developed IBTR, initial lymph node metastases and short interval to IBTR were significant risk factors for subsequent distant metastasis.

CONCLUSIONS. Young age, positive surgical margin, and omission of radiation therapy seemed to be important factors in relation to local control. The authors' results also indicated that IBTR is significantly associated with subsequent distant metastasis. Patients with positive nodal status at primary operation or with short interval from primary operation to IBTR are at especially high risk of distant metastasis. It remains unclear, however, whether IBTR is an indicator or a cause of subsequent distant metastases. *Cancer* **2006;106:35–41.**

KEYWORDS: breast cancer, breast-conserving treatment, ipsilateral breast tumor recurrence, distant metastases.

A long time has passed since breast-conserving therapy (BCT) became the standard treatment modality for early stage breast cancers.[1–2] The increasing number of patients treated with BCT resulted in a corresponding increase of ipsilateral breast tumor recurrence (IBTR). The main concern for both physicians and patients is, therefore, the risk of IBTR in the preserved breast.

Postoperative irradiation to the remaining breast has significantly reduced the incidence of IBTR.[1–5] The results of the recent National Surgical Adjuvant Bowel and Breast Project (NSABP) B-21, showed that radiation therapy was so effective that it would even benefit early breast cancers at minimal risk for IBTR.[6] Therefore, postoperative irradiation was thought to be an important part of standard procedure for BCT.

In addition to radiation therapy, some factors were reported to have an influence on IBTR. For example, young women were generally thought to have a higher frequency of local recurrence.[7–11] Kroman et al. recently reported a relation between young age and increasing risk of IBTR, from a study of BCT with over 2000 patients.[12] The European Organization for Research and Treatment of Cancer (EORTC) trial also confirmed the impact of age.[13]

The presence or absence of cancer cells at the resection margin, and their quantity, are also major factors affecting IBTR.[14–19] Park et al. reported that the 8-year accrued rate of IBTR was 7% in patients with negative and close margins, 14% in those with focally positive margins, and 27% in those with extensively positive margins.[14] Although the definitions of positive margin are obscure, the importance of pathologic margin status in relation to the risk of IBTR has been shown.

Many studies have shown that IBTR is associated with subsequent distant metastases (DM) and worse survival.[20–28] Whether IBTR is an indicator or a cause of subsequent DM is debatable.[26,29–33] It has been proposed that IBTR is not the cause but is simply a significant indicator of subsequent DM. Other groups have recently suggested that IBTR may be a cause of DM.[32,34,35]

In the current study, we summarized the long-term follow-up results of BCT for Japanese women with breast cancer, and we focused on IBTR, particularly its incidence, risk factors, and predictive significance for subsequent DM. In Japan, BCT was adopted later than in western countries. Therefore, there are few studies summarizing the results of BCT for Japanese women.[36,37] This is the first long-term report of large-scale results of BCT in this ethnic group.

MATERIALS AND METHODS

Included in this study were 1901 patients with unilateral breast cancer ≤ 3 cm in diameter who underwent BCT at 18 major institutes from 1986 to 1993. Patients who had received primary systemic therapy, and those with past history of breast cancer, were excluded. Postoperative irradiation or adjuvant therapy were not exclusion criteria. The surgical procedure consisted of wide excision or quadrantectomy plus axillary lymph node dissection.

Questionnaire forms were sent to the members of this study in November 2001 to collect clinical patient data. The questionnaire asked for data as follows: age at primary operation, menopausal status, date of primary operation, initial tumor size by palpation, histologic type, pathologic lymph node status, histologic margin status, lymphovascular invasion, nuclear grade, extensive intraductal component (EIC), estrogen receptor status (ER), progesterone receptor status (PgR), adjuvant endocrine therapy, adjuvant chemotherapy, postoperative irradiation, boost radiation, date of IBTR, method of salvage operation, systemic therapy after IBTR, secondary local recurrence and its date, distant metastases, date of distant metastases, contralateral breast cancer, death, cause of death, and date of death or last visit. Serial sections of resected specimens were meticulously examined at all institu-

tions. Margins ≤ 5 mm from the cut edge of the specimen were usually regarded as positive margins. Measurement methods and cutoff levels of the hormone receptors were not standardized, and they varied between institutions.

IBTR was defined as all events which occurred in the remaining breast after BCT. No distinction was made between recurrence because of residual cancer cells or because of new primary cancer.

Local-free, disease-free, distant disease-free, and overall survival rates were calculated using the Kaplan–Meier method. The statistical differences of local, distant, disease-free rates, and overall survival were proved using a log-rank test for univariate analysis. Multivariate analyses for local free and distant disease-free rates were performed using the Cox proportional hazards model. In univariate and multivariate analysis, age was dealt with as a serial variable and was not categorized at a certain point, such as ≤ 35 years or older. All statistical analyses were performed with Stat View 5.0 software (SAS Institute, Cary, NC).

RESULTS

Systemic Recurrence and IBTR

There were 1901 patients available for analysis of survival and recurrence rates. The median follow-up period was 107 months(range, 2–184 mos). Patient characteristics are shown in Table 1. There were 172 patients who developed IBTR, and 179 patients had recurrences in distant organs or regional lymph nodes. During follow-up, 182 patients died; of these, 128 patients died of their breast cancers. The 10-year overall and cause-specific survival rates were 83.9% and 92.2%, respectively. The 10-year distant disease-free survival was 77.8%. The 10-year cumulative rate of IBTR was 9.6% (8.5% in the group with postoperative irradiation and 17.2% in the group without RT). There was a significant difference between these two groups ($P < 0.0001$).

Risk Factors for IBTR

Factors influencing IBTR are shown in Table 2. In a univariate analysis, younger age at primary operation, tumor size, positive margin status, high nuclear grade, EIC, PgR, omission of endocrine therapy, and omission of postoperative irradiation were significantly associated with IBTR. Of these, younger age, positive margin status, and omission of postoperative irradiation were independently associated with IBTR on a multivariate Cox proportional hazards model analysis.

Time Course of IBTR and Distant Metastasis

The annual rate and cumulative incidence of IBTR after primary operation is shown in Figure 1. The peak of IBTR was seen at 3 to 4 years after primary operation, and the annual rate decreased gradually thereafter. Figure 2 shows the clinical outcome of patients with and without IBTR. Patients who developed IBTR had a significantly greater risk of developing DM ($P < 0.0001$).

TABLE 1
Patient Characteristics

Characteristic	No. of patients
Age, yrs	
Median	49
Range	21–89
≤ 35	135
> 36	1766
Clinical tumor size, cm	
Median	17
Range	0–30
Lymph node metastasis	
Positive	380
Negative	1476
Unknown	45
ER status	
Positive	779
Negative	482
Unknown	640
PgR status	
Positive	510
Negative	430
Unknown	961
Surgical margin	
Positive	263
Negative	1503
Uncertain	135

ER: estrogen receptor; PgR: progesterone receptor.

Risk Factors for Distant Metastasis

Both distant disease-free and overall survival rates were significantly lower in the IBTR group. To determine whether IBTR is related to DM and patient prognosis, we verified risk factors for DM. Univariate analysis showed that initial age, lymph node metastases, margin status, lymphovascular invasion, nuclear grade, EIC, PgR, and IBTR were all significantly correlated with DM (Table 3). In a multivariate analysis, IBTR was independently associated with DM as well as with lymph node metastases. The hazard ratio (HR) associated with distant metastasis was 3.93 (95% confidence interval [CI], 2.676–5.771) in IBTR, and 3.34 (95% CI, 2.365–4.724) in node-positive patients (Table 3).

Of 1901 patients, 172 developed IBTR, and 51 developed subsequent DM after IBTR; 27 of these patients developed distant metastases within 1 year after IBTR.

TABLE 2
Factors Influencing Ipsilateral Breast Tumor Recurrence (IBTR), Results of Univariate and Multivariate Analysis

Variable	Univariate analysis *P* value	Multivariate analysis HR	*P* value	95% CI
Age	< 0.0001	0.943	< 0.0001	0.917–0.970
Size	0.0257	1.017	0.2557	0.988–1.047
Histologic type				
DCIS/IDC/special	0.6053			
Lymph node metastasis				
+/−	0.141			
Surgical margin				
+/−	< 0.0001	2.849	0.0004	1.587–5.012
ly +/−	0.8768			
v +/−	0.5236			
Nuclear grade				
3/1, 2	0.0650			
EIC +/−	0.0106	1.422	0.1857	0.847–2.398
ER −/+	0.0493	0.696	0.1464	0.427–1.135
PgR −/+	0.0036			
Chemotherapy				
−/+	0.0878			
Endocrine therapy				
−/+	0.0180	1.543	0.0824	0.397–1.057
Radiation therapy				
−/+	< 0.0001	3.861	< 0.0001	0.155–0.433

HR: hazard ratio; CI: confidence interval; DCIS: ductal carcinoma in situ; IDC: invasive ductal carcinoma; Special: lobular carcinoma, medullary carcinoma, squamous cell carcinoma, etc.; ly: lymphatic invasion; v: vascular invasion; EIC: extensive intraductal component; ER: estrogen receptor; PgR: progesterone receptor.

