Metastasectomy of Krukenberg Tumors May Be Associated with Survival Benefits in Patients with Metastatic Gastric Cancer

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Abstract. *Background: The current standard treatment for patients with metastatic gastric cancer (MGC) is systemic chemotherapy. For gastric cancer patients with ovarian metastases, i.e. Krukenberg tumors, it is not known whether metastasectomy is associated with additional benefits. Patients and Methods: All patients who were diagnosed with gastric cancer and ovarian metastases between March 2000 and July 2010 in a medical center were included in the current study. The clinicopathological features and the treatment records were reviewed in detail and their association with overall survival (OS) was analyzed. Results: A total of 85 patients were identified. Thirty five (41.2%) and 50 (58.8%) patients did and did not undergo metastasectomy of Krukenberg tumors, respectively. The performance status and the proportion of patients receiving subsequent systemic therapy were well-matched between the two groups. Regarding disease status, patients who underwent metastasectomy had significantly larger Krukenberg tumors, pronounced bilateral disease and less extensive metastases outside the ovaries than patients who did not undergo metastasectomy. Patients who underwent metastasectomy had a better OS [median=14.1 months; 95% confidence interval (CI)=8.6-19.6 months] than patients who did not undergo metastasectomy (median OS=8 months; 95% CI=5.6-10.4 months, p=0.001). There was no aberrant postoperative morbiditie rate observed, and the median length of hospital stay after metastasectomy alone was 6 days. Based on multivariate analysis, metastasectomy remained an independent predictor of better OS (hazard ratio=0.36, p=0.002). The administration of subsequent systemic therapy, the use of platinum-based chemotherapy, and a better performance status also predict a better OS. Conclusion: Metastasectomy of Krukenberg tumors may be associated with survival benefits in patients with MGC. Further prospective studies are warranted.*

Gastric cancer is the fourth most common malignancy and the second most common cause of cancer deaths worldwide (1, 2). Gastric cancer is primarily treated by surgical resection; recurrence rates remain high despite adjuvant chemotherapy (3, 4). Many patients with gastric cancer eventually have distant metastases. Although systemic chemotherapy, the current standard treatment, provides symptom palliation and prolonged survival in patients with metastatic gastric cancer (MGC), the median overall survival (OS) remains disappointing. In most of the phase III studies, the median OS ranged from 8-13 months (5-8).

Krukenberg tumors were originally defined as malignancies arising from the ovarian stroma with characteristic mucin-filled signet-ring cells (9, 10). The term Krukenberg tumor was later applied to all glandular carcinomas, especially carcinomas arising from gastrointestinal tracts metastasizing to the ovaries. Gastric cancer is one of the most common primary malignancies of Krukenberg tumors (11, 12). Several studies have explored the use of metastasectomy of Krukenberg tumors in patients with gastric cancer and ovarian metastases (13-17). However, the survival benefit of such surgery remains unclear, and the role of metastasectomy of Krukenberg tumors in these patients is also unknown.

This study aimed to explore whether metastasectomy of Krukenberg tumors is associated with survival benefits in patients with gastric cancer and ovarian metastases. We analyzed patients with gastric cancer and Krukenberg tumors in the National Taiwan University Hospital and determined the associations between metastasectomy of Krukenberg tumors, other clinicopathological features, and survival outcome.

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Key Words: Gastric cancer, Krukenberg tumors, metastasectomy.

Patients and Methods

Study population. All of the patients who were diagnosed with gastric cancer and ovarian metastases at the National Taiwan University Hospital (NTUH) in Taipei, Taiwan between March 2000 and July 2010 were enrolled in the study. The clinicopathological features and the treatment records were reviewed in detail. All patients had a pathological diagnosis of adenocarcinoma of the stomach. The diagnosis of Krukenberg tumors was made based on the pathological evaluation of the metastasectomy specimens or by imaging studies (computed tomography or ultrasonography). Patients with synchronous (Krukenberg tumors as the initial presentation of MGC) and metachronous diseases (detection of Krukenberg tumors upon relapse or disease progression) were both included. Patients were divided into two groups: the metastasectomy and the non-metastasectomy groups. The type of metastasectomy included total abdominal hysterectomy (TAH) plus bilateral salpingo-oophorectomy (BSO), subtotal hysterectomy (STH) plus BSO, and oophorectomy alone. Optimal cytoreductive surgery was not required. The primary objective of this study was to compare OS, which was defined as the time from diagnosis of ovarian metastases until death, between patients who did and did not undergo metastasectomy of Krukenberg tumors. This study was approved by the Institute Research Ethical Committee of NTUH.

