ORIGINAL SCIENTIFIC REPORT

Proposal of a Useful Surrogate Endpoint of the Overall Survival in Patients Undergoing Pulmonary Metastasectomy: The Time to Local Therapy Failure

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Abstract

Background A recent study demonstrated remarkable discrepancy between the relapse-free survival (RFS) and overall survival (OS) after pulmonary metastasectomy (PM) in the current era. As the RFS may not be a suitable parameter after PM, a more suitable parameter is needed for PM as a surrogate marker for OS.

Methods A total of 134 consecutive patients who underwent PM were retrospectively analyzed. In the present study, we introduced a new endpoint, time to local treatment failure (TLTF). This endpoint was defined as the time interval between the first PM and the first untreatable recurrence by local treatment with curative intent or death due to any cause. We analyzed the correlation between the RFS and OS and between the TLTF and OS to validate whether or not the TLTF is a better parameter than the RFS after PM.

Results Thus far, 78 patients have experienced relapse. Of these, 37 patients (47%) underwent local therapy with curative intent, 29 of whom are alive without local treatment failure. The 5-year OS, RFS and TLTF were 70.9%, 36.5%, and 57.6%, respectively. The concordance proportions for the RFS and OS and for the TLTF and OS were 0.634 and 0.851 for all patients, respectively. The Spearman's rank correlation coefficient for the RFS and OS was 0.639, while that for the TLTF and OS was 0.875.

Conclusions The TLTF may be a good surrogate parameter for the OS after PM in the current era.

Introduction

Pulmonary metastasectomy (PM) is an established therapy for pulmonary metastasis from various types of tumors [1–4]. Since the first report about PM by Thomford et al. [5], the indications for PM have been discussed. Kondo et al. summarized the principle criteria for the indication of PM in the current era. In brief, when a patient has a good general condition and the primary disease or other metastatic disease are resected/controlled, the pulmonary metastases which are deemed completely resectable are indicated for PM [6]. The outcomes of PM are conventionally expressed by the relapse-free survival (RFS) (also called the disease-free survival or progression-free survival [PFS] in this field) and the overall survival (OS).

A recent study revealed a remarkable discrepancy between the RFS and OS after PM for pulmonary metastasis from CRC in the current era. In our institute, the RFS curve and OS curve after PM for pulmonary metastasis from CRC were similar in patients who underwent PM before 2002, while a remarkable discrepancy was noted between the RFS and OS in patients who underwent PM after 2003 [7]. This discrepancy means that patients who experienced relapse after the first PM survive longer in the current era than in the

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past. Possible reasons for this discrepancy between the RFS and OS in the current era are as follows: First, the rate of patients who undergo local therapy with curative intent, including repeat PM for relapse after the first PM, is increasing [7, 8]. Second, if patients do not receive local therapy with curative intent for the relapse after the first PM, the survival time is prolonged thanks to advancements in systemic therapy in the current era. These advancements for recurrent diseases are not limited to CRC. Repeat PM procedures are performed in various types of tumors [9–12], and systemic therapy for different tumors is also advancing [13–15]. Therefore, the discrepancy between the RFS and OS is likely not limited to CRC.

Considering the phenomenon discussed above, the RFS is not a suitable parameter after PM, and a more suitable one is needed, both as a marker for the effectiveness of PM and as a surrogate marker for the OS. Recently, a remarkable report on this issue was published by surgeons managing hepatic metastases from CRC. Oba et al. proposed a new potential surrogate endpoint, called time to surgical failure (TSF) after hepatectomy [16]. The TSF was defined as the time until unresectable relapse or death. They concluded that the correlation between the TSF and the OS was stronger than that between the RFS and the OS after curative hepatic resection in patients with hepatic metastases from CRC. We expand this concept and herein propose a new endpoint after PM: the time to local therapy failure (TLTF). This endpoint is defined as the time interval between the first PM and the first untreatable recurrence by local therapy with curative intent or death due to any cause.

In the present study, we analyzed the correlation between the RFS and OS and the TLTF and OS in order to validate whether or not the TLTF is a better parameter after PM than the RFS after PM in the current era.