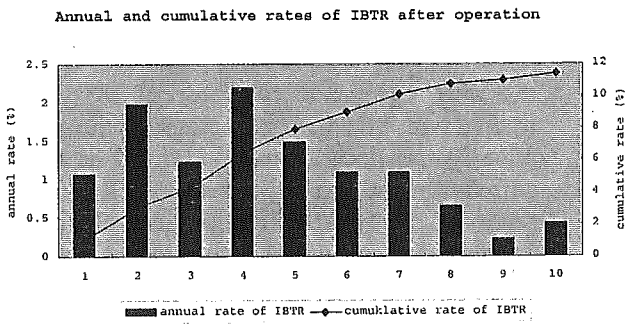

FIGURE 1. Annual and cumulative rates of ipsilateral breast tumor recurrence (IBTR) after primary operation are represented. The bar graph shows annual rates of IBTR. It was 1 to 2% up to 7 years from primary operation. After that, the incidences decreased slightly, but they did not reach zero. The incidence was highest at 4 to 5 years after primary operation. The line graph shows cumulative incidence of IBTR. It was linear to 7 years and a little flattened thereafter.

Factors associated with distant metastases among patients who developed on IBTR were analyzed. Univariate analysis showed that nodal status, lymphovascular invasion, and period to IBTR were potential risk factors for DM. Initial nodal status and interval to IBTR were independent risk factors for DM by Cox proportional hazard model (Table 4). Annual rates of DM for primary operation in patients with or without IBTR were compared (Fig. 3). The incidences of DM in the group of patients with IBTR were higher than those in the group of patients without IBTR regardless of the time after operation. More interestingly, the annual rates of distant metastases in the group of patients with IBTR showed two

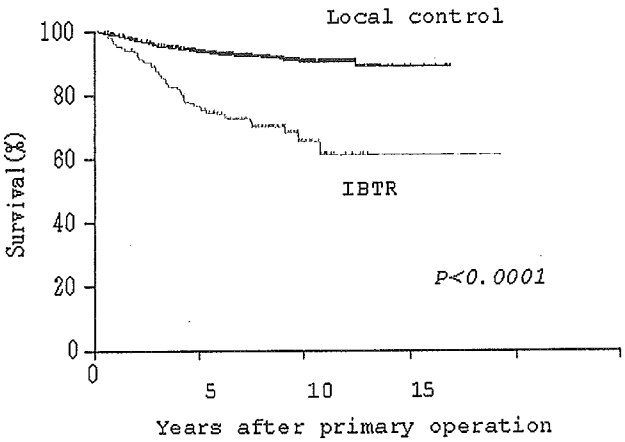

FIGURE 2. Distant-free survival after primary operation is shown according to local relapse. The distant-free survival curve shows that patients with IBTR are more likely to develop subsequent distant metastases. There was a statistically significant difference between the two groups ($P < 0.0001$). The actuarial distant-free survival rate at 10 years was 89.7% in the local control group and 70.3% in the IBTR group.

TABLE 3
Risk Factors for Distant Metastases After Breast Conserving Surgery, Results of Univariate and Multivariate Analysis

Variable	Univariate analysis HR	*P* value	Multivariate analysis HR	*P* value	95% CI
Age	0.979	0.004	0.99	< 0.30	0.978–1.008
Size	1.013	0.10			
Lymph node metastasis					
+/−	3.55	< 0.0001	3.34	< 0.0001	2.365–4.724
Surgical margin					
+/−	1.46	0.03	1.30	0.20	0.873–1.926
ly +/−	2.16	< 0.0001			
v +/−	1.98	0.002			
Nuclear grade					
3/1, 2	3.32	0.006			
EIC +/−	0.57	0.03			
ER −/+	0.79	0.16			
PgR −/+	0.64	0.01			
IBTR +/−	3.72	< 0.0001	3.93	< 0.0001	2.676–5.771

HR: hazard ratio; CI: confidence interval; ly: lymphatic invasion; v: vascular invasion; EIC: extensive intraductal component; ER: estrogen receptor; PgR: progesterone receptor; IBTR: ipsilateral breast tumor recurrence.

TABLE 4
Risk Factors for Subsequent Distant Metastases After IBTR, Results of Univariate and Multivariate Analysis

Variable	Univariate analysis *P* value	Multivariate analysis HR	*P* value	95% CI
Age	0.1724			
Size	0.5618			
Lymph node metastasis				
+/−	< 0.001	2.68	0.008	1.291–5.574
Surgical margin				
+/−	0.3113			
ly +/−	0.0161	1.21	0.599	0.888–2.506
v +/−	< 0.0001			
Nuclear grade				
3/1, 2	NE			
EIC +/−	0.2134			
ER −/+	0.4057			
PgR −/+	0.2230			
DFI	< 0.0001	0.99	0.008	0.999–1.000

HR: hazard ratio; CI: confidence interval; ly: lymphatic invasion; v: vascular invasion; EIC: extensive intraductal component; ER: estrogen receptor; PgR: progesterone receptor; DFI: disease free interval.

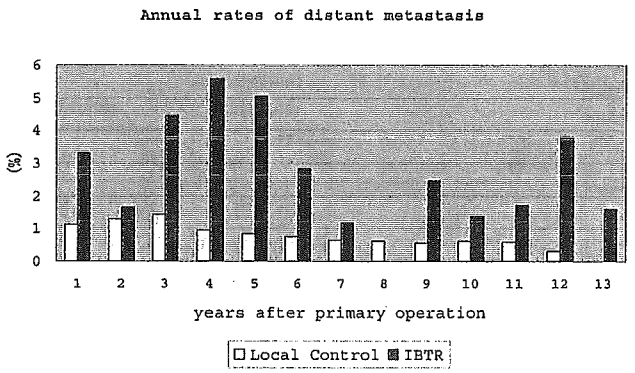

FIGURE 3. The time distribution of distant metastases after primary operation compares the local control group (LC) and IBTR group. In the group of patients without IBTR, the incidence of DM was high at 2 to 4 years after primary operation, and it gradually decreased thereafter. By contrast, in the group of patients with IBTR, the annual rates of distant metastases showed two peaks, 4 to 5 years and 12 to 13 years after primary operation. The proportion of DM after 9 years was remarkably high.

peaks, and the incidence of DM after 9 years was remarkably high. By contrast, in the group of patients without IBTR, the incidence of DM was high at 2–4 years after primary operation and subsequently decreased.

DISCUSSION

The current study was conducted to clarify the risk factors for IBTR, as well as the impact of IBTR on distant metastases in patients with early stage breast cancer treated with BCT. We first summarized the results of BCT cases in Japan with long-term follow-up. As previously reported,[36,37] the survival rates and local control rates of BCT in Japan were favorable. Risk factors of IBTR were younger age, positive margin status, and omission of postoperative irradiation. These results were consistent with previous reports.

The 10-year cumulative rates of IBTR were 8.5% and 17.2% in patients with and without radiation therapy, respectively. On a Cox proportional hazards model, postoperative irradiation decreased the risk of IBTR by about one-fourth (HR, 0.259, 95% CI, 0.214–0.431, $P < 0.0001$). This result is similar to the result of Early Breast Cancer Trialists' Collaborative Group (EBCTCG) metaanalysis.[38]

In the current study, positive surgical margins were also associated with an increased risk of IBTR as previously reported.[14–18] However, definitions of margin status are not standardized. Some researchers defined it only as "positive" or "negative".[16,20] Other studies have assessed surgical margin according to distance from the cut edge,[17] but these distances varied by < 1 mm, < 2mm, or < 10mm.[14,19,39] In the current study, the majority of close margins (≤ 5 mm from the cut edge of the specimen) were regarded as positive margins. Although judgment of margin status depends on each institution, meticulous histologic assessment was done in all institutions. (The removed specimens are examined by expert pathologists at each institute, by using 5 mm sections.)