Statistical analysis. Statistical analyses were performed using the SAS statistical software (version 9.1.3; The SAS Institute, Cary, NC, USA). A two-sided p-value <0.05 was considered statistically significant. The baseline patient characteristics between the two groups were compared using an independent t-test for continuous variables and the chi-square test for nominal variables. The Kaplan Meier method was utilized to estimate survival, which was compared by the log-rank test (univariate analysis) between patients who did and did not undergo metastasectomy.

Other clinically relevant variables, including age, performance status, chronology of disease, bilaterality and size of Krukenberg tumors, presence of signet-ring cells, other metastases, gastrectomy, and subsequent systemic therapy, were also analyzed univariately for the association of OS. Variables with significant association of OS by univariate analyasis were adjusted in multivariate analysis with a Cox proportional hazards model.

Results

A total of 85 patients were enrolled in this study; 35 (41.2%) and 50 (58.8%) patients did and did not undergo metastasectomy of Krukenberg tumors, respectively. The baseline patient characteristics are listed in Table I. The years of diagnosis, the performance status and the proportion of patients receiving subsequent systemic therapy after the diagnosis of ovarian metastasis were not significantly different between the two groups. Patients who underwent metastasectomy compared to patients who did not had significantly larger Krukenberg tumors (median, 9.05 *vs*. 4.5 cm, p<0.001), bilateral disease (88.6% *vs*. 56%, p=0.001), less extensive metastases outside the ovaries (62.9% *vs*. 90%, p=0.003), a greater percentage of signet-ring cells, based on pathological evaluation (82.9% *vs*. 60.4%, p=0.028), and were more likely to undergo resection of primary gastric tumors (65.7% *vs*. 42%, p=0.031). The use of chemotherapy compounds was similar between the two groups, with most patients receiving platinum agents and 5-fluorouracil.

Seventy four patients had died by the data cut-off date (31 January 2011), with a median follow-up of 8.27 months. The median OS of all patients was 9.47 months. Patients who

Table I. *Baseline characteristics*.

	Metastasectomy group N=35	Control group N=50	p-Value
Median age, years (range)	45 (30-67)	44 (39-77)	0.546
Presenting symptoms			
Abdominal pain or distention	22 (62.9%)	26 (52%)	
Menstrual irregularity	5 (14.3%)	3 (6%)	
Weight loss	3 (8.6%)	6 (12%)	
Other	2 (5.7%)	15 (30%)	
Year of diagnosis			
2000-2002	12 (34.3%)	9 (18%)	0.223
2003-2006	11 (31.4%)	21 (42%)	
2007-2010	12 (34.3%)	20 (40%)	
ECOG performance status[a]			
0-1	27 (79.4%)	34 (69.4%)	0.309
2-3	7 (20.6%)	15 (30.6%)	
Chronology			
Synchronous	21 (60%)	24 (48%)	0.275
Metachronous	14 (40%)	26 (52%)	
Median tumor size, cm (range)	9.05 (1-22)	4.5 (2.07-14)	<0.001
Bilaterality			
Bilateral	31 (88.6%)	28 (56%)	0.001
Unilateral	4 (11.4%)	22 (44%)	
Signet-ring cells[b]			
Positive	29 (82.9%)	29 (60.4%)	0.028
Negative	6 (17.1%)	19 (39.6%)	
Other types of metastasis	22 (62.9%)	45 (90%)	0.003
Peritoneum	19 (54.3%)	34 (68%)	0.139
Liver	1 (2.9%)	8 (16%)	
Bone	4 (11.2%)	9 (18%)	
Bone marrow	0 (0%)	4 (8%)	
Other	5 (14.3%)	5 (10%)	
Gastrectomy			
Yes	23 (65.7%)	21 (42%)	0.031
No	12 (34.3%)	29 (58%)	
Subsequent systemic therapy	26 (76.47%)	38 (84.44%)	0.371
Platinum	20 (57.1%)	33 (66%)	0.145
5-Fluorouracil	21 (60%)	37 (74%)	
Capecitabine, UFUR or S-1	8 (22.9%)	4 (8%)	
Taxanes	7 (20%)	19 (38%)	
Irinotecan	2 (5.7%)	5 (10%)	
Cetuximab	1 (2.9%)	7 (14%)	
Bevacizumab	3 (8.6%)	5 (10%)	
Other	5 (14.3%)	7 (14%)	

