

Krukenberg tumors. Prognostic factors, surgical treatment and survival benefit. A literature review

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Abstract

The Krukenberg tumor (KT) represents a metastatic lesion to the ovary from a primary gastrointestinal tumor (GI) most frequently the stomach being the site from which the malignant cells disseminate to the ovaries. KT are generally bilateral metastatic ovarian tumors which are associated with a low overall survival rate and a poor prognosis. Usually, it develops in women at the age of 40-50 years. The purpose of this article is to review the prognostic factors for KT, the surgical treatment and its impact on survival in women with KT of the ovary. A Pubmed database search for English language articles using key words (e.g. "ovarian cancer"; "Krukenberg tumors"; "treatment"; "surgery") has been conducted. Systematic reviews, retrospective studies, controlled and randomized clinical trials were selected if the research subjects were treated with surgery. Detection of a unilateral KT, the absence of any other metastases, the primary tumor originating in the colon or rectum as well as the identification of the primary GI tumor during the resection of the KT have been recognized as favourable prognostic factors associated with the postoperative evolution of women diagnosed with KT. A complete resection of the KT (negative margins, R0) improves the overall survival rate especially in women with colorectal cancer and no other medical or surgical comorbidities. In women with gastric cancer and metachronous KT, the absence of any other distant visceral metastases represents an indication for the complete resection of the KT. Women with primary gastric cancer and KT's have generally a poor prognostic.

Keywords: ovarian cancer, Krukenberg tumor, surgery, survival

Introduction

The Krukenberg tumor (KT) is an uncommon type of metastatic ovarian cancer (OC)^(1,2) which has been initially described by Friedrich Ernst Krukenberg in 1896⁽³⁾. About 6 years later, Schlagenhauser⁽⁴⁾ showed that the KT's represent in fact metastases from another primary malignant tumor which originates in the gastrointestinal tract (GI), either gastric or colorectal cancers⁽⁵⁾. The incidence of the KT varies between 0.7% and 6.7%⁽⁶⁾.

KTs represent almost 40%-50% of all the metastases to the ovaries from other primary tumors with a poor prognosis and a high rate of recurrences⁽⁷⁾. Owing to its low incidence and the absence of studies on the treatment and prognostic of the KT's, nowadays data regarding the prognostic factors and the optimal treatment of women with KT as well as the impact of surgery and chemotherapy on the prognosis are lacking^(8,9). The existing studies have shown that a limited extent of the disease (i.e. metastases identified only on one of the ovaries), a complete resection (R0) of the KT as well as the identification of a colorectal malignant tumor as the primary site of dissemination to the ovaries are the factors associated with a better prognosis and an improved overall survival (OS) rate^(9,10). With regard to the adjuvant treatment of the KT, the prognostic value of the postoperative chemotherapy and its impact on the survival have not been yet confirmed⁽¹¹⁻¹⁴⁾.

However, a better 5-year survival rate after the adjuvant chemotherapy has been observed in women with well or moderately differentiated tumors in whom a complete resection of the KT (R0) has been achieved^(15,16,17).

Tumor dissemination from a primary malignant gastric tumor develops mainly through direct extension⁽¹⁸⁾. It has been reported that approximately 10% of women with gastric cancer is diagnosed with a KT of the ovary, the failure of the identification or the incomplete resection of the KT being responsible for the appearance of distant recurrences^(15,19). A hematogenous route of dissemination to the ovaries is encountered in women with primary advanced colon cancer which also involves the mesenteric lymph nodes⁽²⁰⁾.

Studies reporting the effects of the surgical treatment of the KT originating either from gastric either from colon cancer are still inconclusive in order to establish the optimal management of the KT. Cheong et al.^(9,13) analyzed a series of 54 patients who developed KT after a curative gastric resection for stomach cancer and showed that patients who developed metachronous KT's after the primary gastric tumor resection had the longest median survival. However, even after a curative resection and despite the radical resections, some patients develop recurrences that often impair surgery, consequently having a poor prognosis⁽²¹⁾. R1 resections owing to a high extent

of the KT, a poor tolerance of the patient for surgery, and a high peri- and intra-operative morbidity rate are the most frequent variables that often discourage the surgeon to attempt the complete radical resection when KT are diagnosed pre-operatively⁽²²⁾.

The purpose of this article was to review the prognostic factors for KT originating from primary GI tumors as well as the assessment of the outcomes and survival benefit of the surgical management of patients with KT of different origins.

Major prognostic factors

Firstly, we will consider the impact of the adjuvant chemotherapy on the survival outcome. The majority of the studies investigating the prognostic value of the adjuvant chemotherapy in the treatment included only women who were submitted to primary resection of the GI cancer and have metachronously developed ovarian metastasis. The results were of poor relevance, the overall conclusion being that adjuvant chemotherapy does not impact the OS rate and the prognosis^(23,24). On the other hand, the study of Lu et al.⁽²⁵⁾ included 44 women with KT who initially presented with gynecological complaints. After the complete resection of the KT, 32 patients underwent adjuvant chemotherapy while the remaining 12 have remained under observation without receiving chemotherapy. The adjuvant chemotherapy consisted of four to six consecutive cycles of chemotherapy with 5-fluorouracil and cisplatin or paclitaxel plus carboplatin. After finalizing this aggressive chemotherapeutic regimen it has been observed that the group of 32 women had over four times longer median survival than the group of 12 women who did not receive any chemotherapy (20.4 months versus 4.7 months). Moreover, the follow of a non-aggressive chemotherapy (the same regimen but less than 4 cycles has resulted in a 1.5 times longer median survival (7.5 months versus 4.7 months) than patients who remained under observation. When it comes to the survival outcomes of the group which had aggressive chemotherapy versus the group who received non-aggressive chemotherapy, an intensive chemotherapeutic treatment resulted in a longer median survival rate (20.4 months versus 7.5 months), hence suggesting that aggressive intravenous chemotherapy after optimal cytoreductive surgery improves the median overall survival.

