

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

Meme kanseri hastalarında pulmoner metastazektominin uzun dönem sonuçları ve prognostik faktörleri: Sistemantik derleme

Ainaz Sourati,¹ Mona Malekzadeh Moghani,² Samira Azghandi²

Institution where the research was done:

Shahid Beheshti University of Medical Sciences, Emam Hossein Hospital, Tehran, Iran

Author Affiliations:

¹Department of Radiotherapy and Oncology, Shahid Beheshti University of Medical Sciences, Emam Hossein Hospital, Tehran, Iran

²Department of Radiation Oncology, Shohadaye Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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

ÖZ

Meme kanseri, gelişmekte olan ülkelerde kadınlarda kansere bağlı ölümlerin başlıca nedenidir. Bu sistemantik derlemede, meme kanserli hastalarda akciğer metastazektomisinin uzun dönem sonuçları ve prognostik faktörleri değerlendirildi. MEDLINE, Web of Science ve Scopus veri tabanlarında belirli anahtar sözcükler kullanılarak kapsamlı bir tarama yapıldı. Bu derlemeye Nisan 1990 - Nisan 2016 tarihleri arasında meme kanserli hastalarda pulmoner metastazektominin sonuçları ve prognostik faktörlerine ilişkin çalışmaların tümü dahil edildi. Çalışmaların 10'unda hastaliksız geçen süre, üçünde metastaz bölgesi, beşinde metastaz sayısı ve rezeksiyon genişliği ve altısında hormon reseptör statüsünün prognostik faktör olduğu belirlendi. Çalışma sonuçlarımıza göre, sırasıyla hastaliksız geçen süre, hormon reseptör statüsü, metastaz sayısı, metastatik rezeksiyon genişliği ve metastaz bölgesi meme kanserli hastalarda pulmoner metastazektominin önemli prognostik faktörleridir.

Anahtar sözcükler: Meme kanseri; akciğer metastazı; metastaz; pulmoner metastazektomi.

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



Available online at
www.tgkdc.dergisi.org
doi: 10.5606/tgkdc.dergisi.2017.13770
QR (Quick Response) Code

Received: August 04, 2016 Accepted: December 24, 2016

Correspondence: Mona Malekzadeh Moghani, MD. Department of Radiation Oncology, Shahid Beheshti University of Medical Sciences, Shohadaye Tajrish Hospital, 1989934148 Tehran, Iran.

Tel: +989123098543 e-mail: mona_malekm@yahoo.com

©2017 All right reserved by the Turkish Society of Cardiovascular Surgery.

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 develops 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

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

No	Author	Publishing date	Number of patients	Age (years)		DFI (years)		Survival (months)		Overall five-year survival (%)	Prognostic factor
				Mean	Median	Mean	Median	Mean	Median		
1	Lanza et al. ^[16]	1992	37	55	-	Not reported		-	47	49.5	DFI >12 months, positive ER,
2	Staren et al. ^[17]	1992	33	50	-	4	-	55	-	36	None
3	McDonald et al. ^[18]	1994	60		58	-	2.2	-	42	37.8	None
4	Friedel et al. ^[19]	1994	89	53	-	Not reported		-	31	27	DFI >2 years, positive-ER, number of metastases, complete resection
5	Livartowski et al. ^[20]	1997	40	Not reported		Not reported		-	70	54.8	Number of metastases, complete resection
6	Simpson et al. ^[21]	1997	17	59	-	5.1	-	Not reported		62	DFI
7	Friedel et al. ^[22]	2002	467	53	-	-	3.6	-	35	38	DFI ≥3 years, complete resection
8	Ludwig et al. ^[23]	2003	21	-	54	-	8.3	-	96.9	53	DFI >2 years
9	Planchard et al. ^[24]	2004	125	-	53	-	3	-	50.4	45	DFI >3 years, size of metastasis >2 cm
10	Welter et al. ^[25]	2008	47	56.2	-	-	3.7	-	32	36	Positive-ER, positive HER2-neu receptor
11	Yoshimoto et al. ^[26]	2008	90	55.1	-	5.6	-	-	75.6	54	DFI ≥3 years, tumor stage at breast surgery, size of metastasis >2 cm
12	Chen et al. ^[27]	2009	41	-	55	-	4.6	Not reported		51	DFI ≥3 years, number of metastasis <4
13	Yhim et al. ^[28]	2010	15 Metastasectomy	-	49	-	2.5	Not reached		4 years: 82.1	DFI ≥2 years, biological subtypes including positive HR and HER-2
14	Kycler et al. ^[29]	2011	33	53.4	-	4.32	-	-	73.2	54.5	DFI >3 years, complete resection
15	Meimarakis et al. ^[30]	2013	81	-	58.2	Not reported		-	82.4	35.6 for complete resection 42.1 for incomplete resection	Size of metastasis >3 cm, number of metastases, width of resection (complete or partial), HR status
16	Mimoto et al. ^[31]	2014	17	-	62	-	8.2	Not reached		72	Oligometastasis, ER-positive DFI >8 years

