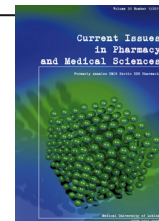


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OPEN**Current Issues in Pharmacy and Medical Sciences**

Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA, SECTIO DDD, PHARMACIA

journal homepage: <http://www.curiipms.umlub.pl/>

Surgical treatment of gastric carcinoma with ovarian metastases

TOMASZ OLESINSKI

Maria Skłodowska-Curie Institute – Oncology Center, W. K. Roentgena 5, 02-781 Warsaw, Poland

ARTICLE INFO

Received 24 October 2017
Accepted 29 December 2017

Keywords:

Krukenberg tumor,
gastric cancer.

ABSTRACT

Ovarian metastases from extragenital neoplasms are rare. The prevalent sites of the primary tumors were the breast, colorectum and the stomach. The Krukenberg tumor (KT) is defined as a gastrointestinal cancer which metastasized to the ovaries. Metastasis to the ovary may appear at the time of diagnosis of the primary tumor (synchronous) or during observation (metachronous). Common clinical presentations are abdominal distention, pain, palpable mass, bloating, ascites or pain during sexual intercourse. Diagnosis can be made by ultrasound examinations, CT or EMR scans, laparotomy and/or a biopsy of the ovary. The current standard treatment for patients with metastatic gastric cancer is systemic chemotherapy, however, treatment strategy for KTs from gastric cancer has not been clearly established and surgical treatment is considered mainly for metachronous tumors. The prognosis of patients with ovarian metastasis of gastric cancer origin is poorer compared with that of other primary tumors. Although the results of cytoreductive surgery – especially in combination with modern chemotherapy – seems to be promising, the optimal therapeutic strategies for such patients requires further prospective studies.

INTRODUCTION

For many years, incidences of gastric cancer (GC) have been decreasing, but this malignancy remains the fourth most commonly diagnosed solid tumor and the second leading cause of cancer deaths worldwide [1]. Surgery is the main therapeutic option, but the efficacy of surgical treatment may be limited due to the risk of peritoneal dissemination of cancer cells seeded from the primary tumor, especially in the case of deep invasion of the gastric wall [2]. An accurate preoperative staging is necessary in order to identify patients with increased risk of intraperitoneal spread, ovarian metastases and recurrence. This allows the implementation of appropriate preventive measures, such as hyperthermic intraperitoneal chemotherapy (HIPEC) [3].

Ovarian metastases from extragenital neoplasms are rare. An analysis of 325 patients with metastasis to the female genital tract [4] reported 149 (45.8%) cases with extragenital origin. Common sites of the primary tumors were the breast, colorectum and the stomach. Similar localization of primary tumors is confirmed by the work of other Western authors [5-7]. In Asia, where stomach cancer occurs nearly 10 times more often, GC remains the most common primary

site [8,9]. The Krukenberg tumor (KT) is defined as a gastrointestinal cancer which metastasized to the ovaries. For unknown reasons, most often, metastasis to the ovaries originate from GC than the colorectal cancer. KTs occur in 0.3–6.7% of all the operated upon GC patients [5,6], and its incidence is much higher in the autopsies (33–41%). This may have an impact on the difference in the metastatic pathways from the primary site.

Potential routes for ovarian metastasis from GC include hematogenous spread, lymphatic spread and surface implantation [10]. With regard to the aforementioned, microscopic examination of KT shows that the rate of lymphatic pathway from the stomach was significantly higher than that from the colon. Several authors also have indicated that the rate of intravascular metastasis to the ovary from the colorectum is higher than that from the stomach [10]. A multifactorial analysis of 690 female gastric cancer patients shows that the incidence of ovarian metastasis from GC is closely associated with the extent of lymph node involvement [11] and increases especially in cases of metastasis to more than 6 lymph nodes [12].

Ovarian metastases from GC tend to be bilateral rather than unilateral [12,13] and predominantly solid [14]. It has also been reported that ovarian metastases from GC are more

* Corresponding author
e-mail: tolesinski@coi.waw.pl

commonly found in premenopausal women [12,15]. This situation is probably due to higher blood flow in premenopausal ovaries [16].

CLINICAL COURSE

Metastasis to the ovary may appear at the time of diagnosis of the primary tumor (synchronous) or during observation (metachronous). An analysis of 73 women with Krukenberg tumors of GC origin revealed that 39.7% (29 pts) were synchronous and 60.3% (44 pts) metachronous, with a median time to diagnosis of 15.5 months (5-46 months) [13]. In an Italian study (9 centres of origin) of 63 women with KT, 47% (30 pts) developed synchronous, and 53% (33 pts) developed metachronous ovarian metastases during follow-up [17]. Due to symptoms which may occur earlier, synchronous cases often appear prior to the detection of the primary tumor (40.9-58.5%) [13,18]. The most common clinical presentation of KT are abdominal distention, pain, a palpable mass, bloating, ascites or pain during sexual intercourse [13,14,16,17]. The presence of the metastases can also occasionally provoke a reaction of the ovarian stroma which leads to hormone production that results in vaginal bleeding, a change in menstrual habits, hirsutism, or occasionally virilization as a main symptom [5,14,19,20].

