Review Article

Krukenberg tumours: which patients should be considered for surgery?—a narrative literature review

Sabina Ioana Nistor[1]^, Hooman Soleymani majd[1,2]^

[1]Department of Gynaecology Oncology, Churchill Hospital, Oxford University Hospitals National Health Service (NHS) Foundation Trust, Oxford, UK; [2]Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, UK

Contributions: (I) Conception and design: Both authors; (II) Administrative support: H Soleymani majd; (III) Provision of study materials or patients: H Soleymani majd; (IV) Collection and assembly of data: SI Nistor; (V) Data analysis and interpretation: SI Nistor; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Hooman Soleymani majd, MD. Department of Gynaecology Oncology, Churchill Hospital, Oxford University Hospitals National Health Service (NHS) Foundation Trust, Old Rd, Headington, Oxford OX3 7LE, UK; Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, UK. Email: hooman.soleymanimajd@msd.ox.ac.uk.

Background and Objective: Krukenberg tumours (KTs) are metastatic signet ring cell (SRC) adenocarcinomas of the ovary, arising from the stomach in most cases (70%). Other common primary sites are the colon, appendix and breast. The use of the term "Krukenberg tumour" is inconsistent in the literature which makes data interpretation difficult. Prognosis of KTs is dismal and, in the absence of randomised controlled trials, the best treatment strategies remain controversial. Evidence from retrospective studies suggests that metastectomy is associated with improved survival. Our narrative literature review set out to determine which patients gain maximal survival benefit from surgical management.

Methods: A comprehensive literature search was performed using PubMed and Google Scholar databases, from 1 January 2000 to 15 July 2024, with the terms 'Krukenberg', 'metastatic mucinous adenocarcinoma of ovary'. This search identified 20 full-text manuscripts, including data on 1,815 patients.

Key Content and Findings: We found that the overall prognosis of these patients remains poor, with a median overall survival (mOS) ranging between 9 and 50 months. Metastectomy is associated with survival benefit only when all visible disease is removed (R0): mOS in patients with microscopic residual disease (R1) or gross residual disease (R2) is similar to mOS in unresected patients (11 *vs.* 10 months). The following other factors have been identified as independent prognostic factors for survival in multivariate analyses: heated intraperitoneal chemotherapy (HIPEC), adjuvant chemotherapy, curative surgery for the primary tumour, i.e., gastrectomy, no ascites, non-gastric origin, a good performance status, less extensive metastatic disease, i.e., no extra-ovarian disease or no extra-pelvic disease, no peritoneal carcinomatosis or a low Peritoneal Cancer Index (PCI), smaller size of lesion, no SRC features, expression of oestrogen receptor-β (ER-β) and progesterone receptors (PR), metachronous tumours, linitis plastica, tumour grade.

Conclusions: Multiple retrospective analyses have demonstrated that metastectomy is associated with a survival benefit in patients with metastatic mucinous ovarian adenocarcinomas. However, patients with poor prognostic factors are less likely to benefit from surgery and should be counselled accordingly. Diagnostic laparoscopy could be considered before debulking surgery, to assess resectability of disease and to avoid a futile exploratory laparotomy. HIPEC after cytoreductive surgery (CRS) remains controversial, with possible survival benefit for KTs of gastric origin, particularly when peritoneal dissemination is present but the PCI is low.

Keywords: Krukenberg; ovarian; metastatic; mucinous; adenocarcinoma

Submitted Jun 03, 2024. Accepted for publication Sep 20, 2024. Published online Oct 29, 2024.
doi: 10.21037/tcr-24-904
View this article at: https://dx.doi.org/10.21037/tcr-24-904

^ ORCID: Sabina Ioana Nistor, 0009-0000-1228-1602; Hooman Soleymani majd, 0000-0003-3293-5321.

Introduction

Krukenberg tumours (KTs) are metastatic signet ring cell (SRC) adenocarcinomas of ovary. The term has been used by some authors to describe all metastatic ovarian carcinomas, irrespective of the histological type (1), but this practice is discouraged. Other authors only use the term "Krukenberg tumours" for metastatic ovarian tumours with a gastric primary (2-4). Prognosis of KTs is poor and, in the absence of randomised controlled trials (RCTs), the best treatment strategies remain controversial. Evidence from retrospective studies suggests that metastectomy is associated with improved survival. Our narrative literature review set out to determine which patients gain maximal survival benefit from surgical management. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-904/rc).

Methods

A comprehensive literature search was performed using PubMed and Google Scholar databases, from 1 January 2000 to 15 July 2024, with the terms 'Krukenberg', 'metastatic mucinous adenocarcinoma of ovary'. We selected retrospective studies assessing independent prognostic factors for survival in patients with KTs, studies in which a multivariate analysis was performed. This search identified 20 full-text manuscripts, including data on 1,815 patients.

Our search strategy summary is detailed in *Table 1*. We present, in *Table 2*, a list of retrospective studies assessing the effect of metastectomy in patients with metastatic mucinous adenocarcinoma. In *Table 3*, we present the retrospective studies looking at independent factors associated with overall survival (OS) in multivariate analysis, in patients with metastatic mucinous adenocarcinoma.

Definition and history

Paget, in 1854, in his "Lectures on surgical pathology", first described a distinctive form of ovarian tumour associated with mammary or gastric cancer of "fibrous hard" nature (29).

In 1896, Friedrich Ernst Krukenberg, a 25-year-old student working in the laboratory of pathologist Felix Marchland in Marburg, Germany, published a series of five cases describing a new type of ovarian tumour, which he called "fibrosarcoma ovarii mucocellulare carcinomatodes". Krukenberg thought these were a mucin-producing type of primary ovarian fibro-sarcomas (30). Krukenberg's criteria required: presence of tumour in the ovary, evidence of intracellular mucin secretion by the formation of signet cells, and diffuse infiltration of the stroma giving a sarcoma-like picture (31). Krukenberg went on to practice as an ophthalmologist in his hometown of Halle, Germany. His brother, Georg Heinrich Peter Krukenberg, was a professor of Gynaecology at the University of Bonn.

In 1902, Schlagenhaufer established the metastatic nature of this lesion from a primary tumour of epithelial origin and with the most common site of primary tumour being the stomach (32).

In 1938, Novak and Gray defined KTs as mucin-secreting SRC carcinomas in the dense fibroblastic stroma of the ovary (33).

The World Health Organisation (WHO) criteria for KTs are currently based on the 1973 description by Serov and Scully (34), according to which the following three histopathological features are all required for diagnosis: stromal involvement, mucin producing neoplastic SRCs and ovarian stromal sarcomatoid proliferation.

Primary sites and mechanisms of spread

The primary site of tumour is the stomach in most cases (70%). The gastric tumours usually originate from the pylorus and are adenocarcinomas of SRC type, either infiltrative or diffuse gastric adenocarcinomas. Other common primary sites can be: the colon, the appendix, the breast (invasive lobular carcinoma) (35). Rare primary sites reported are: the lung (4), the gallbladder, the ampulla of Vater, the uterine cervix, the urinary bladder or the urachus, the pancreas (35). Primary carcinomas, particularly those from stomach or breast (35) may be very small and careful work-up is required to identify them.

The mechanism of spread to the ovary is thought to be either lymphatic or haematogenous. Transperitoneal spread is also possible but less likely.

