Gynecology and Minimally Invasive Therapy 2 (2013) 52–56

Contents lists available at SciVerse ScienceDirect

Gynecology and Minimally Invasive Therapy

journal homepage: www.e-gmit.com

Original article

Identification of prognostic factors for Krukenberg tumor

Weiqi Lu [a,c], Lei Yuan [b,c], Xishi Liu [b,c], Sun-Wei Guo [b,*]

[a] Institute of General Surgery, Shanghai Zhongshan Hospital, Fudan University, Shanghai, China
[b] Shanghai Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China

ARTICLE INFO

Article history:
Received 15 December 2012
Received in revised form
18 February 2013
Accepted 25 February 2013
Available online 2 April 2013

Keywords:
Chemotherapy
Diagnosis
Krukenberg tumor
Prognostic factor
Survival

ABSTRACT

Aims: A Krukenberg tumor (KT) is an uncommon type of ovarian cancer (OC) with poor prognosis. We sought to identify prognostic factors for KT originating from primary gastrointestinal (GI) tumors.
Methods: Forty-four patients with KT were assessed with follow-up. The primary endpoint was overall survival (OS) after first gynecological or GI surgery.
Results: The use of postoperative chemotherapy, unilaterally involved ovarian mass, resection of primary tumors, absence of metastatic residuals, and diagnosis of GI tumors synchronously with or after gynecological surgery were identified to be prognostically favorable. For OS after the first cancer-related surgery, only the resection of primary tumor and absence of metastatic residuals were found to be favorable prognostic factors. The use of postoperative chemotherapy correlated with intraoperative intraperitoneal use of chemotherapy, but not with patients' clinicopathological characteristics, which were not found to be associated with any factors.
Conclusion: The prognostic value of a factor depends on how survival is defined. Optimal cytoreductive surgery followed by aggressive chemotherapy may improve survival in KT patients. KT patients with unilaterally involved ovarian mass, resected primary tumors, and the absence of metastatic lesion residuals also seem to have a more favorable prognosis.

Introduction

A Krukenberg tumor (KT) is an uncommon type of metastatic ovarian cancer with poor prognosis and can account for 30–40% of metastatic cancers to the ovaries.[1–3] There is a lack of consensus on the optimal treatment modality for KT, and the role of surgery and chemotherapy in improving patient survival still remains controversial.[4] No universally accepted prognostic factors for KT are currently available.[5]

Owing mainly to its poor prognosis, various attempts have been made to identify prognostic factors for KT. These attempts are often tenuous because of the rarity of KT. Kim et al[6] found that the absence of residual disease after treatment and limited disease extent are favorable prognostic factors. Cheong et al[4,7] found that metastasectomy is associated with improved survival. McCormick et al[8] reported that metastasectomy is a favorable prognostic factor for survival. Very recently, Jiang et al[9] reported that KT patients from colorectal cancer experience a better prognosis than those from gastric cancer and benefit more from metastasectomy.

For early-stage ovarian cancer and in patients with well or moderately differentiated early-stage ovarian cancer confined to the pelvis, surgical treatment alone may be curative. However, the variable 5-year survival rates prompted for all kinds of adjuvant treatment, mostly chemotherapy.[10] For patients with advanced primary ovarian cancers, surgical treatment combined with platinum-based adjuvant chemotherapy may improve overall and recurrence-free survival.[11] For KT, postoperative adjuvant chemotherapy conceivably may be of value in prolonging overall survival in patients with KT. Unfortunately, the prognostic value of postoperative chemotherapy in KT has not been fully investigated, due, again, to the rarity of the disease.

In this study, we sought to identify prognostic factors for KT among 44 women with surgically confirmed metastatic ovarian cancer originating from the gastrointestinal (GI) tract via multivariate analysis. In addition, we sought to identify the interrelationship, if any, among various potential prognostic factors. Unlike many published studies on KT which focused exclusively on patients who had undergone primary resection of GI tumors and metachronously developed ovarian metastasis, we attempted to identify prognostic factors for KT based on gynecological patients.