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.

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.^[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.^[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.^[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.^[34,35]

In another study, Yhim et al.^[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.^[13] also reported similar findings between pulmonary metastasectomy and systemic treatment patients. However, all of these studies were retrospective, but not prospective clinical trials.^[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.

REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase International Agency for Research on Cancer; 2012. Report No. 11
2. World Health Organization IAFRoC. GLOBOCAN Cancer Fact Sheets: Breast cancer - IARC. World Health Organization; 2012 [Updated 2012; Cited]; Available from: <http://globocan.iarc.fr/old/FactSheets/cancers/breast-new.asp>
3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;61:69-90.
4. Saadat S, Yousefifard M, Asady H, Moghadas Jafari A, Fayaz M, Hosseini M. The Most Important Causes of Death in Iranian Population; a Retrospective Cohort Study. *Emerg (Tehran)* 2015;3:16-21.
5. Kolahdoozan S, Sadjadi A, Radmard AR, Khademi H. Five common cancers in Iran. *Arch Iran Med* 2010;13:143-6.
6. Sadjadi A, Nouraei M, Mohagheghi MA, Mousavi-Jarrahi A, Malekezadeh R, Parkin DM. Cancer occurrence in Iran in 2002, an international perspective. *Asian Pac J Cancer Prev* 2005;6:359-63.
7. Mousavi SM, Gouya MM, Ramazani R, Davanlou M, Hajsadeghi N, Seddighi Z. Cancer incidence and mortality in Iran. *Ann Oncol* 2009;20:556-63.
8. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. *Oncologist* 2005;10:20-9.
9. Kreisman H, Wolkove N, Finkelstein HS, Cohen C, Margolese R, Frank H. Breast cancer and thoracic metastases: review of 119 patients. *Thorax* 1983;38:175-9.
10. Cabuk D, Basaran G, Teomete M, Dane F, Korkmaz T, Seber S, et al. Clinical outcome of Turkish metastatic breast cancer patients with currently available treatment modalities--single center experience. *Asian Pac J Cancer Prev* 2014;15:117-22.
11. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;23:11-9.
12. van Dongen JA, van Slooten EA. The surgical treatment of pulmonary metastases. *Cancer Treat Rev* 1978;5:29-48.
13. Staren ED, Salerno C, Rongione A, Witt TR, Faber LP. Pulmonary resection for metastatic breast cancer. *Arch Surg* 1992;127:1282-4.
14. Wright JO, Brandt B, Ehrenhaft JL. Results of pulmonary resection for metastatic lesions. *J Thorac Cardiovasc Surg* 1982;83:94-9.
15. Bartlett EK, Simmons KD, Wachtel H, Roses RE, Fraker DL, Kelz RR, et al. The rise in metastasectomy across cancer types over the past decade. *Cancer* 2015;121:747-57.
16. Friedel G, Pastorino U, Ginsberg RJ, Goldstraw P, Johnston M, Pass H, et al. Results of lung metastasectomy from breast cancer: prognostic criteria on the basis of 467 cases of the International Registry of Lung Metastases. *Eur J Cardiothorac Surg* 2002;22:335-44.
17. Treasure T, Milošević M, Fiorentino F, Macbeth F. Pulmonary metastasectomy: what is the practice and where is the evidence for effectiveness? *Thorax* 2014;69:946-9.
18. Van Raemdonck D. Pulmonary metastasectomy: common practice but is it also best practice? *Future Oncol* 2015;11:11-4.
19. Lanza LA, Natarajan G, Roth JA, Putnam JB Jr. Long-term survival after resection of pulmonary metastases from carcinoma of the breast. *Ann Thorac Surg* 1992;54:244-7.
20. Staren ED, Salerno C, Rongione A, Witt TR, Faber LP. Pulmonary resection for metastatic breast cancer. *Arch Surg* 1992;127:1282-4.
21. McDonald ML, Deschamps C, Ilstrup DM, Allen MS, Trastek VF, Pairorero PC. Pulmonary resection for metastatic breast cancer. *Ann Thorac Surg* 1994;58:1599-602.
22. Friedel G, Linder A, Toomes H. The significance of prognostic factors for the resection of pulmonary metastases