Data are number of patients (%), unless otherwise indicated; ECOG: Eastern Cooperative Oncology Group. [a]Missing data in one patient of each group. [b]Missing data in one patient of control group.

Table II. *Univariate and multivariate analyses of overall survival.*

Variable	Univariate		Multivariate[a]	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Metastasectomy	0.43 (0.26-0.73)	0.002	0.36 (0.19-0.68)	0.002
Age (1 year increment)	1.01 (0.98-1.04)	0.726	-	-
ECOG PS 0-1 (*vs*. 2-3)	0.32 (0.19-0.55)	<0.001	0.44 (0.24-0.83)	0.011
Synchronous disease	1.11 (0.70-1.77)	0.651	-	-
Bilateral ovarian metastases	0.91 (0.55-1.50)	0.711	-	-
Size of Krukenberg tumor >10 cm	0.55 (0.30-1.02)	0.058	-	-
Signet-ring cells	0.71 (0.43-1.19)	0.195	-	-
Other types of metastasis	3.59 (1.83-7.03)	<0.001	1.90 (0.75-4.86)	0.178
Peritoneal carcinomatosis	2.32 (1.40-3.85)	0.001	1.01 (0.52-1.96)	0.971
Gastrectomy	0.58 (0.36-0.93)	0.025	0.69 (0.39-1.23)	0.209
Subsequent systemic therapy	0.14 (0.07-0.27)	<0.001	0.21 (0.08-0.57)	0.002
Subsequent platinum-based chemotherapy	0.25 (0.14-0.45)	<0.001	0.36 (0.16-0.82)	0.014

HR: Hazard ratio. [a]Including all clinical variables which showed significance in univariate analysis.

underwent metastasectomy had a significantly better OS [median=14.1 months; 95% confidence interval (CI)=8.6-19.6 months] than patients who did not undergo metastasectomy (median OS=8 months; 95% CI=5.6-10.4 months, p=0.001; Figure 1).

Based on univariate analysis, the following were associated with better survival: better performance status; gastrectomy; no distant metastases other than ovaries; no peritoneal carcinomatosis; subsequent systemic therapy; and subsequent platinum-based regimen. After adjusting the covariates in multivariate analysis, metastasectomy remained an independent predictor of better OS (hazard ratio=0.36, p=0.002), along with better performance status, subsequent systemic therapy, and subsequent platinum-based chemotherapy (Table II). Long-term survivals with complete remission were observed in patients who underwent surgery and subsequent chemotherapy. One such patient is demonstrated in Figure 2.

The median time from diagnosis of Krukenberg tumors to metastasectomy was 15 days (range=0-235 days). Fifteen (42.9%) patients underwent TAH plus BSO, 5 (14.3%) patients underwent STH plus BSO, and 15 (42.9%) patients underwent oophorectomy alone. Six (17.1%) patients underwent gastrectomy and metastasectomy at the same time. The surgery was generally well-tolerated and there were no major postoperative complications. Only two patients suffered from sepsis and hypovolemic shock respectively, which prolonged their hospital stay. The median length of hospital stay after the surgery was 12 days (range=11-14 days) for patients who underwent simultaneous gastrectomy plus metastasectomy and 6 days (range=4-14 days) for patients who underwent metastasectomy alone. There were two postoperative mortalities within 30 days and the 60-day postoperative mortality rate was 17.1% (6/35).

