World J Surg (2017) 41:771–779
DOI 10.1007/s00268-016-3802-9

ORIGINAL SCIENTIFIC REPORT

Histology is a Prognostic Indicator After Pulmonary Metastasectomy from Renal Cell Carcinoma

Yoichi Ohtaki[1,2] · Kimihiro Shimizu[1,2] · Keiju Aokage[3] · Masayuki Nakao[4] · Junji Yoshida[3] · Mitsuhiro Kamiyoshihara[5] · Masayuki Sugano[6] · Yusuke Takahashi[7] · Seshiru Nakazawa[1,2] · Toshiteru Nagashima[1,2] · Kai Obayashi[1,2] · Tomoyuki Hishida[3] · Masahiro Tsuboi[3] · Shohei Mori[4] · Mingyon Mun[4] · Sakae Okumura[4] · Hitoshi Igai[5] · Noriyuki Matsutani[7] · Akira Mogi[1] · Hiroyuki Kuwano[1]

Published online: 28 November 2016

Abstract

Objectives There are only a few detailed reports concerning the prognosticators following surgical resection of pulmonary metastases (PMs) from renal cell carcinoma (RCC). We investigated the prognosis of patients with RCC PMs undergoing pulmonary metastasectomy and identified prognostic factors in a multi-institutional retrospective study.

Methods We retrospectively evaluated 84 patients who underwent resection of PMs from RCC between 1993 and 2014. We assessed the clinicopathological characteristics, focusing on the histological findings of PMs. We classified the histology into three types: pure clear cell carcinoma ($N = 68$), clear cell carcinoma combined with other histology type ($N = 8$), and non-clear cell carcinoma ($N = 8$). We examined the relationship between these histological types and the prognosis of patients with PMs from RCC.

Results Complete resection was achieved in 78 patients (93%). The 5-year overall survival rate after metastasectomy was 59.7%. In multivariate analysis, three factors were found to be independent favorable prognostic factors of overall survival after lung metastasectomy [tumor size <2 cm, hazard ratio (HR) = 0.31, 95% confidence interval (CI) 0.13–0.78, $P = 0.012$; clear cell type, HR = 0.37, 95% CI 0.16–0.83, $P = 0.025$; and complete resection, HR = 0.27, 95% CI 0.10–0.78, $P = 0.015$].

Conclusions This study indicates that a histological finding of the clear cell type is a significant favorable prognostic factor in addition to complete resection and a tumor size <2 cm. Histological evaluation of PM lesions is important for predicting survival after metastasectomy.

Abbreviations

CI	Confidence interval
DFI	Disease-free interval
HR	Hazard ratio
ND	Nodal dissection
OS	Overall survival
PM	Pulmonary metastasis

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/06CPsS.

Electronic supplementary material The online version of this article (doi:10.1007/s00268-016-3802-9) contains supplementary material, which is available to authorized users.

✉ Kimihiro Shimizu
kmshimizu@gmail.com

1 Division of General Thoracic Surgery, Integrative Center of General Surgery, Gunma University Hospital, Maebashi, Gunma, Japan

2 Department of Thoracic and Visceral Organ Surgery, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

3 Division of Thoracic Surgery, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

RCC Renal cell carcinoma
RFS Recurrence-free survival

Introduction

Renal cell carcinoma (RCC) accounts for 2–3% of all cancers [1–3]. Approximately 30% of patients with RCC have evident metastases at the initial diagnosis [4], and the lung is the most common site of RCC metastasis. Although no randomized controlled trials have shown that pulmonary metastasectomy extends survival, many previous reports have suggested the effectiveness of pulmonary metastasectomy in patients with RCC [5–13]. Several favorable prognostic factors after metastasectomy have been reported, including complete resection [5–11], younger age [13], longer disease-free interval (DFI) between primary RCC resection and pulmonary metastasectomy [6, 7, 10], metachronous metastases [11], smaller numbers of pulmonary metastases (PMs) [5–7], smaller metastatic tumor size [5, 8, 11, 12], and negative lymph node metastases [6, 8, 11, 12]. However, there is little evidence concerning the prognostic impact of the tumor histology of PMs. Although clear cell carcinoma is the most prevalent subtype of RCC, there are several other histological subtypes, such as the papillary type, chromophobe type, and multilocular cystic type, as well as the coexistence of a sarcomatoid component with these types. Histological findings of the primary tumor, such as nuclear grade and sarcomatoid differentiation, were shown to be prognostic factors in metastatic RCC, including unresectable cases [14]. However, only a few studies have evaluated the prognostic impact of the histological findings of PMs in patients undergoing PM resection [11, 12].

In this multi-institutional retrospective study, we investigated the prognostic factors of RCC patients with PMs undergoing metastasectomy and clarified whether PM histology and other previously reported clinicopathological factors are prognostic.

[4] Department of Thoracic Surgical Oncology, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

[5] Department of General Thoracic Surgery, Maebashi Red Cross Hospital, Maebashi, Gunma, Japan

[6] Department of General Thoracic Surgery, National Hospital Organization Takasaki General Medical Center, Takasaki, Gunma, Japan

[7] Department of General Thoracic Surgery, Teikyo University School of Medicine, Tokyo, Japan

Methods

Patient selection and follow-up

This was a multi-institutional joint retrospective study conducted by researchers at Gunma University Hospital, National Cancer Center Hospital East, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Maebashi Red Cross Hospital, National Hospital Organization Takasaki General Medical Center, and Teikyo University School of Medicine. The study protocol was approved by the Institutional Review Board of each participating institution.

Between July 1993 and July 2014, 93 patients who underwent surgical resection for intrathoracic metastases from kidney cancer at the participating institutions were identified. In this study, we only included patients who underwent metastasectomy of intrapulmonary metastases from RCC for the first time. After excluding patients with diseases other than RCC (one renal pelvic carcinoma, one paraganglioma, one urothelial carcinoma), two patients with pleural metastases, and four patients with recurrent PM, 84 patients with PMs from RCC were included in this study.

