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Salvage radiotherapy for second oligo-recurrence in patients with breast cancer

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ABSTRACT

A new concept designated 'oligo-recurrence (OR)' has been proposed, which indicates one to several distant metastases/recurrences in one or more organs, which can be treated with local therapy, after the primary site of the cancer has been controlled. The purpose of this study was to assess the efficacy and toxicity of salvage radiotherapy (RT) for the second OR of breast cancer. The second OR was defined as once-salvaged patients with OR who had a second failure that was also detected as the state of OR. Twenty-one patients with second OR were treated with salvage RT and were retrospectively analyzed. The sites of the second OR were locoregional recurrence in 7 patients and distant metastasis in 14 patients. Salvage RT was performed at a median total dose of 60 Gy. Nineteen (90%) patients had an objective response. The median overall survival and progression-free survival (PFS) times were 41 and 24 months after salvage RT for the second OR, respectively. The 3-year local (in-field) control (LC) rates were 93%. The toxicities were mild; acute toxicities ≥Grade 3 were seen in one patient with Grade 3 dermatitis, and no late toxicity ≥Grade 2 was observed. In conclusion, salvage RT for the second OR was able to achieve a better LC rate and longer PFS time without inducing severe toxicity, and therefore may be a potentially effective modality for inducing long-term survival in select patients.

Keywords: breast cancer; recurrence; radiotherapy; oligometastases; oligo-recurrence

INTRODUCTION

Despite significant advances in the primary treatment for breast cancer patients, locoregional recurrence (LRR) occurs in 3–20% of patients treated with breast-conserving therapy, and in 2–12% of patients receiving mastectomy in large clinical trials [1]. However, several studies have demonstrated that some patients with an isolated LRR have long-term survival after salvage local treatment [2–7]. Chagpar *et al.* reported the clinical outcomes in 130 patients with an isolated LRR; time to recurrence of >24 months and node-negative status at presentation were strong predictors of a longer survival prognosis, particularly if the patients were treated with radiotherapy (RT) [7]. On the other hand, several studies have indicated that surgical resection for isolated pulmonary metastases after mastectomy or breast-conserving therapy may result in long-term survival for a substantial number of patients, and that patients with a longer disease-free interval have an excellent prognosis after complete resection [8–10]. Recently, curative-intent RT to salvage the isolated pulmonary metastasis also demonstrated favorable clinical outcomes [11]. These findings confirm that a subset of breast cancer patients with isolated LRR or distant metastasis can be salvaged.

Hellmann *et al.* defined the term 'oligometastases' as a limited metastasis with a maximum of 3 to 4 clinically detectable metastases [12]. Patients with oligometastases have a better prognosis, and curative local therapy (such as radiotherapy, surgical resection and radiofrequency ablation) plays an important role in further development of the disease. Recently, Niibe *et al.* proposed a new concept referred to as 'oligo-recurrence (OR)' to eliminate the uncontrolled primary site with several distant metastases from the oligometastases, and defined the conditions of OR as follows: (i) one to

several distant metastases/recurrences in one to several organs; (ii) primary site of the cancer controlled; (iii) one to several distant metastases/recurrences that can be treated with local therapy; and (iv) no distant metastases/recurrences other than those in (iii) [13]. Therefore, the state of OR indicates that all gross metastatic or recurrent sites could be treated with local therapy. A previous study demonstrated that first failure was detected as the state of OR, such as isolated LRR and pulmonary metastasis after mastectomy or breast-conserving therapy, and could be salvage by local therapy; however, a subset of once-salvaged patients with OR could have a second failure that was also detected as the state of OR. We have often experienced this situation in patients with breast cancer and have defined it as 'second OR.' In many cases, definitive RT has been selected to salvage the second OR at our institutions. However, to the best of our knowledge, there have been no reports of salvage RT for the second OR. The purpose of this study was to assess the efficacy and toxicity of salvage RT for the second OR of breast cancer and to identify the predictors of survival.