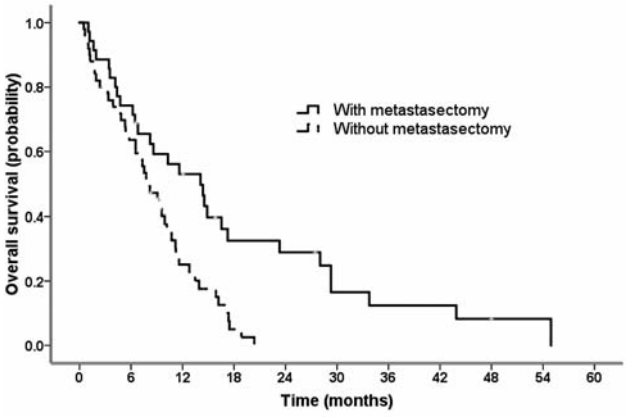

Figure 1. *Kaplan-Meier analysis of overall survival in patients with or without metastasectomy of Krukenberg tumors (p=0.001, log-rank test).*

The causes of 60-day postoperative mortalities were pneumonia in one patient, sepsis in another and disease progression in the remaining four patients.

Discussion

The current study reported on survival benefits associated with metastasectomy of Krukenberg tumors in patients with MGC. The median OS was 14.1 months for patients who underwent metastasectomy, which was significantly longer than the 8 months for patients who did not. The survival benefit was independent of performance status, disease extent, and other local or subsequent systemic therapy.

Several studies have explored the issue of metastasectomy and cytoreductive surgery for Krukenberg tumors; however,

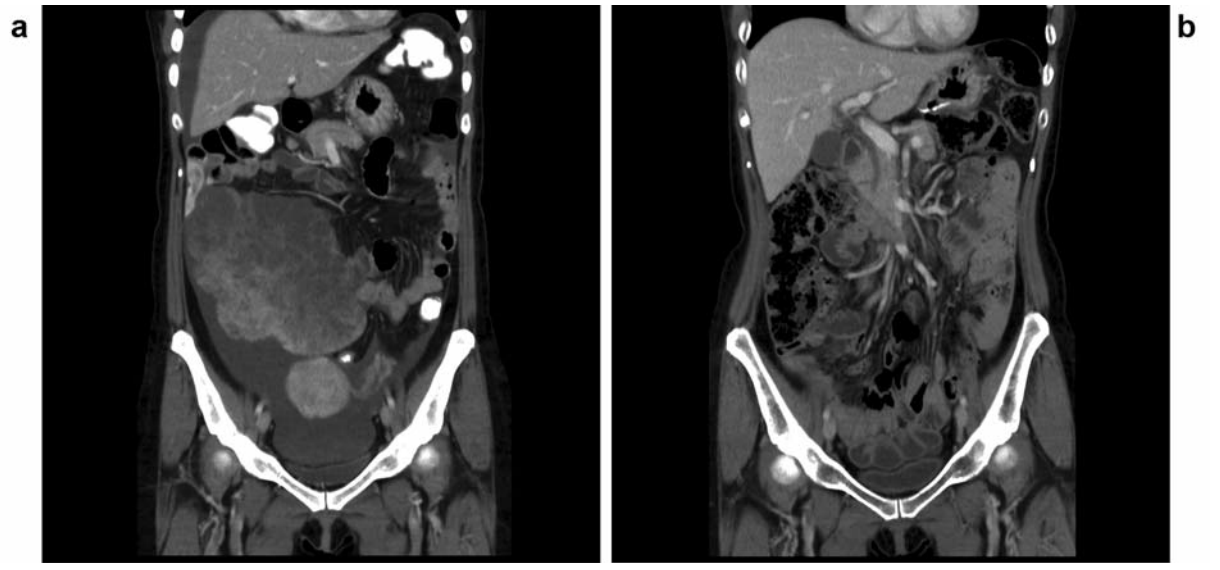

Figure 2. *a: Computed tomographic scans of a 51-year-old woman with presentation of bulky pelvic masses and ascites. b: The patient remained disease-free for four years after metastasectomy of Krukenberg tumors plus subtotal gastrectomy, and postoperative chemotherapy.*