* Corresponding author. Shanghai Obstetrics and Gynecology Hospital, Fudan University, 419 Fangxie Road, Shanghai 200011, China.
E-mail address: hoxa10@gmail.com (S.-W. Guo).
[c] These three authors contributed equally to this work.

2213-3070/$ – see front matter
http://dx.doi.org/10.1016/j.gmit.2013.02.006

But we also sought to identify prognostic factors for overall survival after the first cancer-related surgery and compared them with those for overall survival after gynecological surgery.

Materials and methods

Patients

In a 12-year period spanning from 1995 to 2007, 1416 patients were surgically diagnosed with ovarian cancer at Shanghai Obstetrics and Gynecology Hospital, Fudan University. Among them, 45 cases were confirmed to be KT, accounting for 3.2% of all ovarian cancers. For these 45 patients, we retrieved their clinicopathological information through medical charts and histology review with assistance of an experienced gynecological pathologist. With one exception in which we could not track down the patient, we successfully followed up all these patients, retrieving information on date of death, results of pelvic and sonographic examinations, CA-125, and results from computer tomography (CT)/magnetic resonance imaging (MRI) scans, when available.

This research was approved by the Institutional Ethics Review Board of Shanghai Obstetrics and Gynecology Hospital.

Statistical analysis

The comparison of distributions of continuous variables between two or among three or more groups was made using the Wilcoxon rank test and Kruskal–Wallis test, respectively. Fisher's exact test was used to detect whether there is any relation between two categorical variables. Pearson's correlation coefficient was used when evaluating correlations between two variables when both variables are continuous. When at least one variable is ordinal, Spearman's rank correlation coefficient was used instead.

The overall survival was represented in months, which was defined as the interval between the date of gynecological surgery and the date of death or of the last follow-up when alive. Overall survival curves were estimated by the Kaplan–Meier method, and difference in survival was evaluated using the log-rank test. For multivariable analysis, the Cox regression model was used, along with the stepwise backward elimination procedure. The potential covariates of interest included age at diagnosis, menopausal status, timing of operation, laterality of ovarian mass, mass volume, presence of ascites, intraoperative intraperitoneal chemotherapy, and use of aggressive adjuvant chemotherapy postoperatively. A p value of 0.05 or less was regarded as statistically significant. All computations were made with R 2.12.2[12] (www.r-project.org).

Results

The clinicopathological characteristics of the 44 patients are listed in Table 1. Among them, 39 (88.6%) died from cancer complications. The age of menopausal patients ranged from 44 years old to 75 years old, with a median of 56 years old. In the premenopausal patients, their ages ranged from 20 years old to 52 years old, with a median of 40 years. The median (range) age of patients who had GI cancer diagnosed prior to diagnosis of metastatic ovarian cancer was 45 (33–60) years, as compared with 51 (20–75) years and 45 (31–70) years, respectively, in patients who had synchronous diagnosis of GI and ovarian cancers and after diagnosis of ovarian cancer. Although the age in the first group was slightly younger, the difference did not reach statistical significance ($p = 0.27$).

All patients admitted into the hospital complained of abdominal distention, abdominal pain, pelvic mass, and, in a few cases, postmenopausal vaginal bleeding. At the time of operation, 13 patients (29.6%) had already had a curative resection of GI tumors previously, 21 (47.7%) were found to have primary GI tumors synchronously during gynecological surgery, and the remaining 10 (22.7%) were suspected to have primary GI tumors during surgery, and later confirmed by either endoscopy or CT/MRI examination after surgery. The sites of the GI tract were stomach ($n = 42$, 95.5%) and intestines ($n = 2$, 4.5%) in all patients.