The influence of young age on the risk of IBTR is striking. It has been supported by many previous studies.[7–11] Jobsen et al. reported that age < 40 years was the only significant predictor of IBTR for women treated with BCT with pathologic T1 tumors and negative lymph node status.[10] Harrold et al. showed a correlation with young age and IBTR by using a cut-point age of 40 years.[40] Freedman et al. also found age to be a risk factor of IBTR, but their cut-point age was 55 years.[9] Fourquet et al. categorized patients into 4 age groups (< 32, 32–45, 46–55, > 55).[7] In our series, age was analyzed as a serial variable. The results are that the younger the patient, the higher the risk of IBTR. It was noteworthy that younger age was a risk factor of IBTR regardless of age cut-point.

Our results also showed that IBTR was significantly correlated with DM, as shown by several other reports.[19–24] The HR was 3.93 by multivariate analysis. This ratio was very similar to that of NSABP B-06.[20] When compared with the relative risk (3.34) of lymph node metastasis for distant metastasis, IBTR has almost the same impact on DM.

One of the aims of this study was to clarify what type of IBTR is likely to develop subsequent DM. Univariate analysis showed that initial lymph node metastases,

lymphovascular invasion, nuclear grade, and the interval from primary operation to IBTR were significantly associated with DM. Short DFI was reported to be highly correlated with subsequent DM.[21,25,26,31,41–44] These risk factors appear to reflect the inherent aggressive characteristics of primary tumors.[38,39] Thus the risk of developing DM would be predetermined before treatment, with local recurrence being a manifestation of this risk.

The time distribution of annual rates of DM among patients with IBTR showed a noteworthy pattern. Two peaks in the incidence of DM were observed; 4 to 5 years and 12 to 13 years after primary operation. In patients without IBTR, a peak of incidence was seen 3 to 4 years after primary operation, with a gradual decrease thereafter. Our results agreed with the long-term results of NSABP B-06 and some other studies.[32,33] Some groups have presumed that the second peak of DM was due to IBTR.[28,29] Considering that late distant metastases are not likely to develop so frequently after mastectomy, IBTR may be a cause of DM in such cases. Up to now, many investigators thought that IBTR was only a marker for DM[19,20,23,24] because many cases of IBTR that subsequently developed DM had more aggressive primary tumor characteristics. Recently, however, it appears that additional radiation may lead to a survival benefit, suggesting IBTR may, in part, be a cause of DM, especially in cases of IBTR who develop late DM.[45]

Classifying IBTR into true recurrence (TR) or new primary tumor (NP) is one of the concerns. The finding that cumulative incidence of IBTR is linear to 7 years and flattens slightly thereafter (Table 1. line graph) suggests that not a few cases of late recurrence may be NP recurrence. In the current study, we did not distinguish a second primary breast cancer from true recurrence because it is difficult to correctly diagnose. Some studies suggest the prognostic significance of IBTR from this viewpoint. True recurrence is generally thought to have worse prognosis than a new primary tumor.[46–48] Haffty and colleagues speculated that a certain portion of IBTR contained new primary tumor and biologic behaviors were quite different.[48,49] So it is noteworthy that IBTR represent two distinct entities, and classifying IBTR may help our understanding of the complicated behavior of IBTR.

In summary, young age, positive surgical margin, and omission of radiation therapy are independent risk factors for IBTR, and IBTR was certainly correlated with subsequent DM. Initial nodal status and the interval to IBTR were significantly associated with DM after IBTR. It remains unclear whether IBTR is an indicator of DM or a cause of it. Further study is needed to solve this question.

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CASE REPORT

Intracystic papillary carcinoma of the breast in a male patient diagnosed by core needle biopsy: a case report

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CASE REPORT

Intracystic papillary carcinoma of the breast in a male patient diagnosed by core needle biopsy: a case report

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KEYWORDS
Intracystic papillary carcinoma;
Male breast carcinoma;
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Summary We report a case of intracystic papillary carcinoma (IPC) of the breast in a 71-year-old man in whom diagnosis was made by core needle biopsy. He came to our hospital complaining of a left subareolar mass. Imaging diagnosis was a cyst with an intracystic component. Since aspiration biopsy cytology was interpreted as a borderline lesion, the decision was made to proceed with core needle biopsy.

Pathological examination of the specimen revealed the intracystic component to be non-invasive papillary carcinoma. So the patient underwent simple mastectomy without axillary node biopsy. From the final pathological result, no invasion was identified.

Introduction

Male breast cancer is an uncommon disease with an incidence of approximately 1% of all breast cancers.[1] Intracystic papillary carcinoma (IPC) forms a small subgroup of breast carcinomas with a favorable prognosis.[2,3] Core needle biopsy has been increasingly utilized as initial approach for the diagnosis of mammographic abnormalities and palpable breast lesions. In this report, we describe a case of mammary IPC diagnosed in a 71-year-old man by core needle biopsy. We discuss the clinicopathological features of cystic breast cancer in the male and review the literature and the present case.

Case report

A 71-year-old man, complaining of a round mass in his subareolar region with bloody nipple discharge,

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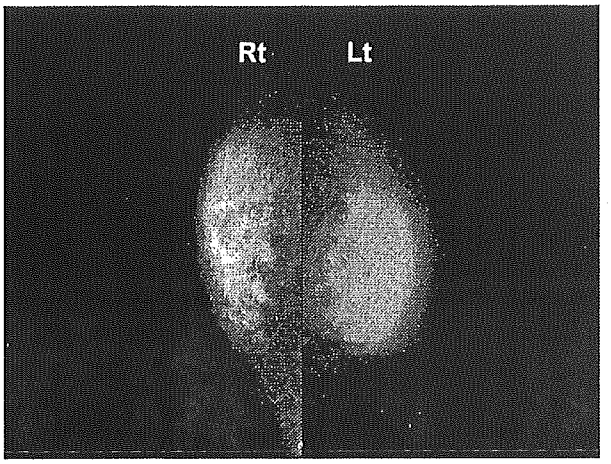

Figure 1 Mammogram revealed a 6 cm lobulated mass in his left breast and subareolar gynecomastia in his right breast.

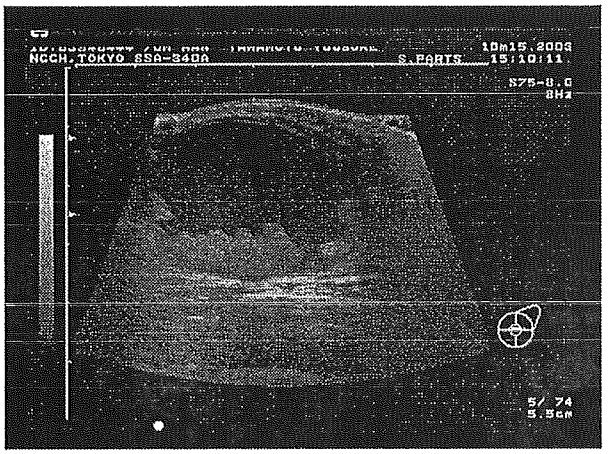

Figure 2 Ultrasound studies showed a cystic lesion with an intracystic component.

visited the National Cancer Center Hospital in October 2003. He had a past history of lung cancer and gastric cancer. There was no reported history of breast trauma. He had gynecomastia in his right breast. The tumor was $6 \times 5\,cm^2$ in size with a smooth surface and clear margin. No overlying skin retraction and no palpable axillary lymph nodes were noted.

Mammogram revealed a 6 cm lobulated mass in his left breast and subareolar gynecomastia in his right breast (Fig. 1). Ultrasound studies showed a cystic lesion with an intracystic component (Fig. 2).

We diagnosed intracystic papilloma or carcinoma from the radiological appearance of the intracystic lesion. So, the decision was made to proceed with core needle biopsy. Three passes with 16-gauge biopsy gun were performed. The diagnosis of non-invasive papillary carcinoma was made on core needle biopsy (Fig. 3). Finally, we diagnosed the

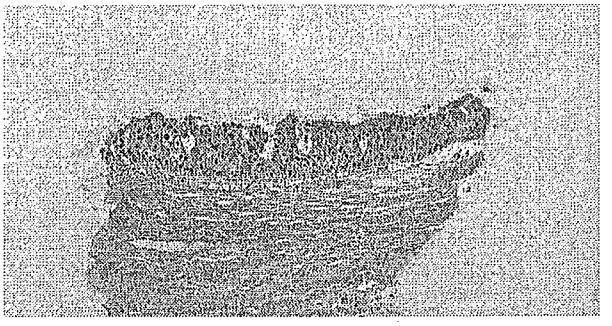

Figure 3 Core needle biopsy demonstrates a solid epithelial proliferation composed of papillary structures with fibrovascular cores lined by a uniform population of neoplastic cuboidal cells. No invasion was identified.

tumor as intracystic carcinoma from these combined informations. The patient underwent simple mastectomy without axillary lymph node biopsy. Because the role of adjuvant therapy is not clearly defined for this type of tumor, no other treatment was performed.

