

Krukenberg Tumor: A Review of Prognostic Factors and Management

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Received date: September 28, 2020; **Accepted date:** October 10, 2020; **Published date:** October 17, 2020

Citation: Bocanegra MV, Ortiz Sanchez AC, Vásquez JA, et al. (2020) Krukenberg Tumor: A Review of Prognostic Factors and Management. *Onco Tum Res* 1(1): pp. 1-4.

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ABSTRACT

Aim: This review aims to summarize current evidence on Krukenberg Tumors (KT), addressing the main prognostic determinants and its management.

Background: Krukenberg Tumors are rare metastatic tumors of the ovary. They were initially described by Friederich Ernst Krukenberg in 1896. They arise from extra-ovarian primary signet-ring cell carcinomas, being the gastrointestinal tract the most common site of origin. The most common clinical presentation of KT is an abdominal mass or discomfort in a premenopausal 40 to 50 year old woman. The prognosis is extremely poor compared to primary ovarian cancer.

Results: Overall survival may vary significantly according to the choice and timing of treatment. The effective treatment strategies for KT are still controversial. However, therapeutic options include surgical resection as the mainstay of treatment when possible and the application of different Chemotherapy (CT) regimens.

Conclusions: Several factors negatively affect prognosis: an incomplete metastasectomy, extensive disease at diagnosis and the origin of the tumor are the main factors that most authors agree incur in a worse prognosis. KT's optimal therapeutic strategies are still a matter of debate, raising the need for more studies to achieve consensus.

Keywords:

Krukenberg Tumor, Prognostic factors, Management, Colorectal cancer, Gastric cancer

Abbreviations:

KT: Krukenbert Tumor; OS: Overall Survival; HIPEC: Hyperthermic Intraperitoneal Chemotherapy; CRS: Cytoreductive Surgery; CK7: Cytokeratin 7; CK20: Cytokeratin 20; CT: Chemotherapy; CA-125: Cancer Antigen 125, CEA: Carcinoembryonic Antigen, ER: Estrogen Receptor; PR: Progesterone Receptor; PDL1: Programmed Death-Ligand 1, ECOG: Eastern Cooperative Oncology Group; KPS: Karnofsky Performance Status; SRC: Signet-Ring Cells; 5-FU: 5-Fluorouracil; PAS: Periodic Acid-Schiff; FOLFIRI: Leucovorin Calcium, Fluorouracil, Irinotecan Hydrochloride.

Introduction

Krukenberg tumors (KT) are rare metastatic tumors of the ovary secondary to signet-ring cell carcinomas. They were initially described by Friederich Ernst Krukenberg in 1896 [1,2]. They arise from primary signet-ring cell carcinomas, being the gastrointestinal tract the most common site of origin. It is unclear why some primary tumor sites are more likely to metastasize to the ovaries than others. The most common clinical presentation of KT is an abdominal mass or discomfort in a 40 to 50-year-old in a premenopausal state. The prognosis is extremely poor compared to primary ovarian cancer because of its aggressiveness, diagnostic difficulties, and poor response to current treatment [3,4]. Due to the low incidence of the disease, there isn't a consensus on the adequate management of these tumors, and therefore there aren't many effective measures to

increase overall survival in these patients.

Background

Metastatic ovarian malignancies account for 5-30% of all ovarian malignancies, while KT represents 1-2% [4-7]. KTs generally occur in premenopausal women, with the mean age of diagnosis from 40 to 45 years, and 35-45% being under 40 years of age [2,8]. The presentation may occur before the diagnosis of the primary tumor (synchronous metastases) in 1.3-10% of cases, or after resection of the primary tumor (metachronous metastases) in 1.3%-2.4% [2,3,9,10]. However, the incidence rate on autopsy results ranges from 33-44% in females with gastric cancer [11-13].

KT arises mainly from the gastrointestinal tract. The most common location is gastric (76%), followed by colorectal tract (11%), breast (4%), gallbladder (3%), appendix (3%), and other organs such as pancreas, uterus, urinary bladder, and renal pelvis (15%) [2,8,14-16]. There is variability between countries, some authors report gastric or colorectal cancer as the main origin of KT depending on the incidence of each cancer in their region [7,16,17]. Most of KTs present bilaterally (72-83%); unilateral presentation is seen more frequently in colorectal origin, being the right ovary the most commonly affected [2,18].

