The Japanese nationwide cohort data of proton beam therapy for liver oligometastasis in breast cancer patients

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Abstract

**Purpose:** A nationwide multicenter cohort study on particle therapy was launched by the Japanese Society for Radiation Oncology in Japan in May 2016. We analyzed the outcome of proton beam therapy (PBT) for liver oligometastasis in breast cancers.

**Methods:** Cases in which PBT was performed at all Japanese proton therapy facilities between May 2016 and February 2019 were enrolled. The patients were selected based on the following criteria: the primary cancer was controlled, liver recurrence without extrahepatic tumors, and no more than three liver lesions.

**Results:** Fourteen females with a median age of 57 (range, 44–73) years and twenty-two lesions were included. The median lesion size, fraction size, and biological effective dose (BED) were 44 (20–130) mm, 6.6 (2-8) gray (Gy) (relative biological effectiveness [RBE])/fraction (fr), and 109.6 (52.7-115.2) Gy, respectively. The median follow-up period was 22.8 (4-54) months. The 1-, 2-, and 3-year local control (LC) rates of liver metastasis from breast cancer were 100% for all. The 1-, 2-, and 3-year overall survival rates were 85.7%, 62.5%, and 62.5%, respectively. The 1-, 2-, and 3-year progression free survival (PFS) rates were 50.0%, 33.3%, and 16.7%, respectively. The median PFS time was 16 months. Only one patient did not complete PBT due to current disease progression. One patient had grade 3 radiation-induced dermatitis. None of the patients experienced radiation-induced liver failure during the acute or late phase.

**Conclusions:** Owing to the low incidence of adverse events and the high LC rate, PBT appears to be a feasible option for liver oligometastasis in breast cancers.

Headings

- We analyzed the outcome of proton beam therapy (PBT) for liver oligometastasis of breast cancers using data of the Japanese nationwide multicenter cohort.

- The 1-, 2-, and 3-year overall survival rates were 85.7%, 62.5%, and 62.5%, respectively.

- Owing to the low incidence of adverse events and the high LC rate, PBT appears to be a feasible option for liver oligometastasis in breast cancers.

Introduction

Approximately 50% of breast cancer patients develop distant metastasis, which is a major cause of cancer-related mortality\(^1,2\) Most metastatic patients may have systemic disease; therefore, only a limited number of patients are candidates for local treatment. To improve the treatment outcome, various local treatments, such as surgery, radio frequency ablation (RFA), transcatheter arterial chemoembolization (TACE), and radio therapy including stereotactic body radio therapy (SBRT) and particle therapy (PT) have been applied, in combination with chemotherapy or performed alternative to, chemotherapy. Many cases are inoperable, or the patients do not wish to undergo surgery due to underlying disease, age, or the patients’ other conditions. If surgery is not possible, radiotherapy is one alternative treatment.

PT, such as proton beam therapy (PBT) and carbon-ion beam therapy (CIBT), has been reported to have excellent therapeautic effects on liver tumors due to the physical properties of the Bragg peak\(^3–5\) However, the clinical benefit for oligometastatic liver tumors is still controversial. There is also little evidence on the use of PBT for liver metastatic tumors\(^6–9\) The number of cases of liver metastasis at each institute is not large, and the number of institutions offering PBT is also small. Therefore, there are few studies that can provide sufficient evidence for the treatment of liver metastasis. There are no reports of CIBT, and there are only two reports of PBT on liver metastasis from breast cancer\(^10,11\)

In Japan, a nationwide multicenter cohort study on PT was started in May 2016 for all facilities that performed PBT and/or CIBT. Using these data, we analyzed data on PBT for liver metastasis of breast cancers. The present study was performed and managed by the Oligometastatic Cancer Working Group in the Particle Beam Therapy Committee and the Subcommittee at the Japanese Society for Radiation Oncology (JASTRO).
Materials And Methods

Study Design and Patient Enrollment

This was a nationwide multi-institutional cohort study. The study population included patients in whom PBT was performed at all Japanese PBT facilities between May 2016 and February 2019. These criteria almost all corresponded to the requirements to provide PT for oligometastatic diseases in the JASTRO system as follows:

i) Analysis on the Japanese multi-institutional cohort study dataset of PT.

