REVIEW ARTICLE

The evolution of the role of surgery in the management of breast cancer lung metastasis

Omar M. Rashid, Kazuaki Takabe

Division of Surgical Oncology, Department of Surgery, Virginia Commonwealth University and Massey Cancer Center, Richmond, Virginia, USA

ABSTRACT Breast cancer is the second leading cause of cancer death among women in the United States. Patients with metastatic disease have a median survival of 12 to 24 months and most present with disseminated disease; however, some present with isolated pulmonary metastases which may benefit from surgical resection. Although the initial experience with resection of pulmonary metastases in the late 19th and early 20th centuries produced some encouraging results, patient selection criteria for resection were strict until the mid-1960's when a significant improvement in survival resulted from aggressive management of pulmonary metastasis in osteosarcoma patients. The application of this approach to breast cancer patients similarly produced encouraging results, with five year survival rates in select patients ranging from 36-54%, but this was not without controversy. In this review, we discuss the evaluation of the breast cancer patient with a pulmonary nodule, the historical evolution of the role of surgery in the management of pulmonary metastasis, as well as the latest evidence to guide patient selection and management.

KEY WORDS Breast cancer lung metastasis

J Thorac Dis 2012;4(4):420-424. DOI: 10.3978/j.issn.2072-1439.2012.07.16

Introduction

Breast cancer is the second leading cause of cancer death among women in the United States (1). Breast cancer progresses from local tumor invasion, to regional lymph nodes, and then to distant organs such as the lung, brain, bone and liver. In fact, breast cancer is considered a systemic disease even during early stages of the disease. Patient mortality in breast cancer is due to metastatic disease with a median survival in metastatic breast cancer patients of only 12-24 months (1,2). Unfortunately, metastatic disease in breast cancer is often widespread, in which case surgery offers no benefit to control disease or prolong survival. However, there are instances where patients present with limited metastatic disease for which surgical resection of the metastatic lesion should be considered.

The challenge for clinicians is to determine which patients will benefit from surgical intervention. When appropriately selected, for example, a series of patients with metastatic breast cancer demonstrated a 0.4% rate of solitary lung metastasis amenable to complete resection with a subsequent five year survival of 35.6% after surgery (3). As the experience with pulmonary metastasectomy has increased over the last 130 years, the approach to the breast cancer patient with pulmonary metastasis has evolved with an important role for surgery in select cases. In this review, we discuss the approach to the breast cancer patient with a pulmonary nodule, the evolution of the role of surgery in the management of pulmonary metastasis, and the latest evidence to guide patient selection and management.

Evaluation of the breast cancer patient with a pulmonary nodule

The breast cancer patient who presents with a pulmonary mass must be evaluated for metastatic disease, which can pose a diagnostic challenge because of nonspecific radiographic findings. It should be noted that most lung metastases are asymptomatic and found incidentally. Symptoms only occur in 15-20% of patients, which usually reflects proximity to central airways, such as cough, hemoptysis or dyspnea (4). Chest computed tomography is the standard imaging modality to evaluate a pulmonary nodule, and because of the high likelihood

Corresponding to: Kazuaki Takabe, M.D, Ph.D, FACS. Surgical Oncology/VCU, P.O. Box 980011, West Hospital 7-402, 1200 East Broad Street Richmond, VA 23298-0011 USA. Email: ktakabe@vcu.edu.

Submitted Jul 18, 2012. Accepted for publication Jul 27, 2012.
Available at www.jthoracdis.com

ISSN: 2072-1439

of disseminated disease, a scan within 4 weeks of resection is required (5,6). In addition, positron emission tomography should also be considered as an additional modality to determine if there is evidence of other metastatic disease not detected on physical examination or other imaging (5,6).

Histologic diagnosis is an important factor in management because of the possibility of a primary lung cancer or a benign, inflammatory, or infectious pulmonary process in a patient with breast cancer. In breast cancer patients with lung nodules, series have reported a rate of 34.2-75% of metastatic lesions, 11.5-48.1% of primary lung cancer, and 13.5-17.7% of benign lesions (7,8). Tissue diagnosis can be obtained by imaging guided biopsy (radiologic or endoscopic) or by surgical excisional biopsy (6). The choice of approach depends on the location and size of the mass, the experience of the institution, and the preference of the patient.