Patients and methods

Patients and treatment

The present study was a retrospective analysis of 134 consecutive patients who underwent complete resection of pulmonary metastasis in our hospital between 2010 and 2016. The study protocol was approved by the Ethical Review Board for Clinical Studies at Osaka University (control number 18373).

Patients with pulmonary metastasis from lung cancer were excluded from this study because it is often difficult to distinguish second primary lung cancer from pulmonary metastasis following primary lung cancer. When pulmonary metastasis from various tumors was detected, the treatment strategy was decided by the cancer board of our hospital.

The patients who met the following criteria underwent pulmonary metastasis as previously described [7]: (1) the pulmonary nodule was deemed completely resectable; (2) apparent mediastinal lymph node metastasis was absent on a preoperative radiological examination; (3) the metastatic disease was limited to the lungs, or extrapulmonary distant metastasis was controlled or controllable if present; (4) locoregional control of the primary tumor was achieved; and (5) the patient had a good overall general condition, and their respiratory function was sufficient to tolerate lung resection.
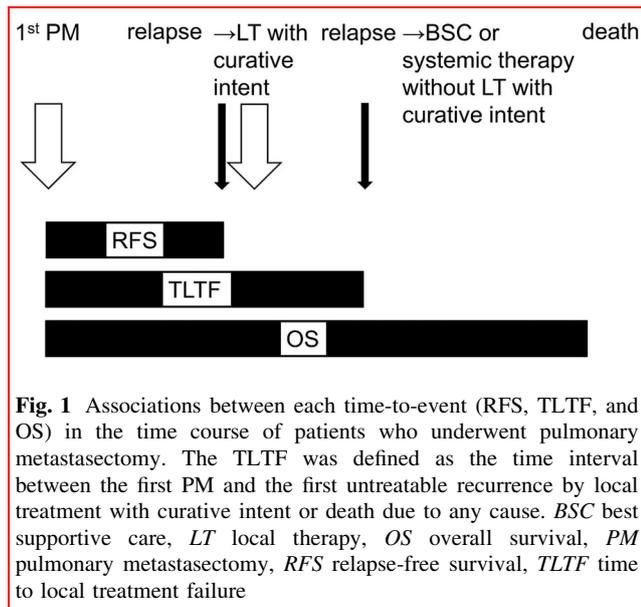
The type of resection was selected according to the size and location of the tumor, the overall general condition, and the respiratory function of the patient; lesser resection was preferably selected as long as curative resection was possible as previously described [7]. In terms of the surgical approach, video-assisted thoracoscopic surgery (VATS) was the first choice. Thoracotomy was selected when the preoperative computed tomography (CT) findings suggested that the palpation of the nodule during surgery was necessary for detecting the pulmonary nodule or ensuring a sufficient margin. All of the specimens obtained from pulmonary resection were reviewed by pathologists.

The treatment strategy for re-recurrence after the first PM was decided by the department in which the primary tumor was treated. Repeat PM was proactively performed for recurrent disease with pulmonary metastasis alone [8, 9]. Local treatment with curative intent for recurrence besides lung was decided based on both the general condition of the patients and the number of metastases.

Follow-up was generally based on the findings from chest CT, a physical examination, and laboratory blood tests performed every 6–12 months after treatment. Follow-up information was obtained from the hospital medical records. The time interval between pulmonary resection and the latest follow-up in the present study ranged from 1 to 99 months (median 36 months, mean 44 months).

Definitions of the survival

The OS was defined as the time interval between the first PM and death by any cause, while the RFS was defined as the time interval between the first PM and the first recurrence of primary tumor cancer or death due to any cause. In the present study, we introduced a new endpoint: the TLTF, defined as the time interval between the first PM and the first untreatable recurrence by local treatment with curative intent or death due to any cause (Fig. 1).