MATERIALS AND METHODS

Patients

From December 2000 to October 2013, patients with recurrent or metastatic breast cancer were prospectively recorded in the database for RT at the authors' institutions. During the same period, 487 consecutive patients with recurrent or metastatic breast cancer were treated with RT. There were 21 consecutive breast cancer patients with second OR who were treated with salvage RT. All of the 21 patients satisfied the following requirements of our definition for second OR and were included in this retrospective study: (i) patients had a pathologically confirmed breast carcinoma; (ii) disease-free status after initial therapy for clinically localized breast cancer had been confirmed once based on the results of a physical examination, postoperative pathological findings and computed tomography (CT); (iii) first failure was detected as OR (first OR), and disease control of the first OR after salvage local therapy was confirmed, while simultaneously there were no other distant metastases/recurrences, based on the results of a physical examination and longitudinal CT; (iv) second failure was also detected as OR (second OR), and was treated with salvage RT when the primary site and the first OR were under control before the diagnosis of the second OR (Fig. 1). Written informed consent for treatment was obtained from all patients. The study was approved by the authors' Institutional Review Boards.

The patient characteristics for the second OR are listed in Table 1. For the initial therapy, mastectomy was performed in 13 patients and breast-conserving surgery in 8. The tumor/node/metastasis (TNM) stages (based on the International Union Against Cancer TNM classification, 6th edition) were pathologically evaluated at the initial surgery: Stage I in one patient, Stage IIA in eight patients, Stage IIB in eight patients, Stage IIIA in two patients, and Stage IIIB in two patients. After the initial surgery, 7 patients were treated with postoperative RT, and 7 patients received adjuvant chemotherapy after the initial surgery as follows: FEC (cyclophosphamide, epirubicin, 5-fluorouracil) in 2 patients, CAF (cyclophosphamide, adriamycin, 5-fluorouracil) in 2 patients,

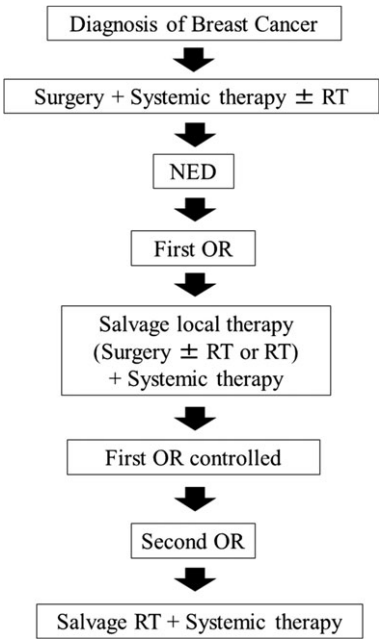

Fig. 1. Diagram showing the therapeutic process in patients who were included in this retrospective study. RT = radiotherapy, NED = no evidence of disease, OR = oligo-recurrence.

trastuzumab in 2 patients, and tegafur-uracil in 1 patient. Nine patients were treated with hormonal therapy after the initial surgery. Only one patient was treated with neoadjuvant chemotherapy, including FEC and docetaxel, before the initial surgery.

The period between the initial surgery and first OR ranged from 4 to 108 months (median, 35 months). The numbers of sites of the first OR were as follows: one site in 20 patients (locoregional recurrence in 14 patients and distant metastasis in 6 patients) and two sites in 1 patient (Table 1). The local therapies for the first OR were as follows: RT alone in 10 patients, surgery alone in 5 patients, and surgery plus postoperative RT in 6 patients. Five patients received systemic chemotherapy for the first OR followed by local therapies as follows: capecitabine in 3 patients, and EC (cyclophosphamide and epirubicin) in 2 patients. Four patients were treated with concomitant systemic therapy during the course of RT as follows: docetaxel in 2 patients, paclitaxel in one patient, and tegafur-uracil in one patient. Seven patients received adjuvant chemotherapy after local therapy for the first OR using tegafur–uracil in 2 patients, trastuzumab in one patient, trastuzumab in combination with eribulin in one patient, docetaxel in one patient, eribulin in one patient, and cisplatin in one patient. Hormonal therapy for the first OR was also used in 9 patients.

