Palliative surgery for Krukenberg tumors – 12-year experience and review of the literature

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AIM
To determine the clinical characteristics of patients undergoing palliative surgery for Krukenberg tumors, including disease presentation, outcomes, and prognostic factors.

METHODS
This was a retrospective clinical study of all patients who underwent palliative surgery for Krukenberg tumors between January 2004 and December 2015. Patient information was obtained from inpatient and outpatient case notes as well as the hospital electronic records. Patients who underwent potentially curative resection, and patients with Krukenberg tumors who did not undergo surgery were also excluded from the study. Palliative surgery was defined as those performed for either alleviation of symptoms or for asymptomatic patients for whom surgical removal of the tumors were deemed necessary following a multidisciplinary consensus. Tumors were diagnosed pre-operatively by computed tomography.
INTRODUCTION

A Krukenberg tumor is a rare ovarian tumor which has metastasized from a primary site, accounting for 1%-2% of all tumors of the ovary[1]. The stomach was previously described to be the most common primary site, followed by the colon, appendix and breast[2]. Recent literature reveals an increased incidence of tumors originating from the colon[2]. Compared with primary ovarian tumors, the prognosis of patients with Krukenberg tumors is bleak, even with metastatic disease confined to the ovaries.

Various studies have been published over the past decade with regards to the prognostic factors and outcomes of surgery for Krukenberg tumors. Metastectomy, or surgical removal of one or both involved ovaries, has been found to improve overall survival[3-5]. Cytoreductive surgery incorporating Krukenberg tumor removal has also been found to have a beneficial effect, with a 7% overall 5-year survival[6]. However, extensive cytoreductive surgery may have significant associated morbidity and mortality. To our knowledge, no previous study focuses exclusively on the group of patients for whom surgery is considered palliative.

Here we discuss the existing literature and report our experience with palliative surgery for Krukenberg tumors, including clinical characteristics of patients, disease presentation, surgical outcomes, safety, and prognostic factors.

RESULTS

Over the study duration, 38 female patients underwent palliative surgery for Krukenberg tumors at our institution. Mean age was 54.2 ± 11.7 years. The colon was the most frequent primary source of metastases (n = 21) followed by the stomach (n = 4). Prophylactic palliative surgery was performed for eight (21.1%) asymptomatic patients. Median post-operative length of stay was 8 d (IQR 6-12 d). Five patients (13.2%) experienced post-operative complications, although high grade morbidity was only seen in one patient (2.6%). Median overall survival from surgery was 17 mo (95%CI: 12.1-21.9) at a median follow-up duration of 12 mo (IQR 8-17 mo). The median survival was shorter for patients who underwent emergency surgery, younger patients, those with a colorectal primary, larger tumors, or synchronous peritoneal or hepatic metastases.

CONCLUSION

Palliative surgery for Krukenberg tumors can be performed safely with acceptable complication rates. Bilateral oophorectomy should be performed to prevent the risk of symptomatic contralateral tumors.

Key words: Krukenberg tumor; Palliative surgery

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Core tip: Krukenberg tumors represent metastases to the ovary and convey a poor prognosis. By reporting our 12-year experience with palliative surgery for Krukenberg tumors and discussing the existing literature, we hope to shed light and establish best practices on the approach to management of the disease. Palliative surgery for patients with Krukenberg tumors can be performed safely in an experienced unit with acceptable complication rates. Where possible, bilateral oophorectomy should be performed to obviate the risk of the contralateral ovary developing symptomatic tumors. Appropriate selection by a multidisciplinary consensus is essential for asymptomatic patients who may benefit from prophylactic surgery.
at the time of this study were censored. Survival rates were calculated using the Kaplan-Meier method and the differences in median survival times between groups assessed using the log-rank test. Cox proportional hazards model was used to determine the hazard ratios of variables affecting survival. $P < 0.05$ was taken as significant.

RESULTS

Patient and disease characteristics
Between January 2004 and December 2015, 38 female patients underwent palliative surgery for Krukenberg tumors at our institution. Patient and disease characteristics are summarised in Tables 1 and 2 respectively. Mean patient age was 54.2 ± 11.7 years. Almost 40% of the patients with Krukenberg tumors presented with abdominal pain or had pain as their most significant symptom. Median tumor size was 11.8 cm [Interquartile range (IQR) 7.8–16.0 cm]. Apart from the ovaries, all patients had at least one other site of metastases, mostly commonly the peritoneum or liver. The colon was the most frequent primary source of metastases followed by the stomach. In one patient, the primary tumor was not identified despite extensive investigation. The Krukenberg tumor was diagnosed during the same setting as the primary in just under half of the patients. Amongst the patients who had ovarian metastases detected metachronously, the median duration of diagnosis of the Krukenberg tumor from the primary was 19.5 mo (IQR 9-24 mo).