The reported factors that negatively impact the OS rate and the prognosis have been described in the same study and include: bilateral ovarian mass, failure to resect primary GI tumors, presence of residuals metastatic lesions, and GI cancer diagnosed prior to metastatic ovarian cancer. These are in concordance with anterior reports focusing on the evolution course of women with KTs⁽²⁶⁾.

Another aspect that requires attention refers to the sequence of the surgical treatment of the KT respectively the first cancer-related surgery or the gynecological surgery.

It has been stated that women who were diagnosed with KT after the primary GI tumor resection may have had a more aggressive tumor, and hence a poor prognosis

in comparison to those patients who presented metastatic OC prior to or synchronously with the metastatic GI tumor, and who proved to have longer survival rates (median survival of 18.0 versus 10.1 months)^(26,27). However, if survival is considered after gynecological surgery, the beneficial effect of chemotherapy is null because of a significant difference found in survival between patients who have been previously diagnosed with GI tumors (i.e. presumably, they had already lived for some time) and those diagnosed after or synchronously during the surgical treatment.

Surgical treatment of KT. Outcomes and impact in survival

Generally, as stated in other studies, the prognosis of the KT is considered to be poor compared to that of women with primary OC⁽²⁸⁾. In the report of Jiang et al.⁽¹²⁾, the 5-year survival rate after the KT resection was approximately 12.1%. A lower rate has been registered in the study conducted by Webb and coworkers⁽²⁹⁾ who obtained a 5-year survival rate of 5.4% in patients with metastatic ovarian tumors that came from the GI tract. As mentioned above, one of the prognostic factors of the KTs is the achievement of a complete resection of the tumor. In this respect, the role and prognostic significance of the complete resection (R0) of the KT has been presented in the same study conducted by Jiang and his coworkers⁽¹²⁾. Thus, it has been confirmed a statistically significant advantage for patients with microscopic residual disease (RD) after metastasectomy compared to those with macroscopic RD, the 5-year survival rates being 23.4% and 0%, respectively. Furthermore, another confirmation of the suitability of the complete resection which originates in a gastric malignant tumor has been presented by Cheong et al. in a report published in 2004⁽¹³⁾. A radical R0-metastasectomy has been associated with a median survival of 18 months compared to a median overall survival of 9 months when a suboptimal resection (R1) has been performed. Other similar results have been reported in other published studies^(8,9,10,13,27), hence being acknowledged that a complete metastasectomy represents the optimal treatment option which can improve the OS rate as well as the life quality of women with KT.

Another feature that impacts the clinical outcome of the patients with ovarian metastatic carcinoma is the primary site of the KT, the prognosis of patients with primary tumor in the stomach being poorer than those with colorectal or breast cancer⁽²⁸⁾. The statement is based on the hypothesis that a gastric cancer patient has usually a lower performance status (i.e. Karnofsky performance status score), serious anaemia, and generally a worse prognosis than those with advanced colorectal or breast cancer.

Complete cytoreductive surgery (CS) leaving no gross RD combined with intraperitoneal chemotherapy as treatment for KT play an essential role in improving the survival time of patients with advanced gastric cancer^(9,29). However, in the same studies it has been observed that the drug delivery method- intraperitoneal versus intravenous

chemotherapy has no impact on the survival outcome, the achievement of an intraoperative complete resection of the metastasis being the most significant prognostic factor of the OS rate.

Returning to the importance of the sequence of operation, it has been assumed that the diagnosis of an ovarian metastasis means that the primary gastric cancer is in an advanced stage which is generally characterized by severe anemia, coagulation dysfunction, and cachexia which generally represent contraindications to primary surgery, hence implying a poorer prognosis of the disease. On the other hand, other studies have reported no statistically significant difference in the OS rate between patients who received metastasectomy synchronously and those with metachronously resected KT^(12,30,31). For example, Cheong et al.^(9,12) have obtained better survival rates for patients with metachronous KTs and no other distant metastases in whom a complete R0 resection has been performed: 30.7 months versus 10.6 months respectively for patients with extensive metastases. On the basis of these results, the performance of a metastasectomy for KT in the absence of other distant metastatic disease appear to be save and associated with a relative good median survival.

As regarded the extent of the KT, as stated above, a single tumor limited to one of the ovaries can be easier

resected and is correlated with a better survival outcome compared with bilateral tumors with multiple and diffuse spreads^(10,11,12,28).

Prophylactic oophorectomy in premenopausal and postmenopausal women at the time of GI cancer surgery has been brought into attention in recent years⁽¹⁰⁾, but apparently, the majority of women with GI cancer would not have KT. This may account as explanation why no guidelines are available so far concerning prophylactic oophorectomy in these women.

Conclusions

Optimal CS followed by aggressive chemotherapy may improve survival in KT patients, particularly in those with good performance. The recognized favorable prognostic factors refer to unilateral ovarian mass, complete resection of the primary tumor, and the absence of metastatic disease.

Metastasectomy may play a critical role in the management of KT in selected patients. However, prognosis is still pessimistic, particularly, in patients with KT from gastric cancer. Therefore, the extent of disease, feasibility of leaving no gross RD as well as the selection of the potential candidates for surgery must be carefully evaluated preoperatively. ■

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