During the operation, 19 cases (43.2%) and 23 cases (52.3%) were found to have unilateral and bilateral ovarian mass, respectively, and two (4.6%) were found to have microscopic bilateral metastatic lesions (Table 1). Of all patients, 24 cases (54.5%) were found to have metastatic lesions in both the abdomen and the pelvis. For patients with ovarian mass, their sizes were measured (Table 1). Thirty-two cases (72.7%) had moderate to massive pelvic ascites.

All 44 patients underwent gynecological surgical treatment. Ascites were collected during surgery for cytological examination.

Table 1
Clinicopathological characteristics of 44 patients with Krukenberg tumor (KT) and statistical significance of their impact on overall survival.

Variable	Distribution	p^*	p^*
Age at diagnosis (y), mean ± SD	47.9 ± 11.6		
Range	20–75	0.57[a]	0.93[a]
Median	47.5		
Menopausal status, *n* (%)			
Premenopausal	21 (47.7)	0.78	0.74
Menopausal	23 (52.3)		
Laterality			
Unilateral	19	0.13	0.10
Bilateral	23		
Unknown	2		
Size of ovarian tumor			
<5 cm	11	0.50	0.96
5–10 cm	17		
>10 cm	14		
Unknown	2		
Presence of moderate/massive pelvic ascites, *n* (%)			
No	12 (27.3)	0.44	0.11
Yes	32 (72.7)		
Sequence of tumor discovery, *n* (%)			
GI tract first, ovarian second	13 (29.6)	0.61	0.0005
Synchronously	21 (47.7)		
Ovarian cancer first, then GI tract	10 (22.7)		
Type of surgery			
TAH + BSO ± omentectomy	36	NA[b]	NA[b]
BSO only	3		
TAH + BSO + en bloc resection of primary tumor	4		
Exploratory laparotomy	1		
Platinum-based intraoperative intraperitoneal chemotherapy, *n* (%)			
No	25 (56.8)	0.58	0.53
Yes	19 (43.2)		
Postoperative adjuvant chemotherapy, *n* (%)			
None	12 (27.3)	6.3×10^{-5}	0.24
Nonaggressive	15 (34.1)		
Aggressive	17 (38.6)		
Presence of residuals of metastatic lesions, *n* (%)			
No	23 (52.3)	0.15	0.005
Yes	21 (47.7)		
Resection of primary GI tumors, *n* (%)			
Yes	17 (38.6)	0.54	3.6×10^{-5}
No	27 (61.4)		
Serum CA-125 level (U/mL)			
Mean ± SD	136.5 ± 171.2	0.51[a]	0.02[a]
Range	0.1–747		
Median (number of missing values: $n = 11$)	44.0		

*The first column of p values is for overall survival starting from gynecological surgery, whereas the second column is for overall survival starting from the first cancer-related surgery.

[a] Based on univariate Cox regression analysis.

[b] Analysis not performed owing to very small sample sizes in some subgroups.

Both intraoperative frozen section-based pathological and postoperative pathological examinations identified metastatic ovarian adenocarcinoma with KT-characteristic mucin-filled signet ring cells in all patients.[13] Among the 13 patients who had GI tumor surgery previously, 11 (84.6%) had a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO) with or without omentectomy, 1 (7.7%) had BSO only, and the remaining 1 (7.7%) received explorative laparotomy only because of unresectable lesions. All patients received postoperative chemotherapy with 5-fluorouracil plus cisplatin. In the remaining 31 patients who had primary GI cancer diagnosed synchronously with ovarian cancer or after, two (6.5%) had BSO only, and 29 (93.5%) had TAH + BSO with or without omentectomy. In these 31 patients, four cases (12.9%) also received en bloc resection of primary GI tumors but the remaining 27 cases (87.1%) did not, either because of unresectable GI lesions or because the patients and their families declined further treatment.

Of all patients, 40 cases (90.9%) received TAH + BSO with or without omentectomy, three (6.8%) received BSO only, and in one case an explorative laparotomy was performed because of unresectable lesions. Twenty-one (47.7%) cases had residues of metastatic lesions and the remaining 23 (52.3%) did not. Nineteen (43.2%) patients received platinum-based intraoperative intraperitoneal chemotherapy and the other 25 (56.82%) did not.

