Growth rate of chemotherapy naïve lung metastasis from colorectal cancer could be a predictor of early relapse after lung resection

Koji Kawaguchi[1], Keisuke Uehara[2], Goro Nakayama[3], Takayuki Fukui[1], Koichi Fukumoto[1], Shota Nakamura[1], Kohei Yokoi[1]

[1]Department of Thoracic Surgery, [2]Division of Surgical Oncology (Surgery I), [3]Department of Gastroenterological Surgery (Surgery II), Nagoya University Graduate School of Medicine, Nagoya, Japan

Corresponding Author:

Koji Kawaguchi

Department of Thoracic Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

Tel: +81-52-744-2376

Fax: +81-52-744-2383

E-mail: gucci@med.nagoya-u.ac.jp

Abstract

Purpose

The aim of this study is to elucidate a potential risk factor of early relapse after pulmonary metastasectomy of colorectal cancer and to propose an optimal treatment strategy for lung metastasis with an aggressive nature.

Methods

Seventy patients who underwent pulmonary metastasectomy for diachronically measurable pulmonary lesions were retrospectively analyzed. We calculated the tumor doubling time (TDT) as the growth rate of lung metastasis and divided the study population into the two groups according to the TDT (the Rapid (≤100 days) or Slow (>100 days) group).

Results

Patients consisted of 47 males and 23 females, with a mean age of 63 years. Forty-two patients had a relapse after pulmonary metastasectomy with a median follow-up duration of 24 months. There was a significant difference in the relapse-free survival between the Rapid and Slow groups ($p = 0.047$). Using a multivariate analysis, no preoperative chemotherapy and a high level of serum CEA were proven to be significant risk factors for relapse after metastasectomy. Meanwhile, multivariate analyses among 37 patients without preoperative chemotherapy indicated the TDT was the sole

significant factor for relapse-free survival. In addition, eight of nine patients with relapse within 12 months were placed into the Rapid group.

Conclusions

Despite of a preliminary study with a small number of patients, lung metastases demonstrating a TDT of 100 days or less were suggested to have a high risk for early relapse after metastasectomy.

Keywords: Colorectal cancer, lung resection, metastasectomy, tumor doubling time, growth rate

Introduction

Pulmonary metastasectomy of colorectal cancer is widely accepted with the aim of maintaining long-term survival or potential cure. From recent multi-institutional large series studies, the five-year survival rates after pulmonary metastasectomy reached approximately 50% [1, 2], and several factors, such as the number or size of metastases, the lymph node involvement, the completeness of resection, and the serum level of carcinoembryonic antigen (CEA), were also considered to be poor prognostic factors. Recently, new chemotherapeutic agents have been developed against colorectal cancer, and the criteria or indications for metastasectomy may thus be changing [3]. In fact, surgical treatment may be feasible to reduce the necessity of chemotherapy, which has been administered as first-line therapy for a long time.

Nevertheless, we occasionally encounter early relapse after pulmonary metastasectomy, and these interventions are proven to be of little benefit for such patients. This poor outcome may be related not to the previously mentioned prognostic factors but to the aggressiveness of the tumor itself. One of the factors presenting tumor aggressiveness was supported to be the growth rate of the tumor, which could be calculated by the tumor doubling time (TDT). Several reports have suggested the TDT to be a prognostic factor, however, whether the TDT was a risk factor for early relapse after metastasectomy has not yet been reported [4, 5]. If this assumption is proven to be

significant, then it could be hypothesized that tumor aggressiveness could be restrained by preoperative chemotherapy, rather than immediate lung resection. Therefore, we conducted this preliminary study to elucidate the risk factors of early relapse after pulmonary metastasectomy with the aim to propose an optimal treatment strategy against it.

Methods

Study design

From January 2002 to December 2012, 78 patients underwent initial pulmonary metastasectomy from colorectal cancer in our hospital. To focus on the tumor aggressiveness of the lung metastases, we selected patients who received computed tomography (CT) of the chest at least twice before pulmonary metastasectomy. Patients who underwent incomplete resection or had malignant disease of other organs which were not excised concurrently were excluded from this study. Bilateral lung metastases which were removed metachronously were also determined to be a contraindication for the study. Ultimately, 70 patients were included in this retrospective analysis.

