Acta Med. Okayama, 2024
Vol. 78, No. 1, pp. 15–20

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Lung Oligometastasis of Breast Cancer: Prospective Cohort Study of Treatment Strategies (SBP-06)

Reina Maeda[a,b], Tadahiko Shien[a]*, Mina Takahashi[c], Kengo Kawada[d], Yukiko Kajiwara[b], Shinichiro Kubo[e], Daisuke Takabatake[f], Shoichiro Ohtani[b], Kinya Matsuoka[g], Hajime Hikino[h], Yutaka Ogasawara[d], Naruto Taira[i], Shozo Osumi[c], Masahiko Ikeda[e] and Hiroyoshi Doihara[a]

[a]*Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama 700-8558, Japan,*
[b]*Department of Breast Surgery, Hiroshima City Hiroshima Citizens Hospital, Hiroshima 730-8518, Japan,*
[c]*Department of Breast Oncology, NHO Shikoku Cancer Center, Matsuyama 791-0280, Japan,*
[d]*Department of Breast and Endocrine Surgery, Kagawa Prefectural Central Hospital, Takamatsu 760-8557, Japan,*
[e]*Department of Breast and Thyroid Surgery, Fukuyama City Hospital, Fukuyama, Hiroshima 721-8511, Japan,*
[f]*Department of Breast Surgery, Kochi Health Sciences Center, Kochi 781-8555, Japan,*
[g]*Department of Breast and Thyroid Surgery, Ehime Prefectural Central Hospital, Matsuyama 790-0024, Japan,*
[h]*Department of Breast Surgery, Matsue Red Cross Hospital, Matsue 690-8506, Japan,*
[i]*Department of Breast and Thyroid Surgery, Kawasaki Medical School, Kurashiki, Okayama 701-0192, Japan*

While local treatment of metastases is considered to be unrelated to prognosis, previous studies have suggested that local treatment of isolated lung metastases may have positive prognostic impact. We designed this prospective cohort study to investigate the clinical situation and its outcomes. We enrolled patients with fewer than 3 lung nodules suspected of being oligometastases after curative breast cancer surgery. Treatments, including local and systemic therapy, were selected by the physician and patient in consultation. The primary outcome was overall survival (OS); secondary outcomes were the efficacy and the safety of the surgery for lung oligometastases. Between May 2015 and May 2019, 14 patients were enrolled. Resection of lung nodules (metastasectomy) was performed in 11 (78.6%) of 14 patients, and one of these cases was diagnosed as primary lung cancer. Metastasectomies were all performed employing video-assisted thoracic surgery (VATS) without perioperative complications. Systemic therapies were administered to all patients except one. The respective 3-year and 5-year OS rates of patients with lung oligometastases were 91.6% and 81.5%, respectively. Progression occurred in 6 patients: 3 of the 10 with metastasectomy and all 3 without this surgical procedure. Lung metastasectomy was worthwhile as a diagnostic evaluation and may provide long-term benefit in some patients.

Key words: oligometastasis, breast cancer, lung, metastasectomy

Recently, the continual emergence of new biological anticancer agents has allowed long-term control of symptoms due to metastases and prolonging the lives of patients with breast cancer. For patients diagnosed with metastatic breast cancer between 2008 and 2017, the median overall survival (OS) was 38.8 months and the 5-year survival rate was 33.8% [1]. However, cure is not deemed possible for these patients because the cancer cells have already spread systemi-

Received February 25, 2023; accepted August 9, 2023.
*Corresponding author. Phone: +81-86-235-7265; Fax: +81-86-235-7269
E-mail: tshien@md.okayama-u.ac.jp (T. Shien)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

cally. In fact, the mechanisms of cancer metastases may be more heterogeneous than originally conceived. Fisher first suggested the systemic hypothesis, *i.e.* that clinically apparent cancer is a systemic disease [2]. Hellman advocated the spectrum hypothesis, which involves some cancers remaining locoregionally confined, while others are metastatic at presentation, and some progress from locoregional confinement to metastatic disease [3]. Then, Hellman and Weichselbaum together proposed the term "oligometastatic" disease for certain tumors that concentrate their metastases in a single organ or a limited number of organs, such that local therapy might actually be a curative treatment when administered either alone or combined with systemic therapy [4].