After surgery, all patients were evaluated once a month in the first 6 months and then once in 3 months, and then twice a year. Thirty-two patients (72.7%) received adjuvant chemotherapy postoperatively and the remaining 12 (27.3%) received none. Chemotherapy options included mostly 5-fluorouracil plus cisplatin or paclitaxel plus carboplatin. Among the 32 patients who received postoperative chemotherapy, 17 (38.6%) received aggressive chemotherapy, defined here as receiving four to six consecutive cycles of chemotherapy, and the other 15 patients (34.1%) thus received nonaggressive chemotherapy (i.e., <4 cycles).

The interval between surgical diagnosis of a primary carcinoma in the GI tract and subsequent discovery of ovarian involvement for the 13 patients ranged from 4 months to 96 months or 8 years, with a median of 2 years and a mean (SD) of 34.1 (28.2) months, in agreement with the literature.[14]

Survival and potential prognostic factors

The overall median survival period was 9.8 months [95% confidence interval (CI) = 7.5–15.4 months], with 1- and 2-year survival rates of 37.9% and 10.2%, respectively. Survival rate beyond 35.6 months was unavailable due to censoring.

Univariate analysis suggested that postoperative chemotherapy is the only factor that is significantly associated with survival (Table 1, Fig. 1). The median survival time was 4.7 months, 7.5 months, and 20.4 months, respectively, for patients who received no, nonaggressive, and aggressive chemotherapy. For patients who had GI tumor diagnosed before, during, or after gynecological surgery, their median survival was 13.2 [95% CI = 9.2–NA (not available)], 10.1 (95% CI = 4.7–23.0), and 9.1 (95% CI = 4.9–NA) months, respectively. The difference, however, did not reach statistical significance.

Cox regression analysis identified bilateral ovarian mass, postoperative chemotherapy, whether primary tumor was diagnosed before metastatic ovarian cancer surgery or not, the presence of residuals of metastatic lesions, and resection of primary GI tumors or not as five prognostic variables (Table 2). Marginally, the median survival of unilateral and bilateral presence of ovarian carcinoma in these patients was 11.2 (95% CI = 10.1–NA) months and 6.2 (95% CI = 4.0–18.3) months, respectively. That is, KT patients with unilateral ovarian mass had approximately 80% longer median survival

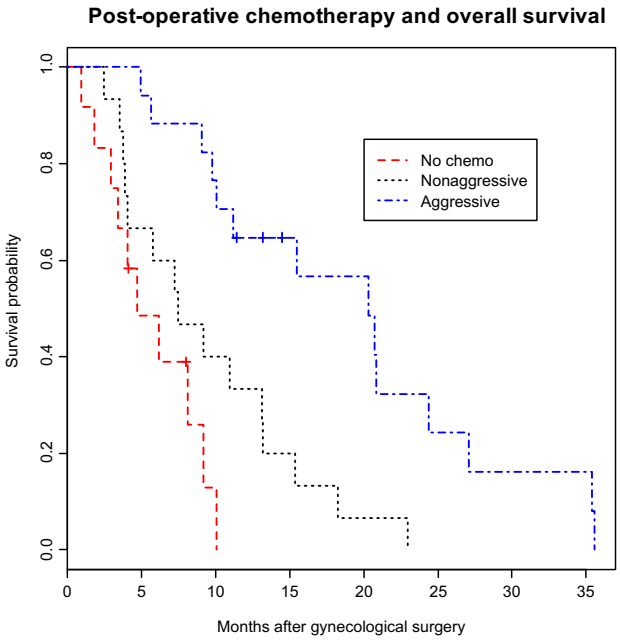

Fig. 1. Postoperative adjuvant chemotherapy and overall survival. Aggressive chemotherapy is defined in the text.

than those with bilateral ovarian mass. For patients who had GI cancer diagnosed first, the median survival was 9.1 months, as compared with 10.9 months in patients who had GI cancer diagnosed during or after gynecological surgery. The difference in median survival between patients who did not receive resection of primary GI tumors and who did was very small (10.1 vs. 9.8 months). By contrast, the difference in median survival between patients who had residuals of metastatic lesions and who did not appeared to be considerable: 9.2 vs. 13.2 months.