Pathologic findings

The specimen consisted of a simple mastectomy with an overlying ellipse skin with nipple. A $4.1 \times 2.0\,cm^2$ well-circumscribed, partially hemorrhagic cystic mass was identified under the areola. At lower-power magnification, the cyst wall was lined by multilayered flat epithelial cells, and papillary epithelial lesions with a fibrous stalk present in the wall (Fig. 4A).

At higher magnification, this solid papillary proliferation is composed of neoplastic cells with mild nuclear atypia and a high mitotic index (Fig. 4B). Since no evidence of stromal invasion was found, the lesion was diagnosed as IPC, high grade.

The immunohistological examination for cancer cells revealed positive for estrogen and progesterone receptor, and negative for HER-2 and p53 protein.

Discussion

IPC of the breast in the male is a very rare disease and it also shows a good prognosis. IPC represents a small subgroup of breast cancers and accounts 0.5–2% of breast cancer in women.[2] Some studies have suggested that they form a higher percentage in men, with an incidence range of 5–7.5%.[4,5] Furthermore, increased risk in men with gynecomastia has been reported.[6] Pacelli,[7] in a recent review of the literature, reported that nine

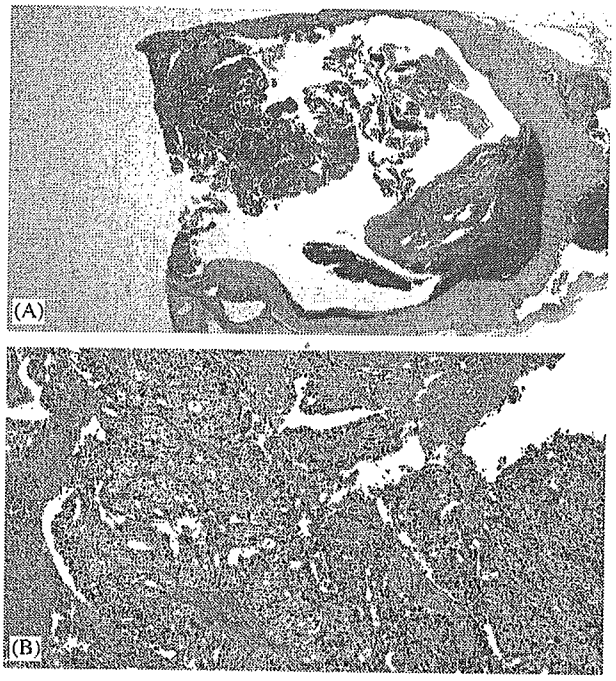

Figure 4 (A) Microscopic feature of the cystic lesion. The cyst wall was lined by multilayered flat epithelial cells, and a papillary epithelial lesion with a fibrous stalk is present in the wall. (B) At higher magnification, this solid papillary proliferation is composed of neoplastic cells with mild nuclear atypia and a high mitotic index. Since no evidence of stromal invasion was found, the lesion was diagnosed as IPC, high grade.

patients underwent fine-needle aspiration, but only four cases were positive for malignant cells. In the remaining patients, fine-needle biopsy gave either negative (two cases), or borderline results (three cases). Imoto,[8] in a review of Japanese literature, also stated that the difficulty in obtaining a definite diagnosis of malignancy by fine-needle aspirate can attributed to the cystic and hemorrhagic nature of these lesions. Only one case was reported that was diagnosed by core needle biopsy.[7] Fine-needle aspiration cytology in male breast lesions is a useful technique and has been shown to be highly sensitive and specific with good cytohistologic correlation.[9,10] However, many institutions have chosen core needle biopsy as alternative to fine-needle aspiration cytology due to the level complexity involved in the interpretation of breast cytology.[11] In our case, core needle biopsy was very useful in decision of operating procedure because of a favorable prognosis of this tumor.

The majority of the reports confirm excellent prognosis associated with pure IPC. The low frequency of axillary node metastases with pure IPC does not justify axillary lymph node dissection.[12] The role of sentinel node biopsy has not been evaluated in this disease, but sentinel node biopsy may be an excellent alternative to full axillary dissection in patients with IPC and associated invasive carcinoma. Lumpectomy is an option for pure IPC. However, the role of radiotherapy in these patients remains undefined. The majority of patients with IPC will have associated DCIS or invasive cancer, or both, and should be treated on the basis of this associated pathology.

Our case report demonstrates that the ICP can be accurately diagnosed by core needle biopsy and the radiological feature of the tumor in a male patient. Because of a favorable prognosis of this tumor, histologic finding is very important in decision of operating procedure.

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Characteristics of Patients with Prostate Cancer Who Have Initially been Treated by Hormone Therapy in Japan: J-CaP Surveillance

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Objective: Hormone therapy for prostate cancer has empirically prevailed in Japan. We planned to evaluate the trends and outcome of hormone therapy for establishing an adequate guideline.

Methods: Patients with prostate cancer who were initially treated by hormone therapy were registered through the J-CaP registration system. This report summarizes the background factors.

Results: From January 2001 to October 2003, 17 872 patients were registered from 395 institutes throughout Japan. The background factors of 17 312 patients were analyzed. The 17 872 patients were estimated as composing more than half of newly diagnosed prostate cancer patients in Japan. Of these, 22.9, 35.1, 32.9 and 8.6% belonged to T1, T2, T3 and T4, respectively. For the purposes of hormone therapy, 77.5% was primary hormone therapy. Neoadjuvant setting and adjuvant setting were 18.1 and 4.3%, respectively. About 60% of the hormone therapy was combined hormone therapy with LH-RHa plus anti-androgens.

Conclusion: Irrespective of patients' age, TNM, stage of illness, or histological background, the majority of prostate cancer patients in Japan are receiving hormone therapy. It is necessary to evaluate whether this trend is merely a continuation of past experience of Japanese urologists or if there is a difference in the profile of effect and side-effect in the case of Japanese patients compared to therapy given in Westerners.

Key words: prostate cancer – hormone therapy – endocrine therapy

INTRODUCTION

In prostate cancer treatment, hormone therapy has been used in Europe and North America mainly to provide temporary relief for advanced cancers. However, the CaPSURE report (1), released in 2003, indicates that there is a rapid increase in the use of hormone therapy on localized cancer in the United States, which suggests a drastic change in the role of hormone therapy. Meanwhile, in Japan, hormone therapy has been used over many years in a considerable number of patients with localized or locally advanced prostate cancer. In recent years, while clinical trial data (2,3) indicating its usefulness have been accumulating, the outcomes have yet to be accurately analyzed. As typically seen in the early prostate cancer (EPC) studies of recent years in Europe and North America (4), clinical trials are being reported that point to the effectiveness of hormone therapy in localized cancer (5,6). Against this backdrop, in 2001 the Japan Study Group of Prostate Cancer (J-CaP Study Group) was inaugurated with financial support from the Japan Kidney Foundation. This project has been authorized by the Japan Urological Association. The purposes of this study group were to gather information about the hormone therapy administered to Japanese prostate cancer patients living in Japan and to analyze the outcomes of treatment in order to create a guideline for optimal hormone therapy. This report summarizes the background factors of patients receiving hormone therapy across most of Japan.

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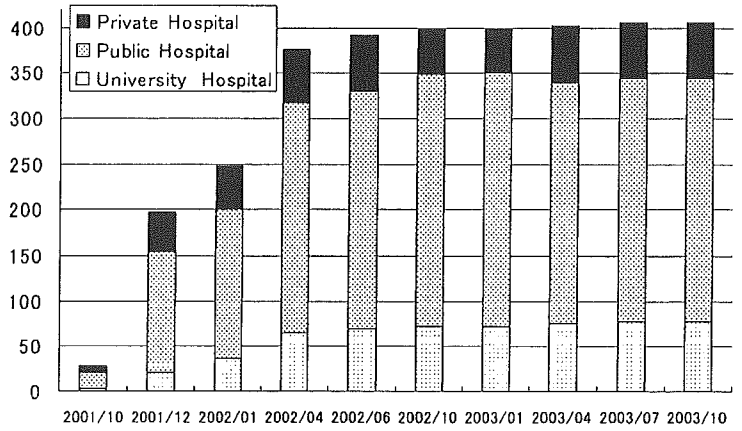

Figure 1. Overview of the year of registration and type of institution.