Although the criteria for surgical resection of PMs were decided independently at each institution, surgical resections were performed generally in accordance with the following criteria: (1) PMs were diagnosed as completely resectable by preoperative radiological examination; (2) metastatic diseases were limited to the lung, or extrapulmonary distant metastasis was absent or controlled if present; (3) loco-regional control of the primary RCC was achieved; and (4) good overall general conditions and adequate respiratory function to tolerate lung resection were confirmed. For criteria (1), we included patients with bilateral or multiple PMs without regard to PM number, on condition that they were expected to be completely resected.

The extent of resection was chosen according to the tumor size and location. Limited lung resections were preferred, and wedge resections were applied for peripheral tumors. Segmentectomy, lobectomy, or pneumonectomy was selected for centrally located tumors or when the surgical margin could not be secured by wedge resection. Surgical approaches (open thoracotomy or thoracoscopic surgery) were selected at the discretion of each surgeon. Pre- and post-metastasectomy treatment information, such as immunotherapy, cytotoxic chemotherapy, and molecular-targeted therapy, was collected. However, as the information was collected retrospectively, it was unclear whether these treatments were performed as adjuvant therapy or as treatment for residual or recurrent lesions.

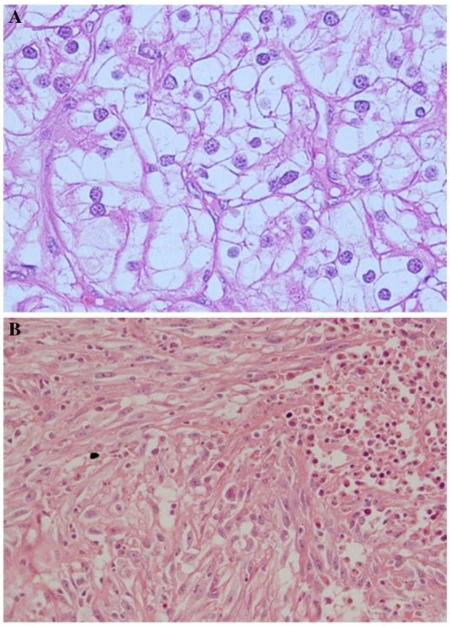


Fig. 1 Histological findings of metastatic lesions. Clear cell carcinoma of low nuclear grade is shown in (**a**). In **b** sarcomatoid cell carcinoma with coagulative tumor necrosis is shown

Histological classification

Histopathological findings obtained postoperatively from surgical PM specimens were collected from the participating institutions. Histologic classification was performed according to a review of written reports. We classified histological subtypes into three groups. PMs comprising only clear cell carcinoma were classified as the clear cell type (Fig. 1a). Clear cell carcinoma combined with another histology component was classified as the combined type. Those that did not contain any clear cell carcinoma component were classified as the non-clear cell type. Figure 1b shows a non-clear cell type, sarcomatoid cell carcinoma.

Statistical analysis

Tumor size was dichotomized at 2 cm, because the tumor size cutoff of 2 cm was used most frequently with significant results in previous reports [5, 9, 12]. The DFI was dichotomized at 24 months for the same reason [6, 10, 14]. The overall survival (OS) was defined as the time interval between the date of pulmonary metastasectomy and date of death from any cause or the last follow-up. The recurrence-free survival (RFS) was defined as the time interval between the date of resection of PM and the date of any recurrence detected or death from other cause than cancer death or last follow-up. For univariate analyses, the survival rates were estimated by the Kaplan–Meier method, and differences in survival between subgroups were compared by the log-rank test. Multivariate analyses were performed using the Cox proportional hazard model. Forward and backward stepwise procedures were performed to determine the prognostic effect of combined factors. Chi-squared test was performed to evaluate the relationship between PM histology and clinicopathological features.

All of the reported P values were two-sided, and the significance level was set at less than 0.05. The analyses were performed using SPSS Statistics 20 statistical software (Dr. SPSS II for Windows; standard version 20.0; SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

The patient characteristics of the 84 patients are listed in Table 1. There were 70 men and 14 women, and the median age was 62 years (range 32–84 years). Eleven patients had PMs synchronously with primary RCCs, and the median DFI was 43.0 months (range 0–260.5 months). Fifty-five patients (65%) had a single metastatic lesion, and the maximum number of metastases was six. Wedge resection was performed in 55 patients (65%), and greater anatomical lung resection was performed in 29 patients (35%). Nodal dissection (ND) was performed in all of the anatomical lung resection patients except one undergoing simple segmentectomy. Of the 28 patients who underwent ND, two had nodal involvement. Complete resection was achieved in 78 patients (93%). Incomplete resection refers to residual tumors of the contralateral lung after resection of unilateral lesions in patients initially scheduled to undergo complete resection of bilateral PMs. Pre-metastasectomy therapy was administered in 35 patients (42%), and any post-metastasectomy therapy was administered in 33 patients (39%). The clear cell type was observed in 68 patients. The combined type was observed in eight patients: Five patients had the combined type with sarcomatoid cell carcinoma, one had granular cell carcinoma, one had papillary and sarcomatoid cell carcinoma components, and one had unspecified carcinoma. The non-clear cell type was observed in eight patients: Five had granular cell carcinoma, two had sarcomatoid cell carcinoma, and one had

Table 1 Patient characteristics

Characteristics	Patients ($N = 84$)	
	N	%
Age		
Median, years (range)	62 (32–84)	
<65	47	56
≥65	37	44
Sex		
Male	70	83
Female	14	17
Stage of primary renal cell carcinoma		
Stage I	16	19
Stage II	12	14
Stage III	13	15
Stage IV	12	14
Unknown	31	37
Synchronous pulmonary metastasis with primary tumor		
(−)	73	87
(+)	11	13
DFI		
Median, months (range)	43.0 (0–260.5)	
Laterality		
Right	49	58
Left	26	31
Bilateral	9	11
Pre-metastasectomy therapy		
Yes	35	42
Immunotherapy	25	30
Cytotoxic chemotherapy	8	10
Molecular target therapy	2	2
Others	3	4
No	31	37
Unknown	18	21
Max tumor size of pulmonary metastasis		
Median, cm (range)	1.5 (0.4–12.0)	
Number of metastatic lesions		
Median (range)	1 (1–6)	
1	55	65
2	15	18
≥3	14	17
Extent of resection		
Pneumonectomy/bilobectomy	4	5
Lobectomy	18	21
Segmentectomy	7	8
Wedge resection	55	65
Nodal dissection		
ND (−)	56	67
ND (+)	28	33
Hilar lymph node dissection	9	11
Mediastinal lymph node dissection	19	23
Pathological nodal involvement		
pN (−)	26	31
pN (+)	2	2
Unknown	56	67
Histologic subtype		
Clear cell type	68	81
Combined type	8	10
With sarcomatoid cell carcinoma	5	6
With granular cell carcinoma	1	1
With papillary and sarcomatoid cell carcinoma	1	1
With unspecified carcinoma	1	1
Non-clear cell type	8	10
Granular cell carcinoma	5	6
Sarcomatoid cell carcinoma	2	2
Granular cell with sarcomatoid cell carcinoma	1	1
Completeness of resection		
Complete resection	77	92
Incomplete resection	7	8
Post-metastasectomy therapy		
Yes	33	39
Immunotherapy	23	27
Cytotoxic chemotherapy	6	7
Molecular target therapy	8	10
Others	1	1
No	31	37
Unknown	20	24

