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Is a Surgical Approach Justified in Metachronous Krukenberg Tumor from Gastric Cancer? A Systematic Review

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Keywords
Krukenberg tumor · Gastric cancer · Overall survival

Summary
Background: The treatment of metachronous Krukenberg tumor (mKT) from gastric cancer remains unexplored. We performed a literature review to evaluate whether or not surgical treatment improves survival. **Methods:** A systematic review according to PRISMA guidelines was performed. Studies reporting on patients who underwent surgical treatment for mKT from gastric cancer were selected. Metachronous disease was divided as follows: confined to the ovaries, confined to the pelvis, or beyond the pelvis. Outcomes evaluated included overall survival (OS), progression-free survival (PFS), resection rate (R0), and factors predicting survival. **Results:** 13 retrospective reports fulfilled the selection criteria (512 patients). Most of the patients presented at a premenopausal age. The median presentation interval from gastrectomy ranged from 16 to 21.4 months. Median OS ranged between 9 and 36 months. 1-year OS ranged between 52.5 and 59%, and 3-years OS between 9.8 and 36.5%. Resection margin, peritoneal seeding, and chemotherapy regimen and cycles influenced survival. **Conclusion:** Surgical treatment and adjuvant chemotherapy in patients with mKT from gastric cancer seems to be associated with improved survival and is justified especially in young patients. Disease location and R0 resection should be considered when selecting patients.

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Introduction

Gastric cancer is the fourth most common malignancy and the second most common cause of cancer-related death worldwide [1]; furthermore, it has been reported that it is the most common primary malignancy causing metastasis to the ovaries [2–4]. Despite the name referring to gastrointestinal cancer metastatic to the ovaries, Krukenberg tumors (KT) are generally secondary to gastric cancer and are associated with poor prognosis. First described by Friedrich Ernst Krukenberg in 1896, a synchronous diagnosis of KT is considered as a stage IV presentation precluding treatment with curative intent and offering poor survival. Ovarian relapse after gastrectomy with curative intent is not rare and is one of the most common causes of treatment failure [5, 6]. The incidence of ovarian metastasis after curative resection of gastric cancer is approximately 0.3–6.7%, although some autopsy studies have reported incidence rates ranging from 33 to 41% [7, 8]. Nowadays, most of the reports concerning metachronous presentation of KT (mKT) focus on incidence and clinicopathologic findings, intermixing metastasis from various organs rather than analyzing the possibility of offering a survival benefit using different treatment modalities [9–11]. Furthermore, no separate analysis in the subgroup of patients with primary gastric cancer who underwent curative-intent gastrectomy is available. In this setting, the role of surgery in the management of mKT disease remains unexplored, with few articles reporting oncologic outcomes [12–14]. Furthermore, the role of chemotherapy in addition to surgical resection is unclear as well as regimens and modalities.

The aim of this systematic review was to evaluate the presenting features of mKT from gastric cancer and investigate whether or not a surgical approach with or without systemic treatment provides a survival benefit for these patients, pooling the evidence available in the literature.

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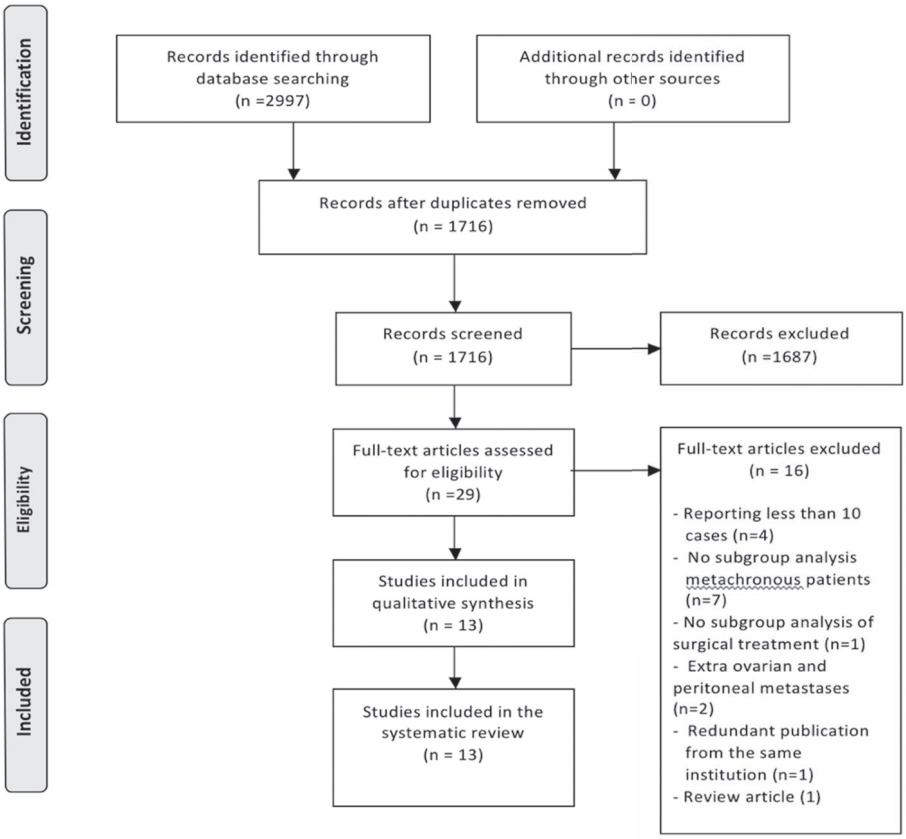