The retrograde lymphatic spread theory would explain the association of KTs with early gastric cancers, which are confined to the mucosa and submucosa (layers which have a rich lymphatic plexus) (35). Cancer cells are thought to metastasise to the perigastric nodes in the first instance and to form emboli which block the upward lymphatic flow. They then travel to the para-aortic and pelvic lymph nodes by a retrograde flux. Ovaries, with their rich lymphatic

Table 1 Search strategy summary

Items	Specification
Date of search	1 May 2024 and 15 July 2024
Databases and other sources searched	PubMed, Google Scholar
Search terms used	Krukenberg, metastatic mucinous adenocarcinoma of ovary
Timeframe	1 January 2000–15 July 2024
Inclusion criteria	Retrospective studies assessing independent prognostic factors for survival in patients with Krukenberg tumours published in English
Selection process	Both authors, S.I.N. and H.S.m., independently selected studies for inclusion in the review

network, are preferentially reached by cancer cells (36). Histopathology findings support this theory: carcinomatous emboli have been found in lymphatic vessels of the ovarian hilus, mesovarium, mesosalpinx (1) and ovarian cortex (36), while surface involvement is rare in KTs (36).

Haematogenous spread via the thoracic duct has also been proposed (37). KTs are prevalent in premenopausal women, which have a greater vascularity of the ovaries (38). The histopathological findings supporting haematogenous diffusion in addition to a lymphatic one are hilar metastases and lymphovascular invasion.

Peritoneal spread is less likely, as KTs are often identified in the absence of peritoneal disease (39) and the surface of tumour is not usually infiltrated (35). The "tumour cell entrapment hypothesis" suggests that free intraperitoneal cancer cells may become entrapped in the ovary during the time of ovulation (40).

Qiu *et al.* [2010] investigated factors associated with ovarian metastases from primary gastrointestinal carcinomas, in a retrospective study including 42 patients with metachronous tumours. They found that invasion depth (T stage) of the primary carcinomas was the only significant risk factor (relative risk 3.2, P=0.004), with 93% of these patients having advanced (T3/T4) disease. The deeper the primary tumour invaded, the earlier the metastasis occurred. The 1- and 2-year metastasis-free survival rates were, respectively, 48.5% and 18.2% in the T3 group, compared with 14.3% and 0% in T4 group (P=0.031) (41).

Epidemiology

The incidence of KTs varies across the globe, following the patterns of gastric carcinomas. While in the west they are rare, accounting for 1–2% of ovarian tumours, in countries with a high incidence of gastric cancer, such as Japan, they amount to 17% of ovarian tumours (42).

One to two percent of women diagnosed with colorectal cancer develop ovarian metastases (40). For gastric cancer, the reported incidence of ovarian metastatic disease varies: 0.3% to 6.7% (23).

KT in pregnancy

KTs have been described in pregnancy, with poor maternal and foetal outcomes. Glišić *et al.* [2006] report the case of a 38-year-old woman who presented with severe abdominal pain at 24 weeks gestation. Imaging identified large bilateral complex ovarian cysts. She underwent right oophorectomy and partial resection of left ovary. Intraoperatively, ascites, as well as a gastric pyloric tumour invading the serosa were identified. Postoperative imaging confirmed liver and lung metastases. An emergency caesarean section (CS) was performed at 25 weeks gestation due to foetal concerns. The baby died a few days later. The mother died one week later due to respiratory failure (43).

Sandmeier *et al.* [2000] reported the case of a 35-year-old patient who had a CS at 35 weeks gestation due to deranged liver function tests and vomiting. Bilateral ovarian masses were identified at the time of CS. Biopsy confirmed a SRC carcinoma. A subsequent gastroscopy identified a gastric ulcer in the proximal antrum and biopsies were also suggestive of SRC carcinoma. The patient underwent total gastrectomy, omentectomy, left segmental colectomy, bilateral salpingo-oophorectomy. She died 5 months after the CS due to progressive peritoneal carcinomatosis, despite chemotherapy treatment (44).

Mendoza-Rosado *et al.* [2021] describe the case of a 38-year-old patient who presented with abdominal pain at 25 weeks gestation and was found to have bilateral ovarian masses. She underwent caesarean hysterectomy and right

Table 2 Retrospective studies assessing the effect of metastectomy in patients with metastatic mucinous adenocarcinoma

Author	Year	Region	Period	Patients	Primary	S/M	Metastectomy	R0	mOS, months
Rayson *et al.* (5)	2000	Canada	1984–1998	38	Colorectal	M 27, S 11	38 (100%)	R0 19/38 (50%)	20
Kim *et al.* (6)	2001	South Korea	1987–1996	34	Gastric	M 34	22/34 (65%)	15/22 (68%)*	7.7
Cheong *et al.* (7)	2004	South Korea	1987–2000	34	Gastric	M 34	34 (100%)	R0 18/34 (53%)	11
Cheong *et al.* (8)	2004	South Korea	1987–1998	54	Gastric	M 54	33/54 (61%)	<1 cm 31/33 (94%)	9
McCormick *et al.* (9)	2007	USA	1980–2005	39	Colorectal	M 12, S 28	39 (100%)	<1 cm 29/39 (73%)	30
Jiang *et al.* (10)	2009	China	1997–2003	54	Gastric 26; colorectal 23; other 5	M 41, S 13	54 (100%)	R0 32/54 (59%)	17.8
Tan *et al.* (11)	2010	Singapore	1992–2004	25	Colorectal	S 16, M 9	25 (100%)	Not recorded	16.5
Kim *et al.* (12)	2010	South Korea	1994–2006	158	Gastric 73; colon 61; other 13	M 71, S 87	158 (100%)	<2 cm 93/158 (59%)	15
Ojo *et al.* (13)	2011	USA	1994–2010	26	Colorectal	M 4, S 22	25/26	R0 8/26 (31%)	27.5
Jun *et al.* (14)	2011	South Korea	1981–2008	22	Gastric	M 22	22 (100%)	R0 16/22 (76%)	18.8
Wu *et al.* (15)	2013	China	2000–2010	62	Gastric	M 62	62 (100%)	PCI <16 after CRS 14/32 (44%)	–
Lu *et al.* (3)	2012	Taiwan	2000–2010	85	Gastric	S 45, M 40	35 (41%)	Not recorded	9
Peng *et al.* (16)	2013	China	1998–2011	133	Gastric	S 69, M 64	133 (100%)	R0 83/133 (62%)	16
Cho *et al.* (17)	2015	South Korea	2004–2012	216	Gastric	S 84, M 132	107 (50%)	R0 41/107 (38%)	–
Wu *et al.* (18)	2015	China	1990–2010	128	Gastric 41; colorectal 58; other 21; unknown 8	S 36, M 92	114 (89%)	Not recorded	16
Rosa *et al.* (2)	2015	Italy	1990–2012	63	Gastric	M 33, S 30	53 (84%)	R0 33/53 (62%)	23
Brieau *et al.* (19)	2016	France	2001–2014	35	Gastric	S 21, M 14	17 (49%)	Not recorded	15.5
Xu *et al.* (20)	2017	China	1994–2013	57	Colorectal	S 21, M 36	57 (100%)	R0 26/57 (46%)	35
Yu *et al.* (21)	2017	China	2005–2014	152	Gastric	M 59, S 92	89 (59%)	R0 57/90 (63%)	–
Ganesh *et al.* (22)	2017	USA	1999–2015	195	Colorectal	M 100, S 85	195 (100%)	R0 114/195 (58%)	23
Yan *et al.* (23)	2018	China	2004–2015	103	Gastric	S 103	54 (52%)	R0 32/54 (59%)	15.8
Ma *et al.* (24)	2019	China	2006–2016	182	Gastric	S 94, M 88	128 (70%)	R0 60/128 (47%)	–
Lin *et al.* (25)	2022	China	2011–2021	130	Gastric	S 82, M 48	88 (68%)	Not recorded	13
Fang *et al.* (26)	2023	China	2011–2020	92	Gastric	S 92	46 (50%)	R0 26/46 (56%)	14
Ostowari *et al.* (27)	2024	USA	2012–2021	45	Colorectal	S 45	43 (96%)	Not recorded	50.3
Bildersheim *et al.* (28)	2024	Canada	2014	26	Colorectal	S 5, M 21	10 (39%)	Not recorded	30.4