Fig. 1 Associations between each time-to-event (RFS, TLTF, and OS) in the time course of patients who underwent pulmonary metastasectomy. The TLTF was defined as the time interval between the first PM and the first untreatable recurrence by local treatment with curative intent or death due to any cause. *BSC* best supportive care, *LT* local therapy, *OS* overall survival, *PM* pulmonary metastasectomy, *RFS* relapse-free survival, *TLTF* time to local treatment failure

Statistical analyses

The follow-up and survival periods were estimated using the Kaplan–Meier method. Surviving patients were censored at the time of the last follow-up. The correlations between the RFS and OS events and between the TLTF and OS events were each evaluated using the concordance proportion, as previously described [16]. Spearman's rank correlation coefficient was used to estimate the correlations between the survival function of the RFS and OS and between the survival function of the TLTF and OS, as predicted using the Cox proportional hazards model in all patients. The statistical analyses were conducted using JMP Pro 13 and SAS 9.4 SAS/STAT 14.3 software programs (SAS Institute, Berkley, CA, USA).

Results

The characteristics of the patients in the two groups are shown in Table 1. The mean age of the patients was 59.1 years. The most frequent type of primary tumor was CRC ($n = 50$, 37%) followed by soft tissue sarcoma/osteosarcoma ($n = 19$, 14%) and gynecologic malignancies ($n = 16$, 12%).

Surgical factors are described in Table 2. One hundred and seven patients (80%) underwent video-assisted thoracic surgery (VATS), and 107 patients (80%) underwent sublobar resection. Lymph node metastasis was pathologically confirmed in 6 patients (4%). Postoperative therapy was performed in 41 patients (31%). Regimens of postoperative therapy are also shown in Table 2.

Table 1 Patient characteristics

Characteristics	Number of patients ($n = 134$)
Sex	
Male	71 (53%)
Female	63 (47%)
Age (years)	
Mean ± SD	59.1 ± 14.2
Range	19–84
Primary tumor	
Colorectal cancer	50 (37%)
Soft tissue sarcoma/osteosarcoma	19 (14%)
Gynecologic malignancies	16 (12%)
Renal cell carcinoma	11 (8%)
Esophageal cancer	6 (4%)
Head and neck squamous cell carcinoma	5 (4%)
Urinary tract transitional cell carcinoma	5 (4%)
Salivary gland tumor	3 (2%)
Thyroid cancer	3 (2%)
Melanoma	3 (2%)
Breast cancer	2 (1%)
Pancreatic cancer	2 (1%)
Seminoma	2 (1%)
Nonseminomatous germ cell tumor	2 (1%)
Others	5 (4%)
Treatment mode for primary tumor	
Treatment includes surgery	127 (95%)
Chemoradiotherapy or radiotherapy	7 (5%)
Disease-free interval (months)	
Median	27
Range	0–160
0 (synchronous)	20 (15%)
1–24	46 (34%)
> 24	68 (51%)
Laterality	
Unilateral	121 (90%)
Bilateral	13 (10%)
Number of lesions	
1	99 (74%)
2	18 (13%)
3	9 (7%)
≥ 4	8 (6%)
Size of target lesion (cm)	
Mean ± SD	1.85 ± 1.48
Range	0.4–10.0
Metastasis besides the lung at the time of PM	37 (28%)
Preoperative chemotherapy before PM	42 (31%)

PM pulmonary metastasectomy, *SD* standard deviation

Table 2 Surgical factors and regimen of postoperative therapy

Characteristics	Number of patients (n = 134)
Approach	
Thoracotomy	26 (20%)
Video-assisted thoracoscopic surgery	107 (80%)
Type of resection	
Pneumonectomy	1 (1%)
Bilobectomy	2 (1%)
Lobectomy	34 (25%)
Segmentectomy	30 (22%)
Partial resection	67 (50%)
Lymph node dissection	
Not done	75 (56%)
Sampling	30 (22%)
Hilar	20 (15%)
Mediastinal	9 (7%)
Type of tumor/regimen of postoperative therapy	
Colorectal cancer (n = 16)	
FOLFOX	4
Capecitabine	4
IRIS + bevacizumab	2
UFT	2
UFT + folinic acid	2
Capecitabine + oxaliplatin	1
TS-1 + oxaliplatin	1
Soft tissue sarcoma/osteosarcoma (n = 6)	
ICE	2
Doxorubicin + ifosfamide	1
Paclitaxel	1
Gemcitabine	1
Pazopanib	1
Uterine corpus malignancy (n = 5)	
TAC	2
Paclitaxel + carboplatin	1
GLIF	1
Medroxyprogesterone acetate	1
Ovarian cancer (n = 3)	
Paclitaxel + carboplatin	3
Breast cancer (n = 2)	
Trastuzumab + docetaxel	1
Trastuzumab + capecitabine	1
Head and neck squamous cell carcinoma (n = 2)	
TPF	1
Urinary tract transitional cell carcinoma (n = 2)	
Gemcitabine + nedaplatin	1
Doxifluridine	1
Adenoid cystic carcinoma of salivary gland (n = 1)	
TS-1	1
Urethral carcinoma (n = 1)	