Once the mass is diagnosed as a metastatic lesion, there are several considerations required before proceeding with surgery. First, it must be determined if the primary tumor can be controlled prior to or contemporaneously with the lung metastasis (6). Second, there must be a thorough evaluation for extrathoracic disease which would otherwise prevent any benefit from controlling thoracic disease (6). Third, the number and resectability of pulmonary disease as well as the ability of the patient to physiologically tolerate resection as opposed to other treatment alternatives must be considered (6). Fourth, the disease-free interval from resection of the primary tumor and development of metastatic disease as well as the tumor doubling time should be considered in evaluation of the potential benefits of resection (6). How clinicians have weighed these factors in patient selection has changed over time as experience has evolved in the management of these lesions.

Historical evolution of patient selection criteria

The first resections of pulmonary metastasis were reported in the age of Billroth in the 1880's in Vienna by Dr. Weinlechner and Zurich by Dr. Kronelin (9), and the first in North America in the 1930's by Drs. Barney and Churchill where a patient with metastatic renal carcinoma survived disease free for over 20 years (4). However, from 1940-1960 resection of isolated pulmonary metastasis was restricted to specialized centers in only highly selected patients (4). At Memorial Sloan-Kettering Cancer Center (MSKCC), patients had to have a long disease free interval between primary tumor resection and presenting with metastatic disease, and had to have only three lesions or fewer in one lung, or else surgery was thought to provide no benefit (10). Applying such criteria, only 25 such patients were treated surgically from 1940-1965 (10).

During the same time frame the Mayo Clinic also applied similar restrictions and treated 205 patients surgically (11). However, a review of outcomes demonstrated that during that era patients with osteogenic sarcoma with pulmonary metastasis had an 81% five year mortality rate due to pulmonary metastasis when not resected (12,13). Therefore, in the 1960's a more aggressive approach was applied to the management of lung metastases in osteogenic sarcoma which increased five year survival from 17% to 32% in 22 consecutive patients at MSKCC who had undergone 59 thoracotomies to achieve complete resection of pulmonary disease (6). Because of this experience in the 1960's, since the 1970's a more aggressive approach was applied to the management of lung metastases for other cancers, including breast cancer (12,13).

The experience at M.D. Anderson from 1981 to 1991 in 44 women with metastatic breast cancer demonstrated a five year survival rate of 49.5% when all pulmonary metastatic disease was removed (14). When compared to a median survival of 12 to 24 months, those outcomes in breast cancer patients further supported the more aggressive approach applied since the 1970's in patients who could tolerate thoracic surgery and pulmonary resections. A Japanese series of 90 patients treated between 1960 and 2000 demonstrated 54% and 40% five year and ten year survival rates in patients with complete resection of lung metastases (15). That study also demonstrated that disease free interval and initial stage at diagnosis were important prognostic factors (15). The International Registry of Lung Metastases published five year survival rates after complete versus incomplete pulmonary metastasectomy in 467 breast cancer patients was 38% versus 16% (16). In the complete resection group five, ten and fifteen year survival rates were 38%, 22% and 20%, respectively (16). When the authors further selected patients by subgroup analysis applying disease free interval, number of metastases, and complete resection as additional criteria, the five year survival rate was 50%, ten and fifteen year survival rates were both 26%, and median survival was 59 months (16). However, in the era of multimodality therapy, there has been controversy whether surgery has been the determining factor for this observed survival benefit.