*, no gross residual disease. S, synchronous; M, metachronous; R0, removal of all macroscopic disease; mOS, medium overall survival; PCI, Peritoneal Cancer Index; CRS, cytoreductive surgery.

salpingo-oophorectomy at 26 weeks gestation. Histology confirmed a poorly differentiated adenocarcinoma with extensive SRCs. Endoscopy identified a gastric tumour. She was readmitted with intra-abdominal sepsis secondary to bowel perforation. At laparotomy disseminated peritoneal carcinomatosis was identified. She received palliative therapy and died 2 months later (45).

The occurrence of gastric carcinoma is in pregnancy is rare. Unfortunately, the diagnosis of gastric carcinoma is usually delayed, as symptoms may be attributed to pregnancy, and patients already have metastatic disease at the time of diagnosis (43-45). Sex steroid hormones during

Table 3 Retrospective studies reporting overall survival in patients with metastatic mucinous adenocarcinoma

Author	Year	Patients	Primary	Multivariate analysis—independent prognostic factors for overall survival
Kim *et al.* (6)	2001	34	Gastric	No gross residual disease (RR 0.40, 95% CI: 1.17–0.94, P=0.036) 10.9 *vs.* 7.5 months
				Disease confined to ovaries (RR 0.06, 95% CI: 0.01–0.39, P=0.003) 13.1 *vs.* 10.9 months
Cheong *et al.* (7)	2004	34	Gastric	R0 (RR 0.155, 95% CI: 0.055–0.435) 18 *vs.* 9 months
Jiang *et al.* (10)	2009	54	Gastric 26, colorectal 23, other 5	Gastric *vs.* colorectal origin (chi sq. 7.98, P<0.01) 13 *vs.* 29.6 months
				Macroscopic residual disease (chi sq. 7.35, P<0.01) 10 *vs.* 29.6 months
				Lower KPS scores (chi sq. 4.57, P=0.03)
Kim *et al.* (12)	2010	158	Gastric 73, colon 61, other 13	Primary site (RR 1.203, 95% CI: 1.024–1.414, P=0.025) gastric 12 *vs.* colorectal 17 months
				Adjuvant chemotherapy (RR 2.347, 95% CI: 1.309–4.219, P=0.004) 17 *vs.* 8 months
				Residual disease <2 *vs.* ≥2 cm (RR 1.311, 95% CI: 1.084–1.587, P=0.005) 29 *vs.* 15 months
Ojo *et al.* (13)	2011	26	Colorectal	Age <50 years (P=0.008)
				Extent of metastasis (P=0.007)
Wu *et al.* (15)	2013	62	Gastric	CRS + HIPEC *vs.* CRS only (HR 2.996, 95 % CI: 1.245–7.208, P=0.014) 15.5 *vs.* 10.4 months
				PCI high (≥16) *vs.* low (<16) (HR 3.235, 95% CI: 1.366–7.662, P=0.008) 7.4 *vs.* 10.4 months
Lu *et al.* (3)	2012	85	Gastric	Metastasectomy (HR =0.36, P=0.001) 14.1 *vs.* 8 months
				ECOG PS 0–1 (HR 0.44, P=0.011)
				Subsequent systemic therapy (HR 0.21, P=0.002)
				Subsequent platinum-based chemotherapy (HR 0.36, P=0.014)
Peng *et al.* (16)	2013	133	Gastric	Gastrectomy (P=0.048) 19 *vs.* 9 months
				Absence of ascites (P=0.008) 21 *vs.* 13 months
Cho *et al.* (17)	2015	216	Gastric	metastasectomy (HR 0.458, 95% CI: 0.287 to 0.732, P=0.001)
				Signet-ring cell pathology (HR 1.583, 95% CI: 1.057 to 2.371, P=0.026)
				Peritoneal carcinomatosis (HR 3.081, 95% CI: 1.610 to 5.895, P=0.001)
Wu *et al.* (18)	2015	128	Gastric 41, colorectal 58, other 23, unknown 8	Synchronous metastasis (HR 1.898, 95% CI: 1.182–3.049, P=0.008)
				Pelvic invasion (HR 2.156, 95% CI: 1.170–3.974, P=0.0138) 13.5 *vs.* 23 months
				Ascites (HR 4.820, 95% CI: 2.537–9.157, P<0.0001) 13 *vs.* 23 months
				No metastasectomy (HR 4.878, 95% CI: 1.572–15.15, P=0.0060)
Rosa *et al.* (2)	2015	63	Gastric	S *vs.* M (RR 8.69, 95% CI 4.2–45.6, P=0.0001) 17 *vs.* 36 months
				R0 *vs.* R1/R2 (RR 7.93, 95% CI: 3.9–43.6, P=0.001) 34 *vs.* 11 months
				HIPEC + CT *vs.* CT only (RR 6.98, 95% CI: 1.86–23.7, P=0.007) 33 *vs.* 20 months
Brieau *et al.* (19)	2016	35	Gastric	Metastectomy (HR 0.24, 95% CI: 0.10–0.62, P<0.01) 26.9 *vs.* 10.6 months
Xu *et al.* (20)	2017	57	Colorectal	Complete cytoreduction (HR 0.135, P=0.001) CC0:CC1:CC2 56 *vs.* 28 *vs.* 13 months
				Less extensive metastases (HR 0.287, P=0.029) Movary 54 months *vs.* M1 35 months *vs.* M2 13 months
				Systemic chemotherapy (HR 0.345, P=0.012) 47 *vs.* 30 months

Table 3 (*continued*)

Table 3 (*continued*)

