Long-term outcomes and prognostic factors of pulmonary metastasectomy in breast cancer patients: a systematic review

Meme kanseri hastalarında pulmoner metastazektomisinin uzun dönem sonuçları ve prognostik faktörleri: Sistematik derleme

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ABSTRACT

Breast cancer is the leading cause of cancer-related deaths in women in developing countries. The aim of this systematic review was to evaluate long-term outcomes and prognostic factors of pulmonary metastasectomy in patients with breast cancer. A comprehensive search was performed in the MEDLINE, Web of Science, and Scopus databases using selected keywords. All studies regarding the outcomes and prognostic factors of pulmonary metastasectomy in patients with breast cancer between April 1990 and April 2016 were included in this review. Disease-free interval was identified as a prognostic factor in 10, size of metastasis in three, number of metastases and width of resection in five, and hormone receptor status in six studies. According to our study results, disease-free interval, hormone receptor status, number of metastases, width of metastatic resection and size of metastases, in a descending order, are important prognostic factors for pulmonary metastasectomy in patients with breast cancer.

Keywords: Breast cancer; lung metastasis; metastasis; pulmonary metastasectomy.

Breast cancer is the second most common cancer worldwide, and it is the most common cancer among women both in developed and in less developed countries.[1,2] Its incidence is higher in less developed countries than developed countries (883,000 cases vs 794,000 cases).[1,2] Its incidence also varies across the world, ranging from 27/100,000 in the Middle Africa and Eastern Asia to 92/100,000 in the Northern America.[1,2]

Although breast cancer is the fifth cause of cancer-related deaths, it is the leading cause of cancer-related deaths in women in developing countries (14.3%) and
is the second cause of cancer-related deaths after lung cancer in developed countries (15.4%). Breast cancer accounts for 25% of all cancer cases and 14% of the cancer deaths.[2,3] Its incidence (99,000 new cases) and mortality (42,000 deaths) in Turkey and in the Middle East is relatively lower than the other parts of the world.[2]

According to a recent report, cancer is the third cause of death after coronary artery disease and traffic accidents in the Iranian population.[4] Among all cancers in Iran, breast cancer is the third cause of cancer-related deaths and is the leading cancer diagnosed in women,[5,6] accounting for 24.4% of all cancer cases.[7]

About 20 to 30% of patients with primary breast cancer develop distance metastasis[8] and the lung is a common site for distance metastasis in these patients (12%).[9] As lung metastasis usually is regarded as incurable and advanced systemic disease, only palliative and systemic therapies are recommended for these patients.[10,11]

On the other hand, the introduction of pulmonary metastasectomy in 1882 has opened new horizons for curative treatment of breast cancer with an isolated pulmonary metastasis.[12] Similar to other malignancies such as colorectal cancer, pulmonary metastasectomy was used for the treatment of metastasis from primary breast cancer with favorable effects in improving five-year survival.[13,14] As of 2000 to date, the rate of pulmonary metastasectomy has dramatically increased among common cancer types, as well as breast cancer.[15]

In this systematic review, we aimed to evaluate long-term outcomes and prognostic factors of pulmonary metastasectomy in breast cancer patients in the light of literature data.

MATERIALS AND METHODS

In this systematic review, all documents about pulmonary metastasectomy in breast cancer between April 1990 and April 2016 were evaluated. Three international databases including the MEDLINE (via PubMed-NCBI), ISI Web of Science, and Scopus were searched according to their specified instructions. Search was performed using selected keywords including “pulmonary metastasectomy”, “lung metastasectomy”, “breast neoplasms”, “breast cancer”, “breast tumor”, “breast carcinoma”, “surgical procedures”, “operative”, and “resect” as well as their combination using appropriate operator “OR” and “AND”.

In the initial search, 357 documents including 254 for PubMed, 80 for Scopus, and 23 for Web of Science were obtained. In the next step, letters, meeting abstracts, review articles, case reports, and any documents, except for original articles, were excluded. In addition, only documents in English language were selected and documents in other languages were excluded. The results from three databases were, then, incorporated and duplicate articles were also removed.

Finally, only 56 documents were obtained. The title, topic, and the abstract of these articles were studied and those with unrelated topics were removed. After screening, 16 documents were obtained. The full text of these articles were provided or downloaded from free databases or purchased. These articles were studied carefully and data were extracted.

RESULTS

Of 16 studies, a total of 1,213 patients with a lung metastasis from breast cancer whom underwent pulmonary metastasectomy were evaluated. Data including publishing date, number of patients, mean age of patients, disease-free survival, median disease-free interval (DFI) from primary breast cancer surgery to lung metastasis, median survival, and five-year survival are summarized in Table 1.

The earliest document was published in 1992, while the most recent article was published in 2014. The mean age of patients at the time of diagnosis of lung metastases ranged from 49 to 62 years. The number of patients evaluated in these studies ranged from 15 to 467. In these studies, the median DFI ranged from 2.2 to 8.3 years. Overall five-year survival after surgery also ranged between 27 and 72%.

