Surgical therapy for pulmonary metastasis of breast cancer

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Abstract: Metastatic breast cancer (MBC) is a disease with heterogeneous manifestations that arise from a variety of modes of spread from the primary disease. The lung is a common site of metastasis from breast cancer. A solitary lung nodule appearing on radiological examination following breast cancer treatment is likely to be diagnosed as pulmonary metastasis from breast cancer. However, the reported final pathological diagnoses include primary lung cancer and MBC in approximately 48–67% and 23–43% of cases, respectively. Moreover, some pulmonary metastases of breast cancer have radiological and histological characteristics similar to those of primary lung cancer. Thus, the differential diagnosis of a solitary lung nodule after treatment of breast cancer is challenging. Oligometastatic disease (OMD) is characterized by solitary or limited numbers of detectable metastatic lesions. OMD in the lung from colorectal cancer can be considered for locoregional treatments either alone or in combination with systemic therapy. In MBC patients, the indication for locoregional treatments for pulmonary metastasis is controversial, whereas surgical intervention can be performed to obtain tissue for histological and molecular confirmation and occasionally for curative intent in selected MBC patients. While several retrospective studies have examined the clinical impact of pulmonary metastasectomy (PM) in MBC patients, no prospective randomized trials have been conducted. Our systematic review of PM in MBC patients found that PM might offer a survival advantage in selected MBC patients with a long disease-free interval (DFI), small number of pulmonary metastases, complete resection, and/or hormone receptor positivity. Metastases are usually detected by radiological examinations such as computed tomography (CT) and positron emission tomography-CT. The detectability of these radiological examinations mainly depends on tumor size (size-dependent manner). By contrast, the amount of circulating tumor DNA (ctDNA) released by apoptotic or necrotic tumor cells depends on the tumor burden in the whole body, regardless of radiological detectability (dose-dependent manner). Since ctDNA assays reportedly reveal residual disease several weeks earlier than radiologic imaging does, monitoring for radiological tumor size and ctDNA concentration during the clinical course may help to inform the indication for local treatment in patients with MBC and may improve their clinical outcomes. This article reviewed the current status of PM in MBC patients with pulmonary metastasis and discussed future perspectives.

Keywords: Pulmonary metastasectomy (PM); oligometastasis; differential diagnosis

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Introduction

Metastatic breast cancer (MBC) encompasses primary breast cancers with distant metastasis and recurrence after surgery. In general, cure is rarely achieved in patients with MBC; thus, systemic therapy is the standard of care for this disease. Although recent advances in systemic therapies have led to improved survival in patients with MBC (1-3), their clinical outcomes remain unsatisfactory. The elucidation of patient subgroups that may benefit from different treatment strategies is of great interest. The lung is an important site of metastasis from breast cancer (4-6). Multiple pulmonary metastases are commonly observed in patients with MBC; however, a solitary or limited number of metastases may also be detected (4). Cases in which a solitary lung nodule is detected in patients previously treated for breast cancer require histological confirmation for differential diagnosis and treatment strategy because this manifestation represents something other than recurrent disease such as primary lung cancer or benign lung tumor (7,8). Women treated for breast cancer have an increased risk of second malignancies, including lung cancer, compared to the general population (9,10). Most pulmonary metastases show typical radiological features of smooth and ovoid margins but occasionally show radiological signs similar to those of primary lung adenocarcinomas, such as margin notching or irregularity (8). The histological diagnosis of MBC and primary lung adenocarcinoma is also difficult (11).

Oligometastatic disease (OMD) is characterized by a solitary or limited number of detectable metastatic lesions (12,13). Patients with OMD may receive locoregional treatments either alone or in combination with systemic therapy with curative intent (14). In colorectal cancer, the clinical practice guidelines from the European Society for Medical Oncology (ESMO) (15) and National Comprehensive Cancer Network (NCCN) (16) recommend surgical intervention or other locoregional treatments in patients with “resectable” OMD. The reported 5-year survival rates after surgical intervention range from 20% to 45% for complete resection of liver or pulmonary metastasis. In MBC (15). OMD accounts for 1–10% of all newly diagnosed patients (17,18), and locoregional treatment remains controversial in this population.

This review presents and discusses available data on MBC of the lung for differential diagnosis and local treatment, especially surgical treatment, which may be associated with improved survival in select patients.

Clinical features of pulmonary metastasis in breast cancer

At the time of diagnosis, only 5–10% of breast cancer patients have distant metastasis (19,20). However, more than 30% of breast cancer patients experience recurrence (6). The bone, liver, lung, and brain are common sites of distant metastasis in breast cancer (21,22). At diagnosis, most pulmonary metastases are asymptomatic; however, progression may cause serious conditions and symptoms such as cough, hemoptysis, pleural effusion, and pulmonary dysfunction, which profoundly affect patients’ quality of life and survival (6). There is a need to establish better treatment strategies for pulmonary metastasis in breast cancer.