Author	Year	Patients	Primary	Multivariate analysis—independent prognostic factors for overall survival
Yu *et al.* (21)	2017	152	Gastric	Metastasectomy (HR 0.486, 95% CI: 0.323–0.729, P<0.001)
				Peritoneal carcinomatosis (HR 1.938, 95% CI: 1.230–3.049, P=0.004)
				Expression of ER-β (HR 0.404, 95% CI: 0.251–0.648, P<0.001)
				Expression of PR (HR 0.496, 95% CI: 0.301–0.817, P<0.001)
Yan *et al.* (23)	2018	103	Gastric	Metastasectomy (HR 0.486, 95% CI: 0.323–0.729, P<0.001) 18.9 *vs.*12.4 months
				Signet ring cells (HR 1.938, 95% CI: 1.182–3.175, P=0.009)
				Peritoneal carcinomatosis (HR 1.934, 95% CI: 1.230–3.049, P=0.004)
				Expression of ER-β (HR 0.404, 95% CI: 0.251–0.648, P<0.001)
				Expression of PR (HR 0.496, 95% CI: 0.301–0.817, P<0.001)
Ma *et al.* (24)	2019	182	Gastric	Metastasectomy (HR 0.537, 95% CI: 0.344–0.839, P=0.006) 14 *vs.* 8 months
				Ascites (HR 1.523, 95% CI: 1.058–2.193, P=0.024)
				Linitis plastica (HR 1.995, 95% CI: 1.115–3.571, P=0.020)
				Systemic chemotherapy (HR 0.456, 95% CI: 0.280–0.742, P=0.002)
Lin *et al.* (25)	2022	130	Gastric	Fibrinogen (HR 0.483, 95% CI: 0.300–0.777, P=0.003)
				Tumour >5 cm (HR 1.808, 95% CI: 1.178–2.776, P=0.007) 10 *vs.* 16 months
				Chemotherapy after ovarian metastasis (HR 0.19, 95% CI: 0.1–0.37, P=0.0) 15 *vs.* 8 months
				Oophorectomy (HR 1.720, 95% CI: 1.066–2.778, P=0.026) 16 *vs.* 8 months
				Peritoneal metastasis (HR 2.742, 95% CI: 1.606–4.682, P=0.000) 10 *vs.* 25 months
Fang *et al.* (26)	2023	92	Gastric	Ovarian metastectomy before systemic chemotherapy (HR 0.339, 95% CI: 0.143–0.799, P=0.013)
				R0 resection (HR 0.387, 95% CI: 0.164–0.913, P=0.030)
				Peritoneal carcinomatosis (HR 2.308, 95% CI: 1.087–4.902, P=0.029)
Ostowari *et al.* (27)	2024	45	Colorectal	Poor tumour grade (HR 10.69, 95% CI: 1.20–95.47, P=0.03) well-differentiated 53.7 months, moderately differentiated 50.7 months *vs.* poorly differentiated 22.1 months
Bildersheim *et al.* (28)	2024	26	Colorectal	Synchronous metastasis (HR 7.23, 95% CI: 1.57–33.28, P<0.05)

Independent factors associated with overall survival in multivariate analysis. RR, relative risk; CI, confidence interval; R0, removal of all macroscopic disease; KPS, Karnofski performance status; CRS, cytoreductive surgery; HIPEC, heated intraperitoneal chemotherapy; HR, hazard ratio; PCI, Peritoneal Cancer Index; ECOG PS, Eastern Cooperative Oncology Group performance status; S, synchronous; M, metachronous; R1, microscopic residual disease; R2, gross residual disease; CT, chemotherapy; CC0, no macroscopic residual tumour; CC1, maximal diameter of residual tumour <2.5 mm; CC2, maximal diameter of residual tumour ≥2.5 mm; Movary, ovary-only metastasis; M1, metastasis confined to the pelvis; M2, metastasis beyond the pelvis; ER-β, oestrogen receptor-β; PR, progesterone receptor.

pregnancy may promote the development and diffusion of gastric cancer by stimulating the underlying precancerous lesions (45).

Clinical presentation

The mean age at presentation for KTs is 45–46 years (1,2,25,29,33,35,46,47). This age distribution is younger than that of women with primary gastric, colorectal or breast cancers without ovarian metastases (36). A possible explanation for this would be that, during reproductive age, ovaries may be more receptive as a site of metastases (36).

The most common presenting symptoms are abdominal distension, pain, weight loss (47). Patients can also be asymptomatic, with ovarian tumours found incidentally on imaging or at laparoscopy or CS. Ascites is present in 40–50% of patients (35,47).

The clinical presentation may be dominated by symptoms

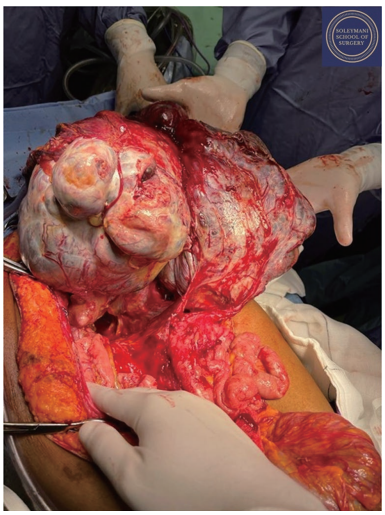

Figure 1 A rare finding of an enormous Krukenberg tumour arising from a colorectal primary, measuring 30 cm × 26 cm × 8 cm.

related to other metastatic lesions, i.e., pain related to bone metastases, pulmonary symptoms due to pulmonary effusion or metastatic lesions, breast symptoms, symptoms of ureteric obstruction. Liver metastases are rare (46).

KTs may be hormonally functional, as the ovarian stroma may go through reactive changes and become luteinised, leading to production of sex steroid hormones (1,2,29,35,48). Patients may therefore experience either oestrogenic or androgenic endocrine symptoms: abnormal uterine bleeding, breast soreness, virilisation or hirsutism without virilisation (47). Acanthosis nigricans has also been described (49).

Tumour markers such as cancer antigen 125 (CA125), carcinoembryonic antigen (CEA), cancer antigen 19.9 (CA 19.9) levels can be elevated (17,23).

KT may be diagnosed before the primary lesion (anachronous), at the same time as the primary lesion (synchronous) or after the diagnosis of the primary lesion (metachronous).

In metachronous tumours with a gastric primary, the average time from gastric cancer surgery to the diagnosis of KT is 17 months (7).

Radiological findings

On ultrasound, KTs are usually bilateral, solid and sometimes cystic ovarian masses. They have clear, well-defined tumour margins. An irregular hyperechoic solid pattern, and moth-eaten cyst formation are considered characteristic features (50,51). These ultrasonographic findings reflect the characteristic pathological findings of KTs: an encapsulated lesion, diffuse infiltration of mucin-producing cancer cells, and sarcomatous stroma (50). Intra-tumoral cysts have been described which are well demarcated, with a prominent vascular signal along the wall (51). The "lead vessel sign" depicts the main peripheral vessel in solid ovarian metastases, seen in a tree-shaped configuration, traversing into the central part of a solid ovarian mass (52). In contrast, primary epithelial ovarian tumours have ill-defined margins, irregular thick septations, irregular hypoechoic solid components with solid papillary projections, moderately echogenic cystic locules of varying size (53).

Computed tomography (CT) identifies lobulated, mostly solid tumours with homogeneous enhancement of the solid portion (36).

On T2-weighted magnetic resonance imaging (MRI), the solid tumour components typically show heterogeneous low to high signal intensity. Areas of decreased intensity are either randomly or peripherally located and correspond histologically to increased cellularity seen with fibrous stroma. Areas of increased intensity represent connective tissue oedema (38). Intra-tumoral cysts may also be present (54).

While KTs from a gastric primary are predominantly solid tumours, in KTs arising from a colorectal primary, solid components are usually contained within a predominantly cystic tumour (38). On CT/MRI, these are either unilocular or multilocular masses, with a "stained glass" appearance, containing various degrees of solid components (38).