The time between the initial surgery and salvage RT for the second OR ranged from 22 to 197 months (median, 61 months). The time between the local therapy for the first OR and salvage RT for the second OR ranged from 6 to 89 months (median, 25 months). Table 1 shows the patient characteristics. The Eastern Cooperative Oncology Group performance status was evaluated at

Table 1. Patient characteristics

Variable	$n = 21$ (%)
Median age (range)	66 (47–82)
Initial surgery for primary breast cancer	
Total resection	13 (62)
Partial resction	8 (38)
Site(s) of the first OR	
One site	20 (95)
LRR	
Supraclavicular LN	6
Chest wall	6
Axillary LN	2
Distant metastasis	
Bone	4
Lung	2
Two sites	1 (5)
Supraclavicular and parasternal LN	1
Local therapy for the first OR	
RT alone	10 (48)
Surgery alone	5 (24)
Surgery+postoperative RT	6 (29)
Site(s) of the second OR	
One site	17 (81)
LRR	
Axillary LN	4
Supraclavicular LN	3
Distant metastasis	
Bone	5
Mediastinal LN	3
Brain	1
Lung	1
Two sites	2 (10)
Parasternal LN and pleura	1
Thoracic spine and iliac bone	1
Three sites	2 (10)
Multiple lung metastases	1
Supraclavicular (contralateral), cervical and parasternal LN	1

OR = oligo-recurrence, LN = lymph node, RT = radiotherapy, LRR = loco-regional recurrence.

the start of the salvage RT for the second OR. The subtype status was based on the original region. Two of the 21 patients were pathologically diagnosed as having second OR, and the remaining 19 patients were diagnosed based on longitudinal computed tomography (CT) scans and tumor marker levels; in some cases, magnetic resonance imaging ($n = 3$) and/or ^{18}F-fluorodeoxyglucose positron emission tomography/CT ($n = 2$) were also used. The sites of the second OR are listed in Table 1.

The treatment methods for the second OR are shown in Table 2. Two of the 21 patients received systemic chemotherapy for the second OR followed by salvage RT as follows: tegafur–uracil in one patient, and trastuzumab in one patient. Six patients were treated with concomitant systemic chemotherapy during the course of RT as follows: vinorelbine in 2 patients, docetaxel in 2 patients, paclitaxel in one patient, and tegafur-uracil in one patient. Four patients received adjuvant chemotherapy after the salvage RT for the second OR using capecitabine in one patient, tegafur–uracil in one patient, docetaxel in one patient, and paclitaxel in one patient. Hormonal therapy for the second OR was also used in 9 patients.

Salvage RT for the second OR

All the 21 patients were treated with external RT (Table 2). The total radiation dose of the salvage RT, using a 4, 6 or 10 MV linear accelerator, ranged from 40 to 76 Gy (median, 60 Gy), the daily dose was 2.0–3.0 Gy (median, 2.0 Gy), and, exceptionally, one patient with brain metastasis was treated with whole-brain RT (30 Gy in 10 fractions) plus stereotactic RT (35.2 Gy in 8 fractions). Computed tomography–assisted three-dimensional treatment planning (Xio or FOCUS; CMS Japan, Tokyo, Japan) was used to determine the radiation fields in all of the 21 patients. Prophylactic nodal irradiation for axillary or supraclavicular lymph node (LN) lesions was administered in 4 patients; the clinical target volume (CTV) was defined as the gross tumor volume (GTV) and the axillary LN area plus a 0.5 cm margin. Prophylactic irradiation was also performed for the mediastinal LN region in 2 patients and whole brain in one patient. The planning target volume (PTV) included the CTV plus a 1.0–2.0 cm margin for the daily set-up variation. Normally, the initial field area covered the PTV with a two-field or four-field box technique, and the field was then shrunk to the GTV (tumor of the second OR) with 0.5–1.5 cm margins at a dose of 40–50 Gy for the boost doses of 10–20 Gy using a multifield beam arrangement or conformational therapy. The remaining patients were treated without prophylactic irradiation and with RT using a three-dimensional conformal technique; the CTV was defined as