Fig. 1. Study selection.

Materials and Methods

Literature Search

The PRISMA statement guidelines for conducting and reporting systematic reviews were followed. The research protocol was registered with the International Prospective Register of Systematic Reviews (*www.crd.york.ac.uk/PROSPERO*; registration number: CRD 42017076010). A systematic literature search was independently performed by 2 authors (PA and GB) using PubMed, EMBASE, Scopus, and the Cochrane Library Central. The search was limited to studies in humans and written in English. No restrictions were set for the type of publication, date, or publication status. The search strategy was based on different combinations of words for each database. For the PubMed database, the following combination was used: *(Krukenberg) AND (gastric OR stomach) AND (cancer) AND (ovarian OR ovary) AND (metastases)*. The same key words were inserted in the search manager fields of Scopus, EMBASE, and the Cochrane Library Central (Appendix). Extensive crosschecking of the reference lists of all retrieved articles that fulfilled the inclusion criteria further broadened the search. For all databases, the last search was run on October 31, 2017.

Appendix (Search Strategy)

For the Scopus database, the following combination was used: *TITLE-ABS-KEY ('Krukenberg') AND TITLE-ABS-KEY ('gastric OR stomach') AND TITLE-ABS-KEY (cancer) AND TITLE-ABS-KEY (ovarian OR ovary) AND TITLE-ABS-KEY (metastases)*.

For the EMBASE search, the following combination was utilized: *('Krukenberg') AND ('gastric' OR 'stomach') AND ('cancer') AND ('ovarian' OR 'ovary') AND ('metastases')*.

For the Cochrane Library database, the following combination was used: *(Krukenberg) AND (gastric OR stomach) AND (cancer) AND (ovarian OR ovary) AND (metastases)*.

Study Selection

The same 2 authors independently screened the titles and abstracts of the primary studies that were identified in the electronic search. Duplicate studies were excluded. The following criteria were set for inclusion in this systematic review: i) studies reporting patients undergoing surgical treatment for mKT from gastric cancer; ii) studies reporting at least 1 perioperative or long-term outcome; iii) studies reporting outcomes of at least 10 patients; and iv) in the case of more than 1 report from the same center, only the most recent or the highest-quality study was included in the review. Every duplicate from the same institute was attentively screened; where applicable, a second report was included if evaluating a different patient population. The following exclusion criteria were set: i) original studies not reporting surgical treatment; ii) studies reporting only surgical treatment for synchronous metastases; iii) studies reporting only surgical treatment of patients with metastatic disease to solid organs other than uterus, ovaries, and peritoneum (namely liver, lungs, and bones); iv) original articles not reporting a separate analysis of patients undergoing surgical treatment for metachronous disease; v) review articles, letters, comments, and case reports; and vi) studies in which it was impossible to retrieve or calculate data of interest. Cohen's kappa statistic was used to quantify agreement between the investigators.

Data Extraction

The same 2 authors extracted the main data as follows: i) first author, year of publication, and study type; ii) number and characteristics of patients as well as disease-free interval (DFI) considering time from resection of gastric primary and diagnosis of metastases; iii) metachronous disease location divided as follows: confined to the ovaries, confined to the pelvis, and beyond the pelvis; iv) adjuvant treatment; and v) treatment outcomes including R0 resection rate, overall survival (OS), progression-free survival (PFS), and factors influencing survival. All relevant texts, tables, and figures were reviewed for data extraction, and whenever further information was required, the corresponding authors of the papers were contacted by e-mail. Discrepancies between the 2 reviewers were resolved by consensus discussion.

Risk of Bias

The Downs and Black checklist was used for the assessment of study quality [15].