Table 2 continued

Characteristics	Number of patients (n = 134)
Gemcitabine + cisplatin	1
Esophageal cancer (n = 1)	
Docetaxel	1
Thyroid cancer (n = 1)	
Radioactive iodine	1
Melanoma (n = 1)	
Nivolumab	1

FOLFOX, folinic acid, fluorouracil, oxaliplatin, IRIS; irinotecan, TS-1; ICE, ifosfamide, carboplatin, etoposide; TAC, paclitaxel, doxorubicin, carboplatin; GLIF, gemcitabine, folinic acid, irinotecan, fluorouracil; TPF, docetaxel, cisplatin, fluorouracil

Thus far, 78 patients have experienced relapse. The sites of relapse were the lung alone in 29 (37%), other sites besides the lung and primary tumor or regional lymph nodes in 22 (28%), lung and other sites in 11 (14%), pleura in 6 (8%), mediastinal lymph nodes in 4 (5%), local relapse of primary tumor or regional lymph nodes in 4 (5%), and surgical margin relapse of pulmonary metastasis in 2 (3%). The clinical course after the first PM is shown in Fig. 2. Of the 78 patients who experienced relapse, 37 (47%) underwent local therapy with curative intent, 21 underwent repeat pulmonary resection, 9 underwent surgery for other organs besides the lung, 6 underwent radiotherapy, and 1 underwent chemoradiotherapy. Of these, 29 patients remain alive without local treatment failure.
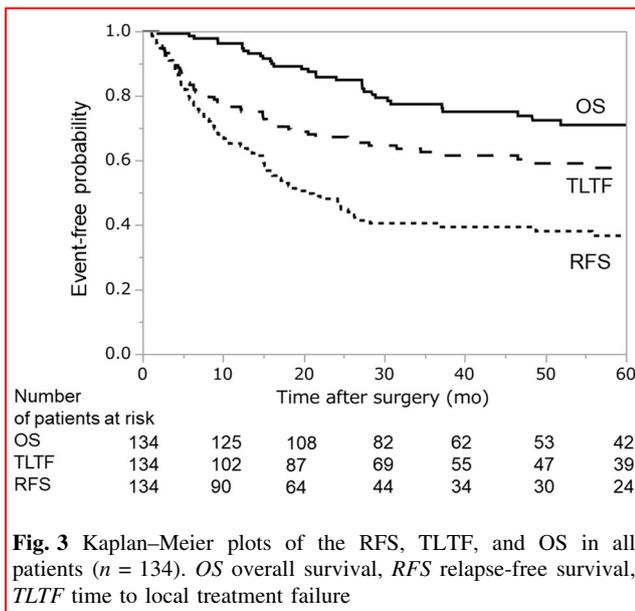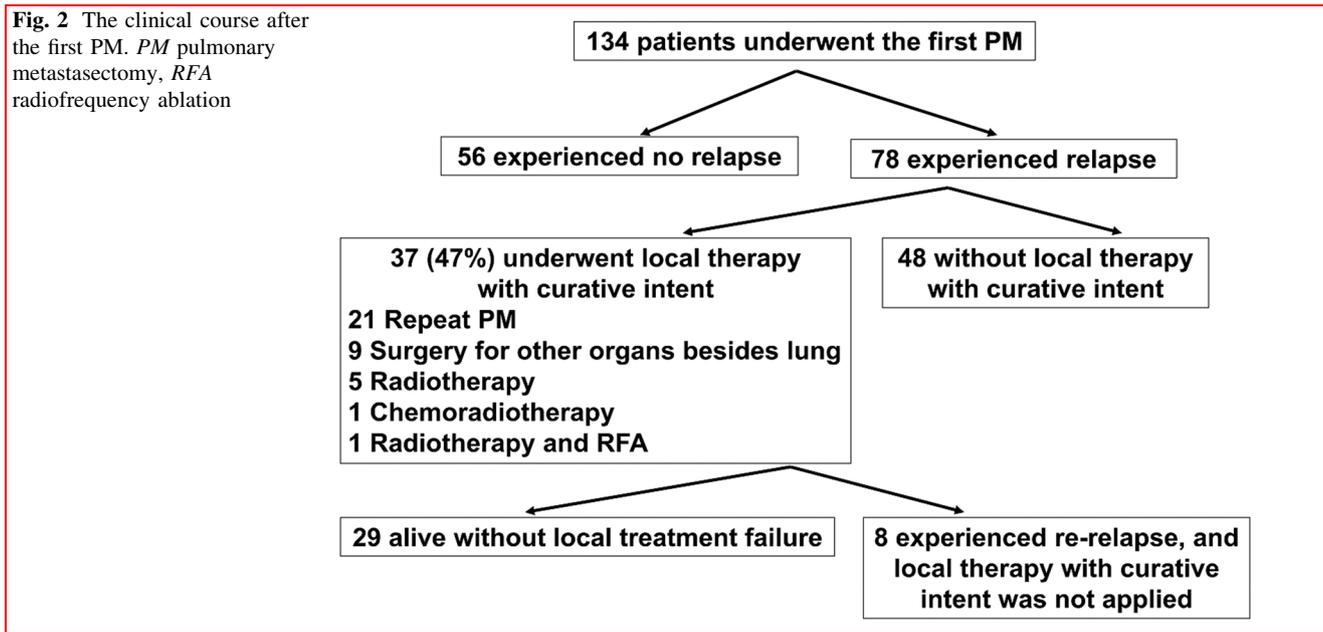
The 5-year OS, RFS, and TLTF were 70.9%, 36.5%, and 57.6%, respectively (Fig. 3). Table 3 shows the concordance proportions for RFS and OS, and TLTF and OS, and Spearman's rank correlation coefficient for RFS and OS, and TLTF and OS in each patient group [all patients (n = 134), colorectal cancer (n = 50), carcinoma (n = 105), and sarcoma (n = 22)]. These results show that the correlation between TLTF and OS was stronger than that between RFS and the OS in all patient groups.

Discussion