Table 2. Treatment methods for the second oligo-recurrence

Variable	$n = 21$ (%)
Salvage RT for the second OR	
Median total dose (Gy, range)	60 (40–76)
Median daily dose (Gy, range)	2 (2–3)
Tumor response to neoadjuvant systemic therapy before salvage RT for the second OR	11 (52)
Hormonal therapy	
NC	4
PD	5
Chemotherapy	
NC	1
PD	1
Concurrent systemic therapy during the salvage RT for the second OR	15 (71)
Hormonal therapy	9
Chemotherapy	6
Adjuvant systemic therapy after the salvage RT for the second OR	10 (48)
Hormonal therapy	6
Chemotherapy	4

OR = oligo-recurrence, RT = radiotherapy, NC = no change, PD = progressive disease.

the GTV plus 0.5 cm, and the PTV was the CTV plus 0.5–1.5 cm for the daily set-up variation and respiratory movement.

Four (19%) of the 21 patients were also treated with hyperthermia during the salvage RT. Hyperthermia was applied after irradiation once per week for radiosensitization via the 8-MHz radiofrequency-capacitive regional hyperthermia system (Thermotron RF-8; Yamamoto Vinita, Osaka, Japan) [14, 15]. The heating duration was adjusted from 40 to 50 min based on the patient's tolerance (median, 50 min). The number of hyperthermia treatments during the RT ranged from 2 to 5 (median, 5).

Evaluation and follow-up

The objective tumor response was evaluated by measuring the tumor size by CT before and 1–6 months after salvage RT for the second OR, and follow-up evaluations were performed by CT every 1–6 months. The treatment response was evaluated according to the World Health Organization criteria [16]. A complete response (CR) was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks. A partial response (PR) was defined as a minimum 50% reduction in the sum of the products of the longest perpendicular diameters of all measurable lesions.

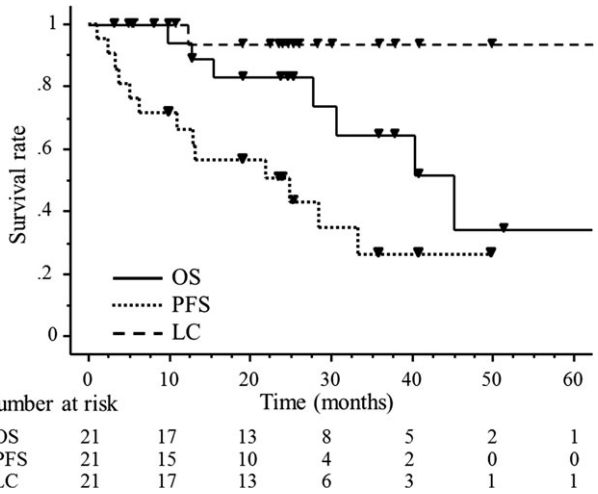

Fig. 2. Overall survival (OS), progression-free survival (PFS), and local (in-field) control rates (LC) after salvage radiotherapy (RT) for the second oligo-recurrence (OR).

Progressive disease (PD) was defined as either a 25% increase in measurable lesions or the appearance of any new measurable or non-measurable lesions. Patients who did not meet the definitions of response or progression were classified as having no change (NC).

The overall survival (OS), progression-free survival (PFS) and local control (LC) (defined as failure to have a recurrence within the radiation field for the second OR) rates were calculated from the start of the salvage RT for the second OR using the Kaplan–Meier method. The statistical significance of the difference between the actuarial curves was assessed using the log-rank test. To identify the prognostic factors for the OS and PFS rates, univariate analyses were performed. A multivariate analysis was not performed due to the small number of patients.

