Original Article

Metachronous Krukenberg Tumors from Colorectal Cancer — A 12-year Study in a Medical Center

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Key Words
Colorectal cancer;
Krukenberg tumor;
Metachronous;
Survival benefit

Purpose. We performed this study to evaluate the clinical presentation and survival after proper surgical intervention for Krukenberg tumor (KT) from colorectal cancers (CRC) and these tumors were identified during postoperative follow-up. This will help to establish the optimal strategy for improving the survival.
Materials and Methods. A total of 2,191 female patients with primary CRC were diagnosed at our hospital between January 2001 and December 2012, and 26 patients (1.19%) with metachronous KT from CRC were collected for survival analyses. Parameters included patient age at the time of ovarian relapse, the size of the tumor, the initial TNM stage of the colorectal cancer, the interval to metastasis and the presence of gross residual disease after treatment for KT.
Results. The average age of the patients with metachronous KT was 49.77 years (range: 31 to 75 years) and the average survival time of the 26 patients was 23.94 months with a range of 3 to 93 months after the diagnosis of KT. The 5-year survival rate was 6.6% for all patients with KT from CRC and the 5-year survival rate for patient with R0 resection was 18.8%. The survival rate for patients without gross residual disease was longer than those with gross residual disease ($p < 0.001$). In contrast, menstrual status, the lymph node involvement status, and the interval to metastasis were not prognostic indicators for survival after the development of KT.
Conclusions. Early diagnosis and complete resection had benefits to improve survival. The 5-year survival rate was 6.6% for all patients with KT from CRC and the 5-year survival rate for patient with R0 resection was 18.8%. Therefore, attempts to resect tumors as the second tumor reduction seem worthwhile.
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Krukenberg tumor (KT) is a metastatic tumor of the ovary that originates from the gastrointestinal tract. The characteristic of tumor shows the presence of mucin-filled signet-ring cells, which account for at least 10% of the tumor.[1] The diagnostic criteria of the WHO are based on the pathological description by Serov and Scully for making the diagnosis of KT.[2] In older literature, gastric carcinomais cited

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as the most frequent primary malignancy that metastasizes to the ovary through mechanisms of direct extension or drop metastasis.[3] However in some recent studies, colorectal cancer (CRC) is the most common primary malignancy, accounting for 3-53.4% of the KT.[4-7] The KT which arises from primary CRC is developed in 3.6-7.4% of patients at the time of initial laparotomy and metachronously in 1.5% of patients within 2 years after primary CRC resection, and is associated with poor prognosis.[8] Treatment for KT includes ovarian metastasectomy, chemotherapy and radiotherapy; however optimal treatment has not yet been established. KT of colorectal origin is less responsive to chemotherapy.[9] Many studies have shown that aggressive surgical treatment may provide survival benefits in selected patients.[6,8,10] The aim of this study is to analyze clinicopathological characteristics and treatment outcomes in patients with colorectal cancer with metachronous KT.

Materials and Methods

All patients with histologically metachronous KT from CRC origin who received surgical resection at our hospital between January 2001 and December 2012 were collected in the study. Their medical records were retrieved from the hospital database after the study was approved by the hospital ethics committee. A total of 2,191 female patients with primary CRC were diagnosed in the study period. All the metachronous KT from CRC cases had surgical resection for the primary tumor. Data were collected and analyzed including: age, site of colorectal primary tumor, staging of colorectal cancer, KT size, serum carcinoembryonic antigen (CEA) level, type of operation performed, and metastasis to other organs.

Survival analyses focused on KT survival, defined as the time since the diagnosis of KT to death or the last follow-up status. Death and recurrence were treated as events, while patients who were still alive at the last follow-up were censored. Metachronous KT was defined by metastasis found 6 months after the primary tumor being diagnosed. Right-side colon tumors were referred to tumors located at cecum, ascending colon, hepatic flexure, and transverse colon. Left-side colon tumors were referred to tumors located at splenic flexure, descending colon, and sigmoid colon. Resection margin evaluation was defined by the residual classification published in the *AJCC* Cancer Staging Manual, *7th Edition*. R0 indicated no residual tumor. R1 and R2 indicated microscopic and macroscopic residual tumors.

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS 20.0, SPSS Inc., Chicago, IL, USA) software. Statistical analysis was performed using nonparametric statistics (chi-squared test or binomial test). Survival curves were generated using the Kaplan-Meier method. Comparisons of overall survival by univariate analysis were calculated using log-rank test. A p value of less than 0.05 was considered to be statistically significant.