PATIENTS AND METHODS

The rules for the J-CaP study group are summarized in the Appendix.

ELIGIBLE INSTITUTIONS

Eligible institutions are Japanese urological institutions endorsing the purpose of this study that are able to obtain the approval of their own ethics committees (or IRB). Institutions that have not yet established their own ethics committee (or IRB) but can be vetted instead by an affiliated institution or can obtain approval from the person responsible for the institution are also included. As a rule, in each eligible institution, all cases of patients newly starting hormone therapy for prostate cancer in and after January 2001 will be regarded as subjects of the study.

PERIOD OF RESEARCH

Registration will commence when approval is obtained from the J-CaP Study Group. The term of case registration is for 3 years and the follow-up period is for 2 years.

METHOD

Data under the following headings for each registered case will be relayed to the secretariat server over the Internet: date of birth, family history, date of PSA reading, PSA value, PSA kit name, testosterone value, biopsy date, Gleason score, histological grade, clinical stage, case history, details of hormone therapy, whether or not there has been progress observation, whether or not surgery was carried out, date of surgery, operative procedure, whether or not radiotherapy is being conducted, irradiation method, irradiation date, progress. TNM classification used was the 5th edition (7). Histological grade and other criteria were adopted in accordance with the Japanese Urological Association/Japan Society of Pathology 3rd Edition of General Rules for Clinical and Pathological Studies on Prostate Cancer (8).

FOLLOW-UP METHOD

The registered cases, as a rule, are to be updated once every 3 months with regard to test data, change in treatment and progress data. The secretariat immediately contacts institutions not updating information, requesting data input. The secretariat forwards input forms for data addition, and confirms registered cases as of that date as necessary. Additionally, assistance can be given on adding test data and entering changes in treatment and progress data.

This report concerns patient background factors, tumor factors and treatment details of registered cases between 2001 and October 2003.

RESULTS

PARTICIPATING INSTITUTIONS

By October 2003, 395 institutions throughout Japan had registered, acquiring IDs and passwords. Eleven institutions of the 395 later withdrew registration. Fig. 1 gives an overview of the year of registration and type of institution. The number of university hospitals registering was 76 (60.2% of university hospitals in Japan); in detail, 35 national university hospitals (83.3%) have been included.

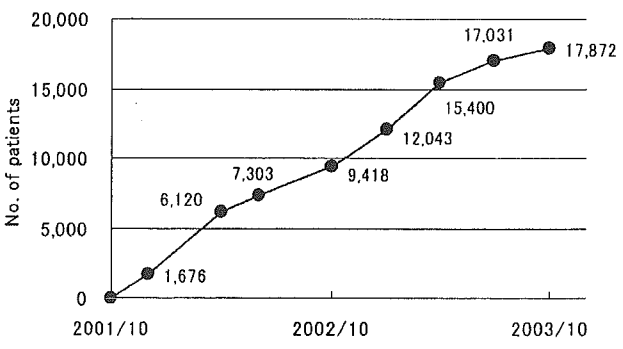

Figure 2. Cumulative number of patients registered.

Table 1. Patient backgrounds; family history of prostate cancer, age at diagnosis and PSA value at diagnosis

	2001	2002	2003	Total	%
Family history					
No history	5959	6104	1771	13 834	79.9
Within 2nd degree of relationship	120	128	29	277	1.6
Within 3rd degree of relationship	11	8	3	22	0.1
Don't know	1412	1453	314	3179	18.4
Total	7502	7693	2117	17 312	100.0
Age at diagnosis					
<60	329	320	61	710	4.1
60–64	596	620	161	1377	8.0
65–69	1197	1265	331	2793	16.1
70–74	1935	2037	567	4539	26.2
75–79	1798	1889	562	4249	24.5
≥80	1647	1562	435	3644	21.0
Total	7502	7693	2117	17 312	100.0
PSA at diagnosis					
<4	255	269	73	597	3.4
4–<10	1680	1863	556	4099	23.7
10–<20	1470	1628	493	3591	20.7
20–<50	1459	1514	387	3360	19.4
≥50	2612	2401	606	5619	32.5
No description	26	18	2	46	0.3
Total	7502	7693	2117	17 312	100.0

Number of Registered Patients

As shown in Fig. 2, 17 872 patients were registered by October 2003. This survey investigated patients who were first diagnosed with prostate cancer at the registered institutions during this period. Respectively, 7952 and 8195 new patients were reported in 2001 and 2002 by 246 and 216 institutions. Of these new patients, 5969 and 6064 were newly administered hormone therapy, and 5646 and 5651 were registered with J-CaP. In summary, it is shown that 75% of new patients were given hormone therapy in some form and 70% registered with J-CaP.

Patient Background Factors

Of the 17 872 registered patients at the time of data compilation, data were collected from 17 312 patients. 529 cases without any record of hormone therapy commencement date were excluded, as were 31 cases whose therapy was reported as commencing in 2000. Family history, age at diagnosis and PSA value at diagnosis are given in Table 1.

Tumor Background Factors

A summary of Gleason score, histological grade, TNM classification and clinical stage (TNM) is given in Table 2.

Table 2. Tumor backgrounds; Gleason score, histological grade, TNM classification, TNM clinical stage

	2001	2002	2003	Total	%
Gleason score					
2–4	654	551	150	1355	7.8
5	696	744	251	1691	9.8
6	1029	1250	401	2680	15.5
7	1595	1958	579	4132	23.9
8–10	1801	2337	590	4728	27.3
No description	1727	853	146	2726	15.7
Total	7502	7693	2117	17 312	100.0
Histological differentiation					
Well	1489	1554	453	3496	20.2
Moderate	3360	3362	990	7712	44.5
Poor	1995	1997	513	4505	26.0
Unknown	103	119	16	238	1.4
No description	555	661	145	1361	7.9
Total	7502	7693	2117	17 312	100.0
T stage					
T0	1	3	0	4	0.0
T1	1630	1813	518	3961	22.9
T2	2566	2680	832	6078	35.1
T3	2597	2509	589	5695	32.9
T4	673	657	157	1487	8.6
Tx	27	25	12	64	0.4
No description	8	6	9	23	0.1
Total	7502	7693	2117	17 312	100.0
N factor					
N0	6000	6315	1767	14 082	81.3
N1	1004	917	210	2131	12.3
Nx	462	427	119	1008	5.8
No description	36	34	21	91	0.5
Total	7502	7693	2117	17 312	100.0
M factor					
M0	5380	5696	1634	12 710	73.4
M1	157	119	12	288	1.7
M1a	83	77	11	171	1.0
M1b	1496	1428	327	3251	18.8
M1c	100	71	19	190	1.1
Mx	250	268	93	611	3.5
No description	36	34	21	91	0.5
Total	7502	7693	2117	17 312	100.0
Clinical stage					
II	3684	3987	1188	8859	51.2
II	1273	1327	326	2926	16.9
IV	2082	1945	444	4471	25.8
No description	463	434	159	1056	6.1
Total	7502	7693	2117	17 312	100.0

Table 3. Purpose of hormone therapy

	2001	2002	2003	Total	%
Hormonal therapy					
Main	5926	5914	1585	13 425	77.5
Adjuvant	306	366	81	753	4.3
Neoadjuvant	1270	1413	451	3134	18.1
Total	7502	7693	2117	17 312	100.0
Hormonal therapy detail					
Orchiectomy only	236	214	63	513	3.0
Orchiectomy + medication	605	427	96	1128	6.5
LH-RHa only	826	1065	319	2210	12.8
LH-RHa + anti-androgen	4431	4703	1249	10 383	60.0
Anti-androgen only	392	584	251	1227	7.1
Other	1012	700	139	1851	10.7
Total	7502	7693	2117	17 312	100.0

HORMONE THERAPY

As to the reason for hormone therapy, primary application of hormone therapy was the most prevalent, comprising 77.5% of the total, followed by 18.1% neoadjuvant and 4.3% adjuvant (Table 3).

Table 3 also indicates an overview of the types of hormone therapy. The combined use of LH-RHa + anti-androgen drug is the largest, comprising 60%. Anti-androgen monotherapy was 7.1% and LH-RHa monotherapy was 12.8%.