The National Cancer Institute Common Toxicity Criteria version 3 (CTCAE) was used to score the patient toxicity. The highest toxicity grade obtained for each patient was used for the toxicity analysis. The toxicity was defined as acute (during therapy and up to 3 months after the combination therapy) or late (over 3 months after the completion of the combination therapy).

RESULTS

The median follow-up for the surviving patients after the salvage RT for the second OR was 25 months (range, 3–156 months). All patients completed the planned radiation treatments. Nineteen (90%) of the 21 patients experienced an objective response; CR in 12 patients, PR in 7 patients, and NC in 2 patients. The first sites of disease progression after the salvage RT for the second OR were out-field alone in 11 patients (52%) (axillary LN in 3 patients, lung in 2 patients, supraclavicular LN in one patient, brain in one patient, bone in one patient, and multiple organs in 3 patients) and both in-field and out-field in 2 patients (10%); none of the patients had first sites locally (in-field) alone. All of the patients with disease progression after salvage RT for second OR underwent various types of systemic therapy and/or local treatment. Three patients were treated with third salvage RT after second OR, and one patient underwent

Table 3. The results of the univariate analyses of factors predicting the survival rates after the salvage RT for the second oligo-recurrence

Variable	*n*	Overall survival rate		Progression-free survival rate	
		2-year (%)	*P*	2-year (%)	*P*
Age			0.0808		0.199
<60 year	6	83		67	
≥60 year	15	83		45	
Hormonal status			0.964		0.452
Positive	9	86		49	
Negative	12	80		50	
Subtype			0.636		0.877
Triple negative	5	80		40	
Others	16	84		54	
Site of the second OR			0.0405		0.347
Soft tissue	13	90		52	
Visceral organ or bone	8	71		47	
Tumor size of the second OR			0.267		0.824
≥3 cm	8	71		38	
<3 cm	13	91		60	
Pattern of the first and second OR			NR		0.922
LRR→LRR	7	100		54	
LRR→DM or DM→DM	14	77		49	
Total dose of salvage RT for the second OR			0.0561		0.173
≥51 Gy	12	91		56	
<51 Gy	9	71		42	
Objective tumor response			0.129		0.437
CR	12	90		47	
non-CR	9	75		53	
Adjuvant systemic therapy after salvage RT for the second OR			0.777		0.659
Yes	9	88		56	
No	12	79		48	
Period between start of initial surgery and the second OR			0.768		0.951
≥72 months	8	86		50	
<72 months	13	82		52	

RT = radiotherapy, OR = oligo-recurrence, CR = complete response, NR = not reached, LRR = loco-regional recurrence, DM = distant metastasis.

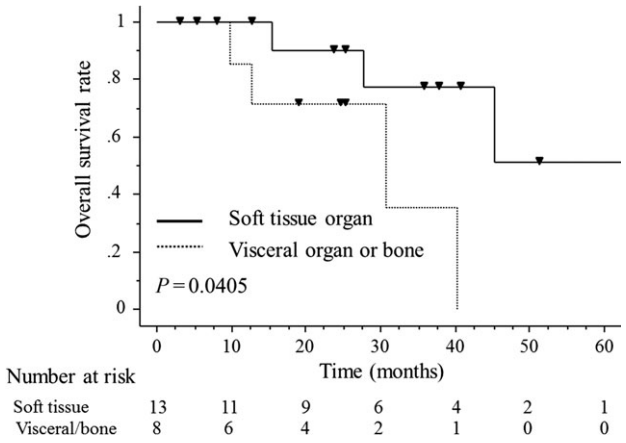

Fig. 3. Presence of the recurrence within soft tissue, compared to that within a visceral organ or bone, was significantly associated with a better overall survival (OS) rate after salvage radiotherapy (RT) for the second oligo-recurrence (OR).