Previous study results have suggested that local treatment, either surgical resection or ablative radiotherapy of isolated lung metastases, may be beneficial and increase OS in highly selective patients [5]. However, those were retrospective findings. As the evidence obtained was insufficient, the Clinical Practice Guidelines continue to recommend lung metastasectomy only for diagnostic purposes, *i.e.*, to distinguish primary lung cancer from metastatic breast cancer [6].

We designed this prospective cohort study (SBP-06) to investigate the therapeutic and diagnostic clinical situation of oligometastatic breast cancer in the lung, as well as the outcomes of patients with this disease.

Materials and Methods

SBP-06 was a prospective cohort study that enrolled patients from 5 centers involved in the Setouchi Breast Project Comprehensive Support Organization. The inclusion criteria were age ≥18 years and ≤80 years, first and only lung metastasis suspected after curative breast cancer surgery, fewer than 3 lung nodules detected by Positron Emission Tomography - Computed Tomography (PET-CT) and/ or CT, and confirmed estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) expressions for the primary breast tumor. Postoperative imaging and blood tests were not stipulated.

Treatments, including local and systemic therapy, were selected by physicians in consultation with their patients. The patients were followed for at least 5 years. The primary outcome in this study of oligometastasis of breast cancer detected in the lung was OS; secondary outcomes were the efficacy and safety of surgery for these lesions in the lung.

Based on the methods of previous studies, the expected 5-year OS rate was assumed to be 30% and the threshold to be 50%, respectively. Based on an α value of 0.05 and a β value of 0.2, the target sample size was defined as 35 patients. Categorical variables were compared using the chi-square test. All statistical analyses were performed using JMP software (version 10, SAS Institute, USA).

This study was approved by the Institutional Review Board (IRB No. 960) of the Okayama University Hospital, Okayama, Japan, and was registered in the clinical trials database UMIN (UMIN000016999) on 31 March 2015. Written informed consent was obtained from all enrolled patients.

Results

Between May 2015 and May 2019, 14 patients were enrolled at 5 centers. Baseline characteristics are listed in Table 1.

Eleven (78.6%) of 14 patients underwent resection of lung nodules. Ten of these 11 patients were pathologically diagnosed as having metastases from breast cancer while one was diagnosed with primary lung cancer. One patient had already been diagnosed as having metastases from breast cancer by biopsy before lung metastasectomy. Two of three patients who did not undergo metastasectomy of the lung were diagnosed by biopsy. ER status had changed to positive for one patient and PgR status had became negative for another, such that the discordance rates between metastases and the primary tumor were 8.3%, 10%, and 0% for ER, PgR, and HER2 expressions, respectively (Table 2).

Operations were all performed employing video-assisted thoracic surgery (VATS) and achieved complete resection. The mean operation time was 87 min (27-186 min), the mean hospitalization period was 10.2 days (5-14 days), and the median blood loss amount was 5 ml (0-160 ml). No perioperative complications were reported.

Treatments and outcomes were evaluated in 13 patients excluding the one found to have primary lung cancer. Systemic therapies such as chemotherapy, as well as endocrine and HER2-directed therapies, were administered to all patients except one who declined all treatments offered, including metastasectomy (Table 1).