DFI disease-free interval, *ND* nodal dissection

granular cell carcinoma combined with sarcomatoid cell carcinoma.

Figure 2 shows the OS curve after resection of pulmonary metastases. The 5-year OS rate after surgery was 59.7%, and median survival time was 6.6 years. When limited to patients with complete resection, the 5-year OS rate was 62.3% (Supplementary Fig. 1a), and the 5-year RFS rate was 45.7% (Supplementary Fig. 1b).

Relationship between histological subtype and survival

The OS curves, stratified by histologic group, are shown in Fig. 3. The survival of the clear cell group was significantly better than that of the combined group ($P = 0.003$). The clear cell group appeared to have better survival than

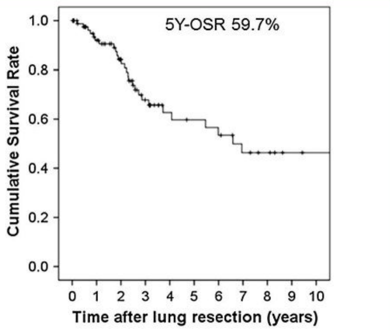


Fig. 2 Overall survival (OS) curve after resection of pulmonary metastases in all patients is shown ($N = 84$). The 5-year OS rate after metastasectomy was 59.7%, and the median survival time was 6.6 years

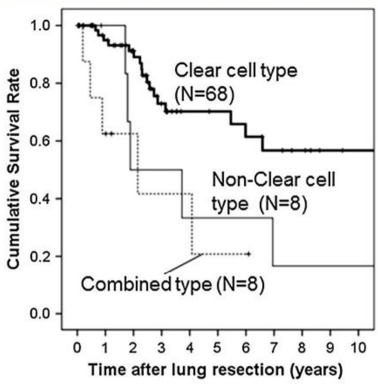
non-clear cell group, but the difference was marginal ($P = 0.056$). There was no statistically significant difference in survival between the combined and non-clear cell groups ($P = 0.515$). Therefore, we combined the combined and non-clear cell group patients collectively as the other group and performed the following analyses.

Prognostic factors after lung metastasectomy

Table 2 shows univariate and multivariate analyses for OS in 84 patients. Univariate analysis showed that tumor size, histology of the metastatic tumor, and complete resection were significantly associated with OS (Fig. 4a–c). Multivariate analysis revealed that the remaining three factors were statistically significant independent prognosticators of OS after lung metastasectomy: tumor size <2 cm: hazard ratio (HR) = 0.31; 95% confidence interval (CI) 0.13–0.78; $P = 0.012$; clear cell type: HR = 0.37; 95% CI 0.16–0.83; $P = 0.025$; and complete resection: HR = 0.27; 95% CI 0.10–0.78; $P = 0.015$ (Table 2).

We also determined prognostic factors for RFS in patients who underwent complete resection (Supplementary Table 1). In 77 cases of complete resection, univariate and multivariate analyses for RFS showed that tumor size and histology of metastatic tumor were independent significant prognostic factors (Tumor size <2 cm: HR = 0.36; 95% CI 0.16–0.80; $P = 0.012$; Clear cell type: HR = 0.33; 95% CI 0.15–0.72; $P = 0.005$).

Fig. 3 Overall survival (OS) curves stratified by histologic classification



P-values in survival difference		
		P-value※
Clear cell type vs	Combined type	0.003
	Non-clear cell type	0.056
Combined type vs	Non-clear cell type	0.515

※ : by log-rank test.

Table 2 Prognostic significance for overall survival

Characteristics	Number of patients (total = 84)	Overall 5YSR*	Univariate analysis *P* value‡	Multivariate analysis	
				Hazard ratio (95% CI)	*P* value§
Age (years)					
<65	47	71.7	0.121		
≥65	37	37.1			
Sex					
Male	70	56.6	0.585		
Female	14	75.5			
Pulmonary metastasis					
Synchronous	11	50.6	0.528		
Metachronous	73	61.3			
DFI					
<24 month	34	60.6	0.800		
≥24 month	50	58.3			
Laterality					
Unilateral	75	61.2	0.941		
Bilateral	9	50.0			
Tumor size					
<2.0 cm	49	84.6	<0.001†	0.31 (0.13–0.78)	0.012†
≥2.0 cm	20	25.3		1	
Number of lesions					
Single	55	61.0	0.890		
Multiple	29	56.5			
Nodal dissection					
ND (−)	56	69.3	0.213		
ND (+)	28	47.6			
Nodal involvement					
N (−) or unknown	82	60.1	0.348		
N (+)	2	50.0			
Histology					
Clear cell type	68	70.2	0.002†	0.37 (0.16–0.83)	0.025†
Other type	16	26.6		1	
Resection completeness					
Complete	77	62.3	0.007†	0.27 (0.10–0.78)	0.015†
Incomplete	7	34.3		1	