Histopathology

Macroscopic findings

KTs are bilateral in 80% of cases (15,35). Their size varies, with an average reported size of 10 cm (46). Unlike primary mucinous ovarian tumours, they are typically not very large tumours and rarely measure more than 20 cm (46). We present, in *Figure 1*, a rare finding of an enormous Krukenberg tumour from a colorectal primary, measuring 30 cm × 26 cm × 8 cm. KTs from a breast primary are relatively small, usually smaller than 5 cm (38). KTs are most often solid but can occasionally be cystic. The capsular surface is typically smooth, with no surface implants or peritoneal deposits. This is in contrast with non-

Krukenberg metastatic tumours of the ovary which tend to be associated with surface implants (50).

Microscopic findings

KTs have two histological components: epithelial (carcinoma) and stromal (non-neoplastic). The epithelial component consists of SRCs and this component should be >10% of the tumour (47). The SRCs are mucin-laden, and the identification of intra-cytoplasmic mucin is essential for the diagnosis of KTs. Mucin-specific stains such as Mayer mucicarmine, Alcian blue, periodic acid-Schiff (PAS) are employed. Cells have an eosinophilic and granular cytoplasm and eccentric, hyperchromatic nuclei. Sometimes they contain a large mucin vacuole with a central eosinophilic body, which given them a "bulls eye" or targetoid appearance (35).

The stroma is typically oedematous and has a fibroma-like cellularity (47). Lutein cells may be present in the stroma, particularly if the patient is pregnant (46).

In "tubular Krukenberg", the SRCs are present in tubules intercalated with stromal cells. The mesenchymal component is of ovarian stromal origin. The cells show minimal cytological atypia or mitotic activity. Tubular KTs can easily be mistaken for Sertoli-Leydig tumours.

Many primary gastric SRC carcinomas have focal gland differentiation. This gland morphology will also reflect in their ovarian metastatic lesions.

Lymphovascular involvement is seen in 52% of KTs, usually demonstrated in the hilum area, or in the mesovarium or mesosalpinx (1).

Immunohistochemistry (IHC)

IHC markers have been employed to help establish the primary source. The following pattern suggest metastatic rather than primary ovarian origin: CA125 negative, CEA positive (50,55). Gastric carcinomas are caudal-type homeobox transcription factor 2 (CDX2) positive, hepatocyte paraffin 1 (Hep Par 1) positive, oestrogen receptor (ER) negative. The expression of cytokeratin 7 (CK7) and cytokeratin 20 (CK20) markers varies widely in gastric cancer (55). Colonic carcinomas are mucin 2 (Muc 2) positive, CDX2 positive, mucin 5AC (Muc 5AC) positive, mucin 1 (Muc 1) negative, Hep Par 1 neg, ER neg. Breast carcinomas are Muc 1 positive, CK7 positive and ER positive (56).

In a cohort of patients with KT and gastric primary, the following three IHC markers correlated with poor survival: cluster of differentiation 44 (CD44), cluster of differentiation 133 (CD133) or sex-determining region Y-box 2 (Sox2). In multivariate analysis, only Sox2 expression was an independent prognostic indicator of OS (P=0.04) (16).

Special AT-rich sequence-binding protein 2 (SATB2) is a highly sensitive marker for KT originated from a primary appendiceal tumour with high specificity (100% sensitivity, 100% specificity if using 4+ strong staining as the cut-off) (57).

Three quarters of gastric primaries stain for CDX2 and only rare examples stain for SATB2. Most colorectal primaries and all appendiceal primaries are positive for CDX2 and SATB2. GATA binding protein 3 (GATA3) stains almost all breast primaries and approximately half of bladder primaries. All pulmonary primaries are positive for thyroid transcription factor-1 (TTF1). Paired box gene 8 (PAX8) is negative in gastric, colorectal, and appendiceal primaries (58) and may help in the differentiation between primary and metastatic mucinous adenocarcinomas. In a recent paper looking at primary mucinous adenocarcinomas, we found that PAX8 was more frequently expressed by expansile tumours, which tend to have a more favourable prognosis (59).

Yan *et al.* [2018] demonstrated a correlation between the expression of oestrogen receptor-β (ER-β) and progesterone receptors (PR) and survival of gastric cancer patients with synchronous ovarian metastases. In their analysis of 102 synchronous KT with a gastric primary, the positive rate of ER-β was 44.7% and that of PR was 28.2% (23). Multivariate analysis revealed a positive association of OS with PR and ER-β expression. The mean OS for ER-β-positive and negative patients was, respectively, 20.4 *vs.* 12.1 months (P<0.001), while the mean OS of PR positive and negative patients was 20.6 *vs.* 13.8 months (P=0.001).

Molecular

Wang *et al.* [2017] found there is major concordance of the expression of human epidermal growth factor receptor 2 (HER2/neu), mesenchymal epithelial transition factor (c-MET), tumour protein 53 (p53), and antigen Kiel 67 (Ki-67) between gastric primary cancers and the paired metastatic tumours. This suggests that the status of these biomarkers remains stable during the metastatic process and may guide therapeutic options in the future (60).

In contrast, Nadauld *et al.* [2014] (61) identified a "genetic divergence" between the primary tumour which

had an amplification of the fibroblast growth factor receptor 2 (*FGFR2*) gene, and the metastases, which had an amplification of the transforming growth factor beta receptor 2 (*TGFBR2*) gene.

Frequent alterations in suppressor of mothers against decapentaplegic (*SMAD4*) and lysine-specific methyltransferase 2D (*KMT2D*) in KTs from colorectal primaries appear to be associated with poor prognosis (22).

Treatment/prognosis

Prognosis for KTs is dismal and, in the absence of RCTs, the best treatment strategies remain controversial.

Evidence from retrospective studies suggests that metastectomy is associated with improved survival (2,3,6,10,12,17,19-25). The evidence for adjuvant chemotherapy, however, is conflicting: some studies have identified a survival benefit (12,24,25), while other studies have not (3,30). Chemotherapy regimens described for KTs included cisplatin, carboplatin, oxaliplatin, docetaxel and 5-fluorouracil. Ovarian metastases from primary colorectal cancer are relatively resistant to chemotherapy compared with non-ovarian metastases (33).

In a recent meta-analysis including 17 retrospective studies and 1,502 patients with stage IV gastric cancer and KTs, Anwar *et al.* [2024] found that the combined approach of surgery and chemotherapy demonstrated the highest survival benefit, with a median OS (mOS) of 16.2 months for surgery and chemotherapy, 12.7 months for surgery only and 6.7 months for chemotherapy only (62).

The association of cytoreductive surgery (CRS) with removal of all visible disease (R0) and heated intraperitoneal chemotherapy (HIPEC) may result in some survival benefit for selected patients (2,15,63,64). Radiotherapy for rectal cancer with lympho-vascular invasion may contribute to reducing the risk of ovarian spread (18). No benefits in terms of population survival were demonstrated for prophylactic oophorectomy during primary resection for colorectal cancer (53). In addition to metastectomy, adjuvant chemotherapy, and HIPEC, the following factors have been identified as independent prognostic factors for survival in multivariate analyses: curative surgery for the primary malignancy, i.e., gastrectomy (16), no ascites (16,18,24), non-gastric origin (10), R0 (2,7,10,20,26), performance status (3,10), smaller size of lesion (25), no SRC features (17), expression of ER-β and PR receptors (23), metachronous tumours (13,18,30,39,44,65), linitis plastica (24), and tumour grade (27). With regards to the extent of disease, patients with disease confined to the ovary only have a better survival than those with disease than those with extra-ovarian disease in the pelvis (18,20), and these have a better survival than those with disease outside the pelvis (20). No peritoneal carcinomatosis (17,25,26), or a Peritoneal Cancer Index (PCI) of less than 16 (15) are associated with improved survival.