Among patients registered in the Japanese multi-institutional cohort study, the dataset of patients who received PBT between May 2016 and Feb 2019 was reviewed to evaluate;

ii) number of metastatic liver tumors ≤ 3 with breast cancer;

iii) absence of recurrence in primary disease site after primary curative treatment;

iv) absence or control of the other cancers and clinically detectable recurrent or metastatic diseases other than the metastatic regions;

v) delivery of PBT to all metastatic regions with curative intent.

Procedure of PBT

The treatment indication and strategy were discussed at cancer boards in each institution. The dose and fraction of PBT were determined by referring to the unified treatment policy established by JASTRO. We used the following protocol: 64 gray (Gy) (relative biological effectiveness [RBE])/8 fraction (fr) for the hepatic periphery area away from the GI tract, and 72.6 GyE/22 fr for the adjacent hilar region type. Regarding safety, the HCC irradiation protocols of 66 GyE/10 fr, 72.6-76 GyE/20-22 fr, and 74-76 GyE/37-38 fr could be used.

Outcomes

The local control (LC), overall survival (OS), progression-free survival (PFS), and adverse events (AEs) were examined. LC was defined as the date of the event when the response evaluation criteria in solid tumor evaluation resulted in progressive disease from PBT initiation. OS was defined as the duration from the date of PBT initiation to death from any cause. PFS was defined as the duration from the date of PBT initiation to the recurrence or death from any cause death. We evaluated AEs using the Common Terminology Criteria for Adverse Events version 5.0.

Statistical Analysis

The LC, OS, and PFS rates were calculated using the Kaplan-Meier method. Factors possibly related to OS, such as tumor size (for multiple lesions, the largest size), number of liver tumors, intervention of chemotherapy, and/or hormone therapy, were investigated. The cut-off values were estimated using the receiver operating characteristic curve and area under the curve. The final cut-off value was selected as the point where the sum of sensitivity and specificity was maximized. Univariate analysis was performed using the log-rank test. P-values of < 0.05 were considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R d4 (R Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of the R commander designed to add statistical functions commonly used in biostatistics.\textsuperscript{12}

Results

Characteristics of Patients and Metastatic Liver Tumors
Fourteen females, with a median age of 57 (range, 44–73) years and twenty-two lesions were included. Nine patients had one lesion, two patients had two lesions, and three patients had three lesions. PBT was selected because nine patients had underlying disease and five patients had general conditions (age, etc.). The median lesion size, fraction size, and biological effective dose using the linear-quadratic model with $\alpha/\beta = 10$ Gy (BED)$_{10}$ were 44 (20–130) mm, 6.6 (2-8) (relative biological effectiveness [RBE])/fraction (fr), and 109.6 (52.7-115.2) Gy,respectively. The characteristics of patients and metastatic liver tumors are shown in Table 1.

**Survival Outcomes**

The median follow-up period of breast cancers was 22.8 (4-54) months. The 1-, 2-, and 3-year LC rates of liver metastasis from breast cancers were 100% for all as shown in Figure 1(a). The 1-, 2-, and 3-year OS rates were 85.7%, 62.5%, and 62.5%, respectively (Figure 1(b)). The 1-, 2-, and 3-year PFS rates were 50.0%, 33.3%, and 16.7%, respectively, and median PFS time was 16 months (Figure 1(c)).

**OS-related Factors**

Tumor size, the number of liver tumors, and the intervention of chemotherapy and/or hormone therapy at any time were not significantly related to the OS. The results are summarized in Table 2.

**Safety Outcomes**

Only one patient did not complete PBT due to current disease progression. The other patients completed PBT without interruption. One patient had grade 3 radiation-induced dermatitis. The other patients had no grade 3 or higher AEs observed. None of the patients experienced radiation-induced liver failure during the acute or late phase.

**Discussion**

Analysis of 439 patients of postoperative recurrence found that median survival times of patients with and without liver metastases were 12 and 26 months, respectively. Patients with liver metastases have a poor prognosis (P < 0.001), and liver metastasis of breast cancer is a fatal and incurable disease.