The medical records of all eligible patients were reviewed for demographic information, stage, and treatment of primary cancer. To elucidate the potential risk factors of early

relapse after pulmonary metastasectomy, the disease-free interval from primary colorectal cancer, the number and laterality of the lung metastases, the history of liver metastasis, the preoperative serum level of CEA, and perioperative chemotherapy were recorded for the analysis. The disease-free interval was defined as the interval between the day of surgery for primary colorectal cancer and the day of first relapse in any organ. In addition, the growth rate of the pulmonary lesion and/or the increasing number of metastatic lesions were defined to be factors indicating tumor aggressiveness. We calculated the TDT as a growth rate of lung metastasis; the equation for the TDT was originally described by Schwartz in 1961 [6]:

$Td = t \cdot \log 2 / [3 \cdot \log Dt/D0]$

(where t = the interval between two CT scans, Dt = the final tumor diameter, and D0 = the initial tumor diameter).

In case of multiple lung metastases, we decided the tumor with the fastest TDT as the representation of the disease. The TDT of colon cancer was shown to be approximately100 days in a previous report [5]. Therefore, we divided the patients into two groups: the Rapid group with a TDT of 100 days or less and the Slow group with a TDT of more than 100 days.

The relapse-free survival was calculated from the date of complete pulmonary metastasectomy to the date of the first documented relapse or the day of the last

follow-up. Early relapse was considered to be a relapse within 12 months after the pulmonary metastasectomy. The patients were followed up in principal by gastrointestinal surgeons every three months during the first three years with physical examinations and chest X-rays and chest CT studies at six-month intervals after the treatment.

We performed univariate and multivariate analyses to elucidate the risk factors in the relapse-free survival after pulmonary metastasectomy using various factors, such as the number and laterality of the metastases, hilar lymph node metastasis, the disease-free interval before the lung metastases, the history of liver metastasis, the TDT, and perioperative chemotherapy.

This study was approved by the Institutional Review Board of Nagoya University Hospital. Written informed consent was waived because of the retrospective nature of this study.

Statistical analysis

The relationships between the clinical factors and TDT were analyzed using the chi-square test or Fisher's exact test. Relapse-free survival curves were estimated according to the Kaplan-Meier method, and differences in survival were assessed using the log-rank test. A multivariate analysis for the relapse-free survival was performed

using the Cox proportional hazard model. The data were analyzed using the SPSS 22.0 software program (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics in this study are shown in Table 1. Forty-seven males and 23 females, with a mean age of 63 years, were included. The primary sites of the tumors, which were completely resected before pulmonary metastasectomy, were in equal distribution between the colon and the rectum. The median disease-free interval from the resection of the primary colorectal cancer was 12 months, and 15 patients had lung metastases detected at the screening before the resection of the primary colorectal cancer. Thirty-two patients had a history of liver metastasis or concurrent liver and lung metastases.

The demographic data of the lung metastases are shown in Table 2. The number of metastases was 1 in 43 patients, 2 in 18 patients, 3 in 5 patients, 4 in 1 patient, 5 in 2 patients, and 7 in 1 patient, respectively. A high level of serum CEA before pulmonary metastasectomy was detected in 25 patients. The maximum diameter of the lung metastasis was 20 mm or less in 54 patients. Among the various chemotherapy agents administered to 33 patients before pulmonary metastasectomy, oxaliplatin was utilized in 16 patients, capecitabine in three patients and bevacizumab in 14 patients,

respectively. The TDT ranged from -198 to 1056 days, with a median of 78 days. Six cases had TDTs less than zero because of the decreasing tumor size during preoperative chemotherapy. Among the 70 patients, 17 patients had rapidly growing metastases even while receiving chemotherapy. In contrast, slow growing metastases were found in 15 out of 37 patients who did not receive any chemotherapy before metastasectomy. Regarding the employed surgical procedure for metastasectomy, wedge resection was the most frequently used procedure, followed by lobectomy. Forty-two patients had a relapse after pulmonary metastasectomy with a median follow-up duration of 24 months. The first relapse site was the lungs in 24 patients, liver in 12 patients and peritoneal region in six patients, respectively. Among them, 27 patients developed an early relapse within 12 months after the lung resection. Figure 1 shows the relapse-free survival curves according to the TDT of the lung metastasis. Relapse after pulmonary metastasectomy was observed in 27 patients of the Rapid group and 15 patients of the Slow group, and there was a significant difference in the relapse-free survival between the two groups (median: 13 months vs 22 months; $p = 0.047$). Table 3 reveals the results of univariate and multivariate analyses of the relapse-free survivals. Using a multivariate analysis, no preoperative chemotherapy (Supplementary Figure 1B) and a high level of serum CEA were proven to be significant risk factors in the relapse-free survival after pulmonary metastasectomy.