The present study showed that the correlation between the TLTF and the OS was stronger than that between the RFS and the OS. The TLTF may be a good surrogate parameter for the OS after PM in the current era.

Local therapy with curative intent, including repeat PM, stereotactic radiotherapy, and radiofrequency ablation, is increasingly frequently indicated for relapse after initial PM in the current era [9–12, 17–19]. In our recent report, the rate of patients who received local therapy with curative intent for isolated relapses was significantly higher in

Fig. 2 The clinical course after the first PM. *PM* pulmonary metastasectomy, *RFA* radiofrequency ablation

134 patients underwent the first PM

56 experienced no relapse

78 experienced relapse

37 (47%) underwent local therapy with curative intent
21 Repeat PM
9 Surgery for other organs besides lung
5 Radiotherapy
1 Chemoradiotherapy
1 Radiotherapy and RFA

48 without local therapy with curative intent

29 alive without local treatment failure

8 experienced re-relapse, and local therapy with curative intent was not applied

Fig. 3 Kaplan–Meier plots of the RFS, TLTF, and OS in all patients (*n* = 134). *OS* overall survival, *RFS* relapse-free survival, *TLTF* time to local treatment failure

patients treated after 2003 than in those treated before 2003 who underwent PM for CRC (64% vs 31%, *p* = 0.04) [7]. When patients underwent successful local therapy for relapse after the first PM, they were free from disease, and a proportion achieved a survival without disease. The presence of these patients subsequently results in a discrepancy between the RFS and OS. In the present study, of the 78 patients who experienced relapse after the first PM, 37 (47%) underwent local therapy with curative intent. Of those patients, 29 remain alive without local therapy failure. Therefore, a remarkable discrepancy between the RFS

and the OS is observed (concordance proportion 0.634, Spearman's rank correlation coefficient 0.639).