Reports on the local treatment of patients with liver metastasis of breast cancer are not sufficient. In surgical outcomes, the 3- and 5-year OS rates were 49–75% and 41–61%, respectively, with a median survival time of 42–64 months. In TACE outcomes, the 1- and 3-year OS rates were 63–76% and 13–48%, respectively, with a median survival time of 18.5–31 months. In RFA outcomes, the 1- and 3-year OS rates were 68–87% and 25.3–49.3%, respectively, with a median survival time of 26–33.5 months. There are few papers reporting treatment of SBRT for breast cancer liver metastases. However, one of the studies was also mixed on cases of lung metastases, and the results for patients with liver metastases simply are not clear.

Regarding SBRT outcomes, the 1- and 2-year OS rates were 85% and 57%, respectively. Regarding PBT outcomes, the 1- and 3-year OS rates were 88–94.1% and 71.7–73%, respectively, with a median survival time of 39.3 months. The summary of clinical results of local treatment for liver metastasis in breast cancer patients is shown in Table 3. A study of prognostic factors predicting survival from first recurrence in patients with metastatic breast cancer reported that i) size of primary tumor, ii) axillary lymph node status, iii) hormonal receptor status, iv) adjuvant radiotherapy, v) disease free interval, and vi) number of recurrence site were prognostic factors.

Many studies have reported that the indications for local treatment (TACE, RFA, and SBRT) are metastatic liver tumors less than 5 or 6 cm from the viewpoint of safety of treatment. One strength of PBT is its ability to treat larger tumors than other local treatments. The present study included seven cases of tumors larger than 5 cm, and the largest tumor was 13 cm. Only one patient suffered from G3 dermatitis, where a 3.2 cm tumor was located near the skin. PBT can be used to treat significantly larger tumors without severe adverse effects. In a past study of PBT for patients with large hepatocellular carcinoma, 22 patients whose tumors were larger than 10 cm were treated with PBT without late treatment-related toxicity of Grade 3 or higher.
In a past report, liver metastases occurred in 47 out of 912 breast cancer patients, an incidence of 5.2%. Ten of 47 patients (22.7%) presented with liver metastases only, 11 patients (25%) had synchronously locoregional recurrence and/or extrahepatic metastases, and 23 patients (52%) developed locoregional recurrence and/or extrahepatic metastases following liver metastases. Liver metastases of breast cancer patients without extrahepatic tumors were only 1.1% among all patients having postoperative recurrence. In breast cancer, tumor cells spread to the liver via systemic circulation from the primary breast local site; thus, isolated liver metastasis without extrahepatic lesion is rare.

Systemic chemotherapy is the most often used treatment for breast cancer metastases; however, local treatment may be significant if the case is appropriately selected. Systemic chemotherapy regimens with new molecular-targeted agents have been developed, but survival of liver metastasis of breast cancer is a median of 3–15 months. Although these prognostic factors, as shown in a previous report, have not been examined and cannot be definitively determined, a comparative study of the effect of systemic chemotherapy with or without TACE as local treatment for liver metastases of breast cancer after mastectomy showed that the group that received TACE had a longer survival time ($P = 0.027$). Therefore, the addition of local treatment to chemotherapy is considered significant.

Although the present study showed a high LC rate, the DFS rate deviates considerably from and is inferior to the LC rate. This is due to the appearance of new distant metastatic lesions, some of which may appear in the liver after initial PBT. This situation can occur with any local treatment. In surgery reports, the additional metastasis rates (recurrence of remaining liver and other metastatic site) after surgery were 26.6% at 1 year, 54.8% at 2 years, and 63.8% at 3 years. Liver function is considerably impaired after hepatectomy, sometimes resulting in adhesions, making repeat hepatectomy difficult. On the other hand, PBT can be used for repeated liver treatment, as evidenced by some past reports.