Results

A total of 2,191 female CRC patients were collected in the study period. Among them, 26 patients had metachronous KT (Table 1), demonstrating an incidence of metachronous KT of CRC of 1.19%. The median age of patients with metachronous KT was 50 (range: 34-74) years old. The most common primary site was the sigmoid colon (46.1%, 12 patients). Two patients (7.7%) had a colorectal primary tumor at the cecum, 4 (15.4%) at the ascending colon, 3 (11.5%) at the descending colon, and 5 (19.2%) at the rectum. The most common clinical presentation on KT was palpable abdominal mass (38.5%; 10 patients), followed by abdominal pain (26.9%; 7 patients), asymptomatic CEA elevation (15.4%;4 patients), incidentally found (11.5%; 3 patients), intestinal obstruction (3.8%; 1 patient), and bloody stool (3.8%; 1 patient). The mean maximum diameter of the KT was 10.3 ± 6.23 cm. The serum CEA level was measured for 25 patients with a mean of 148.6 ± 218.66 ng/ml and elevated in 23 patients (88.5%). CA 125 was measured only in 5 patients (19.2%) with a median of 167.46 U/ml (range: 17.9-404 U/ml) and elevated in 2 patients (40%).

Table 1. Patient characteristics and demographics

	n (%) (N = 26)	*p* value
Menopause		0.556
Pre	15 (57.7)	
Post	11 (42.3)	
Location of primary tumor		0.03
Right colon (cecum to distal transverse)	6 (23.1)	
Left colon (splenic flexure to sigmoid)	15 (57.7)	
Rectum	5 (19.2)	
T staging		< 0.001
T1	1 (3.8)	
T2	1 (3.8)	
T3	1 (3.8)	
T4	23 (88.5)	
N staging		0.607
N0	11 (42.3)	
N1	8 (30.8)	
N2	7 (26.9)	
Primary colorectal cancer stage		< 0.001
I	2 (7.7)	
II	3 (11.5)	
III	5 (19.2)	
IV	16 (61.5)	
Years to relapse		0.857
< 1 year	10 (38.5)	
1-2 year	8 (30.8)	
> 2 years	8 (30.8)	
Operation procedure		0.003
BSO	15 (57.7)	
USO	10 (38.5)	
Nil	1 (3.8)	
Uni or bilateral of ovarian tumor		0.327
Unilateral involvement	10 (38.5)	
Bilateral involvement	16 (61.5)	
Size of ovary tumor		0.845
≥ 10 cm	14 (53.8)	
< 10 cm	12 (46.2)	
Combined metastasis besides ovary		0.166
Nil	10 (38.5)	
Peritoneal seeding	7 (26.9)	
Liver metastases	7 (26.9)	
Peritoneal seeding + liver metastases	2 (7.7)	
CEA at ovarian metastasis		< 0.001
< 5	2 (7.7)	
≥ 5	23 (88.5)	
Nil	1 (3.8)	
Residual tumor classification		0.327
R0	10 (38.5)	
R1-2	16 (61.5)	
Chemotherapy after CRC surgery		0.043
Nil	5 (19.2)	
5FU + LV	7 (26.9)	
FOLFOX	12 (46.2)	
FOLFIRI	2 (7.7)	

On type of operation patients received, unilateral salpingo-oophorectomy was performed for 10 (38.4%) patients, bilateral salpingo-oophorectomy for 15 (57.7%) patients, and laparotomy without bilateral salpingo-oophorectomy (severe adhesion) for 1 (3.8%) patient. Adjuvant chemotherapies were offered to 21 patients (80.8%) after the resection of primary CRC: FOLFOX (5-FU/leucovorin/oxaliplatin) to 12 patients (46.2%), 5-FU/leucovorin to 7 patients (26.9%), and FOLFIRI (5-FU/leucovorin/irinotecan) to 2 patients (7.7%). For stage-IV patients, one patient did not get chemotherapy after primary CRC R0 resection due to old age (ECOG 2).

The overall survival from ovarian resection to death at 3 and 5 years was 19.8% and 6.6%, respectively. The median survival was 13.0 months. One long-term survivor lived more than 5 years. In our study, the median survival after R0 resection is 37.0 months (3-year overall survival was 56.3% and 5-year overall survival was 18.8%) compared to 10.0 months for patients with R1/2 resections only (3 year overall survival was 0% and 5-year overall survival was 0%). R0 resection was found to be significantly associated with prolonging survival ($p < 0.001$) (Fig. 1).

Our results also demonstrated no statistically significant correlations in survival at menopausal status ($p = 0.666$), N-staging in CRC ($p = 0.356$), and relapse after CRC within 1 year or over 1 year ($p = 0.592$).