Indeed, the Cox model concluded that, with everything else being equal, the use of postoperative chemotherapy reduced the risk of death from cancer by over 80%, and bilaterally involved ovarian mass doubled the risk of death as compared with unilateral ovarian cancer (Table 2). The failure to resect primary GI tumors increased the risk of death by almost 7-fold, whereas the presence of residuals of metastatic lesions increased the risk by nearly 3-fold. Among all patients with KT, having their primary GI tumor diagnosed first increased the risk of death by 14.3-fold as compared with those with their primary GI tumor diagnosed synchronously with or after diagnosis of the ovarian metastasis.

There was an indication that the use of aggressive chemotherapy was more effective in prolonging life, and the Cox regression model using two dummy variables suggested that this was the case. The use of both aggressive and nonaggressive chemotherapy was significant ($p = 2.4 \times 10^{-4}$, and $p = 0.030$).

Table 2
Parameter estimates of the Cox regression model on factors associated with overall survival after gynecological surgery.

Covariate	Estimate	Standard error	Hazard ratio (95% CI)	p
Chemotherapy	−1.748	0.174	0.174 (0.063, 0.479)	0.001
Bilaterality of ovarian mass	0.928	0.418	2.529 (1.114, 5.740)	0.027
Failure to resect primary GI tumors	1.899	0.848	6.682 (1.267, 35.230)	0.025
Presence of residual metastatic lesions	1.066	0.382	2.905 (1.374, 6.142)	0.005
GI cancer diagnosed later or synchronously	−2.704	0.926	0.067 (0.011, 0.411)	0.003

Survival since first surgery

From a patient's perspective, it is perhaps of equal interest to focus on survival after the first cancer-related surgery, regardless if it was GI surgery or gynecological surgery. Therefore, we added the time interval between the two surgeries for the 13 patients who had GI surgery previously and re-did the analysis.

We found that 1-, 2-, 3-, 5-, and 8-year overall survival rates were 55.4%, 29.1%, 17.8%, 12.2%, and 0.8%, respectively, which were in broad agreement with the literature.[9] The median survival was 15.5 (95% CI = 10.1–23.0) months. Although survival rates appeared to be increased substantially as compared with overall survival after gynecological surgery, the median survival only increased by approximately 50%, or around 6 months.

In addition, we found that sequence of surgery, presence or absence of residuals of metastatic lesions, resection of primary GI tumors, and CA-125 are significantly associated with overall survival after the first cancer-related surgery (Table 1). In particular, patients with residuals of metastatic lesions had a less favorable survival than those without ($p = 0.005$, Table 1, Fig. 2). We also found that the failure to resect primary GI tumors was associated with worse overall survival ($p = 3.6 \times 10^{-5}$, Fig. 3).

Cox regression analysis identified the presence of residuals of metastatic lesions and the failure to resect primary GI tumors or not as two prognostic variables. It is interesting to note that three factors, that is, chemotherapy after gynecological surgery, sequence of diagnosis, bilaterality of ovarian mass, that were significantly associated with overall survival after gynecological surgery are no longer significant when overall survival after the first-cancer related surgery is considered. However, the resection of primary tumors and the absence of residual metastatic lesions still remain to be the two main prognostic factors, suggesting that these two factors are prognostically important for overall survival not only after the first-cancer related surgery but also after gynecological surgery.