Results

Study Selection

The literature search yielded 2,997 articles; after duplicate removal, 1,716 titles and abstracts were reviewed (fig. 1). Of these, 1,687 papers were excluded because of not addressing the topic of this review. Finally, 29 articles were selected for full-text review, and of these, 16 more were excluded: 4 because of reporting less than 10 cases [9, 10, 16, 17], 7 because of not dividing outcomes according to presentation of the disease (synchronous vs. metachronous) [11, 14, 18–22], 1 because of not dividing outcomes based on treatment (surgical vs. non-surgical) [23], 2 because of including patients with metastasis other than to the ovaries and peritoneum [24, 25], 1 review article [13], and 1 because of redundant series from the same institute [12]. Other papers from the same institute were attentively reviewed with the aim to include them if not reporting outcomes of patients already included in other articles. There was no disagreement regarding eligibility of full-text articles (Cohen's kappa = 1). Finally, a total of 13 articles dated between 2002 and 2017 fulfilled the selection criteria and were therefore included in this systematic review [7, 8, 26–36]; this pool of articles consisted of 13 retrospective reports. Characteristics of the included studies are summarized in table 1. The articles included a total of 512 adult patients who underwent surgical treatment for mKT from gastric cancer. The studies included were assessed for quality, and results are shown in table 2. Outcomes of interest for each single study are summarized in table 3.

Age at Presentation

Six of the included articles reported age at presentation and percentage of pre/postmenopausal patients [7, 26, 27, 31, 34, 36]. Most of the patients presented at a premenopausal age (range 44–48 years; percentage of premenopausal patients over the total: 59.1–76.5%).

Timing and Location of the Disease at Presentation

Six of the 12 included articles reported about the timing of presentation [7, 8, 26, 27, 31, 33], and 6 articles included the disease location [7, 8, 26, 27, 34, 36]. mKT from gastric cancer presented at a median time of 16–21.4 months according to the included studies. 26.4–50% the disease presented confined to the ovaries, 22.7–53% confined to the pelvis, and 0–50% beyond the pelvis but confined to the peritoneal cavity excluding solid organs.

Postoperative Chemotherapy

Six articles reported the percentage of patients undergoing systemic treatment after surgical therapy [7, 8, 26, 31, 34, 36]. 53–100% of patients underwent systemic adjuvant chemotherapy. Interestingly, 32 patients underwent intraoperative hyperthermic

Table 1. Characteristics of the included studies

First author (year)	Country	Study type	Study period	Patients, n	Age, years	Premenopausal, n (%)	DFI, months	Confined to the ovaries, n (%)	Confined to the pelvis, n (%)	Beyond the pelvis, n (%)	Adjuvant chemotherapy, n (%)	Score of study quality[d]
Kikkawa (2002)	Japan	retro	1989–1999	21	NR	NR	NR	NR	NR	NR	NR	10
Kobayashi (2003)	Japan	retro	1987–2000	14	NR	NR	NR	NR	NR	NR	NR	10
Cheong (2004)	Korea	retro	1987–2000	34	44 (24–66)[a]	26 (76.5)	17.5 (2–61)[a]	9 (26.4)	8 (23.5)	17 (50)	26 (76.5)	17
Jeong (2007)	Korea	retro	1992–2000	25	NR	NR	NR	NR	NR	NR	NR	15
Wang (2008)	China	retro	1986–2006	36	NR	NR	16.4 (3–78)[a]	NR	NR	NR	NR	11
Lee (2009)	Korea	retro	1996–2006	34	43.6 ± 10.2[b]	26 (76.5)	21.4 ± 24.5[b]	NR	NR	NR	34 (100)	8
Jun (2010)	Korea	retro	1981–2008	22	48 (24–78)[a]	13 (59.1)	16.5 (3–34)[a]	11 (50)	5 (22.7)	6 (27.3)	15 (68.2)	13
Peng (2013)	China	retro	1998–2011	64	NR	NR	NR	NR	NR	NR	NR	16
Feng (2013)	China	retro	1999–2011	63	45	42 (65.1)	16 (2–240)[a]	– (27)	NR	46 (73)	NR	8
Wu (2013)	China	retro	2000–2010	62	44 (19–71)[a]	NR	NR	30 (47)	32 (53)	0 (0)	32 (53)[c]	11
Yi Jo Jeung (2015)	Korea	retro	2001–2010	64	NR	NR	NR	NR	NR	NR	NR	13
Rosa (2016)	Italy	retro	1990–2012	33	NR	NR	15.9 (3–58)[a]	11(33.3)	15 (45.4)	7 (21.2)	22 (66.6)	12
Yu (2017)	China	retro	2005–2014	40	46.9 (31–62)[a]	NR	NR	NR	NR	11 (27.5)	40 (100)	11

[a]Median (range). [b]Mean ± standard deviation. [c]Patients underwent intraoperative hyperthermic chemotherapy. [d]According to the Downs and Black checklist.
Retro = retrospective; DFI = disease-free interval (from gastric surgery to diagnosis of metastases); NR = not reported.