DFI disease-free interval, *ND* nodal dissection

* 5-year survival rate

‡ Log-rank test

§ Cox proportional hazard model

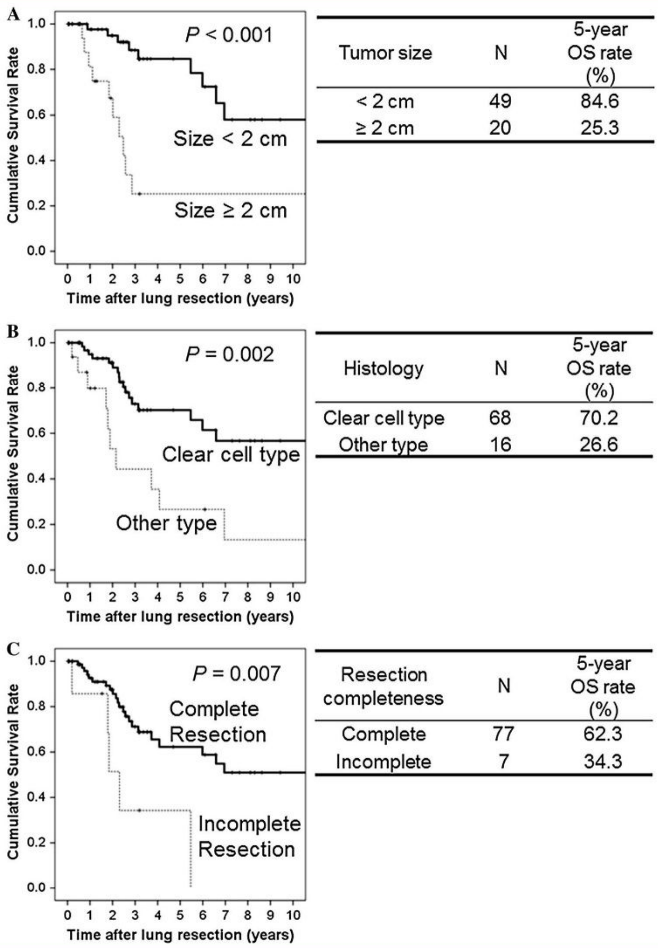
† Significance

Discussion

In this study, we showed the outcomes of patients undergoing surgical resection of RCC PMs in a Japanese population. The overall 5-year survival rate was 59.7%, which was better than that reported in previous studies [5, 8–10]. The reasons remain unclear, but we presume that strict resection criteria and recent progress in systemic control, surgical techniques, and perioperative management might have resulted in better prognoses. For example, there were more patients undergoing resection for a single PM (65%) than reported in the previous literature (47–56%) [5, 8, 9].

In the current study, we showed three independent favorable prognostic factors of OS: clear cell carcinoma

Fig. 4 Overall survival (OS) curves according to independent prognostic factors



histology, complete resection, and a tumor size <2 cm. Histological subtype was reported to be a prognostic factor of primary RCC [15]. Clear cell predominant carcinoma accounts for approximately 90% of RCC and is associated with a better outcome. Other pathological findings such as nuclear grade, coagulative tumor necrosis, and sarcomatoid differentiation were reported to be unfavorable factors of metastatic clear cell RCC [14]. Initially, in the present study, we classified the tumor histology of PMs into clear cell, combined, and non-clear cell types. Because of the identical prognoses, we combined the latter two types into one group, other type. Compared with this group with various subtypes, patients with PMs comprising only clear cell carcinoma had significantly better outcomes after pulmonary metastasectomy. Meimarakis et al. [11] previously reported the negative prognostic impact of tumor histology, but they investigated only the predominant histology in primary tumors. Our study differs from theirs in that we evaluated the prognostic impact of histology in PMs, a finding that has never been reported in the literature to our knowledge. Even if the histologic findings of primary RCC are unknown or lacked during the long course of DFI, we can predict prognosis by meticulously observing histology of RCC PMs in whole resected specimen. And especially for clear cell type, surgical resection of PMs is reasonable because of its prognostic significance. Other pathological findings, such as nuclear grade and tumor necrosis, may also have been prognostic, but we could not collect further detailed pathological findings from multiple participating institutions.

Complete resection was shown to be an independent favorable prognostic factor after the resection of RCC PMs, consistent with other reports [5–11]. Tumor size also was an independent favorable prognosticator when the size cutoff was set at 2 cm. Although the optimum cutoff size of PMs as a categorical prognosticator remains controversial [5, 8, 11, 12], 2 cm was a significant cutoff value in our study, as in many previous reports [5, 9, 12].

Lymph node metastasis has also been commonly reported as an important prognostic factor [5, 6, 8, 11, 12, 16], but its prognostic significance was not evident in our study. One of the reasons may be that only 33% of our study cohort underwent nodal dissection. Likewise DFI, which has also been reported as a prognostic factor [6, 7, 10], was not a significant factor even in univariate analysis in our study. The reason is unclear, but similar to the fact that our patient set had better prognosis when compared with previous literature, and this may also be because of our strict resection criteria. And these results suggested that tumor histology and tumor size might be important to predict post-metastasectomy survival.

The collected variables and characteristics, particularly the pathological findings, were limited because of the retrospective multi-institutional nature of the study and long study period. Because we reviewed the pathological findings only in pulmonary metastatic tumors, the relationship between the pathological findings of the primary lesion and those of PMs is unclear. We need to clarify differences in the prognostic impact of the pathological findings of the primary tumors and that of PMs in future research. In our series, seven patients were diagnosed with granular cell carcinoma. However, the term "granular cell RCC" has now been abandoned for subtyping. Wang et al. [17] and Yang et al. [18] showed that granular cell RCC comprises a heterogeneous group of tumors ranging from benign to highly malignant according to the gene expression profile. In terms of combination with other systemic treatments, such as immunotherapy and molecular-targeted therapy, it remains unclear as to how to apply surgical intervention for RCC PMs, particularly in patients with multiple lesions.

In conclusion, this multi-institutional study showed that histological subtype, tumor size, and resection completeness are significant prognostic factors for OS. Especially, histological evaluation of whole specimen of RCC PMs is necessary to predict survival after metastasectomy. Even if the histologic findings of primary RCC are unknown, we might be able to predict the prognosis by meticulously observing histology of whole PM lesions.

Acknowledgements The authors thank Dr. Jun Atsumi, Dr. Misaki Iijima, Dr. Yoko Azuma, Dr. Toshiki Yajima, and Ms. Kaori Takeshita for their support in data collection.

Compliance with ethical standards

Conflict of interest All authors participated in this study and have agreed on the content of this paper. None has any financial or other relationship that could lead to a conflict of interest. The research was approved by the Institutional Review Board.