Table 4 shows the relations between the purpose of hormone therapy and T category, clinical stage, Gleason score and age. A notable feature is that in all categories, primary use of hormone therapy was the most common.

Table 5 shows the relations between the type of hormone therapy and T category, clinical stage, Gleason score and age. In all categories and ages, combined androgen blockade (CAB) was used in the main. In Table 6, details are given of the main treatment methods when hormone therapy was administered as neoadjuvant, as well as the details of main treatment methods when used as adjuvant.

COMPLIANCE OF SURVEY DATA

Omission of data entry among registered data included 0.2% of patients for whom PSA values were not recorded. Meanwhile, omission of histological grade accounted for 7.8% and omission of clinical stage 6.1%. As for Gleason score, 23% of registered cases in 2001 had no entry, but in 2002 this had decreased to 11.9% and by 2003, to 6.5%. This is thought to be because in the First Edition of the Japanese Urological Association and Japan Society of Pathology's General Rules for Clinical and Pathological Studies on Prostate Cancer, Gleason score entry was not compulsory. Only in the Second Edition did Gleason score become required.

Table 4. Relations between the purpose of hormone therapy and T category, TNM clinical stage, Gleason score and patient age

	Main	Adjuvant	Neoadjuvant	Total	%
T stage					
T0	4 (0.1%)			4	0.0
T1	2689 (67.9%)	218 (5.5%)	1054 (26.6%)	3961	22.9
T2	4260 (70.1%)	333 (5.5%)	1485 (24.4%)	6078	35.1
T3	4965 (87.2%)	174 (3.1%)	556 (9.8%)	5695	32.9
T4	1425 (95.8%)	26 (1.7%)	36 (2.4%)	1487	8.6
Tx	60 (93.8%)	2 (3.1%)	2 (3.1%)	64	0.4
No description	22 (95.7%)		1 (4.3%)	23	0.1
Total	13 425 (77.5%)	753 (4.3%)	3134(18.1%)	17 312	100.0
Clinical stage					
II	5847 (66.0%)	537 (6.1%)	2475 (27.9%)	8859	51.2
III	2263 (77.3%)	145 (5.0%)	518 (17.7%)	2926	16.9
IV	4362 (97.6%)	44 (1.0%)	65 (1.5%)	4471	25.8
No description	953 (90.2%)	27 (2.6%)	76 (7.2%)	1056	6.1
Total	13 425 (77.5%)	753 (4.3%)	3134 (18.1%)	17 312	100.0
Gleason score					
2–4	996 (73.5%)	69 (5.1%)	290 (21.4%)	1355	7.8
5	1214 (71.8%)	91 (5.4%)	386 (22.8%)	1691	9.8
6	1902 (71.0%)	120 (4.5%)	658 (24.6%)	2680	15.5
7	3179 (76.9%)	175 (4.2%)	778 (18.8%)	4132	23.9
8–10	3966 (83.9%)	185 (3.9%)	577 (12.2%)	4728	27.3
Unknown	2168 (79.5%)	113 (4.1%)	445 (16.3%)	2726	15.7
Total	13 425 (77.5%)	753 (4.3%)	3134 (18.1%)	17 312	100.0
Age at diagnosis					
<60	364 (51.3%)	48 (6.8%)	298 (42.0%)	710	4.1
60–64	767 (55.7%)	95 (6.9%)	515 (37.4%)	1377	8.0
65–69	1613 (57.8%)	234 (8.4%)	946 (33.9%)	2793	16.1
70–74	3305 (72.8%)	226 (5.0%)	1008 (22.2%)	4539	26.2
75–79	3808 (89.6%)	116 (2.7%)	325 (7.6%)	4249	24.5
≥80	3568 (97.9%)	34 (0.9%)	42 (1.2%)	3644	21.0
Total	13 425 (77.5%)	753 (4.3%)	3134 (18.1%)	17 312	100.0

FOLLOW-UP DATA

For approximately 92% of the registered cases in 2001 and 75% of the registered cases in 2002, the input of follow-up data was confirmed at least once. The period (median) from the start of hormone therapy to the latest follow-up data entry was 406 days (between 0 and 964) for 2001-registered cases and 189 (between 0 and 615) for 2002-registered cases.

DISCUSSION

In Japan, the General Rules for Clinical and Pathological Studies on Prostate Cancer issued by the Japanese Urological Association and Japan Society of Pathology were first published in

Table 5. Relations between the type of hormone therapy and T category, TNM clinical stage, Gleason score and patient age

	Orchiectomy only	Orchiectomy + medication	LH-RHa only	LH-RHa + anti-androgen	Anti-androgen only	Other	Total	%
T stage								
T0				1 (25.0%)	1 (25.0%)	2 (50.0%)	4	0.0
T1	112 (2.8%)	169 (4.3%)	719 (18.2%)	2333 (58.9%)	427 (10.8%)	201 (5.1%)	3961	22.9
T2	158 (2.6%)	277 (4.6%)	921 (15.2%)	3737 (61.5%)	532 (8.8%)	453 (7.5%)	6078	35.1
T3	196 (3.4%)	466 (8.2%)	490 (8.6%)	3513 (61.7%)	215 (3.8%)	815 (14.3%)	5695	32.9
T4	44 (3.0%)	208 (14.0%)	69 (4.6%)	752 (50.6%)	46 (3.1%)	368 (24.7%)	1487	8.6
Tx	1 (1.6%)	5 (7.8%)	8 (12.5%)	36 (56.3%)	4 (6.3%)	10 (15.6%)	64	0.4
No description	2 (8.7%)	3 (13.0%)	3 (13.0%)	11 (47.8%)	2 (8.7%)	2 (8.7%)	23	0.1
Total	513 (3.0%)	1128 (6.5%)	2210 (12.8%)	10 383 (60.0%)	1227 (7.1%)	1851 (10.7%)	17 312	100.0
Clinical stage								
II	262 (3.0%)	360 (4.1%)	1527 (17.2%)	5366 (60.6%)	841 (9.5%)	503 (5.7%)	8859	51.2
III	111 (3.8%)	157 (5.4%)	325 (11.1%)	1959 (67.0%)	135 (4.6%)	239 (8.2%)	2926	16.9
IV	115 (2.6%)	559 (12.5%)	246 (5.5%)	2449 (54.8%)	132 (3.0%)	970 (21.7%)	4471	25.8
No description	25 (2.4%)	52 (4.9%)	112 (10.6%)	609 (57.7%)	119 (11.3%)	139 (13.2%)	1056	6.1
Total	513 (3.0%)	1128 (6.5%)	2210 (12.8%)	10 383 (60.0%)	1227 (7.1%)	1851 (10.7%)	17 312	100.0
Gleason score								
2–4	31 (2.3%)	54 (4.0%)	187 (13.8%)	820 (60.5%)	157 (11.6%)	106 (7.8%)	1355	7.8
5	65 (3.8%)	91 (5.4%)	247 (14.6%)	1032 (61.0%)	152 (9.0%)	104 (6.2%)	1691	9.8
6	80 (3.0%)	146 (5.4%)	468 (17.5%)	1579 (58.9%)	241 (9.0%)	166 (6.2%)	2680	15.5
7	151 (3.7%)	247 (6.0%)	557 (13.5%)	2515 (60.9%)	267 (6.5%)	395 (9.6%)	4132	23.9
8–10	119 (2.5%)	445 (9.4%)	373 (7.9%)	2796 (59.1%)	232 (4.9%)	763 (16.1%)	4728	27.3
Unknown	67 (2.5%)	145 (5.3%)	378 (13.9%)	1641 (60.2%)	178 (6.5%)	317 (11.6%)	2726	15.7
Total	513 (3.0%)	1128 (6.5%)	2210 (12.8%)	10 383 (60.0%)	1227 (7.1%)	1851 (10.7%)	17 312	100.0
Age at diagnosis								
<60	5 (0.7%)	32 (4.5%)	76 (10.7%)	413 (58.2%)	65 (9.2%)	119 (16.8%)	710	4.1
60–64	11 (0.8%)	88 (6.4%)	176 (12.8%)	816 (59.3%)	120 (8.7%)	166 (12.1%)	1377	8.0
65–69	57 (2.0%)	175 (6.3%)	319 (11.4%)	1674 (59.9%)	239 (8.6%)	329 (11.8%)	2793	16.1
70–74	96 (2.1%)	248 (5.5%)	564 (12.4%)	2826 (62.3%)	300 (6.6%)	505 (11.1%)	4539	26.2
75–79	153 (3.6%)	302 (7.1%)	566 (13.3%)	2556 (60.2%)	259 (6.1%)	413 (9.7%)	4249	24.5
≥80	191 (5.2%)	283 (7.8%)	509 (14.0%)	2098 (57.6%)	244 (6.7%)	319 (8.8%)	3644	21.0
Total	513 (3.0%)	1128 (6.5%)	2210 (12.8%)	10 383 (60.0%)	1227 (7.1%)	1851 (10.7%)	17 312	100.0

1985 (9) and this set of rules has been widely used ever since. The document gives a guideline on diagnosis and a detailed description of rules associated with making entries on patient background, tumor background and treatment method. Most of the papers presented at such meetings, such as the academic conference of the Urological Association, follow these rules and their diffusion rate is extremely high. The J-CaP survey basically followed the rules, and the accuracy of TNM diagnoses and clinical stage diagnoses is considered to be high. The Japanese Urological Association started a prostate cancer registration system from 2001, in accordance with these rules. However, this system is a registration of all prostate cancers. Therefore, when, for example, focusing on hormone therapy, we cannot necessarily expect satisfactory outcome data.