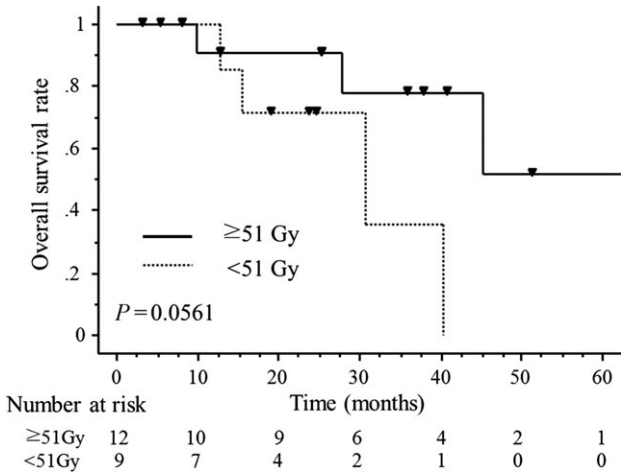

Fig. 4. The total dose of the salvage radiotherapy (RT)_ for the second oligo-recurrence (OR) (≥51 Gy) tended to achieve a significantly better overall survival (OS) rate after salvage RT for the second OR ($P = 0.0561$).

fourth salvage RT. During the follow-up period, 8 (38%) of the 21 patients were alive without disease, and 6 patients (29%) were alive with disease. Seven patients (33%) died after second OR.

The observed toxicities were mild. Acute toxicities ≥Grade 2 occurred in 10 patients (48%): Grade 3 dermatitis in one patient, Grade 2 dermatitis in 7 patients, and Grade 2 esophagitis in 2 patients. No late toxicities ≥Grade 2 were observed.

The 2-year OS, PFS, and LC (in-field) rates after RT for the second OR were 83%, 51% and 93%, respectively (Fig. 2). The 3-year OS, PFS, and LC (in-field) rates were 65%, 26% and 93%, respectively. The median survival times (MST) with regard to the OS and PFS rates after the salvage RT for the second OR were 41

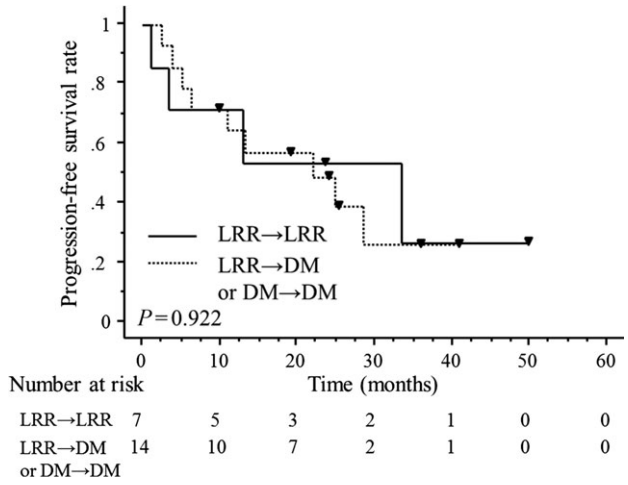

Fig. 5. Patients associated with the first oligo-recurrences (ORs) of loco-regional recurrence (LRR) and the second ORs of LRR did not achieve better progression-free survival (PFS) rate after salvage radiotherapy (RT) for the second OR.

and 24 months, respectively. The univariate analyses indicated that location of the second OR in soft tissue was significant for achieving a better OS rate (Table 3, Fig. 3). The total dose of salvage RT for the second OR (≥51 Gy) and age (<60 years) tended to be significant factors for achieving a better OS rate (Fig. 4). Patients associated with the first OR of the LRR and second OR of the LRR did not show a better PFS rates (Table 3, Fig. 5).

DISCUSSION

The present study is, to the best of our knowledge, the first study to evaluate the efficacy and toxicity of salvage RT for a second OR as a selected type of metastatic/recurrent breast cancer. As most cases of metastatic/recurrent breast cancer are not curable, the standard management of these patients has been systemic chemotherapy; however, as aforementioned, local therapy may play an important role in treating patients with OR. The previously reported therapeutic results for salvage local therapy for the condition of OR can be divided into two categories. One is isolated LRR after disease-free status has been achieved by initial therapy for breast cancer. The other is isolated distant metastasis after the disease-free status (Table 4) [2–6, 8–10, 17–21]. In most of those results, the lesions of OR conformed to the first OR. However, a subset of once-salvaged patients with the first OR may have had second OR. Selecting this subset of patients for study means that, our selection of patients for salvage RT is unique.