A German series from 1998-2007 evaluated 47 patients with metastatic breast cancer who underwent pulmonary metastasectomy and found that the number of metastases, tumor stage at initial presentation, complete resection and pleural/chest wall involvement did not prognosticate survival (2). Instead, estrogen receptor and HER2-neu expression predicted survival with a five year survival rate of 76% versus 12% accordingly for estrogen receptor positive versus negative patients, and similar statistically significant differences by HER2-neu expression (2). Their interpretation of the findings from other series, such as the M.D. Anderson and Japanese series cited above (14,15), was that hormone receptor status was unknown in many of these patients or that the excellent outcomes were due to highly selected patients as illustrated by the importance of disease free interval and initial tumor stage (2). Their implication was

that such prognostic factors were essentially a proxy for such factors as estrogen receptor or HER2-neu expression status, even though their own results did not demonstrate any correlation to the prognostic factors reported in the other studies. However, the limitations of their study did not allow for conclusions to be drawn on the benefits of resection of lung metastasis versus chemotherapy alone (2).

Although the authors conceded that their results were limited by small sample size and a single institution retrospective design, they hypothesized that patients with minimal tumor burden and a complete response to chemotherapy may receive the most benefit from surgical resection (2). However, their study was limited in its ability to provide specific guidelines by estrogen receptor or HER2-neu expression status. Instead, the main contribution of their findings was their suggestion that the surgical approach to lung nodules in breast cancer include (I) diagnosing and treating other primary lung lesions and (II) establishing the histology, grade, estrogen receptor and HER2-neu expression status to guide further medical management (2). When those results and conclusions are taken together with reports that disease free interval, initial tumor stage, and tumor doubling time are important prognostic factors, there may be a greater role in the future for these and other biological markers in selecting the appropriate candidates for surgical management as cancer biology is better understood. As greater advances are made, the role for pulmonary metastasis resection may evolve further for tumor genetic profiling of resected lung metastases in order to further guide medical therapy focused on specific targets to prolong survival. As future therapies are developed, it is conceivable that neoadjuvant therapy may also play a future role in converting patients with unresectable metastatic disease to patients in whom surgical resection may become an option by decreasing the size of pulmonary lesions.

Surgical approach

With technological advances in cardiothoracic surgery and anesthesia, there has been a proliferation of surgical interventions available to the thoracic surgeon. In a recent survey of European surgeons the approaches and preferences for each included anterolateral thoracotomy (36.3%) video-assisted thoracic surgery (28.8%), posterior muscle sparing thoracotomy (26%), posteriolateral thoracotomy (22.6%), horizontal axillary thoracotomy (10.3%, vertical axillary thoracotomy (6.9%), steronotomy (1.4%), bilateral staged thoracotomy (66.2%), single stage sternotomy (26.9%), single stage bilateral sequential thoracotomy (19.3%), bilateral staged versus single stage video-assisted thoracic surgery (12.4%, 7.6%), and clamshell single stage thoracotomy (7.6%) (17).

Although there have been numerous studies which have demonstrated no difference in survival rates between thoracoscopic and open approaches, the determining factor among surgeons was whether there was a need for palpation to localize the lesion (6,17). There has yet to be developed an adequate intraoperative localization alternative to palpation, with studies demonstrating failure rates as high as 56% when comparing CT scan combined with thoracoscopy to intraoperative palpation (6,18). One option to enjoy both the advantages of minimally invasive technology and the increased sensitivity of manual palpation may be our hybrid technique for video-assisted thoracoscopic surgery (VATS) (19,20). As described in detail previously, our hybrid-VATS utilizes an 8-10 cm "utility incision", most commonly in the fifth interspace, in addition to a thoracoscopy port placed in the eighth interspace (19). The original intention of this utility incision was to enable direct visualization, an additional direct light source from headlamp, conventional instrument access, and immediate direct access in case of emergency such as massive bleeding; however, certainly manual palpation for localization can be added to this list. We have reported our experience of 1,170 cases that underwent this technique and demonstrated that it is safe and feasible at community hospital-based practices, which implicates that with our technique it may broaden the indication for this disease (20).

The question of staging resections for bilateral disease is determined by how well the patient can tolerate a single bilateral procedure and the length of recovery required between procedures (6,21). For patients who require staged procedures, it is important to consider once again that beyond an interval of 3-6 weeks the patient must be re-evaluated for progression of metastatic disease with interval computed tomography (21).

