
<tr>
<td>Fraction size (Gy)</td>
<td>2.0 ± 0.2</td>
<td>2.0 ± 0.1</td>
<td>0.490</td>
</tr>
<tr>
<td>(median ± standard deviation)</td>
<td></td>
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<tr>
<td>Beam quality of chest wall irradiation*</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Photon (≤6 MV) (%)</td>
<td>59/79 (74.7)</td>
<td>26/51 (51.0)</td>
<td></td>
</tr>
<tr>
<td>Photon (&gt;6 MV) (%)</td>
<td>6/79 (7.6)</td>
<td>2/51 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Electron (%)</td>
<td>13/79 (16.5)</td>
<td>23/51 (45.1)</td>
<td></td>
</tr>
<tr>
<td>Mixed beam (60Co and X-ray 15 MV) (%)</td>
<td>1/79 (1.2)</td>
<td>0/51 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Wedge filter (yes) (%)</td>
<td>11/66 (16.7)</td>
<td>11/28 (39.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Boost (yes) (%)</td>
<td>7/258 (2.7)</td>
<td>5/81 (6.2)</td>
<td>0.141</td>
</tr>
</tbody>
</table>

*Calculations were performed only for patients who received chest wall irradiation.
Calculations were performed only for patients who received chest wall irradiation using photon beam.

JPCS, Japanese Patterns of Care Study.

et al. (23) reported that PMRT provided clinical benefits for patients with T1-2 disease and positive axillary nodes. However, some other investigators argued that the role of PMRT had not been defined for patients with T1-2 disease and positive axillary nodes (25). Hence further studies should be performed to establish the indications for PMRT. Our surveys showed that among patients with breast cancer who received postoperative radiotherapy, the proportion of PMRT decreased from 22.9% in JPCS-1 to 9.7% in JPCS-2. This observation does not imply a decrease in the absolute number of patients who received PMRT in Japan, but rather suggests an increment in the number of patients who received breast conservative therapy. The proportions of patients with adverse risk factors, including four or more pathologically proven axillary positive nodes and/or advanced T stage, increased from 57 to 72% between the two studies. The eligibility for PMRT may be influenced by the outcome of the prospective randomized trials in the late 1990s, and PMRT came to be avoided for patients with low risk factors (3–5).

A recent meta-analysis demonstrated that PMRT with an optimal radiation dose ranging from 40 to 60 Gy in 2 Gy fractions, and an appropriate target volume, including chest wall and regional lymph node area, was associated with a statistically significant 6.4% increase in absolute survival (7). However, an inappropriate PMRT technique with an inadequate or excessive dose of radiotherapy or an inappropriate target volume failed to show clinical benefit. Our two surveys demonstrated some problems in radiotherapy techniques for PMRT. In the first survey, the majority of patients received regional lymph node irradiation alone, which was known as the hockey-stick technique. In the second survey, the radiotherapy target volume more frequently included the chest wall and regional lymph nodes. Multiple radiation fields covering anatomically complex sites require a high-quality radiotherapy technique, including three-dimensional radiation planning and quality assurance to avoid severe toxicities. The dose distribution is essential to determine the administration of wedge filter and to evaluate the irradiated lung and heart volume. In the United States, dose distribution in the iso-center plane was calculated in ~95% of patients (11). However, in our survey the dose distribution in the iso-center plane was calculated only in 40% patients, and the multiple-plane dose distribution was calculated only in 15% patients. No improvement of quality assurance was found either in the academic or in the non-academic facilities. Although the immobilization cast is an important item to reproduce the irradiation field in daily treatment, it was used in less than half of the patients in our surveys.

The main limitation of our surveys was the eligibility criteria used. The aim of our surveys was to clarify the clinical procedures applied in patients with breast cancer who received postoperative radiotherapy. The eligibility criteria for our surveys were set up to collect data for patients who received postoperative radiotherapy, including breast conservative therapy and PMRT. The population of patients who received breast conservative therapy has been increasing, and the relative size of the population receiving PMRT has decreased. We could not collect data for patients with PMRT to determine the changes in the clinical procedure sufficiently. Our surveys excluded patients with multiple gross tumors and/or diffuse microcalcification on pretreatment mammography, but the survey for PMRT should include these patients to determine the nationwide status of PMRT. In future studies, we should consider the eligibility criteria to determine the changes in the clinical procedure of PMRT.

Donabedian emphasized three components of quality of care: structure, process and outcome (15). Good processes of care help to achieve good clinical outcome for the patients, while poor processes are associated with insufficient outcome. However, we did not evaluate the correlation between poor radiotherapy technique and clinical outcome, including survival and adverse effects, because of the short follow-up time and small sample size. A survey with small sample size cannot clarify the interactions between poor processes and insufficient clinical outcome. “No difference” in the survey with small sample size does not necessarily mean the “same.” Even if the poor process is not significantly associated with poor clinical outcome, this hasty interpretation does not justify by any means that a poor radiotherapy technique is acceptable. In addition, repeated analyses of the correlation between each clinical parameter and the outcome may lead to misunderstanding of the observed phenomenon because of multiplicity. A process survey including large sample size may not be efficient and economical. In contrast, a process survey using a relatively small sample size is convenient and useful to compare the observed clinical practice with the optimal radiotherapy technique that is considered appropriate according to the textbooks or previously reported evidence. However, the definition of optimized sample size for a survey is controversial.
A recent meta-analysis demonstrated that use of an inappropriate radiotherapy technique that applied excessive radiation dose and/or inappropriate target volume was associated with an increment in non-breast cancer mortality (7). In Japan, the infrastructure of radiation oncology units has been insufficient to provide safe medical service in both academic and non-academic facilities (13). The radiation oncology staff, including radiation oncologists, technologists, dosimetrists and oncology nurses, should be enriched to provide good clinical practice for the patients. An efficient monitoring system using optimized surveys combining the structure survey and process survey should be established for good clinical practice.

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