Twenty-six patients (68.4%) had undergone chemotherapy prior to Krukenberg tumor surgery and of these, 19 continued post-operative palliative chemotherapy. A total of 27 patients (71.1%) received chemotherapy post-operatively, including eight patients who commenced chemotherapy for the first time after surgery. Four patients (10.5%) had never received chemotherapy.

Surgical characteristics
Surgical procedures performed were; a unilateral or bilateral salpingo-oophorectomy alone, or a total hysterectomy in addition to a bilateral salpingo-oophorectomy (Table 3). Two other patients underwent additional surgical procedures during the same sitting as the Krukenberg tumor surgery; one patient had a small bowel resection while the other had a right hemicolectomy performed. Prophylactic palliative surgery was performed for eight asymptomatic patients; two were performed for histological confirmation of metastases to guide subsequent treatment, two were for progression of the Krukenberg tumors while on chemotherapy despite adequate extra-ovarian disease control, and four were prophylactic for sizeable tumors which would have likely caused symptoms during the patient’s lifetime. Five patients underwent emergent surgery; two for ruptured Krukenberg tumors, the third for a patient with fever and abdominal pain whose pre-operative CT scan was incorrectly reported as tubo-ovarian abscesses, the fourth for ovarian torsion, and in the last patient for acute intestinal obstruction secondary to compression of the bowel from the Krukenberg tumor.

Peri-operative morbidity
Median post-operative length of stay was 8 d (IQR 6-12 d). The majority of patients had an uneventful recovery period (86.8%). Five patients (13.2%) suffered complications; two Clavien-Dindo grade I, two grade
Survival

The median follow-up duration was 12 mo (IQR 8-17 mo). Two patients were lost to follow-up and one patient returned to her country of origin for continued care shortly after discharge. Twenty patients (52.6%) died during the follow-up period. Median overall survival (OS) from Krukenberg tumor surgery was 17 mo (95%CI: 12.1-21.9) (Figure 1). Based on univariate analysis (Table 4), only emergency surgery was associated with a significantly worse survival outcome. The median survival for patients with a colorectal primary compared to all other origins was 15 mo (95%CI: 10.5-19.5) and 38 mo respectively (95%CI: 5.8-70.2), \( P = 0.845 \). The median OS was also shorter for patients younger than 50 years old (13 mo, 95%CI: 8.0-18.0 vs 20 mo, 95%CI: 16.4-23.6), patients with a pre-operative American Society of Anaesthesiologists (ASA) score of 3 vs 2 (8 mo, 95%CI: 18.6-40.1), larger tumors \( \geq 12 \text{ cm} \) (14 mo, 95%CI: 9.4-18.6 vs 20 mo, 95%CI: 14.8-25.2), those with peritoneal metastases (17 mo, 95%CI: 11.3-22.7 vs 20 mo, 95%CI: 9.7-30.3) and those with hepatic metastases (14 mo, 95%CI: 8.4-19.6 vs 17 mo, 95%CI: 9.8-24.2).

Pre-operative serum tumor marker level did not correlate with OS. Serum CA 125 level was performed in 21 patients (55.3%) before Krukenberg tumor surgery, for which median CA 125 level was 42.4 kU/L (IQR 14.1-206.5). Pre-operative serum carcinoembryonic antigen (CEA) testing was done in 30 patients (78.9%), including 20 out of 21 patients who had a colorectal primary. For these 20 patients, the median CEA level was 30.3 \( \mu \text{g/L} \) (IQR 10.8-144.0). Using a cut-off value of 35 and 30 for CA 125 and CEA respectively (Table 4), it appeared that the pre-operative values of these tumor markers did not reflect patient prognosis. These values were chosen based on the normal reference range of CA 125 (0-35 kU/L) and the median CEA level amongst patients with a colorectal primary in our study.

DISCUSSION

The eponymous Krukenberg tumor was first described in 1896 by the German doctor Friedrich Krukenberg (1871-1946). Representing advanced metastatic disease, this entity clearly conveys a poor prognosis. Gastric cancer was previously reported to account for...
the majority of primary tumors responsible\[7\]. However, recent literature suggests an increased frequency of Krukenberg tumors with a colorectal origin\[2\]. In our study, more than half of the patients had a colorectal primary compared to only 10% with a gastric primary. This is likely related to the increasing frequency of colorectal cancer locally as well as in other developed countries. In Singapore, the age-standardized incidence rate of colorectal cancer is one of the highest among ethnic Chinese populations in the world\[8\]. With the longer survival generally seen in patients with metastatic colorectal cancer as compared with that of gastric cancer, the option of pursuing palliative surgery in these patients may be seemingly more attractive.

Many aspects of Krukenberg tumors still remain controversial, including the mechanism of metastases or even the pathologic tumor characteristics used for diagnosis. The current criteria used by the World Health Organisation, established in 1973 by Serov and Scully\[9\], may not adequately reflect the complexity of the tumor considering the multiple different primary sites possible. Treatment generally consists of surgery, chemotherapy or radiotherapy but guidelines concerning treatment of choice and appropriate timing of intervention have yet to be established.