For previously reported clinical outcomes of the isolated LRR as the first OR, Table 4 indicates that the 5-year OS ranged from 34% to 62% after local salvage therapy. Jeong *et al.* demonstrated the clinical outcomes for surgery plus postoperative RT or RT alone in 71 cases of breast cancer patients with isolated LRR after mastectomy. Second isolated LRR occurred in 5 (7%) patients, 3 of whom received surgery and 1 of whom received RT; single-site metastasis occurred in 26 (37%) patients [6]. Those patients were comparable with the patients who experienced second OR. However, the

Table 4. Major reports of the local therapy for the oligo-recurrence and the results of the current study in patients with breast cancer

Series (Ref.)	Year	No. of patients	No. of patients with the first OR (%)	Site of the OR	Local therapy	Treatment outcomes
Isolated LRR						
Magno [2]	1987	162	162 (100)[a]	LRR	surgery+RT or RT	5-year OS; 34%, 5-year DFS; 28%
Schwaibold [3]	1991	128	128 (100)	LRR	surgery+RT or RT	5-year OS; 49%, 5-year DFS; 24%, 5-year LRC; 43%,
Deutsch [4]	2000	70	70 (100)	LRR	RT	5-year OS; 36%, CR rate; 87%.
Kuo [5]	2008	115	115 (100)	LRR	surgery+RT or RT	5-year OS; 57%, MST; 106 months, MDFS; 52 months
Jeong [6]	2013	71	71 (100)	LRR	surgery+RT or RT	5-year OS; 62%, MST; 87 months, MDFS; 36 months
Isolated DM						
McDonald [8]	1994	60	60 (100)	lung	surgery	5-year OS; 38%, MST; 42 months, MDFS; 18 months
Planchard [9]	2004	125	125 (100)	lung	surgery	5-year OS; 45% , MST; 50 months
Welter [10]	2008	47	40 (85)	lung	surgery	5-year OS; 36%, MST; 32 months
Milano [11]	2009	40	36 (90)	lung	SBRT	4-year OS; 59%, 4-year PFS; 38%, 4-year LC; 89%
Raab [18]	1998	34	29 (85)	liver	surgery	5-year OS; 18%, MST; 27 months
Selzner [19]	2000	17	14 (82)	liver	surgery	5-year OS; 22%, MST; 24 months, 5-year DFS; 17%
Kondziolka [20]	2011	24	N.A.	brain	SRS ± WBRT	MST 17 months
Niibe [21]	2008	7	N.A.	bone	RT	All the patients were alive at the last follow-up.
Present study		21	second OR	various	RT	5-year OS; 34%, MST; 41 months, MPFS; 24 months

OR = oligo-recurrence, LRR = loco-regional recurrence, DM = distant metastasis, SBRT = stereotactic body radiotherapy, SRS = stereotactic radiosurgery, WBRT = whole-brain radiotherapy, OS = overall survival, DFS = disease-free survival, LRC = local and/or regional control, CR = complete response, MST = median survival time, MDFS = median disease-free survival, PFS = progression-free survival, MPFS = median progression-free survival, N.A. = not available. [a]Twenty-seven patients were treated with systemic therapy alone.

treatment outcomes for the second OR were not described. Kuo *et al.* also reported that the 5-year OS rate was 57% in 115 patients with isolated LRR treated with local therapy; 20 (17%) had a second isolated LRR after local therapy, which was comparable with a second OR. However, treatment details for the second OR were not stated [5]. In the present study, 7 patients had isolated LRR as the second OR; they were treated with salvage RT and showed favorable treatment outcomes without severe toxicity; the 2-year OS, LC and PFS after salvage RT for the second OR were 100%, 100% and 54%, respectively.