HIPEC is a technique which has been proposed for treating selected patients with peritoneal metastases from gastric or colorectal cancers. It involves the administration of cytotoxic agents into the peritoneal cavity at a high temperature (66). Hyperthermia and chemotherapeutic agents appear to have a synergistic effect: heat increases the tissue penetration of chemotherapy and is more toxic to cancerous cells than it is to normal cells.

HIPEC is administered after completion of CRS. Patients would only be candidates for CRS and HIPEC when R0 is thought to be achievable. The intra-abdominal tumour burden is determined using the Sugarbaker Peritoneal Cancer Index (PCI), a score which helps determine suitability of surgery. This score, ranging from 1 to 39, quantifies the size and location of cancer lesions throughout 13 abdominopelvic regions, of which four refer to the small bowel. Each of these regions is assigned a score from 0 to 3 based on the size and extent of the tumour implants. The total PCI score is the sum of each region's score (67).

Approximately 17% of patients with metastatic colorectal cancer have peritoneal carcinomatosis, with 2% having the peritoneum as the only site of metastasis. Patients with peritoneal metastases generally have a shorter progression-free survival (PFS) and OS than those without peritoneal involvement (58). The role of HIPEC in patients with metastatic colorectal cancer remains controversial, with two recent randomised trials reporting no survival benefit (68,69).

PRODIGE 7 was a randomised, phase III multicentre trial including 265 patients with colorectal peritoneal carcinomatosis randomised to receive standard treatment alone (systemic chemotherapy before and/or after CRS) or standard treatment and HIPEC with oxaliplatin. This study reported no significant difference in OS, with a mOS of 41.7 months in the HIPEC arm versus 41.2 months in the non-HIPEC arm. The 60-day grade 3–5 morbidity rate was significantly higher in the HIPEC arm (26% *vs.* 16%; P=0.035) (68).

Another randomized, phase III study, PROPHYLOCHIP-PRODIGE 15 investigated the survival benefit of systematic second-look surgery and HIPEC versus surveillance, in

patients at high risk of developing colorectal peritoneal metastases. This study included 150 patients with primary colorectal cancer, with synchronous and localised colorectal peritoneal metastases removed during tumour resection, resected ovarian metastases, or a perforated tumour. All patients completed 6 months of adjuvant systemic chemotherapy with no signs of disease recurrence. They were randomised to either surveillance or second-look surgery and oxaliplatin-HIPEC, or mitomycin-HIPEC alone in case of neuropathy. Three-year disease-free survival (DFS) was worse in the second look surgery and HIPEC group compared to surveillance (44% *vs.* 53%). Forty-one percent of patients in the second-look surgery plus HIPEC group reported grade 3 or 4 complications (69).

The National Comprehensive Cancer Network (NCCN) Colon Cancer guideline recommendation is that CRS and HIPEC can be considered in experienced centres only, for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. However, this approach remains controversial as HIPEC is associated with significant morbidity and mortality (70).

There is slightly more encouraging evidence to support the use of HIPEC in patients with metastatic gastric cancer.

Granieri *et al.* [2021], in their meta-analysis including 12 RCTs and 1,376 patients, investigated the prognostic impact of CRS and HIPEC in patients with metastatic gastric cancer. The addition of HIPEC to CRS in patients undergoing curative surgery was an independent predictor of better prognosis, with a 2.6-fold increase in survival outcome. Patient selection was important, and the authors conclude that the best candidates for the procedure are patients with limited nodal spread of disease, limited peritoneal dissemination, an excellent performance status and no distant metastases (63).

The NCCN guideline for gastric cancer suggests HIPEC may be considered, after multidisciplinary discussion, in patients with a PCI ≤10, no extraperitoneal disease, with stable or improved disease, only when complete cytoreduction is predicted (71).

Rosa *et al.* [2015], in a retrospective review of 63 patients with KT of gastric origin, found that the mOS survival for resected patients, both synchronous and metachronous, who underwent HIPEC procedure followed by postoperative systemic CT was significantly longer compared to patients who underwent postoperative systemic CT or just palliative CT after an explorative laparotomy (33, 20, and 10 months, respectively; P=0.0005) (2).

Wu *et al.* [2013], in a retrospective study including 62 patients with metachronous KT from a gastric primary, compared survival outcomes in patients who underwent CRS and HIPEC *vs.* CRS alone. The mOS in the CRS and HIPEC group was 15.5 *vs.* 10.4 months in the CRS only group, P=0.018 (15). Multivariate analysis using the Cox regression model identified HIPEC and a low PCI (less than 16 pelvic peritoneal metastases) as the major independent predictors for improved survival (15).

Lionetti *et al.* [2019] performed a systematic analysis of 23 retrospective studies, including a total of 1,533 patients with KTs. They found that CRS, particularly when R0 is achieved, was the treatment showing the clearest results in improving OS in KT patients. Their study showed conflicting results regarding chemotherapy. Based on the two studies described above, which included patients with Krukenberg tumours from gastric primaries (2,15), Lionetti *et al.* [2019] found that HIPEC appeared effective, both alone and in combination with CRS. They concluded that the association of R0 CRS with HIPEC seemed to be the most effective and safe therapeutic protocol for KT patients (64).

Conclusions

Metastatic mucinous ovarian adenocarcinomas are rare tumours. The use of the term "Krukenberg tumour" is inconsistent in the literature which makes data interpretation difficult. Many studies describe as KTs all metastatic mucinous adenocarcinomas of the ovary, regardless of the presence or absence of SRCs, approach which is not in keeping with the definition proposed by WHO.

While high-quality evidence is lacking, multiple retrospective analyses have demonstrated that metastectomy is associated with a survival benefit in patients with metastatic mucinous ovarian adenocarcinomas. However, the overall prognosis of these patients remains poor: the mOS ranged between 9 and 50 months in the studies included in this literature review. Adequate patient counselling regarding the possible benefit of surgery is paramount.

Patients with independent risk factors for poor prognosis, such as the presence of ascites, peritoneal carcinomatosis with a high PCI, or disease beyond the pelvis, those who did not undergo curative surgery for their primary tumour or those with poor performance status are less likely to benefit from surgery.

Surgery only results in a survival benefit when all macroscopic disease is removed: the mOS of patients with

R1/R2 is similar to the mOS of unresected patients (11 *vs.* 10 months) (2). Therefore, pre-operative assessment of resectability plays a crucial role. CT has been shown to only have a 50% accuracy for detecting peritoneal carcinomatosis (48). Diagnostic laparoscopy could be considered before debulking surgery, in order to assess resectability of disease and to avoid subjecting patients to a futile exploratory laparotomy (2). The role of HIPEC in the management of patients with KTs remains controversial. An RCT investigating HIPEC in patients with KTs from colorectal primaries showed no survival benefit, but higher morbidity in the CRS and HIPEC arm (68). There is limited evidence suggesting that HIPEC performed after CRS, could potentially improve the survival of patients with KTs of gastric origin, particularly when peritoneal dissemination is present, but the PCI is low (15,63).