Table 2. Study quality according to the Downs and Black checklist

First author (year)	Quality of reporting (max score = 10)	External validity (max score = 3)	Internal validity: bias (max score = 7)	Internal validity: confounding (max score = 7)	Power (max score = 5)	Total score (max score = 27)
Kikkawa (2002)	4	1	3	2	0	10
Kobayashi (2003)	5	1	3	1	0	10
Cheong (2004)	9	3	4	1	0	17
Jeong (2007)	7	3	3	2	0	15
Wang (2008)	6	2	3	2	0	11
Lee (2009)	4	1	2	1	0	8
Jun (2010)	6	3	3	1	0	13
Peng (2013)	8	3	4	1	0	16
Feng (2013)	3	3	1	1	0	8
Wu (2013)	6	2	2	1	0	11
Yi Jo Jeung (2015)	6	2	4	1	0	13
Rosa (2016)	5	3	3	1	0	12
Yu (2017)	3	3	2	3	0	11

Table 3. Primary outcomes of each included study

First author (year)	Patients, n	R0 resection, n (%)	Overall survival	Progression-free survival	Predictors of survival
Kikkawa (2002)	21	NR	11.4[a]	NR	NR
Kobayashi (2003)	14	NR	12.5[a]	NR	NR
Cheong (2004)	34	17 (50)	11 (8–14)[a]	7 (4–10)[a]	R0 resection
Jeong (2007)	25	NR	20[a]	NR	peritoneal seeding
Wang (2008)	36	NR	13.6[a]; 1y 59%, 2y 13%	NR	treatment modality[b], chemotherapy cycles[c]
Lee (2009)	34	NR	9[a]; 3y 36.5%, 5y 5.2%	NR	NR
Jun (2010)	22	14 (63.6)	18.8 (2–59)[a]; 3y 15.8%	NR	R0 resection
Peng (2013)	64	NR	17[a]	NR	NR
Feng (2013)	63	NR	13.6[a]; 1y 52.5%, 2y 22%, 3y 9.8%	NR	peritoneal seeding
Wu (2013)	64	NR	12.9[a]	NR	chemotherapy, PCI
Yi Jo Jeung (2015)	64	NR	30[a]	NR	NR
Rosa (2016)	16	21 (63.6)	36[a]	NR	NR
Yu (2017)	40	NR	21.7 (17.6–25.9)[a]	NR	NR

[a]Data expressed as median (range), months. [b]Surgery alone versus surgery + chemo-radiotherapy. [c]≤ 4 cycles versus > 4 cycles. PCI = Peritoneal carcinomatosis index; NR = not reported; y = year.

chemotherapy (HIPEC) [34]. Chemotherapy protocols differed between studies: most of the centers used 5-fluorouracil chemotherapy protocols [7, 8, 26, 31, 34]; taxane- and cisplatin-based therapies were also reported [7, 8]. In 1 study, paclitaxel and S-1 chemotherapy (tegafur/gimeracil/oteracil) were proposed [36].

Margins

Three studies reported the percentage of patients having clear margins after surgical treatment at a range of 50–63.6% [7, 8, 26].

OS, PFS, and Predictive Factors

All included studies reported oncologic outcomes of the studies cohorts. Median OS ranged between 9 and 36 months. 1-year OS ranged between 52.5 and 59%, 2-year OS between 13 and 22%, and 3-year OS between 9.8 and 36.5%. Only 1 study reported a 5-years OS rate of 5.2%. Cheong et al. [26] reported a median PFS of 7 (4–10) months.

Two studies reported that achievement of an R0 resection was a strong predictor of better survival [26, 31]. Also 2 studies reported that peritoneal seeding was a predictor of worse survival [27, 28]. Postoperative treatment with chemotherapy and the number of cycles were strongly associated with prognosis based on the results of 2 studies [33, 34]. Finally, Wu et al. [34] described that the peritoneal carcinomatosis index (PCI) was a predictor of OS in their study.

