Original Article

"The Law of 3": Prognostic Parameters for Resected Metastatic Pulmonary Tumors

Yasunori Matsuzaki, MD, Tetsuya Shimizu, MD, Masao Edagawa, MD, Masaki Hara, MD, Masaki Tomita, MD, Takanori Ayabe, MD, and Toshio Onitsuka, MD

Metastatic tumors from various organs are found in pulmonary tissue because of the unique anatomical function of the lungs as a filter for systemic venous return. A retrospective study of the clinical factors used to assess the prognosis of 80 patients who underwent resections of metastatic pulmonary tumors in our surgical department between September 1978 and December 2002 is presented. The overall 5-year survival rate in our study was 31.7%. We demonstrated four significant factors used in predicting the prognosis of patients with resected metastatic pulmonary tumors: diameter of the tumor (≤3.0 cm or >3.0 cm), number of tumors (≤3 or >3), disease-free interval (≥3 years or <3 years), and ratio of the diameter of the largest tumor to the diameter of the smallest tumor in patients with multiple metastases (≤3 or >3). Based on our results, we have applied the term "the law of 3" to these valuable prognostic factors. Among these parameters, the ratio of the diameter of the largest to the diameter of the smallest tumor may be applicable as a new prognostic parameter for surgery in patients with multiple foci. (Ann Thorac Cardiovasc Surg 2003; 9: 290–4)

Key words: metastatic pulmonary tumor, surgery, prognostic parameter, retrospective study

Introduction

Various malignancies develop hematogenous metastases in the lungs because of the unique anatomical function of the lungs as a filter for systemic venous return. Friedel et al. have recently reported improved control of metastatic lung tumors using chemotherapy and hormonal treatment.[1] The active application of video-assisted thoracoscopic surgery has introduced further changes with regard to surgical indications for metastatic lung tumors.[2] A retrospective study of clinical factors affecting the prognosis of patients with metastatic pulmonary tumors resected in our surgical department is presented.

Patients

This study included 80 patients (34 males, 46 females) who underwent surgical resections for metastatic tumors between September 1978 and December 2002. Patients with primary lung cancer and with metachronous metastatic tumors were excluded from this study. Patient ages ranged from 7 to 81 years old, with a mean age of 51.9 years. A single lesion was detected in 41 patients, and multiple foci were observed in 39 patients. Unilateral lesions were present in 69 cases; bilateral lesions in 11 cases. As shown in Table 1, surgical techniques included partial resection (65), lobectomy (19), and segmental resection (6). As indicated in Table 2, primary tumors included colonic or rectal cancer (28), soft tissue sarcoma (19), osteosarcoma (13), breast cancer (9), renal cancer (7), and bladder cancer (4).

Methods

In our surgical department, resecting criteria for pulmonary metastases include 1) no distant metastasis without pulmonary lesions, 2) satisfactory local control for primary lesions, 3) the possibility of complete resection for pulmonary lesions, and 4) good risk for surgical intervention. Patient records were examined retrospectively.

From Department of Surgery II, Miyazaki Medical College, Miyazaki, Japan

Received May 14, 2003; accepted for publication July 1, 2003.
Address reprint requests to Yasunori Matsuzaki, MD: Department of Surgery II, Miyazaki Medical College, 5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan.

Table 1. Characteristics of 80 patients with resection of pulmonary metastasis

	No. of patients
Gender	
Male	34
Female	46
Age	
Average	51.9
Range	7-81
No. of pulmonary metastasis	
One	41
Two or more	39
Location of pulmonary metastasis	
Unilateral	69
Bilateral	11
Mode of operation	
Partial resection	65
Segmental resection	6
Lobectomy	19

Table 2. Histologic type of the primary tumor

Colonic or rectal cancer	28
Soft tissue sarcoma	19
Osteosarcoma	13
Breast cancer	9
Renal cancer	7
Bladder cancer	4

The overall 5-year survival rate was determined and evaluated with respect to diameter of the tumor (≤3.0 cm or >3.0 cm), number of tumors (≤3 or >3), disease-free interval (DFI) (≥3 years or <3 years), and ratio of the diameter of the largest tumor to the diameter of the smallest tumor in patients with synchronous multiple metastases (≤3 or >3).