Some patients may remain asymptomatic. When symptoms are present, patients exhibit palpable abdominal mass, lower abdominal discomfort, abdominal or pelvic pain, dyspareunia, weight loss or bloating, and abdominal distension due to ascites [18,19]. There may be a hormonal imbalance that can result in menstrual cycle changes, hirsutism, virilization, and vaginal bleeding [18]. Other findings include anemia and non-specific

coagulation disorders [3].

The diagnostic criteria of KT were initially described by Novak and Gray and include ovarian neoplasm with signet-ring cells producing mucin accounting for more than 10% of the tumor's total volume and sarcomatoid proliferation of the ovarian stroma [5,10,18,20–22].

In ultrasonography, KT are homogeneously hyperechoic and exhibits the “lead vessel sign” which consists of a large vessel penetrating the tumor from the periphery and then branching in a tree pattern. Computed tomography shows solid, lobulated tumors with homogeneous enhancement [18,23].

The precise diagnosis of secondary ovarian tumors is frequently challenging as they can be misdiagnosed as primary ovarian cancer, especially in the case of mucinous adenocarcinomas, which represent the most common metastases in the ovary, accounting for 46.7% of them [7]. The distinction of the latter is very important because it requires a different treatment [6].

In many cases, especially in KTs tumors of unknown origin, traditional diagnostic methods are insufficient, requiring immunohistochemistry analysis for identifying the origin of metastatic tumors. For KT, the predominant immunohistochemical profile was CEA(+), CA125(-). The CK7/CK20 profile varied depending on the histological origin of the KTs: gastric origin present CK7(-), CK20(-); colorectal CK7(-), CK20(+); and breast CK7(+), CK20(-) (24,25). Therefore, CK7/CK20 may have a key role in identifying the primary tumor in patients with KTs of unknown origin. Also, there is evidence that signet-ring cells of KT are positive for Periodic Acid-Schiff (PAS), cytokeratins, and negative for vimentin [26].

Due to the unspecific clinical presentation and broad differential diagnosis, the clinician needs to be aware of the possibility of this tumor to make an early diagnosis and thus a higher postsurgical survival rate [27].

Materials and Methods

Clinical Key, Google Scholar, and PUBMED were searched up to September 2020 to identify English or Spanish-language publications of Krukenberg tumor's prognosis and treatment. Search terms included “Krukenberg tumor”, “immunohistochemistry”, “prognosis”, “treatment”, “management”, “colorectal cancer”, “gastric cancer”, “gastrointestinal cancer”, “overall survival”, “synchronous vs metachronous”, “ovarian metastases” and “chemotherapy”. Articles were screened by their title and abstract and selected for full-text review by the authors. Additional literature was searched through cross-referencing using the retrieved articles. The final reference list was generated based on the relevance of this review. Given the rarity of the Krukenberg tumor, no limits were placed on study methodology.

Prognosis

Throughout history, KT has been a very sombre diagnosis with a very poor prognosis. The estimated 5-year survival is 12.1% [3]. OS varies depending on several factors, but literature has described the median OS of 9 months, 12.4 months, 13.6 months. [11,14,28]. Factors that may influence KT prognosis include:

Primary site origin: the median survival for gastric origin is 13 months, colon 29.6 months, rectum 48.2 months, and other

locations 19.5 months [3,17].

Size: patients with KT <5 cm had longer OS because they were more likely to be treated by metastasectomy and R0 resection, whereas larger metastases indicated longer disease progression and loss of the opportunity for early treatment [8]. Despite these results, other authors have not found any association between the size >5cm or >10 cm and the OS [11,27,29,30].

Age/Menopausal state: both age above 50 years at diagnosis and the menopausal status have been assessed in several studies, but do not appear to have a significant impact on the probability of survival [3,11,27,29].

Functional scales: the functional status has proven to be useful in many studies regarding cancer patients. Patients with KT who present with ECOG 2 to 3, had worse tolerance for aggressive treatment, showing worse outcomes. Patients with ECOG 0 to 1 had a longer OS [8]. Lower KPS scores were also associated with decreased survival [3,11].

Chronology: it has been described that patients with metachronous metastasis had longer OS than those with synchronous metastasis [8,17,27], but other evidence contradicts this fact [3,5,29,32].