There is far less controversy regarding the extent of resection required with 89% of the respondents reporting margin free resection achieved by stapled wedge resection (17). Anatomic segmentectomy and lobectomy rates were 4.8% and 2.1%, respectively (17). Furthermore, over 60% considered pneumonectomy to be a relative contraindication and 23% to be an absolute contraindication to surgical management of metastatic disease (17). In fact, among all pulmonary metastatic resections the International Registry reported a rate of 2.6% with a perioperative mortality rate of 4%. Similar rates were reported in North American centers as well (6). The selection criteria for pneumonectomy are quite strict, limited to a patient with a long disease free interval who has a single central pulmonary lesion with a previous soft tissue or bone tumor and no previous pulmonary resections (22). Because of the results and controversies in the surgical management of pulmonary breast cancer metastases, pneumonectomy has had no role (6).

The role of mediastinal lymph node sampling and dissection in the management of pulmonary metastases is controversial (6). Based on their series, the Mayo clinic advocates systematic implementation of routine mediastinal lymphadenectomy in patients undergoing surgical management of pulmonary

metastasis (6). First, they cite a high rate of positive lymph nodes found after dissection in their series (26%) and in the International Registry (22%) (6,23). Second, in their series and other series lymph node status was an important prognostic indicator in multiple tumor types, and thus may further guide management (6). However, they concede that excluding patients from subsequent surgical therapy because of lymph node status is even more controversial than lymph node staging itself (6). In fact, the International Registry only reported a lymph node dissection or sampling rate of only 4.6% and a survey of European surgeons demonstrated that only 3.4% of respondents routinely did so (17). Furthermore, in the series of breast cancer patients undergoing pulmonary metastasectomy, mediastinal lymph node status was not reported as a prognostic factor. Although this may be due to the fact that it is not routinely performed, even the reported Mayo Clinic series lymph node status was not a significant prognostic indicator among their treated breast cancer patients. Therefore, routine lymph node staging in this patient population remains controversial.

Surveillance after pulmonary metastasectomy should include repeat computed tomography every six months for two years and then yearly for at least five years (5,6). However, if lung palpation was not performed or if tumor doubling time was short, then the patient may be at a higher risk of recurrence and thus may require more frequent surveillance because of the potential for radiographically occult lesions and a subsequently higher rate of recurrence or metachronous lesions (5,6). Unfortunately, recurrent pulmonary metastasis is common, with rates reported as high as 53% among all cancers and a median time to recurrence of 10 months (5,6). Evaluation of these patients entails the same principles described above. In breast cancer patients the International Registry reported 19 cases of resection of recurrent metastases which resulted in a five year survival rate of 53% (16). While the sample sizes are small and there may be an element of survivor bias confounding the results, the European and North American centers advocate surgical management in select patients (6,16).

Conclusions

In summary, breast cancer is a leading cause of cancer death among women and metastatic disease is the leading cause of mortality. Although the great majority of patients with metastatic breast cancer have disseminated disease, there is a small subgroup of patients who present with isolated pulmonary lesions who may benefit from surgical management. In addition to the standard preoperative approach to patients with pulmonary nodules, the breast cancer patient presents with unique characteristics of importance for clinicians to consider. Over the last 130 years there has been a shift towards aggressively managing patients who meet selection criteria, but this has not been without controversy. Although debate continues regarding the factors which determine the survival benefits for patients who meet criteria for resection of pulmonary metastases, as research advances in neoadjuvant therapy and tumor biology, surgical intervention promises to further guide the management of these patients, particularly in the evolving new era of targeted and personalized therapy.

Acknowledgements

Kazuaki Takabe is supported by United States National Institute of Health grants (R01CA160688 and K12HD055881) and Susan G. Komen for the Cure (Investigator Initiated Research Grant (222224) and Career Catalyst Research Grant KG090510).