Table 1 Baseline characteristics, treatment and outcomes

	Age	Stage	Subtype (primary)	Perioperative treatment		DRFS	Lung nodule					Treatment for MBC		Survival	Follow-up period
				Chemotherapy	Hormonetherapy		Number	Maximum diameter (cm)	Pathology	Subtype	Surgery	Systemic treatment (1st line)	PFS		
1	48	IIB	Luminal	DTX	TAM	8Y5M	2 in one lung	0.9	Breast cancer	Luminal	+	TAM	no new lesion	alive	4Y10M
2	54	IIA	Luminal	-	LHRHa + TAM	3Y7M	1	0.5	Breast cancer	Luminal	+	LHRHa + ANA	no new lesion	alive	5Y1M
3	64	IIA	Luminal HER2	AC (EC)→ DTX + trastuzumab	ANA	5Y7M	1	0.8	Breast cancer	Luminal HER2	+	FUL	no new lesion	alive	3Y1M
4	65	I	Luminal	5-FU	ANA	18Y4M	1	0.9	Breast cancer	Luminal	+	TAM	no new lesion	alive	5Y5M
5	47	IIIB	Luminal HER2	FAC (FEC)→ DTX + trastuzumab	TAM	6Y2M	1	1.3	Breast cancer	Luminal HER2	+	DTX + trastuzumab + pertuzumab	no new lesion	alive	4Y3M
6	66	IIA	Luminal	-	TAM	5Y8M	1	1.6	Breast cancer	Luminal	+	TC	no new lesion	alive	3Y11M
7	55	I	Luminal	-	-	17Y8M	1	1.2	Breast cancer	Luminal	+	LET	no new lesion	alive	10M
8	49	IIB	HER2	FAC (FEC)→ DTX + trastuzumab	-	4Y3M	1	0.5	Breast cancer	HER2	+	DTX + trastuzumab + pertuzumab	5M (new lesion in lung)	alive	5Y5M
9	54	I	Triple Negative	TC	-	2Y5M	1	0.7	Breast cancer	Triple Negative	+	S-1	3Y5M (brain)	alive	4Y8M
10	66	IIA	Triple Negative	AC (EC)→DTX	-	2Y2M	1	1.5	Breast cancer	Triple Negative	+	CAP	1Y (chest wall)	dead	3Y5M
11	75	I	Luminal	-	ANA	1Y2M	1	1.7	Lung cancer	-	+	-		alive	6Y10M
12	74	IIB	Triple Negative	AC (EC)→PTX	-	3Y4M	1	-	Breast cancer	Luminal	-	-	10M (lung)	alive	3Y2M
13	72	I	Luminal	AC (EC)	ANA	10Y11M	1	-	Breast cancer	Luminal	-	FUL	1Y (bone)	alive	3Y10M
14	55	IIB	Luminal	TC	LET	1Y1M	2 in one lung	-	not evaluated	-	-	TAM	11M (bone)	dead	1Y6M

One patient (No. 11) was diagnosed with primary lung cancer.
DRFS, distant recurrence-free survival; DTX, docetaxel; AC, doxorubicin+cyclophosphamide; EC, epirubicin+cyclophosphamide; 5-FU, fluorouracil; FAC, 5-FU+AC; FEC, 5-FU+EC; TC, DTX+cycrophosphamide; TAM, tamoxifen; ANA, anastrozole; LET, letrozole; CAP, capecitabine; FUL, fulvestrant; S-1, Tegafur/Gimeracil/Oteracil.

The median follow-up was 51 months (10-82 months). The primary outcome event, death from any cause, occurred in 2 (15%) of 13 patients (Fig. 1). The respective 3-year and 5-year OS rates of patients with oligometastatic breast cancer lesions in the lung were 91.6% and 81.5%. Median progression-free survival (PFS) was 40 months for all patients with oligometastatic breast cancer lesions in the lung. Median PFS was not reached in cases receiving metastasectomy and was 11 months without metastasectomy ($p = .0121$) (Fig. 2).

Progression events occurred in 6 patients: 3 (30%) of the 10 with metastasectomy and all 3 (100%) foregoing this procedure. Whereas 2 of 10 patients with metastasectomy survived 5 years without progression, progression events in all patients without metastasectomy occurred within 1 year.