Statistical analysis

Survival duration was calculated using the date of the initial resection and the date of the last known follow-up or death. The probability of survival was computed according to the Kaplan-Meier method. The statistical significance of the difference between survival curves was determined using the log rank test. Clinical factors relating to prognosis including gender, age, number of tumors, diameter of the tumor, location of the tumor (unilateral/bilateral), DFI, and ratio of the diameter of the largest tumor to the diameter of the smallest tumor in multiple metastases were analyzed for their independent effect on survival by means of the Cox proportional hazard model. A $p<0.05$ was considered significant. All statistical methods were performed using the Statistical Analysis Software (SPSS, version 6.1J for the Macintosh NT, SPSS Inc., Chicago, IL, USA, 1996).

Results

The cumulative survival rate for the 80 patients in this study was 31.7% at 5 years, and the overall median survival rate was 20 months. Figure 1 demonstrates a statistically significant difference in survival rates in patients with tumors with a maximum diameter of ≤3.0 cm and those with tumor diameters of >3.0 cm (p=0.0001). As shown in Fig. 2, the cumulative survival rate for patients with ≤3 metastases (65) was 40.2% at 5 years, and in patients with >3 metastases (15), the survival rate was 18.1% at 2 years (p=0.006), a statistically significant difference. At 5 years, the survival rate for patients with a DFI of ≥3 years (20) was 48.5%, and the survival rate for patients with a DFI of <3 years (60) was 24.8% (p=0.028)

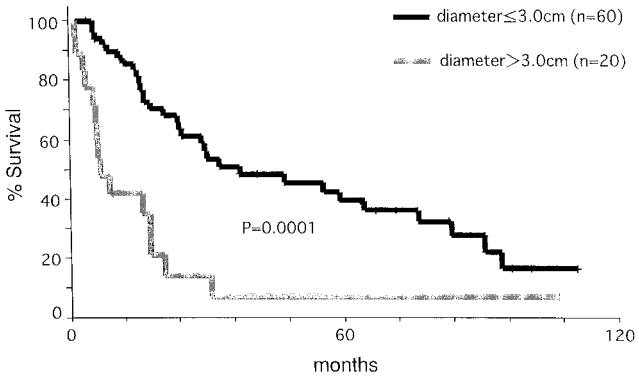

Fig. 1. Patient survival by size of lesions (n=80). Diameter ≤3.0 cm versus diameter >3.0 cm.

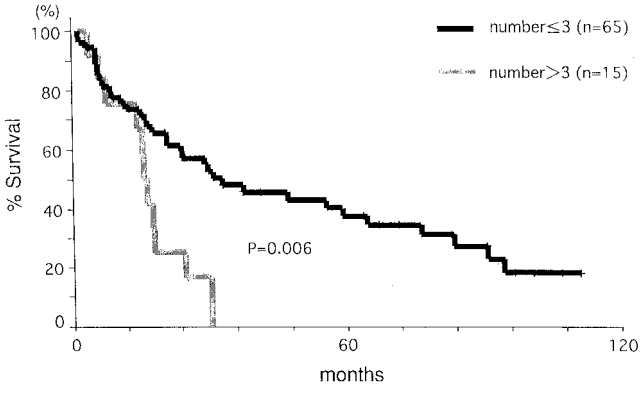

Fig. 2. Patient survival by number of lesions (n=80). Number ≤3 versus number >3.

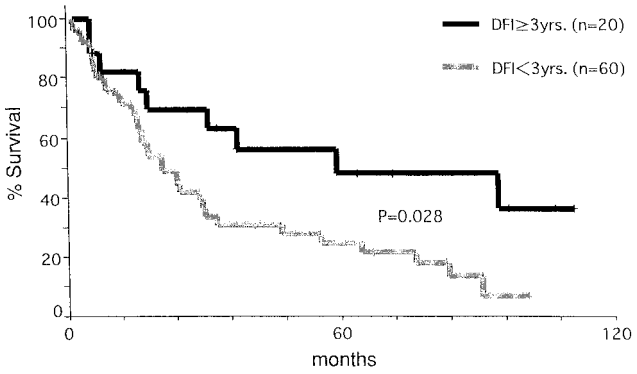

Fig. 3. Patient survival by DFI (n=80).
DFI ≥3 years versus DFI <3 years.
DFI: disease free interval

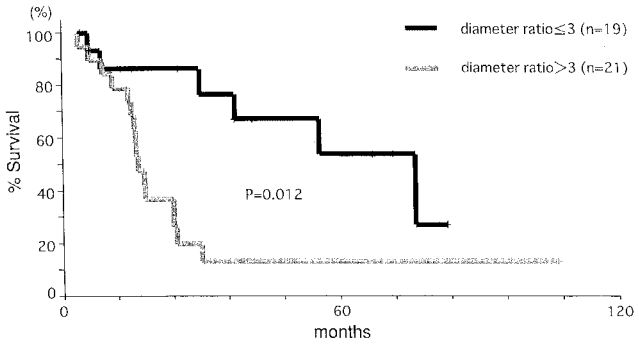

Fig. 4. Patient survival by the ratio of diameter of the largest tumor to the smallest tumor (n=40).
Ratio ≤3 versus ratio >3.