Discussion

In this study, we found that the use of postoperative chemotherapy is a favorable prognostic factor for survival in patients with KT, especially the use of aggressive chemotherapy. We also found that bilateral ovarian mass, failure to resect primary GI tumors, presence of residuals of metastatic lesions, and having GI cancer diagnosed prior to metastatic ovarian cancer diagnosis are risk factors for overall survival after gynecological surgery. Interestingly, for overall survival after the first cancer-related surgery, failure to resect primary GI tumors and the presence of residuals of metastatic lesions are the only two risk factors that are associated with less favorable survival. Moreover, we found that the use of postoperative chemotherapy is strongly correlated with intraoperative use of chemotherapy, but not with patients' clinicopathological characteristics, such as presence of ascites, laterality of ovarian mass, presence of metastatic lesion residuals and so on.

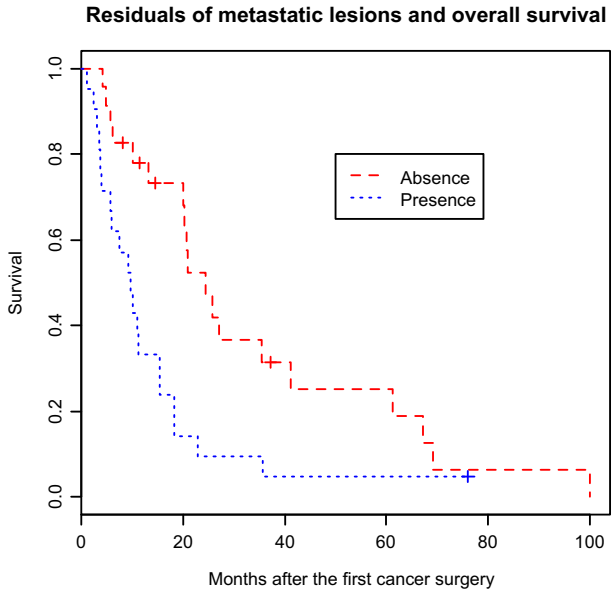

Fig. 2. Presence or absence of residuals of metastatic lesions and overall survival since the first cancer-related surgery.

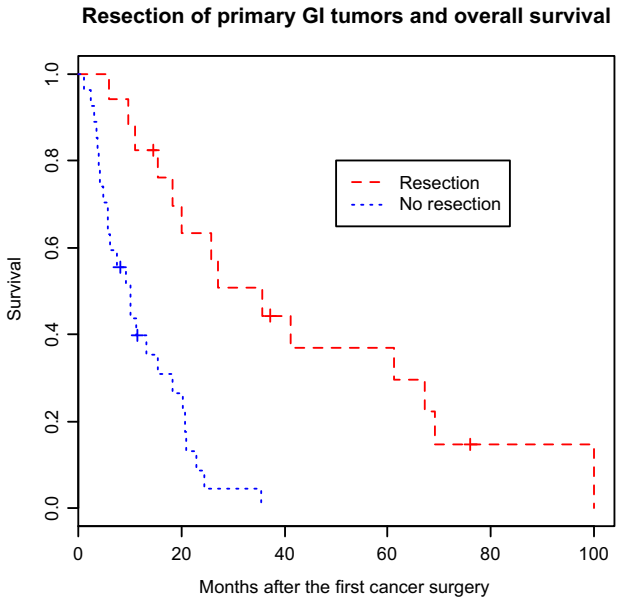

Fig. 3. Timing of diagnosis and overall survival since the first cancer-related surgery.

Although some previously published reports have addressed the prognostic value of chemotherapy in KT, these studies are limited by focusing only on patients who had undergone primary resection of GI tumors and metachronously developed ovarian metastasis, which concluded that postoperative chemotherapy could not yield improved survival.[15,16] By contrast, our study focused mostly on KT patients presented to us initially with gynecological complaints. The main finding of our study indicates that postoperative chemotherapy is significantly associated with longer survival of KT patients, especially aggressive chemotherapy. The median survival in patients receiving aggressive, nonaggressive, and no chemotherapy was 20.4, 7.5, and 4.7 months, respectively. In other words, patients who received aggressive chemotherapy had over four times longer median survival than those who did not, and patients who received nonaggressive chemotherapy had 1.5 times longer median survival. The patients who received aggressive therapy had over twice as long as those who received nonaggressive therapy.