All these symptoms are non-specific and can also arise with a range of problems other than cancer. Hence, a diagnosis can only be made following confirmatory investigations such as ultrasound examinations, CT or EMR scans, laparotomy, and/or a biopsy of the ovary. Distinguishing between metastatic and primary tumors, especially that of non-gynecological origin, is crucial, as misinterpretation may lead to inadequate management and suboptimal treatment outcomes. In patients without a prior history of gastrointestinal cancer, gastric and colon fiberoscopy should be performed. The final diagnosis is based on histopathological examination, although KTs on their hematoxylin and eosin-stained sections often mimic other metastatic or primary ovarian tumors. Immunohistochemically, adenocarcinoma cells are positive for cytokeratins (AE1/AE7) and epithelial membrane antigen, and negative for vimentin and inhibin. Immunohistochemical evaluation may also help distinguish primary ovarian from metastatic carcinomas. Furthermore, the cytokeratin (CK)7-/CK20+ immunophenotype favors primary ovarian carcinoma, whereas the CK7-/CK20+ or CK7+/CK20+ immunophenotypes (CK20 positivity, in particular) favor metastatic gastrointestinal carcinoma. Moreover, MUC5 AC suggests a metastatic gastric carcinoma over primary ovarian adenocarcinoma [21].

TREATMENT

The current standard treatment for patients with metastatic gastric cancer is systemic chemotherapy, however best treatment strategy for KTs from gastric cancer has not been clearly established. Usually surgeons do not remove ovarian neoplasms when KTs are diagnosed preoperatively, although surgical treatment is considered for metachronous metastases

[22,23]. There are many factors, such as peritoneal carcinosis or other site of metastases, a delay in diagnosis which leads to a lower rate of resectability, poor patient tolerance for surgery, and relatively high operation-related morbidity, as well as overall dismal prognosis, that discourages surgeons from operating. Metastatic peritoneal seeding is considered to be the determining factor affecting the prognosis of gastric cancer patients with ovarian metastasis [12]. Surgical intervention in this situation consists mainly of palliative resection to relieve the symptoms and improve quality of life.

An Italian retrospective analysis [17] of 63 women with KTs reported that the probability of resection is higher in metachronous (33/33 pts) than in synchronous tumors (20/30 pts). The median survival time was also longer in the metachronous group (36 vs 17 months, $p < 0.000$). A Taiwanese analysis of 85 women with GC [24], among which 41.2% (35 pts) underwent metastasectomy of Kts, suggests that ovariectomy may improve OS (14.1 vs 8.0 months), although the metastasectomy group had significantly larger Krukenberg tumors, pronounced bilateral disease and less extensive metastases outside the ovaries. The results of this study are similar to that of a Korean study [25] which included 216 KTs patients (125 synchronous, 91 metachronous) placed within two groups (metastasectomy plus chemotherapy vs chemotherapy alone). Both in the synchronous and metachronous groups, ovariectomy increased OS (18.0 vs 8.0 and 19.0 vs 9.0 months, respectively). A retrospective multicentre French study [26] also reported that the median overall survival of patients who underwent ovariectomy was significantly higher than that of patients who had undergone chemotherapy alone (26.9 vs 10.6 months). Thus, applied modern chemotherapy (platinum, irinotecan, taxane plus platinum, or epirubicin plus platinum) in combination with surgical tumor debulking may improve the prognosis of patients with ovarian metastasis from gastric cancer.

A Chinese retrospective study of 62 patients with metachronous KTs after radical gastrectomy assessed the role of HIPEC. This study followed thirty (30) patients who had undergone cytoreductive surgery (CRS) alone, and thirty-two (32) patients who had CRS+ HIPEC. The median survival time in the CRS+HIPEC group was 15.5 vs 10.4 months in the CRS group ($p = 0.018$). A stratified analysis revealed that the median survival period after CRS+ HIPEC was especially significantly higher among the 32 patients who had pelvic peritoneal metastasis ($p = 0.046$). Among the 30 patients who suffered from ovarian metastasis alone, the median survival times were similar in both groups ($p = 0.141$).

CONCLUSIONS

The prognosis of patients with ovarian metastasis of gastric cancer origin is poorer compared with that of other primary tumors. Although the results of cytoreductive surgery (especially in combination with modern chemotherapy) seems to be promising, the optimal therapeutic strategies for such patients requires further prospective studies.

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