(Fig. 3). As shown in Fig. 4, 5-year survival rates based on the ratio of the diameter of the largest tumor to the diameter of the smallest tumor in patients with multiple foci were 53.9% with a ratio of ≤3 (19), and 13.3% with a ratio of >3 (21), respectively (p=0.012). Table 3 illustrates the Cox proportional hazard model for prognosis based on clinical factors in all cases. They reveal that the most significant factor was the size of the tumor (≤3.0 cm or >3.0 cm) followed by the number of tumors (≤3 or >3) and the DFI (≥3 years or <3 years). Among the cases with multiple pulmonary metastases (n=39), the ratio of the diameter of the largest tumor to the diameter of the smallest tumor in multiple metastases (≤3 or >3) was the most significant parameter in Table 4.

Discussion

Metastatic tumors from various organs are found in the lungs because of the unique anatomical function of the lungs as a filter for systemic venous return. Approximately 30% of patients with a malignancy will develop lung metastases.[3] In 1965, Thomford et al.[4] reported the following criteria as indications for surgical resection of metastatic lung tumors: 1) the patient can withstand surgery, 2) the primary focus is controlled, 3) there is no remote metastasis or relapse detected in organs other than

Table 3. Multivariate analysis of prognostic factors (all cases n=80)

Independent prognostic factor	Hazard ratio	95% confidence interval	p value
Age	0.9975	0.9820-1.0132	0.7515
Gender (female)	0.9547	0.6868-1.3272	0.7828
Tumor size (≤3 cm)	2.1796	1.5095-3.1472	0.0000
No. of tumor (≤3)	0.6468	0.4389-0.9532	0.0276
DFI (≥3 years)	1.5498	1.0479-2.2922	0.0282

DFI: disease free interval

Table 4. Multivariate analysis of prognostic factors (multiple metastases n=39)

Independent prognostic factor	Hazard ratio	95% confidence interval	p value
Age	1.0002	0.9760-1.0249	0.9901
Gender (female)	0.8873	0.5383-1.4624	0.6390
No. of tumor (≤3)	0.6499	0.3815-1.1070	0.1127
DFI (≥3 years)	1.8324	0.9578-3.5056	0.0673
Size ratio (≤3)	2.1390	1.1655-3.9256	0.0141

DFI: disease free interval
Size ratio: the ratio of diameter of the largest to the smallest tumor in multiple metastases

the lung, and 4) lung metastasis is localized in the unilateral lung. Since that time, however, surgery has been indicated and aggressively performed in an increasing number of patients to treat multiple or bilateral lesions by one-stage surgery. Furthermore, video-assisted thoracoscopic surgery has been actively applied as a less-invasive surgical procedure for the resection of metastatic lung tumors.[2] Even more recently, the control of distant metastases from primary malignant tumors has improved due to the advancement of chemotherapy or hormonal therapy.[1]

These developments of surgical strategies and multidisciplinary treatments have introduced some changes with regard to surgical indications for pulmonary metastasis. At Miyazaki Medical College Hospital, we have performed aggressive surgical treatment in patients with lung metastasis under the following conditions: 1) no distant metastasis without pulmonary lesions, 2) satisfactory local control for primary lesions, 3) possible complete resection of pulmonary lesions, and 4) good risk for surgical intervention. Furthermore, surgical indication has also been considered in addition to the effects of chemotherapy or hormonal therapy. To further improve the surgical outcome of patients with pulmonary metastases, however, prognostic factors must be clarified.

In this retrospective study, we assessed the effect of clinical factors on the prognosis of patients with metastatic pulmonary tumors resected in our surgical department. In general, the overall 5-year survival rate following surgical resection of metastatic pulmonary tumors has been reported to be 35-50%.[5] In our study, the overall 5-year survival rate was 31.7%. Other studies have reported that post-surgical prognosis is poorer as the number of metastatic tumors increases, especially when there are more than 4 metastases.[6-8] Multiple pulmonary metastases also result in a poorer prognosis. In our investigation, patients with ≤3 foci had a significantly higher survival rate than those with >3 metastases. It has also been reported that long-term survival rates decrease when the maximum diameter of the tumor is more than 5 cm.[9] Our study demonstrated a significant difference in survival rates between patients with tumors of a maximum diameter of ≤3.0 cm and those with tumors with a maximum diameter of >3.0 cm. Some researchers have reported that a prolonged DFI leads to a better prognosis[7,8,10,11] while others have indicated there is no association between DFI and long-term results.[12-15] Our study supports the theory that patients with a DFI of ≥3 years had a better prognosis than those with a DFI of <3 years. We believe the new parameter, the ratio of the diameter of the largest tumor to the diameter of the smallest tumor (≤3 or >3) in patients with multiple pulmonary foci should prove helpful in determining surgical indications for multiple pulmonary metastases. Based on the results of our study, we have applied the term "the law of 3" to these valuable prognostic factors.