As KT is a metastatic ovarian cancer with the potential to spread to all other organs, postoperative intravenous chemotherapy could presumably reduce or eliminate malignant cells or inhibit their growth under certain dosage. Our findings are in agreement with previous reports on treating advanced ovarian cancers[17] and suggest that chemotherapy, especially aggressive chemotherapy, after resection of metastatic ovarian tumors as part of the treatment modality for KT is beneficial for survival. This means that optimal cytoreductive surgery followed by aggressive chemotherapy may improve survival in patients with KT.

We found in our study that patients with KT who were diagnosed with metastatic ovarian cancer prior to or synchronously with metastatic GI tumor diagnosis had a longer survival rate. It is possible that patients who had ovarian cancer diagnosis made after the primary GI tumor may signal a more metastatic and thus more aggressive tumor, and hence represent more advanced KT, whereas those made before could be less advanced. Therefore, time sequence is thus a proxy for invasiveness of the primary tumor and thus for prognosis. In the same vein, the presence of bilateral ovarian masses also signals the severity of KT and thus is of prognostic value.

However, the effect of surgery sequence disappears if survival after the first cancer-related surgery is considered. This is because of an intrinsic bias in favor of those who had primary GI tumors diagnosed during or after gynecological surgery, as those who had GI tumors diagnosed first had already lived for some time. This suggests that, when prognostic factors are of concern, a clear definition of the reference point – the first cancer-related surgery or gynecological surgery – should be given.

Our finding that the use of postoperative chemotherapy is strongly correlated with intraoperative use of chemotherapy, along with the finding that the use of the latter is not associated with any clinical characteristics of the patients, is not very surprising. Ovarian cancer is by far the most fatal gynecological disease and KT usually represents a more advanced and aggressive form of ovarian cancer. As such, the patient's family is often devastated and grief-stricken when a patient's diagnosis is made, and gives up in many cases. The heavy economic burden to patients and their families that is associated with chemotherapy, the low per capita disposable income relative to that in developed countries, and the lack of a social welfare system in China that can absorb the bulk of the cost for the treatment of catastrophic diseases such as advanced ovarian cancer certainly add to the predicament. Even the surgeons who treat patients are somewhat pessimistic, given the poor prognosis of KT.

Yet the survival advantage of chemotherapy after ovarian cancer surgery disappears if survival is considered immediately after the first cancer-related surgery. This may be due to the fact that the patients who had primary GI tumors diagnosed first actually had longer survival rates (median survival = 18.0 vs. 10.1 months) than those who were diagnosed synchronously with or after gynecological surgery. This longer survival rate effectively eliminates any beneficial effect of chemotherapy if survival is considered after gynecological surgery. This is actually corroborated by the significant difference found in survival between patients who had GI tumors diagnosed before and after or synchronously with gynecological surgery.

The 5-year survival rate after resection of GI tumors ranges from 20% to 90%, and it decreases precipitously when metastasis, such as in KT, occurs.[18] Our study found that the median survival in 13 patients with a history of previous GI surgery was approximately 9 months. Therefore, treatment for female patients diagnosed with GI tumors is complicated. Prophylactic oophorectomy in premenopausal and postmenopausal women at the time of GI cancer surgery has been the focus of much attention in recent years,[6] as the ovary is the most common metastatic site. Yet it is apparent that the majority of women with GI cancer would not have KT. This may explain why no guideline has been made so far concerning prophylactic oophorectomy in these patients.

In summary, our study suggests that optimal cytoreductive surgery followed by aggressive chemotherapy may improve survival in gynecological patients with KT. KT patients with unilateral ovarian mass also seem to have a more favorable prognosis than those with bilateral masses. Our study also indicates that the prognostic value of a factor depends on how survival is defined.