References

1. Motzer RJ, Bander NH (1996) Nanus DM renal-cell carcinoma. N Engl J Med 335:865–875
2. Ferlay J, Soerjomataram I, Dikshit R et al (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359–E386
3. Marumo K, Kanayama H, Miyao N et al (2007) Prevalence of renal cell carcinoma: a nation-wide survey in Japan 2002. Int J Urol Off J Jpn Urol Assoc 14:479–482
4. Pantuck AJ, Zisman A, Belldegrun AS (2001) The changing natural history of renal cell carcinoma. J Urol 166(1611–162):3
5. Piltz S, Meimarakis G, Wichmann MW et al (2002) Long-term results after pulmonary resection of renal cell carcinoma metastases. Ann Thorac Surg 73(1082–108):7
6. Pfannschmidt J, Hoffmann H, Muley T et al (2002) Prognostic factors for survival after pulmonary resection of metastatic renal cell carcinoma. Ann Thorac Surg 74:1653–1657
7. Hofmann HS, Neef H, Krohe K et al (2005) Prognostic factors and survival after pulmonary resection of metastatic renal cell carcinoma. Eur Urol 48:77–81 **(discussion 81–72)**
8. Murthy SC, Kim K, Rice TW et al (2005) Can we predict long-term survival after pulmonary metastasectomy for renal cell carcinoma? Ann Thorac Surg 79:996–1003
9. Kawashima A, Nakayama M, Oka D et al (2011) Pulmonary metastasectomy in patients with renal cell carcinoma: a single-institution experience. Int J Clin Oncol 16:660–665
10. Kanzaki R, Higashiyama M, Fujiwara A et al (2011) Long-term results of surgical resection for pulmonary metastasis from renal cell carcinoma: a 25-year single-institution experience. Eur J Cardio Thorac Surg Off J Eur Assoc Cardio Thorac Surg 39:167–172
11. Meimarakis G, Angele M, Staehler M et al (2011) Evaluation of a new prognostic score (Munich score) to predict long-term survival after resection of pulmonary renal cell carcinoma metastases. Am J Surg 202:158–167
12. Assouad J, Petkova B, Berna P et al (2007) Renal cell carcinoma lung metastases surgery: pathologic findings and prognostic factors. Ann Thorac Surg 84:1114–1120
13. Kudelin N, Bolukbas S, Eberlein M et al (2013) Metastasectomy with standardized lymph node dissection for metastatic renal cell carcinoma: an 11-year single-center experience. Ann Thorac Surg 96:265–270 **(discussion 270–261)**
14. Leibovich BC, Cheville JC, Lohse CM et al (2005) A scoring algorithm to predict survival for patients with metastatic clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. J Urol 174:1759–1763 **(discussion 1763)**

15. Gudbjartsson T, Hardarson S, Petursdottir V et al (2005) Histological subtyping and nuclear grading of renal cell carcinoma and their implications for survival: a retrospective nation-wide study of 629 patients. Eur Urol 48:593–600
16. Renaud S, Falcoz PE, Olland A et al (2013) Should mediastinal lymphadenectomy be performed during lung metastasectomy of renal cell carcinoma? Interact CardioVasc Thorac Surg 16:525–528
17. Wang HY, Mills SE (2005) KIT and RCC are useful in distinguishing chromophobe renal cell carcinoma from the granular variant of clear cell renal cell carcinoma. Am J Surg Pathol 29:640–646
18. Yang XJ, Takahashi M, Schafernak KT et al (2007) Does 'granular cell' renal cell carcinoma exist? Mol Histol Reclassif Histopathol 50:678–680

World J Surg (2017) 41:804–809
DOI 10.1007/s00268-016-3786-5

ORIGINAL SCIENTIFIC REPORT

Impact of the Level of Anastomosis on Reflux Esophagitis Following Esophagectomy with Gastric Tube Reconstruction

Makoto Sakai[1] · Makoto Sohda[1] · Tatsuya Miyazaki[1] · Tomonori Yoshida[1] · Yuji Kumakura[1] · Hiroaki Honjo[1] · Keigo Hara[1] · Takehiko Yokobori[2] · Hiroyuki Kuwano[1]

Published online: 31 October 2016

Abstract
Background Among patients who undergo gastric tube reconstruction after esophagectomy, it is generally accepted that the incidence of reflux esophagitis (RE) is significantly lower in patients with neck anastomosis than in those with intrathoracic anastomosis. However, the true impact of the level of anastomosis on RE currently remains unclear.
Methods We examined 53 patients with thoracic esophageal cancer underwent radical esophagectomy with gastric tube reconstruction and neck anastomosis. The level of anastomosis was assessed by measuring the distance from the sternal notch to the stapled ring by computed tomography. The relative level of anastomosis was calculated by the distance from the sternal notch to the most caudal side of the stapled ring (mm)/height (cm).
Results The relative level of anastomosis in 30 (56.6%) patients showed <0, which indicated that anastomosis in these patients was located at a lower level than the sternal notch. The mean relative level of anastomosis was significantly lower in patients with RE (grade A to D) than in those without RE (grade N) (−0.062 vs. −0.012 mm/cm, respectively; $p = 0.043$). RE was more severe with a lower relative level of anastomosis (p for trends = 0.044).
Conclusions The level of anastomosis in patients with gastric tube reconstruction following esophagectomy was associated with the incidence of RE. The displacement of anastomosis into the thoracic cavity was detected in approximately half of the patients with neck anastomosis. RE was more severe with a lower level of anastomosis, even in patients with neck anastomosis.

Introduction

Esophagectomy for esophageal cancer is a highly invasive procedure with serious short-term postoperative complications, such as anastomotic leaks, pneumonia, cardiac events, and sepsis. However, the long-term quality of life of patients who undergo esophagectomy has been attracting attention because of an increase in the postoperative long-term survival rate of patients with esophageal cancer. One of the main complications that may decrease the quality of life of these patients is reflux esophagitis (RE).