Ascites: it has been associated as an independent risk factor for poor survival [12,17,29,33]. One study has found a direct association between massive intraoperative ascites (>1000 mL) and unfavorable OS [34].

Extraovarian involvement: disease confined to the ovaries has a median survival of 30.7 months compared to 17 months when confined to the pelvis, and 9 months when it extends beyond the pelvic cavity with extensive metastases [3,19]. However, some other studies have found extra ovarian metastases not significantly associated with worse OS [25]. Other factors associated with poor prognosis include metastatic peritoneal seeding, vascular tumor emboli, and lymphovascular involvement [3,11,28].

Serum markers (CA 125, CAE, ER, PR): elevated serum CEA levels appear as an unfavorable prognostic factor in KT [29]. The expression of ER-B and PR have shown to be independent risk factors of prognosis, as increased levels are associated with better survival. Increased levels of CA 19-9 show mixed results, as they have been significantly associated with poor prognosis in some studies and with no association in others [12,29]. CA 125 is not significantly associated with OS, even though literature has described that in the scenario of diagnosis of a diffuse gastric adenocarcinoma or any other tumor that may metastasize, levels of CA 125 may be used as screening for early detection of ovarian metastases, including KTs [11,27,29]. In patients with tumor progression the CA 125 levels increased before clinical signs of progression with a median lead time of 97 days [35]. Also, it has proven to be useful in the monitoring of the progression of the disease [11,27,36,37].

PD-L1: the expression of PD-L1 in gastric cancer metastasis has a poor prognosis. PD-L1 expression in colorectal malignancy is associated with an improved prognosis compared to the negative PD-L1 expression [14].

Surgical margin: complete resection of the tumor is one of the most important prognostic factors, as it has shown statistical significance for improved survival in multiple studies. Complete gross resection after metastasectomy has better

results compared to those with the gross residual disease with a median of survival of 18 and 9 months respectively [3,19].

Metastasectomy: complete metastasectomy has a median survival of 29.6 months compared to 10 months in those patients with residual disease after surgery [3].

Results

Overall survival may vary significantly according to the choice and timing of treatment. The effective treatment strategies for KT are still controversial. However, therapeutic options include surgical resection as the mainstay of treatment when possible and the application of different Chemotherapy (CT) regimens.

Surgery is considered by multiple authors as the treatment of choice to maximize survival and quality of life [3,5,17,19,27,30,38,39]. Metastasectomy is associated with improved survival in patients with KT from gastric cancer and more aggressive surgical intervention may be offered for the patients with disease confined to the pelvis (8,19,31). Cytoreductive Surgery (CRS) has proven to be effective in lengthening the OS compared to the absence of such treatment. Furthermore, radical CRS in the absence of residual disease (RO CRS) is related to a significant improvement in OS [4]. Palliative surgery may be offered for all patients with symptomatic disease.

Adjuvant CT choice varies depending on patients' functional status and stage of disease [8]. Regimens for KT of varied origins may include 5-fluorouracil (5-Fu) plus cisplatin, taxanes plus platinum with or without 5-Fu, oxaliplatin plus folic acid plus 5-Fu, and 5-Fu in monotherapy [3,28]. For colorectal cancer origin, CT with FOLFIRI regimen has been used (40). Metastasectomy plus CT offers superior OS when compared to CT alone in gastric cancer with KT regardless of cancer stage [5,11,13,32,41]. In some studies, adjuvant CT failed to be of benefit in prognosis; the adverse effects and lower performance status limit CT treatment for some patients [3,5,27].

Few studies are assessing HIPEC as an alternative to CT, but it has proven to be at least as effective as the latter with the advantage of inducing fewer adverse effects. Therefore, it might be a better option than CT when RO CRS is not achieved [4,5,27].

Conclusion

Differentiating between a primary ovarian malignancy and a metastatic malignancy to the ovary is challenging but fundamental due to the differences in prognosis and the overall management of these disease entities. All authors coincide that factors associated with poor overall prognosis include incomplete metastasectomy (R1 or R2) and the extent and origin of the tumor. KT's optimal therapeutic strategies are still a matter of debate, raising the need for studies to achieve consensus on recommended standardized management and improvement of overall survival for these patients. However, such studies are unlikely because of the rarity of the tumor.

Acknowledgments

None.

Conflict of interests

The authors declare no potential conflicts of interest related to the publication of this review.

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