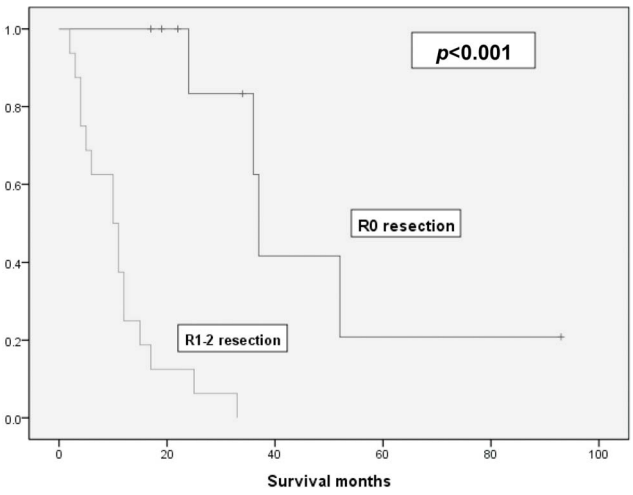

Fig. 1. Overall survival curves for the patients with Krukenberg tumor from colorectal cancer. The patients without gross residual disease survived longer than the patients with gross residual disease ($p < 0.001$).

Discussion

The true incidence of KT from CRC is unclear; the incidences vary from 5% to 31% in autopsy studies and 0% to 8.6% in clinical series.[3,11] The metachronous KT of CRC was rare and the incidence is only 1.2% in our study, while Omranipour et al. has reported low incidences of CRC with synchronous and metachronous KT of 2.7% and 6.6%, respectively. Isolated KT from primary CRC occurred in 3.3% of women undergoing colorectal resection.[11] Kim et al. reported the incidence of metastasis of colorectal tumors to the ovary is 3-14%.[5]

The mechanism of KT is still uncertain. Hematogenous spread has been postulated as the main mechanism of metastasis. This partly explains the incidence in younger generation whose ovarian blood flow is more abundant than that of older patients.[12] Lymphatic dissemination has also been proposed.[13] Omranipour et al. has reported high incidences of peritoneal diseases and transmural tumor extension, and lymphatic diseases were also noted in their series. They suggest that the lymphatic pathway and direct peritoneal dissemination via transmural extension play important roles for ovarian involvement in CRC.[11] Similarly, 15 patients (57.7%) in our study were found to have lymph node involvement and 23 patients (88.5%) to be presented with T4 in CRC.

The influence of age and menstrual status on ovarian involvement is unclear. Several studies have reported a higher relative frequency of KT in premenopausal women, while some other studies have refuted the association between young age and KT, concluding that most women with KT were postmenopausal.[11] In our study, the median age at diagnosis of KT was 50 years, there was no correlation between menopausal status and ovarian involvement ($p = 0.556$).

Serums CA-125, TAG-72, and SLX have been suggested to be useful for the detection of KT from CRC.[14,15] Tottori et al. suggested serum CEA is useful in the follow-up of such patients.[16] However, the CEA levels in subjects with inflammatory diseases are similar to those of patients with benign and/or malignant tumors of the gastrointestinal tract and of other sites which include breast, bronchus, urothelium, ovary, uterus, and cervix. In our department, CEA is more widely used as it has become easily available and is a standard practice in our department. CA-125 is still not commonly utilized as a follow-up marker. Of the patients with metachronous KT from CRC, 25 had performed blood work for serum CEA. Among them, 23 (88.5%) had serum elevation for CEA. Besides, 5 of these patients had serum CA-125 check-up, and 2 (40%) had elevation. These findings suggest that these tumor markers may be used to help detect KT and close follow-up with imaging and tumor markers is important for female patients with colorectal cancer.

It has been shown that differentiation of the primary colorectal tumor is not a risk factor for the development of KT.[11] In our study, no correlation was found between the site of the colorectal primary tumors and the likelihood of KT. Based on our results, KT appears more likely to develop from colorectal primary tumors of the sigmoid colon (46.1%). This result was similar to the results of Tan et al. (2010). Larger studies will be necessary to confirm this finding.

For metachronous KT, reported median time of KT diagnosed after primary tumor resection ranged from 12 to 22.4 months.[6,8,14,17,18] Kim et al. reported 82% relapse within 3 years.[5] Median time of relapse in our study is 19.3 months (range 6-50.4 months, SD 12.8) and 88.5% relapse was found within 3 years. We consider using CA-125 level as a helpful tool for differentiation among selective suspected cases.