Gastric tube reconstruction has been widely performed following esophagectomy for esophageal cancer. The incidence of RE after esophagectomy was previously reported to be between 58 and 72% in patients who underwent gastric tube reconstruction [1, 2]. The pathogenesis of RE after gastric tube reconstruction is known to involve the inactivation of the gastric tube through the vagal denervation of stomach, and the loss of the

✉ Makoto Sakai
maksakai@gunma-u.ac.jp

1 Department of General Surgical Science, Graduate School of Medicine, Gunma University, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan

2 Department of Molecular Pharmacology and Oncology, Graduate School of Medicine, Gunma University, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan

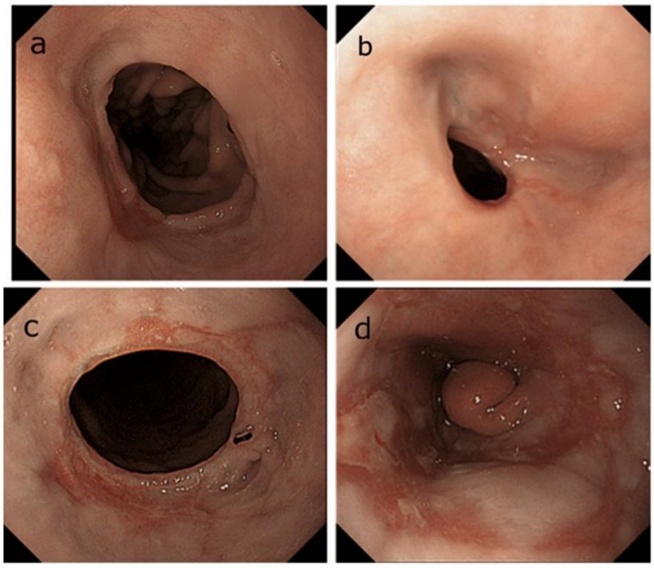


Fig. 1 Representative figures of RE in patients with gastric tube reconstruction. **a** LA grade A, **b** LA grade B, **c** LA grade C, **d** LA grade D

gastroesophageal sphincter mechanism causes the reflux of gastric juices containing acid and/or bile into the remnant esophagus [3, 4]. Although it is generally accepted that the incidence of RE is significantly lower in patients with neck anastomosis than in those with intrathoracic anastomosis [1], the true impact of the level of anastomosis on RE currently remains unclear.

Therefore, the aim of this study was to evaluate the impact of the level of anastomosis on RE in patients who undergo gastric tube reconstruction with neck anastomosis by measuring the distance from the sternal notch to the stapled ring by computed tomography (CT).

Patients and methods

Patients

Between January 2011 and November 2014, 85 patients with thoracic esophageal cancer underwent radical esophagectomy with gastric tube reconstruction and neck anastomosis at the Department of General Surgical Science, Graduate School of Medicine, Gunma University, Japan. We excluded six patients because of an inability to detect the stapled ring using CT, three patients because of short follow-up time (less than 6 months) and 23 patients because of short interval between esophagectomy and first endoscopy to assess mucosal breaks in the residual esophagus (within 6 months), thus, the remaining 53 patients were enrolled in the present study. Esophagogastrostomy was performed using a circular stapling device. Postoperative follow-up ranged between 6.47 and 41.3 months (mean 18.4 months). Helicobacter pylori (H. pylori) infection was determined by the rapid urease test and/or serum antibody test before surgery. If no symptoms of anastomotic stenosis or reflux were present, endoscopic examinations were typically performed and repeated within 12 months in order to survey the upper gastrointestinal tract for a routine follow-up examination. If reflux was present during endoscopy, the severity of RE was recorded. The severity of RE was determined according to the Los Angeles classification [5] (Fig. 1). The time to endoscopy to assess mucosal breaks in the residual esophagus ranged between 6.4 and 36.3 months (mean 13.9 months). This study was approved by the Ethics Committee of Gunma University. Participants provided informed consent before entering the study.

Surgical procedures

Standard esophagectomy was performed using the McKeown method, and three-field (thoracoabdominal and cervical) lymph node dissection was also performed if indicated. All patients underwent curative thoracic esophagectomy that included the esophagogastric junction. The greater curvature gastric tube was created using a linear cutting stapler from the distal side of the lesser curvature to the left side of the cardia and three branches of the right gastric vessels were preserved. Esophagogastric anastomosis was performed by end-to-side anastomosis using a circular stapler device at the cervical esophagus. The digital dilatation of the pyloric ring was routinely performed.

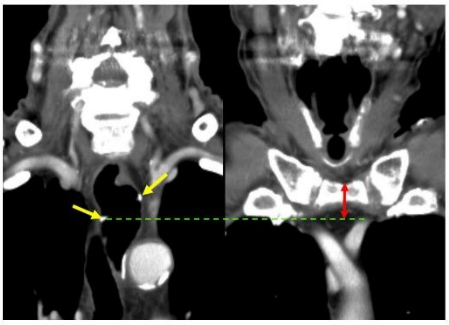


Fig. 2 Coronal contrast-enhanced CT scan at the level of esophagogastric anastomosis, identified by the staples (*yellow arrow*). *Red double-headed arrows* denote the distance from the sternal notch to the most caudal side of the stapled ring

Table 1 Patient characteristics

Characteristic	
Gender (%)	
Female	7 (13.2)
Male	46 (86.8)
Age (mean (sd))	64.72 (9.04)
Reconstruction route (%)	
Retrosternal	3 (5.7)
Posterior mediastinal	50 (94.3)
Antireflux medication after surgery (%)	
None	6 (11.3)
H2-receptor antagonists	18 (34.0)
Proton pump inhibitors	29 (54.7)
Helicobacter pylori infection	
Unknown	8 (15.1)
Negative	30 (56.6)
Positive	15 (28.3)
Severity of esophagitis[a] (%)	
Grade	
N	37 (69.8)
A	2 (3.8)
B	2 (3.8)
C	11 (20.8)
D	1 (1.9)

[a] Los Angeles classification of reflux esophagitis

Assessment of the level of anastomosis

The level of anastomosis was assessed by measuring the distance from the sternal notch to the stapled ring by CT at the routine follow-up examination. By considering differences in patient height, the relative level of anastomosis was calculated by the distance from the sternal notch to the most caudal side of the stapled ring (mm)/height (cm) (Fig. 2).

Statistical analysis

Subject characteristics were compared using Chi-squared tests for categorical variables and the Student's t test for continuous variables. The Jonckheere–Terpstra test was used for a trend analysis. A correlation analysis was performed using Spearman's rank coefficients. A probability value of <0.05 was considered significant. All analyses were performed using R version 2.13.0 (The R Foundation for Statistical Computing, Vienna, Austria) statistical software.