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-904/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-904/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-904/coif). H.S.m. serves as an unpaid editorial board member of *Translational Cancer Research* from September 2023 to August 2025. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Holtz F, Hart WR. Krukenberg tumors of the ovary: a clinicopathologic analysis of 27 cases. Cancer 1982;50:2438-47.
2. Rosa F, Marrelli D, Morgagni P, et al. Krukenberg Tumors of Gastric Origin: The Rationale of Surgical Resection and Perioperative Treatments in a Multicenter Western Experience. World J Surg 2015;40:921-8.
3. Lu LC, Shao YY, Hsu CH, et al. Metastasectomy of Krukenberg tumors may be associated with survival benefits in patients with metastatic gastric cancer. Anticancer Res 2012;32:3397-401.
4. Lim GY, Wong YS, Tawil Z, et al. Krukenberg tumour as the initial manifestation of lung adenocarcinoma. Respirol Case Rep 2023;11:e01133.
5. Rayson D, Bouttell E, Whiston F, et al. Outcome after ovarian/adnexal metastectomy in metastatic colorectal carcinoma. J Surg Oncol 2000;75:186-92.
6. Kim HK, Heo DS, Bang YJ, et al. Prognostic factors of Krukenberg's tumor. Gynecol Oncol 2001;82:105-9.
7. Cheong JH, Hyung WJ, Chen J, et al. Surgical management and outcome of metachronous Krukenberg tumors from gastric cancer. J Surg Oncol 2004;87:39-45.
8. Cheong JH, Hyung WJ, Chen J, et al. Survival benefit of metastasectomy for Krukenberg tumors from gastric cancer. Gynecol Oncol 2004;94:477-82.
9. McCormick CC, Giuntoli RL 2nd, Gardner GJ, et al. The role of cytoreductive surgery for colon cancer metastatic to the ovary. Gynecol Oncol 2007;105:791-5.
10. Jiang R, Tang J, Cheng X, et al. Surgical treatment for patients with different origins of Krukenberg tumors: outcomes and prognostic factors. Eur J Surg Oncol 2009;35:92-7.
11. Tan KL, Tan WS, Lim JF, et al. Krukenberg tumors of colorectal origin: a dismal outcome--experience of a tertiary center. Int J Colorectal Dis 2010;25:233-8.
12. Kim WY, Kim TJ, Kim SE, et al. The role of cytoreductive surgery for non-genital tract metastatic tumors to the ovaries. Eur J Obstet Gynecol Reprod Biol 2010;149:97-101.
13. Ojo J, De Silva S, Han E, et al. Krukenberg tumors from colorectal cancer: presentation, treatment and outcomes. Am Surg 2011;77:1381-5.
14. Jun SY, Park JK. Metachronous ovarian metastases

following resection of the primary gastric cancer. J Gastric Cancer 2011;11:31-7.
15. Wu XJ, Yuan P, Li ZY, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves the survival of gastric cancer patients with ovarian metastasis and peritoneal dissemination. Tumour Biol 2013;34:463-9.
16. Peng W, Hua RX, Jiang R, et al. Surgical treatment for patients with Krukenberg tumor of stomach origin: clinical outcome and prognostic factors analysis. PLoS One 2013;8:e68227.
17. Cho JH, Lim JY, Choi AR, et al. Comparison of Surgery Plus Chemotherapy and Palliative Chemotherapy Alone for Advanced Gastric Cancer with Krukenberg Tumor. Cancer Res Treat 2015;47:697-705.
18. Wu F, Zhao X, Mi B, et al. Clinical characteristics and prognostic analysis of Krukenberg tumor. Mol Clin Oncol 2015;3:1323-8.
19. Brieau B, Auzolle C, Pozet A, et al. Efficacy of modern chemotherapy and prognostic factors in patients with ovarian metastases from gastric cancer: A retrospective AGEO multicentre study. Dig Liver Dis 2016;48:441-5.
20. Xu KY, Gao H, Lian ZJ, et al. Clinical analysis of Krukenberg tumours in patients with colorectal cancer-a review of 57 cases. World J Surg Oncol 2017;15:25.
21. Yu P, Huang L, Cheng G, et al. Treatment strategy and prognostic factors for Krukenberg tumors of gastric origin: report of a 10-year single-center experience from China. Oncotarget 2017;8:82558-70.
22. Ganesh K, Shah RH, Vakiani E, et al. Clinical and genetic determinants of ovarian metastases from colorectal cancer. Cancer 2017;123:1134-43.
23. Yan D, Du Y, Dai G, et al. Management Of Synchronous Krukenberg Tumors From Gastric Cancer: a Single-center Experience. J Cancer 2018;9:4197-203.
24. Ma F, Li Y, Li W, et al. Metastasectomy Improves the Survival of Gastric Cancer Patients with Krukenberg Tumors: A Retrospective Analysis of 182 patients. Cancer Manag Res 2019;11:10573-80.
25. Lin X, Han T, Zhuo M, et al. A retrospective study of clinicopathological characteristics and prognostic factors of Krukenberg tumor with gastric origin. J Gastrointest Oncol 2022;13:1022-34.
26. Fang J, Huang X, Chen X, et al. Efficacy of chemotherapy combined with surgical resection for gastric cancer with synchronous ovarian metastasis: A propensity score matching analysis. Cancer Med 2023;12:17126-38.
27. Ostowari A, Hasjim BJ, Lim L, et al. Clinical Outcomes in Patients With Krukenberg Tumors From Colorectal Cancer. J Surg Res 2024;299:343-52.
28. Bildersheim M, Taqi KM, Nelson G, et al. Incidence of Metastatic Tumors to Ovary (Krukenberg) Versus Primary Ovarian Neoplasms Associated with Colorectal Cancer Surgery. Surgical Oncology Insight 2024;1:100079.
29. Paget J. Lectures on Surgical Pathology [Internet]. Philadelphia: Lindsay & Blakiston; [cited 2024 Jul 15]. 1854:422-34. Available online: https://archive.org/details/lecturesonsurgic00page/page/n7/mode/2up
30. Krukenberg FE. Fibrosarcoma ovarii mucocellulare (carcinomatodes). Archiv für Gynäkologie 1896;50:287-321.
31. McGill FM, Ritter DB, Rickard CS, et al. Krukenberg tumors: can management be improved? Gynecol Obstet Invest 1999;48:61-5.
32. Schlagenhaufer F. Ueber das metastatische Ovarialcarcinom nach Krebs des Magens, Darmes und anderer Bauchorgane (Part 1 of 2). Gynecol Obstet Invest 1902;15:485-506.
33. Novak E, Gray L. Krukenberg tumor of the ovary: clinical and pathological study of four cases. Surg Gynecol Obstet 1938;66:157-65.
34. Serov SF, Scully RF. Histological Typing of Ovarian Tumours [Internet]. American Society of Clinical Pathologists Press; [cited 2024 Jul 15]. 1973:1-56. Available online: https://wellcomecollection.org/works/czjhu3a9
35. Al-Agha OM, Nicastri AD. An in-depth look at Krukenberg tumor: an overview. Arch Pathol Lab Med 2006;130:1725-30.
36. Agnes A, Biondi A, Ricci R, et al. Krukenberg tumors: Seed, route and soil. Surg Oncol 2017;26:438-45.
37. Taylor AE, Nicolson VM, Cunningham D. Ovarian metastases from primary gastrointestinal malignancies: the Royal Marsden Hospital experience and implications for adjuvant treatment. Br J Cancer 1995;71:92-6.
38. Koyama T, Mikami Y, Saga T, et al. Secondary ovarian tumors: spectrum of CT and MR features with pathologic correlation. Abdom Imaging 2007;32:784-95.
39. Miller BE, Pittman B, Wan JY, et al. Colon cancer with metastasis to the ovary at time of initial diagnosis. Gynecol Oncol 1997;66:368-71.
40. Das S, Sahu D, Wani M, et al. A curious discourse of Krukenberg tumor: a case report. J Gastrointest Oncol 2014;5:E117-20.
41. Qiu L, Yang T, Shan XH, et al. Metastatic factors for Krukenberg tumor: a clinical study on 102 cases. Med Oncol 2011;28:1514-9.
42. Yakushiji M, Tazaki T, Nishimura H, et al. Krukenberg tumors of the ovary: a clinicopathologic analysis of 112