In addition, we also analyzed the risk factors of relapse after pulmonary metastasectomy among 37 patients who did not receive preoperative chemotherapy. Using a univariate analysis, the TDT and the level of serum CEA were proven to be significant factors, whereas the number of metastases, hilar lymph node metastasis, and postoperative chemotherapy after pulmonary metastasectomy were not (Table 4 and Figure 2). A multivariate analysis showed that a short TDT was the sole risk factor in the relapse-free survival ($p < 0.01$). Among the 20 relapse cases, nine were detected within 12 months after the metastasectomy. All cases, except one in early relapse, were shown to belong to the Rapid group.

Discussion

The use of pulmonary metastasectomy for the treatment of colorectal cancer has been widely accepted, and a certain degree of patients achieved a long-term survival, or even cure, after the surgical treatment. There are several preferable prognostic factors previously reported by many studies, such as solitary metastasis, a smaller tumor size, longer disease-free interval, normal level of serum CEA, no lymph node involvement, and the presence of extrathoracic disease [1, 2, 7]. Thoracic surgeons as well as other experts have decided the indication of pulmonary metastasectomy basically upon those prognostic factors. However, new chemotherapeutic agents such as oxaliplatin or

molecular-targeted drugs have been recently developed, and the survival of patients with metastatic colorectal cancer could be prolonged without requiring surgical treatments [8]. Therefore, the indications for metastasectomy should be reevaluated, and acquiring a disease-free survival after surgical treatment appears to be more important [3]. However, an early relapse after pulmonary metastasectomy is sometimes experienced, and those cases do not benefit from surgical treatment. One of the reasons for an early relapse is suggested to be due to tumor aggressiveness; however, there is a paucity of data on the risk factors for early relapse. Therefore, it is important to determine the tumor aggressiveness before considering the surgical treatment for lung metastasis.

The TDT is one of the characteristics which indicate tumor aggressiveness or efficacy to therapies. It has been widely used for various malignant diseases and has also been reported to be a prognostic factor [4]. Friberg and colleagues determined that the recognition of basic factors in the tumor cell kinetics is essential in the evaluation of treatment strategies [5]. The TDT of colon cancer was also shown to be approximately100 days in the report. From this study, it was clarified that the lung metastases from colorectal cancer have various TDTs, and patients with TDTs of 100 days or less had a worse prognosis than those with TDTs more than 100 days. Rapidly growing tumors with short TDTs, such as testicular carcinomas, malignant melanoma,

or small cell lung cancer, are mainly treated by chemotherapy and/or radiotherapy instead of surgery [9]. Therefore, it may be preferable to treat rapid-growing lung metastases with chemotherapy rather than by surgery.

The recent improvements in the resolution of CT and intensive follow-up of the surgically treated colorectal cancer patients have led to the detection of lung metastases at a relatively smaller size [10]. In a case of a pulmonary nodule less than 1 cm in diameter, subsequent CT is generally recommended at an interval of one or two months. In the present study, the TDT could be easily calculated from the two metachronous CTs, and we were able to speculate the tumor aggressiveness. Using multivariate analyses among all 70 cases, the TDT, or the tumor aggressiveness, was not indicated to be a risk factor for relapse, whereas preoperative chemotherapy was. Conversely, the TDT was proven to be a sole risk factor among patients with chemotherapy naïve metastases, while it was not a risk factor for relapse in patients who underwent preoperative chemotherapy ($p = 0.724$, data not shown). Therefore, the administration of chemotherapy before metastasectomy could restrict early relapse or raise the curative rate in the tumor aggressive cases with rapid-growing or increasing in number metastases. In practice, we recommended preoperative chemotherapy in Case 3 (Supplementary Figure 1C) of a rapidly progressive lung metastasis to obtain the long-term disease-free survival. In the recently reported National Comprehensive

Cancer Network guideline, preoperative chemotherapy is recommended only for patients with unresectable, but potentially convertible disease [11]. According to the multivariate analyses in this study, we speculate that preoperative chemotherapy should be considered for all patients with aggressive metastases, even those which are resectable.

Hilar or mediastinal lymph node metastasis and the number of lung metastases have been reported as adverse prognostic factors after pulmonary metastasectomy. However, these factors did not influence the relapse-free survival in the univariate analysis in this study. The reason for this finding is suggested to be that the lung metastases were detected at a smaller size with intensive follow-up and had not yet progressed to lymphatic invasion. In addition, the major procedure was wedge resection without lymph node dissection, unless lymph node metastases were suspected on PET/CT. Therefore, the information regarding lymph node metastasis may have been underestimated.

There are several limitations associated with this study. First, this was a retrospective, single institutional study, and the sample size seemed to be too small to derive the definite risk factors. Second, the follow-up period after the pulmonary metastasectomy was relatively short. Third, the chemotherapy regimens before pulmonary metastasectomy were not uniform and changed during the study period.