The prognosis of KT is generally acknowledged to be poor.[14,19,20] However, oophorectomy performed for macroscopic colorectal metastases with a curative aim seems to improve overall survival.[21] Prolonged survival after resection of KT is further supported. Fujiwara et al. reported 5-year overall survival for such patients to be 43.8%, and the 5-year overall survival was 77.9% for patients without peritoneal dissemination.[6] Erroi et al. reported a 5-year survival rate of 80% in patients without peritoneal dissemination.[10] Chung et al. found the 3-year overall survival to be 25.1% and the 3-year overall survival was 64.3% for patients with peritoneal metastasis confined to the pelvis.[8] Our results show overall survival from ovarian resection to be 19.8% and 6.6% at 3 years and 5

years, respectively, with the median survival time of 13.0 months. Among the 26 patients in our study, one patient remained alive with disease-free over 5 years.

The benefit of radical surgery for KT from CRC is unclear. It has been demonstrated that even if bilateral prophylactic oophorectomy had been performed, long-term survival is not affected.[22,23] However, some authors suggest the resection of all gross disease if possible. Fujiwara et al. showed that an R0 resection of metastatic sites was achieved in 15 out of a total of 22 patients, and the median survival time for these patients was 60.5 months (5-year overall survival was 60.6%) compared to 13.5 months for patients with R1/2 resections only (5-year overall survival was 0%). R0 resection was found to be significantly associated with prolonging survival ($p = 0.0002$).[6] Chung et al. found that patients who underwent complete resection of metastases had a significant improvement in survival compared to patients who underwent palliative debulking (3-year overall survival 51.15 vs. 17.4%; $p = 0.0013$).[8] Many studies have showed that patients with microscopic residual disease after surgical resection or with metastasis confined to the ovaries show significantly improved survival.[8,21,24-26] In our study, the median survival after R0 resection is 37.0 months (5-year overall survival was 18.8%) compared to 10.0 months for patients with R1/2 resections only (5-year overall survival was 0%). R0 resection was found to be significantly associated with prolonging survival ($p < 0.001$).

Although the inherent bias from retrospective analysis cannot be eliminated, this study showed that R0 resection for metachronous KT from CRC significantly provided better survival. A metastasectomy should be aggressively evaluated for CRC patients with metachronous KT. Due to the low incidence of metachronous KT in our CRC patients (1.19%), we do not recommend routine prophylactic oophorectomy even in postmenopausal women.[10,27] No benefits in term of survival were demonstrated for prophylactic oophorectomy during primary resection for colorectal cancer.[22,28] However other studies demonstrate the benefits of prophylactic oophorectomy. There is only one prospective randomized trial for prophylactic oophorectomy for CRC.[29] One hundred and fifty-five patients were randomized for an oophorectomy or no oophorectomy at laparotomy for resection of CRC during 11 years. This trial results suggested a survival benefit for an oophorectomy at between 2 and 3 years after surgery, but survival analysis indicated there was not statistically significant and the benefit did not appear to persist for 5 years.

There are several limitations to our study. As a retrospective design, it was based on charts review. The incidence might be underestimated because those KT patients who didn't have significant symptoms were neither treated nor enrolled in the study. Besides, the sample size was not suitable to perform multiple analysis for prognostic factors.

Conclusions

Metachronous KTs originating from CRC are uncommon in this study but with a relative poor prognosis. The regular monitoring of serum CEA and CA-125 should be considered for female patients after the resection of the CRC. A more aggressive surgical approach such as metastasectomy is also recommended to improve the outcome of these patients.

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原　著

源發自大腸直腸癌之異時性庫肯堡氏腫瘤－來自某醫學中心的十二年研究

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目的　本研究主要目的用於評估大腸癌術後庫肯堡氏腫瘤之臨床表現以及手術介入之預後。使我們能夠更恰當地制定治療策略以改善預後。

方法　自 2001 年到 2012 年為止，在本院共 2191 位女性因大腸直腸癌接受手術治療，其中有 26 位 (1.19%) 病患在術後追蹤時發現庫肯堡氏腫瘤並接受手術治療。治療前臨床 TMN 分期、腫瘤大小、病患年紀、手術後是否有殘存腫瘤、以及存活率都被收集與分析。

結果　異時性庫肯堡氏腫瘤病患平均年紀爲 49.77 歲，庫肯堡氏腫瘤診斷後平均存活時間為 23.94 個月，源發自大腸直腸癌之異時性庫肯堡氏腫瘤病患五年存活率為 6.6%，而無殘餘腫瘤之病患五年存活率為 18.8%。手術後無殘存腫瘤的病人較手術後有殘存腫瘤者有較高之存活率並達統計學上之顯著意義 ($p < 0.001$)。

結論　早期診斷以及根治性手術對病人之存活有益。源發自大腸直腸癌之異時性庫肯堡氏腫瘤病患五年存活率為 6.6%，而無殘餘腫瘤之病患五年存活率為 18.8%。因此積極手術治療切除庫肯堡氏腫瘤值得一試。

關鍵詞　異時性、卵巢轉移、大腸直腸癌、存活率。