- of breast cancer. *Thorac Cardiovasc Surg* 1994;42:71-5.
23. Livartowski A, Chapelier A, Beuzedoc P, Dierick A, Asselain B, Darteville P, et al. Surgery of lung metastases of breast cancer: analysis of 40 cases *Bull Cancer* 1998;85:800.
 24. Simpson R, Kennedy C, Carmalt H, McCaughan B, Gillett D. Pulmonary resection for metastatic breast cancer. *Aust N Z J Surg* 1997;67:717-9.
 25. Ludwig C, Stoelben E, Hasse J. Disease-free survival after resection of lung metastases in patients with breast cancer. *Eur J Surg Oncol* 2003;29:532-5.
 26. Planchard D, Soria JC, Michiels S, Grunenwald D, Validire P, Caliendo R, et al. Uncertain benefit from surgery in patients with lung metastases from breast carcinoma. *Cancer* 2004;100:28-35.
 27. Welter S, Jacobs J, Krbek T, Tötsch M, Stamatis G. Pulmonary metastases of breast cancer. When is resection indicated? *Eur J Cardiothorac Surg* 2008;34:1228-34.
 28. Yoshimoto M, Tada K, Nishimura S, Makita M, Iwase T, Kasumi F, et al. Favourable long-term results after surgical removal of lung metastases of breast cancer. *Breast Cancer Res Treat* 2008;110:485-91.
 29. Chen F, Fujinaga T, Sato K, Sonobe M, Shoji T, Sakai H, et al. Clinical features of surgical resection for pulmonary metastasis from breast cancer. *Eur J Surg Oncol* 2009;35:393-7.
 30. Yhim HY, Han SW, Oh DY, Han W, Im SA, Kim TY, et al. Prognostic factors for recurrent breast cancer patients with an isolated, limited number of lung metastases and implications for pulmonary metastasectomy. *Cancer* 2010;116:2890-901.
 31. Kycler W, Laski P. Surgical approach to pulmonary metastases from breast cancer. *Breast J* 2012;18:52-7.
 32. Meimarakis G, Rüttinger D, Stemmler J, Crispin A, Weidenhagen R, Angele M, et al. Prolonged overall survival after pulmonary metastasectomy in patients with breast cancer. *Ann Thorac Surg* 2013;95:1170-80.
 33. Mimoto R, Kobayashi T, Imawari Y, Kamio M, Kato K, Nogi H, et al. Clinical relevance and low tumor-initiating properties of oligometastatic breast cancer in pulmonary metastasectomy. *Breast Cancer Res Treat* 2014;147:317-24.
 34. Fan J, Chen D, Du H, Shen C, Che G. Prognostic factors for resection of isolated pulmonary metastases in breast cancer patients: a systematic review and meta-analysis. *J Thorac Dis* 2015;7:1441-51.
 35. Yamamoto N, Katsumata N, Watanabe T, Omuro Y, Ando M, Narabayashi M, et al. Clinical characteristics of patients with metastatic breast cancer with complete remission following systemic treatment. *Jpn J Clin Oncol* 1998;28:368-73.