most of the studies examined heterogeneous patient populations, with Krukenberg tumors of different origins, including gastric, colon, and breast cancer (14-16). In addition, all the patients in these studies underwent certain types of metastasectomy and there was no corresponding control group for comparison during the same period of time. The role of metastasectomy of Krukenberg tumors was only explored between different primary cancer types, different types of surgery or amounts of residual disease. For a limited proportion of patients with gastric cancer and Krukenberg tumors in two of these studies, worse survival was shown compared to patients with Krukenberg tumors of other origin while optimal cytoreductive surgery yielded no significant survival benefits compared to more limited surgery (14, 15). Therefore, the survival benefits of metastasectomy of Krukenberg tumors from gastric cancer remained obscure. In another study, Cheong *et al*. (17) reported 53 patients with Krukenberg tumors who experienced disease relapse after curative surgery of primary gastric cancer. Thirty three out of the 53 patients who had resections of Krukenberg tumors had a significantly longer median OS than those who did not undergo metastasectomy (17 *vs*. 3 months). Nevertheless, the imbalance between the two groups should cast some doubts on the significance of the findings, because all 33 patients in the resection group underwent subsequent chemotherapy and five patients in the control group received supportive care alone. In addition, there was no multivariate analysis and the median survival in the control group was dismal if compared to historical data in patients with stage IV gastric cancer. Selection bias among the two groups was obvious and the result may be less convincing. To our knowledge, our study is the largest study, focusing on this single disease, to address the issue of survival benefits of metastasectomy of Krukenberg tumors from gastric cancer. The performance status and the proportion of patients who received subsequent systemic therapy were similar between the two groups. The OS in both groups were reasonable and were actually underestimated for MGC because the OS in this study was measured from the diagnosis of Krukenberg tumors, rather than from the time of diagnosis of stage IV disease. Other covariates were adjusted by multivariate analysis and metastasectomy of Krukenberg tumors was still an independent predictor of better OS.

Besides potential survival benefits, metastasectomy of Krukenberg tumors may palliate symptoms, such as abdominal pain and fullness, although information on this issue is scarce. The concerns regarding surgical complications were relatively minor because metastasectomy for Krukenberg tumors is a relatively safe surgical procedure with a short postoperative hospital stay. The median length of hospital stay after metastasectomy alone was similar to that of a cohort of patients who underwent primary ovarian cancer resection (3.5-5.7 days) and the 60-day postoperative mortality rate was only slightly higher than the one observed for the same cohort, with less comorbidity (18). In our study, more than three-quarters of the patients were able to undergo subsequent systemic therapy. The majority of the systemic therapy contained a platinum agent (cisplatin or oxaliplatin) plus 5-fluorouracil, the standard chemotherapeutic regimen in our institute for MGC. All except one patient in this study who received platinum, also underwent 5-FU chemotherapy and survival benefits from receiving this regimen were demonstrated.

There were several limitations in this study. Firstly, because of the retrospective nature of the study, patient selection bias still could not be completely avoided. The two groups in the study were not completely matched. For example, fewer cases of tumor with signet-ring cells existed in the control group, which may be related to less pathological tissue because fewer gastrectomies and no metastasectomies were performed in this group. Moreover, patients in the control group had fewer bilateral Krukenberg tumors but a greater number of other types of metastases. These clinicopathological factors were considered and adjusted in multivariate analysis, although there are always other unknown confounding factors overlooked in a retrospective study. Secondly, the issue of optimal cytoreductive surgery was not addressed. Greater than one-half of the patients had other metastases in our study and most patients had macroscopic residual disease. Nevertheless, metastasectomy for Krukenberg tumors *per se* was still cytoreductive and associated with survival benefits according to the analysis.

In conclusion, our study showed that metastasectomy of Krukenberg tumors is well tolerated and may be associated with survival benefits in patients with MGC. Although further prospective studies are warranted, one can consider this as a rational treatment modality for this patient population.

Conflict of Interest Statement

The Authors declare no conflicts of interest.

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