Over the past decade, a number of retrospective studies have attempted to determine the prognostic factors for patients with Krukenberg tumors. Current evidence suggests a survival benefit for patients who undergo metastasectomy, compared to those without surgery. A recent multivariate analysis of 128 patients with Krukenberg tumors (58 colorectal, 41 gastric origin) showed that synchronous tumors, pelvic invasion and ascites were independent factors predicting for a poorer overall survival\[10\]. Other factors found to negatively influence overall prognosis include R1 or suboptimal resection\[3\], metastatic disease beyond the ovaries\[11\], tumors of gastric origin compared to colorectal origin\[12\], and patients with poorer Karnofsky performance status scores\[4\]. For gastric cancer, metastasectomy in addition to chemotherapy was also found to improve survival compared to palliative chemotherapy alone\[12\]. For colorectal cancers, ovarian metastases have been shown to be less responsive to chemotherapy compared to extra-ovarian sites\[13\]. Surgical resection was therefore recommended for these "metastatic sanctuaries" even in the palliative setting, as they would often progress and result in symptoms while on chemotherapy. In a separate study comparing 83 patients with ovarian metastases from a colorectal primary who underwent an oophorectomy vs 47 historical controls who did not undergo surgery, metastasectomy conferred a significantly longer OS at 20.8 mo vs 10.9 mo\[14\]. In terms of overall survival, surgery for patients with a colorectal primary may confer a greater advantage over that for a gastric primary in view of less aggressive tumor biology.

In contrast to the usually straightforward oophorectomy, the operative circumstances for patients with Krukenberg tumors may be more challenging. These patients often have undergone previous surgeries with resultant intraabdominal adhesions, or have synchronous pelvic peritoneal disease. Therefore, while the benefit of potentially curative metastasectomy is clear, clinicians may be hesitant to subject patients to palliative surgery, particularly if the patient is asymptomatic or in a debilitated state. In our series, five patients (13.2%) experienced post-operative complications, although high grade morbidity was only seen in one patient (2.6%). Both patients with ileus resumed enteral feeding within two weeks and were discharged well. The 30-d mortality rate was zero and median length of stay was about a week.

Close to half of all patients were found to have bilateral ovarian disease. Of these, the diagnosis of contralateral ovarian involvement was not apparent on pre-operative imaging and only established following surgery and histological examination of the resected specimen in a quarter of the cases (n = 4). Even if not synchronously affected there is a high chance of subsequent contralateral ovary involvement resulting in symptoms. We therefore recommend that bilateral ovarian resection be routine if surgery is to be performed for palliation.

Following our analyses, emergency surgery was the only factor that was found to significantly reduce survival prognosis. Although patients who were less than 50 years old, had a higher ASA score, with tumor size larger than 12 cm, or had hepatic or peritoneal metastases tended to have a shorter median survival, this was not found to be statistically significant. Surprisingly, tumors with a colorectal primary tended to fare worse than tumors of all other origins with a median overall survival of 15 mo vs 38 mo. Meaningful comparisons could not be performed for patients with a gastric primary in view of the small sample size (n = 4) with one patient defaulting follow-up and the other continuing further management overseas. While a single study found that a pre-operative CA 125 level of more than 75 kU/L significantly correlated to poorer survival\[15\], in our series no association could be found with this value nor the reference range cut-off. Pre- and post-operative trending of CA 125 levels therefore remains of questionable utility. CEA levels do not appear to prognosticate survival in patients with a colorectal primary, but may serve as an adjunct to imaging for reflecting disease response to chemotherapy.

Over a fifth of the patients in our series were asymptomatic at the time of surgery, all of whom had uncomplicated post-surgery recovery periods. Appropriate patient selection for prophylactic surgery is essential, with patient fitness and prognosis along with tumor size, location and anticipated development of symptoms being key considerations. With emergency surgery conferring a significantly worse outcome, the role of prophylactic surgery should certainly be explored further. The possibility of Krukenberg tumors being chemo-resistant "metastatic sanctuaries" was also evident in two asymptomatic patients in our study who...
had progression of the ovarian tumors despite good systemic control of disease elsewhere.

In conclusion, Palliative surgery for patients with Krukenberg tumors can be performed safely in an experienced unit with acceptable complication rates. The decision to proceed with metastasectomy is influenced by several factors including the presence of symptoms, synchronous disease, and tumor response to chemotherapy, and should be made as part of a multidisciplinary team consensus. Where possible, bilateral oophorectomy should be performed to obviate the significant risk of symptomatic contralateral ovarian involvement. Tumor markers need not be routinely trended peri-operatively. Proper selection is essential for asymptomatic patients who may benefit from prophylactic surgery. Further studies can be done to determine if symptom-free survival can be prolonged or quality of life improved with palliative surgery.

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