Discussion

Metastatic gastric tumors have a poor prognosis since only 4% of patients are alive after 5 years. In 1999, McGill et al. [10] re-

ported an overall incidence of KT in female patients with gastric cancer of 0.9%, which rose to 18.2% in premenopausal women, with an average survival of 12.3 months. The National Comprehensive Cancer Network (NCCN) does not distinguish KT originating from the stomach from other types of recurrences, but the overall survival of KT-oligometastatic patients might be different depending on the histopathology of the primary; for KT of colorectal origin for example, a survival improvement due to surgical treatment has been established [9, 11, 19]. Conversely, whether surgery has a role in the treatment of KT of gastric origin, is still being debated. In our review, patients presenting with metachronous KT from gastric cancer were young (median age ranging from 43 to 48 years) and mostly presenting with premenopausal status (59.1–76.5%). When the surgeon is faced with a young patient presenting with a very aggressive and potentially fatal disease, clinical decision-making is always hard; it is difficult to tell a young woman of fertile age that no surgical therapy is available for her disease, especially when there is no clear evidence to support this decision. The importance of identifying patients that could benefit from aggressive treatment protocols is a crucial step when facing mKT from gastric cancer since it is easier for young patients to withstand more complex surgical procedures and intensive chemotherapy regimens [37]. Survival results suggest a benefit of aggressive surgery in young patients. Furthermore, this review underlines how the improvement in survival rates is closely linked to advances in chemotherapy and surgical protocols. When comparing patients undergoing surgical treatment alone to patients undergoing chemotherapy alone, increased survival was seen among the surgical patients. Furthermore, chemotherapy regimen and number of cycles were shown to be independently linked with prognosis [33]. This suggests that it is mandatory to couple surgical treatment with systemic therapy in order to prolong patients' survival. It is reasonable to believe that HIPEC could improve and strengthen the outcome of surgery and thus be directly linked to survival. In this review, however, the number of patients undergoing HIPEC was n = 34, too small to ascertain its effect, which was also not the purposes of this study. Furthermore, this kind of treatment is generally only performed in patients with peritoneal involvement, which per se is a poor prognostic indicator as shown in this review. Nonetheless, tumor biology still remains fundamental in determining outcome. This becomes clear when analyzing the unpredictable and heterogeneous sites of disease that ranged from the ovaries to the peritoneal cavity. Localized disease, rather than a disseminated presentation in the peritoneal cavity, is strongly associated with survival as shown in this review. An important negative prognostic factor was found to be residual disease after surgical intervention. This is important because it highlights that surgery should be radical rather than cytoreductive in order to obtain long-term survival. Furthermore, residual disease is obviously linked to recurrence, although, in this review, only 1 of the included studies considered PFS as an endpoint. Aggressive surgical treatment with complete resection leaving no gross disease seems to be difficult to obtain given the low and very variable percentages of R0 resections in this systematic review. This raises the question whether it is really the right choice to proceed with an intervention when no certainty of negative margins can be anticipated, especially in patients with peritoneal disease. In this setting, once again tumor biology is the crucial factor; besides correct and detailed preoperative staging, the identification of molecular markers able to identify different progression patterns and possibly different responses to treatment could be a powerful tool to improve patient selection. An important finding of this review was the time interval between curative-intent gastrectomy and metachronous disease presentation: Almost all of the patients presented within 2 years of gastrectomy, indicating that follow-up after surgery of the primary should be intense and comprehensive and include the possibility of pelvic disease sites. Furthermore, the question of delayed presentation of synchronous disease rather than early presentation of metachronous disease should be raised, as this could completely change the management of these patients following the principle of tumor biology as already mentioned. This study, as all systematic reviews on such a specific and poorly studied topic, suffers from some bias: first, most of the included studies were from Asian centers where guidelines, surgical approaches, chemotherapy regimens, and histopathologic workup are very different from those in Western countries. Second, all patients with surgical interventions were selected by oncologists, causing uncertainty in surgical indications and frequency of presentation. Furthermore, all the included studies were retrospective in nature thus carrying an intrinsic risk of selection bias, cohorts were small, and the studies were performed over a long period of time (2002–2016) with possible heterogeneity linked to changes in clinical practice, technology, and surgical and chemotherapy protocols. Changes in adjuvant chemotherapy practice over time in fact may have introduced some selection bias, with patients treated most recently showing better oncologic outcomes due to more effective protocols.

In conclusion, surgical treatment with adjuvant chemotherapy in patients presenting with metachronous KT from gastric cancer is associated with improved survival and is justified especially in young patients provided radical tumor-free resection is feasible. When considering such an approach, disease limited to the pelvis and the possibility to achieve negative margins should be considered as selection criteria in order to improve outcomes.

Disclosure Statement

The authors have nothing to disclose and declare no conflict of interest.

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