Prognostic factors of pulmonary metastasectomy were not reported in two studies. Among 16 studies, DFI was identified as a prognostic factor in 10, size of metastasis in three, number of metastases in five, width of resection (complete versus partial) in five, and hormone receptor (estrogen or progesterone or HER-2) status in six studies. Only one study identified tumor stage at breast surgery as a prognostic factor for pulmonary metastasectomy in patients with breast cancer. Of the studies identified DFI as a prognostic factor, five reported a DFI of >3 years, three reported a DFI of >2 years, and one study reported a DFI of >1 year. However, one study did not report any specific interval for DFI.

In addition, the median survival ranged between 31 and 97 months. According to the results indicated in Table 1, the most optimal results of metastasectomy
were predicted in patients with DFI >3 years, an isolated lung metastasis, positive hormone receptors, the presence of less than two metastases, and small size of metastases (less than 2 cm).

**DISCUSSION**

In this systematic review, all studies relating to surgical resection of pulmonary metastasis from breast cancer were evaluated. The highest number of patients (n=467) evaluated in these studies was reported in the Friedel et al.\(^\text{[16]}\) study. The most important prognostic factors of pulmonary metastasectomy which were identified and confirmed in these studies were DFI (in >60% of studies), hormone receptors (in >37% of studies), number of metastases and width of metastasis resection (complete vs partial) (each in >31% of studies), and size of metastasis (in >18% of studies).

In recent years, surgical resection of an isolated liver and lung metastasis has widely adopted in the management of an isolated metastasis from certain types of cancers, in addition to systemic therapies with good and promising long-term results. However, data on the effectiveness of pulmonary metastasectomy in breast cancer patients are scarce and still controversial.

The most of evidence on the effectiveness of metastasectomy have been obtained from the observational cohorts and there is no randomized clinical trial, yet, which causes uncertainty about the effectiveness of metastasectomy, compared to systemic therapies, such as chemotherapy and radiotherapy.\(^\text{[17,18]}\)

Pulmonary metastasectomy for metastatic breast cancer was begun more than two decades ago and, since then, few studies were performed which reported significant effects of metastasectomy in improving overall and long-term survival.\(^\text{[16,19-33]}\) In a recent meta-analysis, the pooled overall five-year survival rate following pulmonary metastasectomy was found to be 46% in patients with breast cancer, while it was 22.5% following systemic treatment in patients with metastatic breast cancer.\(^\text{[34,35]}\)

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**Table 1. Literature studies about surgical resection of lung metastases from breast cancer**

<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>Publishing date</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>DFI (years)</th>
<th>Survival (months)</th>
<th>Overall five-year survival (%)</th>
<th>Prognostic factor</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Lanza et al.(^\text{[16]})</td>
<td>1992</td>
<td>37</td>
<td>55</td>
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<td>-</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>Staren et al.(^\text{[17]})</td>
<td>1992</td>
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<td>50</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>McDonald et al.(^\text{[18]})</td>
<td>1994</td>
<td>60</td>
<td>58</td>
<td>-</td>
<td>2.2</td>
<td>-</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
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<td>-</td>
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<td>-</td>
<td>31</td>
</tr>
<tr>
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<td>6</td>
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<td>1997</td>
<td>17</td>
<td>59</td>
<td>-</td>
<td>5.1</td>
<td>-</td>
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<td>7</td>
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<td>-</td>
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<td>54</td>
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<td>Blanchard et al.(^\text{[24]})</td>
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<td>-</td>
<td>53</td>
<td>-</td>
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<td>10</td>
<td>Welzer et al.(^\text{[25]})</td>
<td>2008</td>
<td>47</td>
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<td>-</td>
<td>-</td>
<td>3.7</td>
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<td>-</td>
<td>4.32</td>
<td>-</td>
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<td>16</td>
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<td>17</td>
<td>-</td>
<td>62</td>
<td>-</td>
<td>8.2</td>
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</table>

DFI: Disease-free interval from primary breast cancer surgery to lung metastasis; ER: Estrogen receptor; HER-2: Human epidermal growth factor receptor-2; HR: Hormone receptor.
In another study, Yhim et al.\textsuperscript{[30]} compared the results of pulmonary metastasectomy in 15 patients with metastatic breast cancer with 30 patients who received systemic treatment alone, and found significantly longer progression-free survival and overall survival in the metastasectomy group. Consistent with these findings, Staren et al.\textsuperscript{[13]} also reported similar findings between pulmonary metastasectomy and systemic treatment patients. However, all of these studies were retrospective, but not prospective clinical trials.\textsuperscript{[17,18]} Therefore, further randomized, clinical trials are required to confirm the effectiveness of pulmonary metastasectomy, compared to systemic medical treatment in lung metastasis from breast cancer.

In conclusion, based on these results, DFI, hormone receptors status, number of metastases, width of metastasis resection (complete vs partial), and size of metastases, in a descending order, are important prognostic factors of pulmonary metastasectomy in patients with breast cancer. In addition, these results showed that resection of lung metastasis with reasonable survival rates is a promising treatment for lung metastasis from breast cancer.

Based on the studies included in this systematic review, it seems that patients with an isolated lung metastasis, DFI >3 years, positive hormone receptors, few number of metastases (less than 2), and small size of metastases (less than 2 cm) are the best candidates for complete resection of pulmonary metastasis with favorable outcomes. Therefore, these factors should be considered before the selection of patients for pulmonary metastasectomy.

**Declaration of conflicting interests**

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

**Funding**

The authors received no financial support for the research and/or authorship of this article.

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