Results

Patient characteristics and incidence of RE

RE was detected in 16 out of the 53 patients included in this study (30.2%). Severe esophagitis (grades C and D) was noted in 12 (22.7%) (Table 1). No significant correlation was observed between the use of antireflux medication after surgery and the severity of RE ($p = 0.548$) (Table 2). Among 45 patients who underwent examination for H. pylori infection, no significant correlation was observed between H. pylori infection and the severity of RE ($p = 0.675$) (Table 3).

Relationship between the level of anastomosis and RE

The relative level of anastomosis in 30 (56.6%) patients showed <0, which indicated that anastomosis in these patients was located at a lower level than the sternal notch. The mean relative level of anastomosis was significantly lower in patients with RE (grade A to D) than in those without RE (grade N) (−0.062 vs. −0.012 mm/cm, respectively; $p = 0.043$). RE was more severe with a lower

Table 2 Frequency of antireflux medication use after surgery according to the severity of esophagitis

Severity of esophagitis[a]	None ($n = 6$)	H2RAs ($n = 18$)	PPIs ($n = 29$)	p value
Grade				
N	4 (66.7%)	15 (83.3%)	18 (62.1%)	0.548
A	1 (16.7%)	0	1 (3.4%)	
B	0	0	2 (6.9%)	
C	1 (16.7%)	3 (16.7%)	7 (24.1%)	
D	0	0	1 (3.4%)	

H2RAs H2-receptor antagonists; *PPIs* Proton pump inhibitors

[a] Los Angeles classification of reflux esophagitis

relative level of anastomosis (p for trends = 0.044) (Fig. 3).

Discussion

The results of the present study showed that the level of anastomosis in patients with gastric tube reconstruction following esophagectomy may be described as the distance from the sternal notch to the stapled ring, and RE was more severe with a lower relative level of anastomosis in patients with neck anastomosis. Regarding the relationship between the level of anastomosis and RE, it is generally accepted that the incidence of RE is significantly higher in patients with intrathoracic anastomosis than in those with neck anastomosis [6, 7], and this phenomenon has been attributed to negative intrathoracic pressure creating a pressure gradient between the abdomen and thorax [8]. However, few studies have investigated the effects of the level of anastomosis on the incidence and severity of RE, particularly in neck anastomosis. This is the first study to demonstrate the relationship between the level of anastomosis and RE in the cervical remnant after esophagectomy, particularly based on measurements of the distance from the sternal notch to the stapled ring by CT.

To date, several studies have reported the incidence of RE in patients who underwent gastric tube reconstruction following esophagectomy. Shibuya et al. [1] reported that 22 out of 39 patients with neck anastomosis (56.4%) had RE. Yamamoto et al. [2] showed that 28 out of 48 patients with neck anastomosis (58.3%) had RE and severe esophagitis (grades C and D) was detected in 19 (39.6%). Yajima et al. [6] also found that 48 out of 141 patients with neck anastomosis (34%) had RE and severe esophagitis (grades C and D) was found in 34 (24.1%). In our study, the incidence of RE was 30.2% and the incidence of severe esophagitis (grades C and D) was 22.7%. The incidence of RE in the present study was consistent with those of Yajima et al. [1] and lower than that found in those of Shibuya et al. [2] and Yamamoto et al. [6]. These discrepancies in the incidence of RE may be attributable to the heterogeneous patient characteristics, such as surgical procedures, reconstruction route, and the time to endoscopy. The time to endoscopy to assess mucosal breaks in the residual esophagus was not documented clearly in these studies. The severity of reflux esophagitis has been reported to decrease with time after an esophagectomy with gastric tube reconstruction, coupled with progressive recovery of the antropyloroduodenal motor activity [9]. It also has been reported that the denervated stomach as an esophageal substitute recovers normal intraluminal acidity with time [10]. These findings suggest that the incidence of RE might be changed depend on the time to endoscopy. Patients after esophagectomy have been reported to still

Table 3 Status of Helicobacter pylori infection according to the severity of esophagitis

Severity of esophagitis[a]	Negative ($n = 30$)	Positive ($n = 15$)	p value
Grade			
N	20 (66.7%)	12 (80.0%)	0.675
A	1 (3.3%)	1 (6.7%)	
B	0	0	
C	8 (26.7%)	2 (13.3%)	
D	1 (3.3%)	0 (0.0%)	

[a] Los Angeles classification of reflux esophagitis

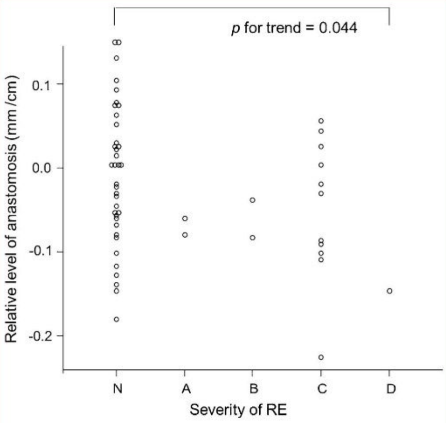


Fig. 3 *Dot plot* graphs of the relative level of anastomosis according to the severity of RE in all 53 patients

suffer from various symptoms (fatigue, dyspnea, appetite loss, dysphagia, esophageal pain, eating problems, etc.) within 6 months after the operation [11, 12]. Thus, considering the effect of surgical invasiveness, we excluded patients with short follow-up time (less than 6 months) and short interval between esophagectomy and endoscopy (within 6 months) in our study. However, suitable timing to assess the RE after esophagectomy remains unclear.