Lastly, it was not possible to clearly determine whether or not the metastases continued to grow in size or in number during chemotherapy. Careful evaluations should be performed for those patients.

In conclusion, a rapidly growing lung metastasis without chemotherapy was suggested to be a sole risk factor for early relapse after pulmonary metastasectomy. Preoperative chemotherapy should be considered in patients with aggressive metastasis, even lesions that are resectable. And for thoracic surgeons, the use of TDT could be useful to determine the eligibility for pulmonary metastasectomy from this preliminary study. A larger number of patients from multi-institutions and consequent prospective study should be needed for the confirmation of the outcomes in this study.

References

1. Onaitis MW, Petersen RP, Haney JC et al. Prognostic factors for recurrence after pulmonary resection of colorectal cancer metastases. Ann Thorac Surg 2009; 87: 1684-1688.

2. Iida T, Nomori H, Shiba M et al. Prognostic factors after pulmonary metastasectomy for colorectal cancer and rationale for determining surgical indications: a retrospective analysis. Ann Surg 2013; 257: 1059-1064.

3. Nordlinger B, Sorbye H, Glimelius B et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. The Lancet 2008; 371: 1007-1016.

4. Usuda K, Saito Y, Sagawa M et al. Tumor doubling time and prognostic assessment of patients with primary lung cancer. Cancer 1994; 74: 2239-2244.

5. Friberg S, Mattson S. On the growth rates of human malignant tumors: implications for medical decision making. J Surg Oncol 1997; 65: 284-297.

6. Schwartz M. A biomathematical approach to clinical tumor growth. Cancer 1961; 14: 1272-1294.

7. Kanemitsu Y, Kato T, Hirai T, Yasui K. Preoperative probability model for predicting overall survival after resection of pulmonary metastases from

colorectal cancer. Br J Surg 2004; 91: 112-120.

8. Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JP. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. Lancet Oncol 2007; 8: 898-911.

9. Takei H, Kondo H, Miyaoka E et al. Surgery for small cell lung cancer: a retrospective analysis of 243 patients from Japanese Lung Cancer Registry in 2004. J Thorac Oncol 2014; 9: 1140-1145.

10. Tjandra JJ, Chan MK. Follow-up after curative resection of colorectal cancer: a meta-analysis. Dis Colon Rectum 2007; 50: 1783-1799.

11. Network NCC. NCCN Clinical Practice Guidelines in Oncology. Version 2.2013.

Table 1 The Characteristics of the Patients according to the Tumor Doubling Time (n = 70)

Characteristic	Total	Rapid	Slow	p value
Median age (years) (range)	63 (29-85)	64	62	0.53
Gender				0.54
Male	47	25	22	
Female	23	14	9	
Site of primary lesion				0.232
Colon	35	17	18	
Rectum	35	22	13	
Primary tumor stage				0.42
II / III / IV	14 / 25 / 31	10 / 13 / 16	4 / 12 / 15	
DFI (months)				0.77
0-12	37	20	17	
>12	33	19	14	
Median (range)	12 (0-73)			
History of liver metastasis				0.57
Yes	32	19	13	
No	38	20	18	

Rapid group: the tumor doubling time of 100 days or less. Slow group: that of more than 100 days. DFI: disease-free interval from primary colorectal cancer

Table 2 Clinical Data about the Lung Metastases according to the Tumor Doubling Time

Variables	Total	Rapid	Slow	p value
Number of lung metastases				0.41
1	43	22	21	
2	18	13	5	
3	5	2	3	
≥4	4	2	2	
Location				0.94
Ipsilateral	63	35	28	
Bilateral	7	4	3	
Serum CEA level				0.30
High	25	16	9	
Normal	45	23	22	
Maximum diameter of lung metastasis (mm)				0.52
Mean (range)	17 (4-65)	17	16	
Chemotherapy before pulmonary metastasectomy				0.50
Yes	33	17	16	
No	37	22	15	

Type of lung resections				0.14
Lobectomy	22	16	6	
Segmentectomy	14	6	8	
Wedge resection	34	17	17	
Hilar lymph node metastasis				0.42
Yes	4	3	1	
No	66	36	30	
Postoperative chemotherapy				0.05
Yes	23	8	15	
No	38	25	13	
Unknown	9	6	3	
Relapse after pulmonary metastasectomy				0.08
Yes (within 1 year)	42 (27)	27 (16)	15 (11)	
No	28	12	16	

Rapid group: the tumor doubling time of 100 days or less. Slow group: that of more than 100 days.