The morbidity of prostate cancer in Japan has been remarkably lower than in Europe and North America (10). Furthermore, due to anxieties about radiotherapy and the slowness of the introduction of technical expertise in radical prostatectomy, in many cases surgical castration or estrogen administration has been conducted across the board (11). However, in recent years Japan has seen an overwhelming increase in morbidity and mortality from prostate cancer (10). Compounding this, the influx of information about prostate and surgical techniques from Europe and North America has led to a rapidly growing debate on the method of treatment. Naturally, the trend towards newer treatment is beginning with reference to European (12) and North American guidelines (13) and the trend is set to continue.

Table 6. Main treatment for adjuvant or neoadjuvant hormone therapy

	Method	2001	2002	2003	Total
Operation					
Hormonal therapy followed by surgery	Retropubic	1609	18		1627
	Laparoscopic	23			23
	Perineal	17			17
	Other	3			3
	Total	1652	18		1670
Surgery followed by hormonal therapy	Retropubic	256	3		259
	Laparoscopic	10			10
	Perineal	2			2
	Other	2			2
	Total	270	3		273
Irradiation					
Hormonal therapy followed by irradiation	External beam	647	468	69	1184
	External + brachytherapy	15	4		19
	Brachytherapy	12	6	1	18
	Other	11	6	1	118
	Total	685	484	71	1339
Irradiation followed by hormonal therapy	External beam	46	62	10	118
	External + brachytherapy	3			3
	Brachytherapy	1	3		4
	Other	1	1		2
	Total	51	66	10	127

At present, with financial assistance from the Ministry of Health, Labor and Welfare, the Japanese Urological Association is working on the drafting of a prostate cancer treatment guideline at the earliest possible date. What is of concern here is that, in addition to the circumstances previously mentioned, there have been very few clinical trials with strong evidence carried out in this country. This causes a desperate lack in clinical data specific to Japan, which is essential to establish such a guideline. Hormone therapy in Japan, which has been administered only empirically, should be re-examined correctly to determine what outcome it is actually providing for the patients. Otherwise, it is likely that Japan's treatment guideline will become a reproduction of those of Europe and North America. Ethnic and philosophical differences, religious background, differences in perceptions about sex, and economic background—these diverse factors must be taken into account in the drafting of the most appropriate guideline for a country. The general attitude toward hormone therapy in Japan is similar to other East Asian countries (14). The recent treatment and clinical trial findings on hormone therapy in Europe and North America aimed at achieving long-term stable results indicate that we should examine the outcome of hormone therapy not only in Japan but throughout the world (4–6). The CaPSURE data reported in 2003 (1) consists of the analyses of 3439 cases, showing that the proportion of primary hormone treatment on localized prostate cancer rose dramatically from 4.6% in 1989 to 14.2% in 2001 and pointed firmly to the need to review the existing guidelines.

The institutions registered with J-CaP cover 60.2% of all university hospitals. According to Japan Cancer Statistics 2003, the number of patients newly diagnosed with prostate cancer in 1998 was 15 814 (15). In view of the proportion of J-CaP registered patients obtained in the survey of new patient numbers mentioned earlier, ~50% of new prostate cancer patients were treated by hormone therapy and registered with J-CaP. J-CaP had requested reports on the number of newly diagnosed prostate cancer patients in the registered institutions. Out of 358 institutions, 246 had responded as of 2001. Based on this report, 7952 patients were newly diagnosed with prostate cancer in those 246 institutions. Of these, 5969 patients (75.1%) were treated by hormone therapy in some form. Among those patients, 5646 (71%) were registered with J-CaP. In other words, 94.6% of the patients who had initiated a hormone therapy in 2001 were registered with J-CaP. This figure is almost the same in 2002. This illustrates the breadth of significance of this study. Patient background factors and PSA values at diagnosis would not represent the general trend because of the bias that patients registered for this study are receiving hormone therapy for the first time. However, we should make a special note of the low frequency of familial prostate cancer.

For the same reason, the background to the tumor in this report would not represent the overall trend of prostate cancer in Japan. Nevertheless, considering the finding that an extremely large number of patients are receiving hormone therapy, we can safely say that they express the overall background factors of prostate cancer in Japan to a fairly high degree of accuracy.

The analysis of the purpose and types of hormone therapy shows that there is a distinctively different trend in Japan compared to Europe or North America. These are the first findings in Japan based on a large-scale organized survey. To summarize: (i) many patients are receiving hormone therapy irrespective of age, TNM, stage of illness or histological background; (ii) more than 70% of them are under primary hormone therapy; and (iii) roughly 60% undergo combined androgen blockade (CAB). Since no clear outcome investigation has yet been carried out, we should evaluate this present status of hormone therapy in Japan either as: (i) it is merely a continuation of past experience, and in the near future, it should be managed carefully by adopting European and American guidelines; or (ii) it is still difficult to judge whether the effect of hormone therapy for Japanese patients is different in the profile of effects and side-effects from that for Westerners. What is more, in T2 treatment no accurate randomized study has been conducted so far globally on whether surgical treatment and radiotherapy are truly more effective than hormone therapy. Therefore, on this point we must reserve any conclusions.

The NCI–PDQ (13) and EAU guidelines (12) attach virtually no significance to hormone therapy on T2 prostate cancer. As for T3, the emphasis is on its significance as neoadjuvant before radiotherapy and little importance is assigned to the sole application of hormone therapy. Even when there is metastasis, there is debate on whether immediate hormone therapy is appropriate and also on whether there is any point in CAB; however, no clear conclusions have been reached (16,17).

In such circumstances, there are two clinical trial results in Japan reported recently that are extremely interesting. The first (2) is the results of a randomized study on hormone therapy given to localized or locally advanced prostate cancer. This was a comparative trial of LH-RHa + chlormadinone acetate (CMA) versus LH-RHa alone on patients in whom radical prostectomy was not chosen as treatment for whatever reason. The results are interim, with an observation period less than 5 years. So far, progression-free survival is good for CAB. Even when both groups are put together, it has been determined that the same survival rate as the one expected for the population of that age group has been obtained. The other study (3) is a comparative trial of LH-RHa + bicalutamide versus LH-RHa + placebo administered for patients with locally advanced or metastatic prostate cancer. The observational period is again short, but in both PSA progression-free survival and time to PSA response, the CAB group was significantly better. Meanwhile, in a successive survey of QOL using FACT-P that was officially translated into Japanese (18), the CAB group showed a significantly better result (19). This is indicative of the perception that the effects of hormone therapy on QOL are different between Japanese and Western patients (20). Therefore, it is important to examine whether or not recent clinical trial results take into account ethnic differences in the broad sense, including the lifestyle and philosophical backgrounds of Japanese and Western people.

In future, in the treatment of prostate cancer in Japan, it is evident that the importance of hormone therapy should be investigated with specific focus on Japanese people. We await the further analysis of the outcome findings, which is the aim of the J-Cap Study.