The present study has several limitations. First, this was not a strictly prospective study, and treatment methods were not necessarily consistent across facilities. In order to eliminate these biases, we standardized the treatment protocols, such as dose fractionation, at all PT facilities in Japan. Furthermore, we have tried to minimize inter-institutional bias by enrolling patients who had been discussed by the cancer board at each facility; each board included physicians and surgeons. Second, the sample size was small. As previous reports have shown, liver metastasis only without extrahepatic lesions is extremely rare, and it is difficult for a single institution to accumulate a fixed number of cases for these diseases. We have been collaborating with nationwide facilities to register and analyze data. In the present study, we tried to increase the number of cases. Third, because of the short observation period, there is room for reconsideration of OS and LC data. The above Japanese nationwide cohort survey has been conducted since 2016, and we will expand the observation period. Our goal is public medical insurance coverage on liver metastatic tumors. We plan to accumulate long-term follow-up data on more cases in the future. As the number of cases and observation period increase, we plan to add multifaceted analyses, including comparisons of the size of the primary tumor, axillary lymph node status, hormonal receptor status, disease-free interval, and treatment prior to and after PBT.

We analyzed the outcome of PBT for hepatic oligometastases of breast cancer using our nationwide multi-institutional cohort study. This cohort study showed the satisfactory LC rate for liver oligometastasis of breast cancer patients. There are few reports of PBT for liver metastases in breast cancer patients and we think current data were useful. In conclusion, based on the low incidence of adverse events and the high LC rate, PBT appears to be a feasible option for liver oligometastasis in breast cancer patients.

**Abbreviations**

PBT: Proton beam therapy

BED: biological effective dose

Gy: gray

RBE: relative biological effectiveness
Declarations

[Conflict of Interest Statement for All Authors]
None

[Funding]
This work was supported by AMED under Grant Number JP16lm0103004.

[Author Contributions]
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by all authors. The first draft of the manuscript was written by Hisashi Yamaguchi, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

[Data Availability]
The datasets generated during and/or analyzed during the current study are not publicly available due to including patients’ personal information but are available from the corresponding author on reasonable request.

[Acknowledgements]

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[Ethics Approval]
All procedures involving human participants performed in this study followed the ethical standards of the institutional and national research committees, as well as the 1964 Declaration of Helsinki and its subsequent amendments. The study was approved by the ethics committee of our institution (approval number 016-0106) and was registered and managed by the University Hospital Medical Information (UMIN). In addition to the UMIN clinical trial registry system, a UMIN case data repository system was implemented (approval number UMIN000022917).
Informed consent was obtained from all individual participants included in the study.

References


Tables
Table 1: Characteristics of patients and metastatic liver tumors
<table>
<thead>
<tr>
<th>Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 (44–73)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
</tr>
<tr>
<td>Performance status*</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Reasons for choosing PBT</td>
<td></td>
</tr>
<tr>
<td>underlying disease</td>
<td>9</td>
</tr>
<tr>
<td>conditions (age, etc.)</td>
<td>5</td>
</tr>
<tr>
<td>Follow-up time (months)</td>
<td>23 (4–54)</td>
</tr>
<tr>
<td>Number of tumors</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>44 (20–130)</td>
</tr>
<tr>
<td>Dose fractionation (Gy [RBE]/fr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>66/10 (40–74)/8–37</td>
</tr>
<tr>
<td>BED_{10} (Gy)</td>
<td>110 (53–115)</td>
</tr>
</tbody>
</table>

Abbreviations: Gy (RBE)/fr, relative biological effectiveness; PBT, proton beam therapy; BED_{10}, biological effective dose using the linear-quadratic model with $\alpha/\beta = 10$ Gy

*According to the Eastern Cooperative Oncology Group.

Each number means the median value with the ranges in parenthesis.

Table 2: Summary of univariate analysis results
<table>
<thead>
<tr>
<th>Factor</th>
<th>Median</th>
<th>Range</th>
<th>Cut-off value</th>
<th>AUC</th>
<th>95% CI</th>
<th>Group</th>
<th>n</th>
<th>Median OS (months)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td>44 mm</td>
<td>20–130</td>
<td>90</td>
<td>0.57</td>
<td>0.201–0.932</td>
<td>&lt; 90</td>
<td>11</td>
<td>NA</td>
<td>0.0768</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 90</td>
<td>3</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Number of tumors</td>
<td>1</td>
<td>1–3</td>
<td>2</td>
<td>0.82</td>
<td>0.581–1</td>
<td>&lt; 3</td>
<td>11</td>
<td>NA</td>
<td>0.085</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 3</td>
<td>3</td>
<td>17.1</td>
<td></td>
</tr>
<tr>
<td>Precedent</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Presence</td>
<td>9</td>
<td>NA</td>
<td>0.488</td>
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<td>Chemotherapy and/or hormone therapy</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Absence</td>
<td>5</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Concurrent</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Presence</td>
<td>3</td>
<td>21.53</td>
<td>0.349</td>
</tr>
<tr>
<td>Chemotherapy and/or hormone therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Absence</td>
<td>11</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Presence</td>
<td>5</td>
<td>17.1</td>
<td>0.365</td>
</tr>
<tr>
<td>Chemotherapy and/or hormone therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Absence</td>
<td>9</td>
<td>4.27</td>
<td></td>
</tr>
</tbody>
</table>