cases. Nihon Sanka Fujinka Gakkai Zasshi 1987;39:479-85.
43. Glisić A, Atanacković J. Krukenberg tumor in pregnancy. The lethal outcome. Pathol Oncol Res 2006;12:108-10.
44. Sandmeier D, Lobrinus JA, Vial Y, et al. Bilateral Krukenberg tumor of the ovary during pregnancy. Eur J Gynaecol Oncol 2000;21:58-60.
45. Mendoza-Rosado F, Nunez-Isaac O, Espinosa-Marrón A, et al. Krukenberg tumor as an incidental finding in a full-term pregnancy: a case report. J Med Case Rep 2021;15:304.
46. Young RH. From krukenberg to today: the ever present problems posed by metastatic tumors in the ovary: part I. Historical perspective, general principles, mucinous tumors including the krukenberg tumor. Adv Anat Pathol 2006;13:205-27.
47. Kiyokawa T, Young RH, Scully RE. Krukenberg tumors of the ovary: a clinicopathologic analysis of 120 cases with emphasis on their variable pathologic manifestations. Am J Surg Pathol 2006;30:277-99.
48. Jacquet P, Jelinek JS, Steves MA, et al. Evaluation of computed tomography in patients with peritoneal carcinomatosis. Cancer 1993;72:1631-6.
49. Rahimi H, Moravvej H. Krukenberg Tumor Manifesting with Hirsutism and Acanthosis Nigricans as the Exclusive Presenting Symptoms. Iran J Public Health 2021;50:1504-8.
50. Zulfiqar M, Koen J, Nougaret S, et al. Krukenberg Tumors: Update on Imaging and Clinical Features. AJR Am J Roentgenol 2020;215:1020-9.
51. Shimizu H, Yamasaki M, Ohama K, et al. Characteristic ultrasonographic appearance of the Krukenberg tumor. J Clin Ultrasound 1990;18:697-703.
52. Roh SJ, Park SC, Choi J, et al. Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy With Mitomycin C Used for Colorectal Peritoneal Carcinomatosis. Ann Coloproctol 2020;36:22-9.
53. Sielezneff I, Salle E, Antoine K, et al. Simultaneous bilateral oophorectomy does not improve prognosis of postmenopausal women undergoing colorectal resection for cancer. Dis Colon Rectum 1997;40:1299-302.
54. Ajani JA, Rodriguez W, Bodoky G, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol 2010;28:1547-53.
55. Crăciun MI, Domşa I. Immunohistochemical diagnosis of Krukenberg tumors. Rom J Morphol Embryol 2017;58:845-9.
56. Chu PG, Weiss LM. Immunohistochemical characterization of signet-ring cell carcinomas of the stomach, breast, and colon. Am J Clin Pathol 2004;121:884-92.
57. Yang C, Sun L, Zhang L, et al. Diagnostic Utility of SATB2 in Metastatic Krukenberg Tumors of the Ovary: An Immunohistochemical Study of 70 Cases With Comparison to CDX2, CK7, CK20, Chromogranin, and Synaptophysin. Am J Surg Pathol 2018;42:160-71.
58. Chiesa-Vottero A. CDX2, SATB2, GATA3, TTF1, and PAX8 Immunohistochemistry in Krukenberg Tumors. Int J Gynecol Pathol 2020;39:170-7.
59. Nistor S, El-Tawab S, Wong F, et al. The clinicopathological characteristics and survival outcomes of primary expansile vs. infiltrative mucinous ovarian adenocarcinoma: a retrospective study sharing the experience of a tertiary centre. Transl Cancer Res 2023;12:2682-92.
60. Wang B, Sun K, Zou Y. Comparison of a Panel of Biomarkers Between Gastric Primary Cancer and the Paired Krukenberg Tumor. Appl Immunohistochem Mol Morphol 2017;25:639-44.
61. Nadauld LD, Garcia S, Natsoulis G, et al. Metastatic tumor evolution and organoid modeling implicate TGFBR2 as a cancer driver in diffuse gastric cancer. Genome Biol 2014;15:428.
62. Anwar J, Abdelhakeem A, Khan MS, et al. Survival Outcomes in Stage IV Gastric Cancer Patients with Krukenberg Tumors: A Systematic Review and Meta Analysis. J Gastrointest Cancer 2024;55:1004-25.
63. Granieri S, Bonomi A, Frassini S, et al. Prognostic impact of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) in gastric cancer patients: A meta-analysis of randomized controlled trials. Eur J Surg Oncol 2021;47:2757-67.
64. Lionetti R, De Luca M, Travaglino A, et al. Treatments and overall survival in patients with Krukenberg tumor. Arch Gynecol Obstet 2019;300:15-23.
65. Jeung YJ, Ok HJ, Kim WG, et al. Krukenberg tumors of gastric origin versus colorectal origin. Obstet Gynecol Sci 2015;58:32-9.
66. Ben Aziz M, Di Napoli R. Hyperthermic Intraperitoneal Chemotherapy [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing; 2023. Available online: https://www.ncbi.nlm.nih.gov/books/NBK570563/
67. Sugarbaker PH, Jablonski KA. Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive

surgery and intraperitoneal chemotherapy. Ann Surg 1995;221:124-32.
68. Quénet F, Elias D, Roca L, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:256-66.
69. Goéré D, Glehen O, Quenet F, et al. Second-look surgery plus hyperthermic intraperitoneal chemotherapy versus surveillance in patients at high risk of developing colorectal peritoneal metastases (PROPHYLOCHIP-PRODIGE 15): a randomised, phase 3 study. Lancet Oncol 2020;21:1147-54.
70. Benson AB. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer Version 3.2024 [Internet]. Nccn.org. 2024. Available online: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
71. Ajani JA. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Gastric Cancer Version 2.2024 [Internet]. Nccn.org. 2024. Available online: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

Cite this article as: Nistor SI, Soleymani majd H. Krukenberg tumours: which patients should be considered for surgery?—a narrative literature review. Transl Cancer Res 2024;13(10):5664-5677. doi: 10.21037/tcr-24-904