Table 3 Univariate and Multivariate Analyses of the Risk Factors in the Relapse-free Survival after Pulmonary Metastasectomy (n = 70)

Factors	Reference	HR (95% CI)	p value
Univariate model			
Sex	Male	1.37 (0.73-2.57)	0.33
Tumor doubling time	Slow group	1.93 (1.01-3.68)	0.05
Increase in the number of LM	No	1.86 (0.73-4.76)	0.20
Number of LM	per 1 increase	1.27 (0.96-1.67)	0.09
Laterality of LM	Ipsilateral	1.38 (0.54-3.52)	0.50
DFI	per 1-month increase	0.98 (0.96-1.00)	0.04
Preoperative chemotherapy	Yes	1.99 (1.07-3.71)	0.03
Serum CEA level	Normal	2.12 (1.14-3.94)	0.02
History of liver metastasis	No	1.39 (**0.75 - 2.56**)	0.30
Hilar LN metastasis	No	2.36 (0.84-6.65)	0.10
Multivariate model			
Tumor doubling time	Slow group	1.56 (0.80-3.06)	0.20
Number of LM	per 1 increase	1.24 (0.93-1.65)	0.15
DFI	per 1-month increase	0.99 (0.96-1.01)	0.22
Preoperative chemotherapy	Yes	1.98 (1.00-3.95)	0.05

Serum CEA level	Normal	2.16 (1.13-4.12)	0.02

HR: hazard ratio. CI: confidence interval. Slow group: the tumor doubling time of more than 100 days. DFI: disease-free interval from primary colorectal cancer. LM: lung metastases. LN: lymph node

Table 4 Univariate and Multivariate Analyses of the Risk Factors in the Relapse-free Survival after Pulmonary Metastasectomy without Preoperative Chemotherapy (n = 37)

Factors	Reference	HR (95% CI)	p value
Univariate model			
Sex	Male	1.18 (0.47-2.96)	0.73
Tumor doubling time	Slow group	6.55 (2.14-20.01)	0.01
Increasing in number of LM	No	1.67 (0.49-5.71)	0.42
Number of LM	per 1 increase	1.28 (0.84-1.96)	0.26
Laterality of LM	Ipsilateral	1.45 (0.33-6.33)	0.62
DFI	per 1-month increase	0.98 (0.95-1.01)	0.12
Serum CEA level	Normal	2.61 (1.05-6.47)	0.04
History of liver metastasis	No	1.35 (0.56-3.26)	0.51
Hilar LN metastasis	No	1.70 (0.39-7.37)	0.48
Postoperative chemotherapy	Yes	2.18 (0.69-6.90)	0.18
Multivariate model			
Tumor doubling time	Slow group	5.89 (1.89-18.32)	0.01
Serum CEA level	Normal	2.01 (0.80-5.09)	0.14

HR: hazard ratio. CI: confidence interval. Slow group: the tumor doubling time of more

than 100 days. DFI: disease-free interval from primary colorectal cancer. LM: lung metastases. LN: lymph node

Figure Captions

Fig. 1. The relapse-free survival curves after pulmonary metastasectomy stratified by the tumor growth rate. A significant difference was seen between the two groups ($p = 0.047$).

Fig. 2. The relapse-free survival curves after pulmonary metastasectomy stratified by the tumor growth rate in patients with chemotherapy naïve lung metastases. A significant difference was seen between the two groups ($p < 0.01$).

Supplementary Fig. 1. Three cases of pulmonary metastasectomy. A) No need of perioperative chemotherapy. A 74-year-old female had a solitary pulmonary nodule of 10 mm in diameter in her left upper lobe at the time of resection for the primary colon cancer (Left). The size of the pulmonary nodule increased to 13 mm seven month after colectomy, and the TDT was calculated to be 189 days (Right). The lesion was proven to be a metastasis by VATS excision, and she is currently in a stable condition 6 years after the metastasectomy without receiving chemotherapy. B) Early relapse after metastasectomy. A 63-year-old male had a lung metastasis in his left lower lobe 20 months after resection of the colon cancer (Left). The pulmonary lesion rapidly grew, and the TDT was 32 days (Right). He had bone metastasis nine months after

segmentectomy for the lung metastasis and died four months later. C) Preoperative chemotherapy followed by metastasectomy. A 71-year-old male had a lung metastasis and the TDT was calculated to be 44 days (Left to Middle). Preoperative chemotherapy was administered, and the tumor size decreased from 15 to 7 mm (Middle to Right). Right upper lobectomy was performed and he is currently in a stable condition 26 months after metastasectomy without relapse.