Discussion

For patients with a first presentation of metastatic disease, pathological examination of an accessible metastatic site should be performed to confirm the diagnosis and re-establish receptor status. When patients undergo surgery for lung metastases of breast cancer, some lung nodules prove to be unrelated to the known cancer, *i.e.*, the lesions may be primary lung cancer, benign tumors, or metastases of another origin, in 12-57% of patients [7, 8], as confirmed by our data.

Reevaluation of the receptor status of metastasis did not affect the selection of treatments in this study; however, Kin *et al.* reported

Table 2 Changes of receptor status

	Positive conversion	Negative conversion	Discordance rates
ER (n = 12)	1	0	8.3%
PgR (n = 10)	0	1	10%
HER2 (n = 10)	0	0	0%

ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

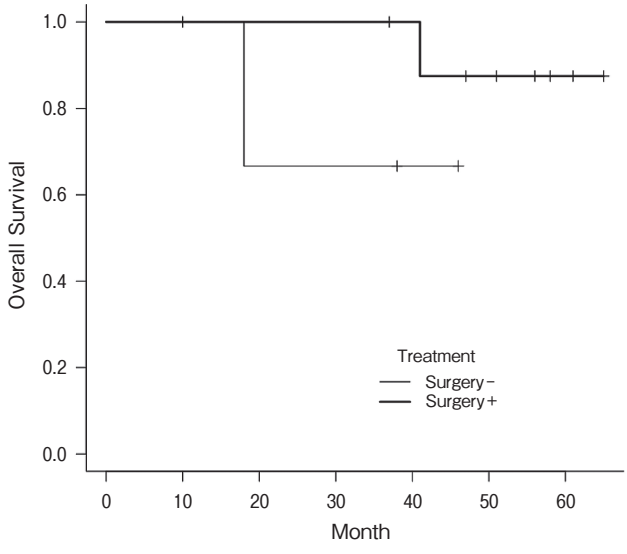

Fig. 1 Overall survival curve for patients with and without metastasectomy.

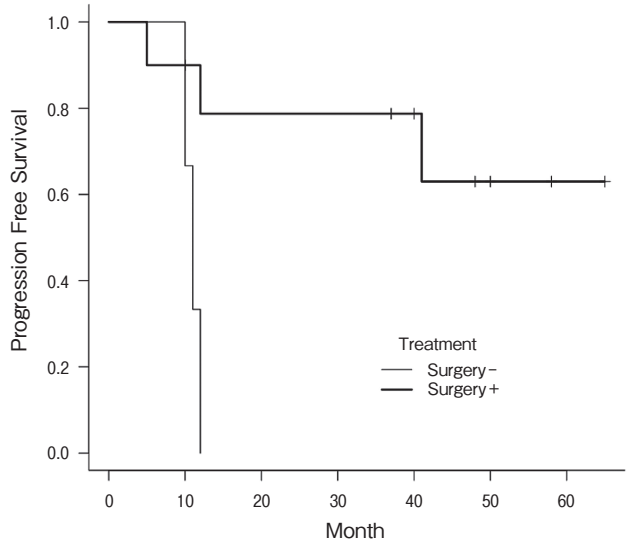

Fig. 2 Progression-free survival curve for patients with and without metastasectomy.

that changes in the subtypes of metastases affected treatment selection in 18% of their patients [9]. Furthermore, gene examination of biopsy tissue may contribute to selecting the optimal approach among the new biological treatments becoming available.