The causes of RE in patients who undergo gastric tube reconstruction following esophagectomy are undoubtedly multifactorial. Several studies have reported its other cause and pathophysiology besides the level of anastomosis. It has been reported that the denervated stomach as an esophageal substitute recovers normal intraluminal acidity with time [10] and the promotion of the duodenal reflux by pyloroplasty facilitates the formation of a damaging refluxate containing pancreatobiliary secretions mixed with gastric acid secretions [6]. Pyloroplasty and bile reflux have been identified as independent risk factors for RE in patients with neck anastomosis [6]. In the present study, antireflux medication did not influence the incidence of RE. This results supports existing data showing that not only acid but bile in the gastric tube has a key role in the development of RE after esophagectomy. H. pylori infection has been reported to influence the acidity in the gastric tube after esophagectomy [13]. In our study, H. pylori infection did not associate with the incidence of RE. Our results suggested that the effect of H. pylori infection on the incidence of RE might not always exist. Nisimura et al. reported that bile reflux could cause RE irrespective of H. pylori infection, while acid reflux could cause RE only in patients without H. pylori infection in the early period after esophagogastrostomy [14]. Although, we did not routinely perform 24-h pH monitoring to investigate the pH of the gastric tube and cervical remnant, our results supports these data showing the effect of H. pylori infection on the incidence of RE might depend on the contents of refluxate.

Another suggestive result of the present study was that the relative level of anastomosis in 30 (56.6%) patients with neck anastomosis was <0, which indicated that the displacement of anastomosis into the thoracic cavity was present in approximately half of patients with neck anastomosis. The most influential factors on the position of the anastomosis are the length of the esophageal remnant. Although, suitable length of esophageal remnant after esophagectomy remain less well defined, redundant esophageal remnant could lead to the displacement of anastomosis into the thoracic cavity and the gastric conduit in these patients as well as in patients with intrathoracic anastomosis may be affected by a negative intrathoracic pressure. Thus, to avoid redundancy of the esophageal remnant is important for preventing RE in patients with neck anastomosis. A routine endoscopic examination and appropriate medication are also important for controlling RE.

Our study has several potential limitations. First, we did not assessed the correlation between the level of anastomosis and clinical symptoms, thus, it remains to be investigated whether the level of anastomosis have any impact on the severity of clinical symptoms. Second, we did not routinely perform 24-h pH monitoring to investigate the pH of the gastric tube and cervical remnant, thus, it was not possible to completely confirm the slight increases observed in the frequency of acid and/or bile reflux with a lower relative level of anastomosis. Third, our method to measure the level of anastomosis cannot access anastomosis without staples, such as hand-sewn anastomosis. Furthermore, it remains unclear whether more severe RE with a lower relative level of anastomosis occurs in patients subjected to other anastomotic techniques. Although the esophagogastric anastomosis technique varies slightly in each institution, further investigations involving a large number of patients are needed in order to confirm the relationship between the level of anastomosis and RE.

In conclusion, the level of anastomosis, described as the distance from the sternal notch to the stapled ring, in patients with gastric tube reconstruction following esophagectomy was associated with the incidence of RE. We also showed that the displacement of anastomosis into the thoracic cavity was present in approximately half of patients with neck anastomosis. Furthermore, RE was more severe with a lower level of anastomosis, even in patients with neck anastomosis.

Author's contribution Study conception and design: MS, acquisition of data: TY, YK, HH, KH, analysis and interpretation of data: MS, MS, TM, TY, drafting of manuscript: MS, critical revision: HK.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest associated with this manuscript.

References

1. Shibuya S, Fukudo S, Shineha R et al (2003) High incidence of reflux esophagitis observed by routine endoscopic examination after gastric pull-up esophagectomy. World J Surg 27:580–583. doi:10.1007/s00268-003-6780-7
2. Yamamoto S, Makuuchi H, Shimada H et al (2007) Clinical analysis of reflux esophagitis following esophagectomy with gastric tube reconstruction. J Gastroenterol 42:342–345. doi:10.1007/s00535-007-2011-6
3. Yuasa N, Sasaki E, Ikeyama T et al (2005) Acid and duodenogastroesophageal reflux after esophagectomy with gastric tube reconstruction. Am J Gastroenterol 100:1021–1027. doi:10.1111/j.1572-0241.2005.41109.x
4. Bonavina L, Anselmino M, Ruol A et al (1992) Functional evaluation of the intrathoracic stomach as an oesophageal substitute. Br J Surg 79:529–532
5. Armstrong D, Bennett J, Blum A et al (1996) The endoscopic assessment of esophagitis: a progress report on observer agreement. Gastroenterology 111:85–92. doi:10.1053/gast.1996.v111.pm8698230
6. Yajima K, Kosugi S, Kanda T et al (2009) Risk factors of reflux esophagitis in the cervical remnant following esophagectomy with gastric tube reconstruction. World J Surg 33:284–289. doi:10.1007/s00268-008-9856-6
7. D'Journo XB, Martin J, Rakovich G et al (2009) Mucosal damage in the esophageal remnant after esophagectomy and gastric transposition. Ann Surg 249:262–268. doi:10.1097/SLA.0b013e31818eec06
8. Bemelman WA, Verburg J, Brummelkamp WH, Klopper PJ (1988) A physical model of the intrathoracic stomach. Am J Physiol 254:G168–G175
9. Nakabayashi T, Mochiki E, Kamiyama Y et al (2013) Impact of gastropyloric motor activity on the genesis of reflux esophagitis after an esophagectomy with gastric tube reconstruction. Ann Thorac Surg 96:1833–1838. doi:10.1016/j.athoracsur.2013.06.034
10. Collard J, Romagnoli R, Salizzoni M (2001) Denervated stomach as an esophageal substitute recovers intraluminal acidity with time. Ann Surg 233:509–514. doi:10.1097/00000658-200104000-00005
11. Viklund P, Wengström Y, Rouvelas I et al (2006) Quality of life and persisting symptoms after oesophageal cancer surgery. Eur J Cancer 42:1407–1414. doi:10.1016/j.ejca.2006.02.005
12. Malmström M, Klefsgard R, Ivarsson B et al (2015) Quality of life measurements as an indicator for timing of support after oesophagectomy for cancer: a prospective study. BMC Health Serv Res 15:96. doi:10.1186/s12913-015-0747-x
13. Mori N, Fujita H, Sueyoshi S et al (2007) Helicobacter pylori infection influences the acidity in the gastric tube as an esophageal substitute after esophagectomy. Dis Esophagus 20:333–340. doi:10.1111/j.1442-2050.2007.00718.x
14. Nishimura K, Tanaka T, Tsubuku T et al (2012) Reflux esophagitis after esophagectomy: impact of duodenogastroesophageal reflux. Dis Esophagus 25:381–385. doi:10.1111/j.1442-2050.2011.01268.x