APPENDIX

J-CAP HOME PAGE: RULES FOR USE

1. The J-CaP Home Page is to be created as an Internet server.
2. Use of the case database on the J-CaP Home Page is restricted to doctors who are joint researchers and the use of the database requires a user ID and password issued by means of prior registration.
3. Communication between the case database server and users is to be protected by encryption (SSL).
4. The names of institutions and patients (initials) displayed in the case database are to be encoded so that individual patients cannot be identified.
5. Information concerning joint researchers' institutions and patient names (initials) will only be accessible to database administrators with a special ID and password and only at the designated location (administrative secretariat).
6. The ID and password of the above-mentioned administrators will be stored as strictly confidential and no record of them will be kept.
7. The disposal of case data and information concerning joint researcher institutions and patient names (initials) after the completion of the J-CaP Study Group's research period will be determined at a later date by administrators.

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CLINICAL INVESTIGATION **Breast**

THE PATTERNS OF CARE STUDY FOR BREAST-CONSERVING THERAPY IN JAPAN: ANALYSIS OF PROCESS SURVEY FROM 1995 TO 1997

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Purpose: To present the results of a process survey on breast-conserving therapy (BCT) in Japan from 1995 to 1997.
Methods and Materials: From September 1998 to December 1999, data on the treatment process of 865 randomly selected BCT patients were collected by extramural audits.
Results: For primary surgery, wide excision or tumorectomy was performed in 372 patients (43.0%), and quadrantectomy or segmental mastectomy was performed in 493 patients (57%). The extent of axillary dissection was equal or beyond Level II in 590 patients (68.2%). Systemic chemotherapy was administered to 103 of 160 node-positive patients (64.4%) and 180 of 569 node-negative patients (31.6%). Tamoxifen was administered to 234 of 323 hormone receptor–positive patients (72.5%) and 68 of 130 hormone receptor–negative patients (52.3%). Photon energy of 10 MV was administered for whole breast irradiation in 38 patients (4.4%) without bolus.
Conclusions: The extent of surgical resection for BCT was large in Japan. Pathologic assessment and the technique of radiation therapy were apparently suboptimal in some cases. Information on prognostic/predictive factors was not fully utilized to individualize systemic adjuvant therapy. Establishment and widespread use of guidelines for BCT for in Japan are desirable. Repeated surveys will demonstrate how such guidelines affect clinical practices. © 2005 Elsevier Inc.

Patterns of Care Study, Breast-conserving therapy, Radiation therapy.

INTRODUCTION

Breast-conserving therapy (BCT) has been proved by many randomized clinical trials to produce survival results equivalent to those of mastectomy (1–6) and is now the treatment of choice for early breast cancers in Western countries. In Japan, BCT was incorporated into practice in the mid-1980s and has recently become increasingly established. The national survey conducted by the Japanese Breast Cancer Society (JBCS) indicated that in 2000 approximately 40% of patients with breast cancer received BCT (7). However, its indication and implementation were not standardized until 1999, when the JBCS published a guideline for BCT, and there still exists considerable variation around the country.

The patterns of care study (PCS) was originally developed in the United States in the mid-1970s. Such studies evaluate the structure of the facility, including both personnel and equipment, and the process of treatment and then feed back the outcome to improve the quality of cancer treatment (8–10). The Japanese version of PCS began in 1996, and treatment processes and outcomes have been reported for uterine cervical cancer, esophageal cancer, and lung cancer to date (11–13).

This study surveyed the treatment process for BCT in Japan between 1995 and 1997 and identified national averages for important factors.

METHODS AND MATERIALS

Eligibility criteria for this analysis were as follows: (1) the patient was treated between January 1995 and December 1997, (2) the patient was female, (3) there were no gross multiple tumors, (4)

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there was no diffuse microcalcification on pretreatment mammography, (5) there were no distant metastases, (6) the patient did not have bilateral lesions, (7) there were no prior or concurrent malignancies, (8) there was no prior history of irradiation of the breast, and (9) the patient did not have any collagen vascular disease other than rheumatoid arthritis.

In 1995, a total of 556 institutions nationwide were stratified into four classifications according to the Japanese facility master list, and 72 institutions were randomly sampled. Then, the subjects of this survey were randomly sampled from the lists of eligible patients supplied by these institutions (two-staged cluster method [10]). Between September 1998 and December 1999, extramural audits of institutions were conducted by the Japanese PCS Working Group. The audits were performed by member physicians of the working group. Consequently, data for the treatment process of 865 BCT patients were collected (Table 1). Although it was our initial intent to collect equal numbers of patients from equal numbers of facilities in each stratum, there were some problems, such as difficulty in getting approval of an external audit from the institutional review board or an unexpectedly large number of ineligible patients in the list provided by the facility. However, the resultant imbalance did not affect the results of this study because calculation of the national average takes these imbalances into account.

A newly developed data format based on the fifth PCS data format developed in the United States was used for this survey. The original format was provided courtesy of the American College of Radiology and modified by the Japanese PCS Working Group to accommodate the staging system of JBCS. The data format is a FileMaker Pro (version 4.0) database (FileMaker, Santa Clara, CA), installed on portable computers. It consists of 316 items, which cover all aspects of the initial treatment of breast cancer. Data were collected primarily from charts of the radiation oncology department. In addition, best efforts were made to obtain required information by using all available resources at the location. In this analysis, the extent of surgery, precision of pathologic evaluation, the technique for postoperative radiation therapy, indication and usage of systemic chemo-endocrine therapy, and the result of functional–cosmetic assessment were evaluated. National averages were calculated where applicable with Sedransk's equation (14). The details of the calculation were described by us previously (15, 16). Of note, national averages were not calculated if the amount of missing data exceeded 20%.

In the tables presented, "unknown" indicates that the item in the format was filled with data "unknown," whereas "missing" means the item in the format was left empty. We combined "unknown" and "missing" in the tables because their meanings are the same in most cases: no valid data were found in the given resources. "Unknown/missing" data for categoric data were included in the ratio calculation, whereas those data for continuous variables were excluded from the ratio calculation, as seen in a corresponding report from the U.S. PCS (17).

RESULTS

Patient backgrounds and the results of pretreatment evaluation are shown in Table 2. Of the entire group of patients, 36.2% were postmenopausal. Approximately 70% of the patients had tumor with a clinical size no larger than 2.0 cm. Approximately 90% of patients were clinically node negative.

Table 1. Definition of facility categories and the number of patients registered in each category

	No. of facilities visited	No. of patients registered
A facilities: university hospitals and cancer centers		
A1 facility (≥300 patients per year)	20	296
A2 facility (<300 patients per year)	19	193
B facilities: community-based hospitals		
B1 facility (≥120 patients per year)	18	256
B2 facility (<120 patients per year)	15	121
Total	72	865

Type and extent of breast-conserving surgery are shown in Table 3. Fifty-seven percent of patients received breast surgery equivalent to quadrantectomy. The most common procedure for the axilla was Level I/II dissection, which was used in 59.7% of patients. The mean number of dissected lymph nodes was 14.3 ± 7.1.

The results of histopathologic assessment are shown in Table 4. Approximately 80% of the patients had invasive ductal cancer. Final microscopic margin was negative in 76.7%. Of note, margin status was not documented in 9.5% of the patients. Only 14.6% of patient records showed quantification of the intraductal component of the specimen. Axillary lymph node was pathologically negative in 78.1%, and only 4.7% of patients had ≥4 positive axillary lymph nodes.

Parameters for treatment planning of tangential fields are shown in Table 5. A fixation system, such as cast or shell, was used in 32.6%. X-ray simulation was the most common method of treatment planning and was used in 67.5% of the patients. Of note, 44% of those X-ray simulations were performed without information from diagnostic CT. Dorsal margins of the tangential fields were matched in 78.7%, and the tilting technique was more commonly used than the half beam technique. Specialized fields, such as the axilla, parasternal, and supraclavicular, were seldom used.

Parameters for treatment delivery of the tangential field are listed in Table 6. The mean interval between final breast surgery and the initiation of radiation therapy was 28.5 ± 21.9 days. Approximately 60% of the patients received photons at an energy level <6 MV. There were 38 patients (4.4%) who received tangential breast irradiation with a 10-MV photon without bolus. Of note, 2.7% of the patients received whole breast irradiation with electron beam alone. The mean cranio–caudal size of the initial radiation field was 17.7 ± 2.6 cm. The most commonly used dose and fractionation was 50 Gy for 25 fractions and 50.4 Gy for 28 fractions. Consequently, overall treatment time for the initial field was 36.4 ± 8.9 days. Of note, 18.6% of the patients received treatment to only one tangential field each day.

Parameters for boost field irradiation are shown in Table 7. Boost to the tumor bed was given in 53.9%, 45.0%, and 11.9% of patients showing positive, close, and negative pathologic margins, respectively. The most commonly used