AUC, area under the curve; CI, confidence interval; OS, overall survival; NA, not available

Table 3: Summary of clinical results of local treatment for liver metastasis of breast cancer patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Year</th>
<th>Treatment</th>
<th>Number of patients</th>
<th>Number of tumors</th>
<th>Median OS rate (%)</th>
<th>MST (months)</th>
<th>AE grade ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porcard [18]</td>
<td>France</td>
<td>2000</td>
<td>Surgery</td>
<td>49</td>
<td>≤ 3</td>
<td>3.8</td>
<td>86</td>
<td>79</td>
</tr>
<tr>
<td>Li [19]</td>
<td>China</td>
<td>2005</td>
<td>TACE</td>
<td>28</td>
<td>S/M</td>
<td>2.8</td>
<td>63</td>
<td>30</td>
</tr>
<tr>
<td>Duan [21]</td>
<td>China</td>
<td>2011</td>
<td>TACE+C</td>
<td>44</td>
<td>S/M</td>
<td>4.6</td>
<td>76.2</td>
<td>66.7</td>
</tr>
<tr>
<td>Meloni [22]</td>
<td>Italy</td>
<td>2009</td>
<td>RFA</td>
<td>52</td>
<td>≤ 5</td>
<td>2.5</td>
<td>68</td>
<td>NA</td>
</tr>
<tr>
<td>Kümler [23]</td>
<td>Denmark</td>
<td>2015</td>
<td>RFA</td>
<td>32</td>
<td>≤ 6</td>
<td>2.0</td>
<td>87</td>
<td>68</td>
</tr>
<tr>
<td>Bai [24]</td>
<td>China</td>
<td>2019</td>
<td>RFA</td>
<td>69</td>
<td>S/M</td>
<td>2.9</td>
<td>81.8</td>
<td>50.1</td>
</tr>
<tr>
<td>Schullian [25]</td>
<td>Austria</td>
<td>2021</td>
<td>RFA</td>
<td>42</td>
<td>S/M</td>
<td>3.0</td>
<td>84.1</td>
<td>NA</td>
</tr>
<tr>
<td>Onal [27]</td>
<td>Turkey</td>
<td>2018</td>
<td>SBRT</td>
<td>22</td>
<td>≤ 5</td>
<td>2.1</td>
<td>85</td>
<td>57</td>
</tr>
<tr>
<td>Mahadevan [28]</td>
<td>USA</td>
<td>2018</td>
<td>SBRT</td>
<td>42</td>
<td>S/M</td>
<td>40 cm³</td>
<td>66.4</td>
<td>NA</td>
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<tr>
<td>Fukumitsu [10]</td>
<td>Japan</td>
<td>2017</td>
<td>PBT</td>
<td>8</td>
<td>S/M</td>
<td>4</td>
<td>88</td>
<td>NA</td>
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<tr>
<td>Kim [11]</td>
<td>Korea</td>
<td>2021</td>
<td>PBT</td>
<td>17</td>
<td>≤ 2</td>
<td>2.4</td>
<td>94.1</td>
<td>88.2</td>
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<tr>
<td>Current study</td>
<td>Japan</td>
<td>2022</td>
<td>PBT</td>
<td>14</td>
<td>≤ 3</td>
<td>4.4</td>
<td>85.7</td>
<td>62.5</td>
</tr>
</tbody>
</table>
OS, overall survival; MST, median survival time; AE, adverse events; S, solitary; M, multi focal; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; PBT, proton beam therapy; USA, United States of America; NA, not available.

Figures

Figure 1

Kaplan-Meier plot of estimated (a) local control, (b) overall survival, (c) progression free survival rates.