Some authors have noted that there is a discrepancy between the RFS and the OS after resection of metastatic diseases. Matsuguma et al. proposed the modified PFS [10]. In that parameter, when the disease-free status continues for longer than 2 years after repeated resection at the last follow-up, the first recurrence is not considered an event. The authors analyzed the outcomes of patients who underwent PM for urinary transitional cell carcinoma, and the 5-year OS and PFS rates were 50% and 26%, respectively, including 3 patients who underwent a second PM for recurrence, 9 patients survived without recurrence for more than 5 years, resulting in a modified 5-year PFS rate of 40%. Therefore, the modified PFS is considered to represent the effects of PM well. However, while the modified PFS seems like a useful parameter, the limitation is that the judge of timing should be 2 years after the repeat PM. This parameter can therefore only be applied in retrospective reviews, not for patients who might undergo repeat PM in the future.

In the present study, we demonstrated that the correlation between the TLTF and the OS was stronger than that between the RFS and the OS in patients who underwent PM for pulmonary metastases from various tumors. The results from the total patients, CRC, carcinoma, and sarcoma have the same tendency. The differences between the TSF proposed by Oba et al. [16] and the TLTF are as follows: local therapy for relapse after the first resection for metastasis is not limited to surgery in TLTF, and the type of tumor is not limited to CRC. However, despite these

Table 3 The concordance proportions for RFS and OS and for TLTF and OS, and Spearman's rank correlation coefficient for RFS and OS and for the TLTF and OS in each patient group

	Concordance proportion for the RFS and OS	Concordance proportion for the TLTF and OS	Spearman's rank correlation coefficient for the RFS and OS	Spearman's rank correlation coefficient for the TLTF and OS
All patients ($n = 134$)	0.634	0.851	0.639	0.875
Colorectal cancer ($n = 50$)	0.600	0.860	0.435	0.790
Carcinoma ($n = 105$)	0.619	0.838	0.614	0.838
Sarcoma ($n = 22$)	0.682	0.909	0.569	0.840

minor differences, the concepts are similar and seem to be viable in both fields.

Two points concerning the newly proposed endpoint of TLTF should be noted. First, the TLTF is a parameter concerning the effectiveness of PM. Second, the TLTF is a surrogate marker for the OS. Recently, stereotactic body radiation therapy (SBRT) has come to be widely performed for the treatment of pulmonary metastasis, and provides a favorable local control rate. Some radiation oncologists use "freedom from failure of local control," which is similar to TLTF, as an endpoint for SBRT for pulmonary metastasis [19]. We believe that TLTF will be useful in studies comparing pulmonary metastasectomy and SBRT. On the other hand, it is difficult to validate the effectiveness of PM, partly because a large proportion of patients receive systemic therapy before and/or after PM, and the effects of such therapy and PM cannot be completely distinguished. Therefore, the TLTF is actually considered to reflect the effects of multidisciplinary treatment, including PM. However, the prediction of the prognosis is important for preparing for palliative treatment in cases requiring terminal care [20]. The present study showed that the TLTF correlates well with the OS, suggesting that it may be useful for predicting the prognosis.

Several limitations associated with the present study warrant mention. First, this was a single-institution study, and the number of patients was limited. There may be differences among physicians or institutions concerning the criteria for deciding whether or not local therapy with curative intent is indicated for relapse after the first PM. Therefore, the TLTF may not correlate with the OS well in other institutions. This point should be analyzed at another institution or in a multi-institutional setting. Second, the present study was a retrospective study. The usefulness of the TLTF must therefore be validated in a prospective cohort in the future.

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