The reported incidence of pulmonary metastasis in patients with breast cancer ranges from 7% to 24% according to histological and molecular subtypes (23). Visceral metastasis such as pulmonary metastasis preferentially occurs in triple-negative breast cancer (TNBC) patients, while bone metastasis is frequent in non-TNBC patients (23-26). The incidence of pulmonary metastasis can reach 40% in TNBC and 20% in non-TNBC patients (26). Different subtypes exhibit distinctive behavior concerning the sites of distant metastasis (6).

Management of a solitary lung nodule after first breast cancer

Solitary lung nodules observed after breast cancer treatment are traditionally considered to represent metastasis from the breast (27). It is difficult to completely avoid misdiagnosis of a solitary lung nodule in patients after treatment of the first breast cancer, and inappropriate treatment is thus possible (28). Although the radiological features on computed tomography (CT) imaging usually differ between primary lung cancer and metastatic lung tumor, differential diagnosis using radiological examination can be misleading because some pulmonary metastases have an irregularly-shaped appearance similar to that of primary lung cancer (8). The final pathological diagnosis of solitary lung nodules include primary lung cancer, MBC, and benign tumor in 48–67%, 23–43%, and 5–10% of cases, respectively (7,27,29). Therefore, in patients with a solitary lung nodule and a history of breast cancer, differentiation of MBC lung...
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retrospectively investigated the clinical outcomes of

PM requires resection of all detectable lung nodules. Partial or sublobar resection is usually performed as PM; however, lobectomy or more extensive resection is occasionally performed to avoid residual tumor (35).

Mediastinal lymph node (LN) dissection is not commonly performed in patients with MBC (35), but lobectomy with mediastinal LN dissection can be performed if primary lung cancer is likely to be considered. Intrathoracic LN metastasis occurs in 39% of patients with thoracic metastasis from breast cancers (36), 13–44% of patients with pulmonary metastasis from colorectal cancers (37,38), and 35% of patients with renal cell carcinomas (39). However, no randomized controlled trials have been conducted to determine the therapeutic effect of LN dissection in these patients, and the indications for LN dissection remain controversial (35).

During surgery, pulmonary metastasis is usually detected by manual palpation by the surgeon’s fingers or the use of surgical instruments. Localization of target lesions can be difficult if they are small, multiple, and/or centrally located. In these cases, multiple localization techniques, including CT-guided use of a short hook wire (40) and bronchoscopic multipot dye-marking (41), have also been applied. Using these techniques and/or manual palpitation, the video-assisted thoracoscopic approach can also be performed for PM (42). However, an open thoracotomy is sometimes needed for more elaborate exploration to confirm the presence of metastasis by palpation and to perform extended resections of large lesions.

**Clinical impact of PM for breast cancer**

Regarding patient selection for PM, in general, it is important that (I) the primary disease site is controlled, (II) there are no other systemic metastases, or if present, they are actively managed, and (III) an adequate disease-free interval (DFI) is present to confirm “oligometastatic” disease (35,43). In most MBC patients, PM is considered for histological confirmation along with the determination of molecular status, and the role of local treatment is limited (35). Yhim et al. retrospectively investigated the clinical outcomes of consecutive recurrent breast cancer patients with a limited number of isolated pulmonary metastases (less than 4), who received PM followed by systemic treatment (PM group) or systemic treatment alone (non-PM group), during 1997–2007 (44). The authors reported a significantly longer 4-year OS in the PM group than that in the non-PM group (82.1% vs. 31.6%, P=0.001).

Our systematic review assessed survival and prognostic
factors for PM in patients with pulmonary MBC. An electronic search of PubMed, complemented by manual searches of the English literature, identified eligible studies using the keywords [“pulmonary metastasectomy” AND “breast cancer”], [“lung metastasectomy” AND “breast cancer”], [“pulmonary resection” AND “metastatic breast cancer”]. After excluding inadequate literature such as case reports, those including other malignancies, and review articles, nine studies were retrieved (45-53) (Table 1).

The patients’ age at PM diagnosis ranged from 50 to 62 years. The DFI, defined as the interval between surgery for primary breast cancer and the appearance of pulmonary metastases, was 26 to 90 months. The 5-year survival rate in MBC patients undergoing PM was 35–72%. The frequently reported significant favorable prognostic factors were DFI (four studies; >3 or 8 years), number of pulmonary metastases (four studies; 1 or <5), complete resection (three studies; R0), and the hormone receptor status of the metastases (three studies: positive). This evidence suggests that PM may be a treatment option in selected patients with MBC; however, prospective randomized trials are necessary to establish an optimal treatment strategy.