Pathological studies are on occasion performed employing a bronchoscopic approach or CT-guided transthoracic needle biopsy, but the accuracies of diagnosis for lung nodules less than 10 mm are reportedly 44% [10] and 70% [11], respectively. The size of the largest lung nodule in the present study was ≤ 10 mm in 6 patients and 11-20 mm in 5 patients. In this trial, we did not decide the modality of radiological examination to diagnose the metastasis, and biopsy of metastasis was not mandatory. Thus, the size of the metastatic lesions in the 3 patients without metastasectomy was not calculated. Lung metastasectomy is more invasive than either the bronchoscopic approach or CT-guided transthoracic needle biopsy; however, VATS has increasingly been performed in recent years because it is less invasive than thoracotomy with fewer intraoperative complications, and in many cases complete resection of parenchymal metastases can be achieved [12]. As complete lung metastasectomy was performed employing VATS all in cases and there were no perioperative complications in this study, our experience indicates that lung metastasectomy by VATS is a reasonable approach to lung oligometastasis of breast cancer.

In general, the role of local management of metastatic breast cancer is palliation of symptomatic sites. However, some studies have raised the possibility of prolonging survival in highly selective patients with good performance status, a long disease-free interval, and/or oligometastatic disease. Local therapy for lung oligometastases from breast cancer has been shown to result in long-term disease control in a retrospective study and meta-analyses [13-15]. In the largest dataset on lung metastasectomy in 467 breast cancer patients, reported by Friedel *et al.*, the median survival was 37 months (5-year OS was 38% and the 10-year OS was 22%) [13]. The present work, a prospective cohort study, also suggested the survival benefit of lung metastasectomy. The outcomes of patients with lung oligometastasis in our study were much better than those reported previously, possibly due to the development of

more effective drug treatments in recent years. Indeed, the lung metastasectomy procedures in the study reported by Friedel were performed between 1960 and 1994 [13]. Another factor explaining improved survival might be advancements in imaging studies allowing early detection of metastasis. On the other hand, follow-up CT scans to detect asymptomatic relapse are not recommended in the Japanese Breast Cancer Society Clinical Practice Guidelines for Breast Cancer. The frequency of CT scans at each facility varies, which may be the reason the number of the patients was only 14, far smaller than the defined sample size of 35; this is an important limitation of this study.

A randomized phase 3 trial might be required to provide definitive evidence of the survival benefit of metastasectomy for lung oligometastasis of breast cancer. NRG-BR002 (NCT 02364557) is an ongoing phase 3 trial designed to determine whether ablative radiotherapy (through stereotactic body radiotherapy) and/or surgical resection of all known metastases in oligometastatic breast cancer patients improves OS.

Prognostic factors impacting local therapy include the number of metastases, length of disease-free interval, and the completeness of resection [13, 16, 17]. Progression events occurred in all 3 patients with a disease-free interval (DFI) < 36 months in our study.

Whether local therapy for metastases with systemic agents prolongs survival may depend on how extensive the micrometastases are. At present, the number of detectable metastases or the DFI can serve as prognostic markers for the severity of micrometastases. New biomarkers such as circulating tumor cells (CTCs) and circulating tumor DNA have been shown to predict poor outcomes [18, 19]. CTCs will be evaluated as a translational primary objective in NRG-BR002, and the results obtained might contribute to the selection of patients who would benefit from local therapy for metastases.

Ablative radiotherapy is an alternative to surgical resection as a local treatment strategy for metastasis and reportedly improves OS [20]. However, surgical resection has the advantage of allowing histopathologic examination; furthermore, ablative radiotherapy is invasive with a treatment-related death rate of 4.5% [20]. Nonetheless, ablative radiotherapy may be useful for treating metastases that are difficult to resect such as central lung metastases or metastatic lesions in unresectable organs.

In conclusion, this prospective cohort study showed that lung metastasectomy by VATS was a reasonable approach to determining the pathological diagnosis and reevaluating receptor status with acceptable safety and invasiveness. Some patients who underwent lung metastasectomy survived 5 years or more without progression events, raising the possibility of achieving long-term benefits of local therapy for metastases. Phase 3 trials might be required to provide definitive evidence and to provide criteria for selecting patients most likely to benefit from this strategy as well as determining the optimal timing of local therapy.

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