Distant metastasis in patients with breast cancer tends to occur in the lung, bone, liver, brain, and lymph nodes [22]. In previously reported treatment results of those distant metastases as the first OR, the 5-year OS rates after salvage local therapy ranged from 18% to 45% (Table 4). McDonald *et al.* reported the clinical outcomes in 60 patients with pulmonary metastasis treated with surgery as the first OR, and observed that pulmonary metastases of the second OR treated with a second thoracotomy occurred in 2 patients. One patient had a wedge excision 9 months after the initial pulmonary resection, but expired due to disease recurrence 33 months after the second thoracotomy. The other patient had a lobectomy 6.3 years after the initial thoracotomy and is still living 24 months later without evidence of disease [8].

Recently, several studies have shown that curative-intent RT using modern techniques in patients with oligometastatic disease, including breast cancer, have resulted in good local tumor control

without severe toxicity [23]. Milano *et al.* reported that a prospective study of curative-intent stereotactic RT in patients with 5 or fewer oligometastatic lesions at various sites demonstrated that breast cancer patients had significant improvements in their OS rates; the 4-year OS rates in the breast cancer and non-breast cancer patients were 54% and 16%, respectively [17]. The same study also reported the clinical outcomes of curative-intent stereotactic RT in 40 patients with oligometastatic breast cancer; 36 (90%) patients were comparable with patients experiencing a first OR; they achieved a 4-year OS of 59% [11]. In the present study, salvage RT for patients with distant metastasis as the second OR also resulted in high local (in-field) control rates. Our results showed a 2-year PFS rate of 49%, which was promising, although the OS rates were relatively low in comparison to the treatment results of the first OR (Table 4).

In the present study, long-term PFS time and high LC rates were observed after salvage RT for the second OR, without severe toxicities. Nevertheless, we believe that additional systemic treatment may also be necessary for the second OR, because the first sites of disease progression were recognized out-field of salvage RT for the second OR in every patient who experienced disease progression. Recently, Milano *et al.* reported that patterns of recurrence after curative-intent RT for oligometastases, and, eventually, new metastases occurred in 73% of patients with the oligometastases [24]. Factors that have previously been reported to be associated with a favorable prognosis in patients with recurrent/metastatic breast cancer include: younger age, complete remission after initial therapy for breast cancer, soft tissue metastasis, smaller recurrent/metastatic tumor volume, and a longer period between the initial surgery and recurrence/metastasis [25–28]. Greenberg *et al.* indicated that younger age was a favorable predictor of a long-term CR in metastatic breast cancer patients who achieved a CR following combination chemotherapy [26]. In the present study, we also found that patients with a soft tissue location for the second OR and younger patients tended to achieve an increased OS time after salvage RT. Therefore, we speculate that additional systemic treatment should be selected, particularly for second OR patients without the aforementioned prognostic factors.

There are limitations associated with this study. Due to the fact that the current study was a small retrospective case series with heterogeneous treatment, the possibility of some selection bias with regard to the prognostic factors could not be ruled out. For example, the addition of prophylactic irradiation in the lymph node area or brain depended on the treatment policy of the attending physician. We considered that prophylactic irradiation was not necessarily needed for salvage RT. However, prophylactic irradiation of the LN area is essentially performed in our recent policy (with the exception of cases in which re-irradiation is performed), because several studies have demonstrated that salvage RT with prophylactic irradiation of the LN area achieved high locoregional control rates without severe toxicity in breast cancer patients with OR in the LNs [6, 29, 30]. A formal prospective trial with detailed treatment protocols is needed in order to determine the efficacy of and prognostic factors for this therapy in breast cancer patients with second OR.

In conclusion, salvage RT in breast cancer patients with second OR may achieve a long-term PFS time and high LC rate without inducing severe toxicity and is a promising treatment that may result in long-term survival in select patients with second OR. Further evaluations with detailed treatment protocols are necessary in order to clarify whether salvage RT could improve survival in breast patients with second OR.

CONFLICTOF INTEREST

There are no conflicts of interest.

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