Our retrospective study, however, may have contained "patient selection bias" such as performance status in determination of surgical indication or "tumor individual bias," which includes tumor growth properties and the biological behavior of the primary tumor. A prospective study excluding any bias is needed in order to establish surgical strategies to distinguish prognostic factors for metastatic pulmonary tumors from each primary organ.

In summary, with regard to the prognosis of patients with resected metastatic pulmonary tumors, our study demonstrated that the most significant factors are the diameter of the tumor (≤3.0 cm or >3.0 cm) followed by the number of tumors (≤3 or >3), and the DFI (≥3 years or <3 years). Also in patients with multiple pulmonary metastases, the ratio of the diameter of the largest tumor to the diameter of the smallest tumor (≤3 or >3) was the significant factor for the prognosis. Among these parameters, the ratio of the diameter of the largest tumor to the diameter of the smallest tumor appears to be useful as a new prognostic factor for surgery in patients with multiple foci.

References

1. Friedel G, Pastorino U, Ginsberg RJ, et al. Results of lung metastatectomy 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.
2. Dowling RD, Keenan RJ, Ferson PF, Landreneau RJ. Video-assisted thoracoscopic resection of pulmonary metastasis. *Ann Thorac Surg* 1993; **56**: 772–5.
3. Mark JB. Surgical management of metastatic neoplasm to the lung. In: Sabiston DC and Spencer FC eds.; Surgery of the Chest. Philadelphia: Saunders, 1990; p 604.
4. Thomford NR, Woolner LB, Clagett OT. The surgical treatment of metastatic tumors in the lungs. *J Thorac Cardiovasc Surg* 1965; **49**: 357–63.
5. Mountain CF, McMurtrey MJ, Hermes KE: Surgery for pulmonary metastasis: a 20-year experience. *Ann Thorac Surg* 1984; **38**: 323–30.
6. Meyer WH, Shell MJ, Kumar APM, et al. Thoracotomy for pulmonary metastatic osteosarcoma. An analysis of prognostic indicators of survival. *Cancer* 1987; **59**: 374–9.

7. Putman JB, Roth JA, Wesley MN, et al. Analysis of prognostic factors in patients undergoing resection of pulmonary metastases from soft tissue sarcomas. *J Thorac Cardiovasc Surg* 1984; **87**: 260–8.
8. Regal AM, Reese P, Antkowiak J, Hart T, Takita H. Median sternotomy for metastatic lung in 131 patients. *Cancer* 1985; **55**: 1334–9.
9. Weiser MR, Downey RJ, Leung DH, Brennan MF. Repeat resection of pulmonary metastases in patients with soft-tissue sarcoma. *J Am Coll Surg* 2000; **191**: 184–91.
10. Mansel JK, Zinsmeister AR, Pairolero PC, Jett JR. Pulmonary resection of metastatic colorectal adenocarcinoma. A ten year experience. *Chest* 1986; **89**: 109–12.
11. Morrow CE, Vassilopoulos PP, Grage TB. Surgical resection for metastatic neoplasm of the lung. *Cancer* 1980; **45**: 2981–5.
12. McCormack PM, Martini N. The changing role of surgery for pulmonary metastases. *Ann Thorac Surg* 1978; **28**: 139–45.
13. Rendina EA, de Vincentiis M, Primerano G, Claudio Mineo T, Ricci C. Pulmonary resection for metastatic laryngeal carcinoma. *J Thoracic Cardiovasc Surg* 1986; **92**: 114–7.
14. Takita H, Merrin C, Didolkar MS, Douglass HO, Edgerton F. The surgical management of multiple lung metastases. *Ann Thorac Surg* 1977; **24**: 359–64.
15. Wright JO 3rd, Brandt B 3rd, Ehrenhaft JL. Result of pulmonary resection for metastatic lesions. *J Thoracic Cardiovasc Surg* 1982; **83**: 94–9.