Monitoring of circulating tumor DNA (ctDNA) levels

A precise determination of disease status (limited or multiple metastases) is important to consider the indication for local treatment in patients with MBC. Disease status is usually diagnosed by radiological examinations such as CT and PET/CT. The detectability of these radiological examinations depends on the tumor size (size-dependent manner) (Figure 1). Circulating cell-free tumor DNA (ctDNA) is released by apoptotic or necrotic tumor cells (54). Using sensitive molecular assays, cancer-specific aberrations can be detected in the ctDNA and used for cancer screening, therapeutic target identification, real-time therapy monitoring, and early diagnosis (54,55). ctDNA levels depend on the tumor burden in the whole body (dose-dependent manner) (Figure 1), and changes in ctDNA levels are associated with tumor volume (56). In clinical course, ctDNA dynamics can be used as a surrogate marker for relapse and metastasis in patients with lung (57) and breast (58,59) cancers. Importantly, ctDNA analysis can detect incipient recurrence earlier than radiological diagnostic modalities with an average lead time of 10 months (range, 2–15 months) (60).

In patients with a limited number of radiologically detectable metastases (solitary or a few), ctDNA levels

| Author       | Country   | Study period      | Type of study | n   | Age (year) median, range | DFI (months) median, range | Median OS (months) | 5-yr OS rate (%) | Favorable prognostic factors |
|--------------|-----------|-------------------|---------------|-----|--------------------------|-----------------------------|--------------------|-------------------|-----------------------------|
| Mimoto (45)  | Japan     | 2004–2011         | Retrospective | 17  | 62 [39–79]               | 90                          | NR                 | NR                | NR                          |
| Meimarakis (46) | Germany   | 1982–2007         | Prospective   | 81  | 50 [28–76]               | NR                          | NR                 | NR                | NR                          |
| Kikler (47)  | Poland    | 1994–2002         | Retrospective | 33  | 53 [33–75]               | 52                          | 72.2               | NR                | NR                          |
| Chen (48)    | Japan     | 1991–2007         | Retrospective | 41  | 50 [35–81]               | 55 [0–192]                 | NR                 | NR                | NR                          |
| Welte (49)   | Germany   | 1998–2004         | Retrospective | 47  | 55 [35–80]               | 44 [0–310]                 | 32                 | 36                | ER/PR positive           |
| Friedel (50) | International | 1990–1996        | Retrospective | 17  | 59 [21–87]               | 43                          | 45                 | 35                | ER/HER2 positive          |
| Simpson (51) | United States | 1984–1996       | Retrospective | 59  | 59 [21–81]               | 26 [1–247]                | 42                 | 37.8              | Not identified           |
| Staren (52)  | United States | 1972–1990       | Retrospective | 33  | 50                       | 48                          | 48                 | 55                | Not identified           |
| DFI, disease-free interval; OS, overall survival; ER, estrogen receptor; PR, progesterone receptor; R0, complete resection; NR, no refer.
Figure 1 Tumor burden and radiological detectability in limited or multiple metastasis. Radiological detectability is mainly affected by tumor size (size-dependent), regardless of tumor burden (TB) in whole body. By contrast, the amount of circulating tumor DNA (ctDNA) is affected by TB in whole body (dose-dependent), regardless of the size of a maximum tumor. In clinical course, monitoring of radiological size and ctDNA amount may help to distinguish limited metastasis from multiple metastasis by comparing the rate of increase in tumor size with the rate of increase of ctDNA. Furthermore, dynamics of ctDNA after local treatment is useful to consider the indication of adjuvant therapy in MBC patients. Exam., examination; MBC, metastatic breast cancer.
increase in proportion to the growth rate of radiologically detectable tumors (Figure 1). By contrast, in patients with multiple undetectable metastases and a limited number of radiologically detectable metastases, ctDNA can be detected at an earlier point of the clinical course and ctDNA levels continue to increase regardless of the growth rate of a radiologically detectable tumor. Monitoring of ctDNA levels may help to determine the treatment strategies for patients with MBC.

Future perspectives
Regarding local treatments other than surgery, remarkable advances have been made in radiotherapy, including the development of stereotactic ablative body radiotherapy (SABR) and thermal ablation therapies including radiofrequency ablation, microwave, and cryotherapy (61-63). The usefulness of these methodologies has been reported for lesions that are difficult to resect. SABR or thermal ablation can benefit patients with pulmonary OMD, particularly those at a high risk for surgery or those who refuse surgery (35).

Currently, various novel anticancer drugs such as cytotoxic cancer drugs, and molecular-targeted drugs, and immune checkpoint inhibitors are being developed. Various ongoing clinical trials are assessing these drugs in monotherapy or combination therapy (64). Since treatment strategies for MBC patients are rapidly changing, the indications for PM in MBC patients should be discussed by multidisciplinary teams including respiratory surgeons, breast cancer physicians, oncologists, and radiation therapists.

Conclusions
Differential diagnosis of a solitary lung tumor is difficult in patients with a history of breast cancer treatment. Some pulmonary metastases in breast cancer have radiological and histological characteristics similar to those of primary lung cancer. In MBC patients with pulmonary metastasis, selected MBC patients with a small number of lung tumors, long DFI, or hormone receptor positivity may benefit from the resection of pulmonary metastasis; however, the selection criteria have not been clearly defined. Using novel technologies and modalities, patient selection for individualized treatment options will help to establish a “cure” for MBC patients.

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