Disclosure: The authors declare no conflict of interest.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-49.
2. Welter S, Jacobs J, Krbek T, et al. Pulmonary metastases of breast cancer. When is resection indicated? Eur J Cardiothorac Surg 2008;34:1228-34.
3. McDonald ML, Deschamps C, Ilstrup DM, et al. Pulmonary resection for metastatic breast cancer. Ann Thorac Surg 1994;58:1599-602.
4. Rusch VW. Pulmonary metastasectomy. Current indications. Chest 1995;107:322S-331S.
5. Detterbeck FC, Grodzki T, Gleeson F, et al. Imaging requirements in the practice of pulmonary metastasectomy. J Thorac Oncol 2010;5:S134-9.
6. Nichols FC. Pulmonary metastasectomy. Thorac Surg Clin 2012;22:91-9, vii.
7. Rena O, Papalia E, Ruffini E, et al. The role of surgery in the management of solitary pulmonary nodule in breast cancer patients. Eur J Surg Oncol 2007;33:546-50.
8. Tanaka F, Li M, Hanaoka N, et al. Surgery for pulmonary nodules in breast cancer patients. Ann Thorac Surg 2005;79:1711-4; discussion 1714-5.
9. Pastorino U, Treasure T. A historical note on pulmonary metastasectomy. J Thorac Oncol 2010;5:S132-3.
10. McCormack PM, Martini N. The changing role of surgery for pulmonary metastases. Ann Thorac Surg 1979;28:139-45.
11. Thomford NR, Woolner LB, Clagett OT. The surgical treatment of metastatic tumors in the lungs. J Thorac Cardiovasc Surg 1965;49:357-63.
12. Martini N, Huvos AG, Miké V, et al. Multiple pulmonary resections in the treatment of osteogenic sarcoma. Ann Thorac Surg 1971;12:271-80.
13. Shah A, Exelby PR, Rao B, et al. Thoracotomy as adjuvant to chemotherapy in metastatic osteogenic sarcoma. J Pediatr Surg 1977;12:983-90.
14. Lanza LA, Natarajan G, Roth JA, et al. Long-term survival after resection of pulmonary metastases from carcinoma of the breast. Ann Thorac Surg 1992;54:244-7; discussion 248.
15. Yamamoto Y, Hirata T, Fukuse T, et al. Diagnosis and surgical treatment of metastatic lung tumors. Gan To Kagaku Ryoho 1996;23:1248-54.
16. Friedel G, Pastorino U, Ginsberg RJ, 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. Internullo E, Cassivi SD, Van Raemdonck D, et al. Pulmonary metastasectomy: a survey of current practice amongst members of the European Society of Thoracic Surgeons. J Thorac Oncol 2008;3:1257-66.
18. McCormack PM, Bains MS, Begg CB, et al. Role of video-assisted thoracic surgery in the treatment of pulmonary metastases: results of a prospective trial. Ann Thorac Surg 1996;62:213-6; discussion 216-7.
19. Kim RH, Takabe K, Lockhart CG. A hybrid technique: video-assisted thoracoscopic surgery (VATS) pulmonary resections for community-based surgeons. Surg Endosc 2010;24:700-4.
20. Kim RH, Takabe K, Lockhart CG. Outcomes of a hybrid technique for video-assisted thoracoscopic surgery (VATS) pulmonary resection in a community setting. J Thorac Dis 2010;2:210-4.
21. Molnar TF, Gebitekin C, Turna A. What are the considerations in the surgical approach in pulmonary metastasectomy? J Thorac Oncol 2010;5:S140-4.
22. Spaggiari L, Grunenwald DH, Girard P, et al. Pneumonectomy for lung metastases: indications, risks, and outcome. Ann Thorac Surg 1998;66:1930-3.
23. García-Yuste M, Cassivi S, Paleru C. Pulmonary metastasectomy in breast cancer. J Thorac Oncol 2010;5:S170-1.

Cite this article as: Rashid OM, Takabe K. The evolution of the role of surgery in the management of breast cancer lung metastasis. J Thorac Dis 2012;4(4):420-424. DOI: 10.3978/j.issn.2072-1439.2012.07.16