Acknowledgments

This work was supported by grant 81270676 (S.-W.G.) from the National Science Foundation of China, and support from Shanghai Key Laboratory of Female Reproductive Endocrine-related Diseases and from the Key Specialty Project from the Ministry of Health of China.

References

1. Hale RW. Krukenberg tumor of the ovaries. A review of 81 records. *Obstet Gynecol*. 1968;32:221–225.
2. Israel SL, Helsel Jr EV, Hausman DH. The challenge of metastatic ovarian carcinoma. *Am J Obstet Gynecol*. 1965;93:1094–1101.
3. Gilliland R, Gill PJ. Incidence and prognosis of Krukenberg tumour in Northern Ireland. *Br J Surg*. 1992;79:1364–1366.
4. Cheong JH, Hyung WJ, Chen J, Kim J, Choi SH, Noh SH. Surgical management and outcome of metachronous Krukenberg tumors from gastric cancer. *J Surg Oncol*. 2004;87:39–45.
5. McGill FM, Ritter DB, Rickard CS, et al. Krukenberg tumors: can management be improved? *Gynecol Obstet Invest*. 1999;48:61–65.
6. Kim HK, Heo DS, Bang YJ, Kim NK. Prognostic factors of Krukenberg's tumor. *Gynecol Oncol*. 2001;82:105–109.
7. Cheong JH, Hyung WJ, Chen J, Kim J, Choi SH, Noh SH. Survival benefit of metastasectomy for Krukenberg tumors from gastric cancer. *Gynecol Oncol*. 2004;94:477–482.
8. McCormick CC, Giuntoli 2nd RL, Gardner GJ, et al. The role of cytoreductive surgery for colon cancer metastatic to the ovary. *Gynecol Oncol*. 2007;105:791–795.
9. Jiang R, Tang J, Cheng X, Zang RY. Surgical treatment for patients with different origins of Krukenberg tumors: outcomes and prognostic factors. *Eur J Surg Oncol*. 2009;35:92–97.
10. Bolis G, Colombo N, Pecorelli S, et al. Adjuvant treatment for early epithelial ovarian cancer: results of two randomised clinical trials comparing cisplatin to no further treatment or chromic phosphate (32P). G.I.C.O.G.: Gruppo Interregionale Collaborativo in Ginecologia Oncologica. *Ann Oncol*. 1995;6:887–893.
11. Hogberg T, Glimelius B, Nygren P. A systematic overview of chemotherapy effects in ovarian cancer. *Acta Oncol*. 2001;40:340–360.
12. Inhaka R, Gentleman RR. R: a language for data analysis and graphics. *J Comput Graph Statist*. 1996;5:1923–1927.
13. Yakushiji M, Tazaki T, Nishimura H, Kato T. Krukenberg tumors of the ovary: a clinicopathologic analysis of 112 cases. *Nippon Sanka Fujinka Gakkai Zasshi*. 1987;39:479–485.
14. Al-Agha OM, Nicastri AD. An in-depth look at Krukenberg tumor: an overview. *Arch Pathol Lab Med*. 2006;130:1725–1730.
15. Benaaboud I, Ghazli M, Kerroumi M, Mansouri A. Krukenberg tumor: 9 cases report. *J Gynecol Obstet Biol Reprod (Paris)*. 2002;31:365–370.
16. Mrad K, Morice P, Fabre A, et al. Krukenberg tumor: a clinico-pathological study of 15 cases. *Ann Pathol*. 2000;20:202–206.
17. Schwartz PE. What is the role of neoadjuvant chemotherapy in the management of ovarian cancer? *Oncology (Williston Park)*. 2008;22:1118–1125. discussion 30, 32, 34.
18. Sivins A, Pedrazzani C, Roviello F, et al. Surgical treatment of gastric cancer in Latvia: results of centralized experience. *Eur J Surg Oncol*. 2009;35:481–485.