Risk factors associated with adverse outcomes in patients with metastatic ovary tumors: multi-center study

Abstract

Objective. The purpose of this study was to investigate the clinical risk factors associated with adverse outcomes in cases of metastatic ovary tumors during a recent 20-year periods.

Patients and methods. One hundred sixty-four patients with metastatic ovary tumors who was confirmed on pathologic diagnosis after surgery in three centers between January 1996 and December 2015. Clinical variables were collected from the patient’s medical records, laboratory results and radiologic data. The patients with metastatic ovary tumors were divided into four subgroups according to original primary tumor sites: gynecologic (n=27), colorectal (n=75), stomach (n=49), and hepatobiliary cancer group (n=13). Cox proportional hazards model was used to investigate risk factors with adverse results in cases of metastatic ovary tumors.

Results. The hepatobiliary tract as primary tumor sites were found to be the most significant risk factor in patients with metastatic ovary tumors. ($p=0.001$). The 2-year survival rate of hepatobiliary cancer group was 23% which was significantly shorter than gynecologic cancer group ($p=0.002$). In multivariate analysis, ovarian metastases from non-gynecologic cancer group and preoperative lymph node positivity in imaging modality were significant unfavorable prognostic factors, respectively ($HR=5.420/p<0.001$, $HR=1.675/p=0.013$). Interestingly, the level of CA19-9 in hepatobiliary cancer group was much higher than the other groups (gynecologic, colorectal, stomach cancer groups). Median value of CA19-9 in hepatobiliary cancer group was 830.5 and 88% of those increased more than 35U/mL. Multiloculation of ovary mass was more frequently observed in non-gynecologic cancer group than gynecologic cancer group and there was a significant difference of ovarian tumor
size between non-gynecologic cancer group and gynecologic cancer group (10.4±5.5cm vs 3.4±3.5 cm, p<0.001).

**Conclusion.** Hepatobiliary cancer group is the most significant risk factor related with poor outcomes in metastatic ovary tumors. Furthermore, CA19-9 may be used to detect hepatobiliary cancer group as an original tumor site among metastatic ovary tumors.

**Keywords:** metastatic ovary tumors, hepatobiliary, CA19-9

**Introduction**

The ovaries are frequent site for metastases from both gynecologic and non-gynecologic cancer origin. Most of metastatic ovary tumors originate from the gastrointestinal tract, breast and gynecologic origins[1-3]. Metastatic ovarian tumors represent 5 to 30% of all ovarian cancer[1-6]. The incidence rate of metastatic ovary tumors is relatively higher in Asia compared to Western countries[1,7-10] and the prevalence of metastatic ovary tumors is affected by the incidence rate and spread pattern of primary malignancy[3].

Regarding prognostic factors for metastatic ovary tumors, primary tumor site was the most significant factor and gynecologic origin showed better prognosis than non-gynecologic cancer groups[1,2,5]. Unfortunately, another risk factors related with prognosis of metastatic ovary tumors were not fully evaluated.

Here we reviewed 164 cases of metastatic ovary tumors that were surgically treated at our institution. The purpose of our study is to investigate risk factors associated with metastatic ovary tumors.
Methods

One hundred sixty-four patients with pathologically confirmed metastatic ovarian carcinoma were retrospectively reviewed. They were treated at Gynecologic Oncology Center in the Catholic University of Korea between January 1996 and December 2015.

For inclusion criteria, ovarian metastasis was confirmed based on histological examination and clinical information. Immunohistochemistry stains (i.e., cytokeratins 7 or 20) were used to give additional information for the diagnosis of primary tumor site. And we excluded patients with primary tumor sites such as breast peritoneum, lung, lymphoma, leukemia, kidney, nasopharynx and unknown origin.

For all patients following data were collected: age, menopause status, family history of malignancy, primary origin site, histologic type, time interval between primary and secondary tumor diagnosis, clinical course, radiologic findings, preoperative serum cancer antigen (CA)-125 and CA19-9 concentration, mass size, bilaterality, ascites, types of operation, outcomes after cytoreductive surgery, and survival on the record of clinical charts.

For the statistical analysis, the study population was divided into four groups on the basis of primary origin site; subgroup 1 (gynecologic cancer group: uterus, endometrium, fallopian tube, vagina), subgroup 2 (colorectum cancer group: colorectum, appendix, cecum, ileum), subgroup 3 (stomach cancer group: stomach), and subgroup 4 (hepatobiliary cancer group: liver, gall bladder, common bile duct, pancreas). Statistical analysis was done using the SAS software (ver. 9.3; SAS Institute Inc., Cary, NC, USA). It included Fisher’s exact test for categorical variables, ANOVA with Bonferroni post-hoc or Kruskal-Wallis test for continuous variables when appropriate. Overall survival curves were estimated by the Kaplan-Meier method, and we analyzed the prognostic variables with the log-rank test (univariate) and the Cox proportional hazards model (univariate and multivariate). P values of 0.05 or less was
regarded as statistically significant.

**Results**

During the past 20 years, 1,530 new cases of ovarian carcinoma were diagnosed, and metastatic ovary tumors accounted for 215 patients (14%, 215/1530). The characteristics of metastatic ovary tumors are summarized in **Table 1**. Colorectal cancer (62/164, 37.8%) was the most common primary tumor followed by stomach cancer (49/164, 29.9%). Primary tumors arising from colorectum and stomach exhibited more than half of metastatic ovarian tumors (67.7%). Gynecologic primary malignancies explained 16.5% (27/164) of metastatic ovary tumors. The primary sites of gynecologic tumors were endometrium (13/164, 7.9%), uterine cervix (10/164, 6.1%), fallopian tube (3/164, 1.8%), and vagina (1/164, 0.6%). Six of ten cervical cancers with ovarian metastases showed adenocarcinoma. Hepatobiliary cancer group occupied 7.9% (13/164) in this study. The mean age of patients was 50.2±11.9 years, more than half of metastatic ovary tumors were premenopausal state (84/164, 51.2%), and women with cancer family history exhibited 7.9% (13/164). Primary malignancies were detected first (metachronous) in 49.4% (81/164) and simultaneously with ovarian metastases (synchronous) in 48.8% (80/164). One hundred fifty three (153/164, 93.3%) were histologically diagnosed as adenocarcinomas. And interval months from primary tumor to ovary metastasis were 12.0±19.6.

**Table 2** summarized the preoperative clinical and radiological findings according to subgroups. One hundred thirty (130/164, 79.3%) cases were preoperatively diagnosed by ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), or positron emitting tomography(PET) CT. Preoperative detection rate using imaging modality was higher in colorectal cancer group (92%) than other groups. (p<0.001). In terms of bilaterality of ovarian involvement and amount of ascites, there was no significant difference
among all subgroups \( p=0.267, p=0.585 \).

Proportion of patients with multiloculation of ovary mass in preoperative image was 67.7%. Multiloculation of ovary mass on image was more frequently observed in non-gynecologic cancer groups than gynecologic cancer group (76.4% vs 26.0%, \( p=0.005 \)). Also, ovarian tumor size was significantly larger in non-gynecologic cancer groups than gynecologic cancer group (10.4±5.5cm vs 3.4±3.5 cm, \( p<0.001 \)).

Preoperative serum CA-125 concentration was measured in 128(78.0%) cases. 62 patients (48.4%) of those had elevated serum CA-125 concentrations (≥35 U/mL), and the mean values of preoperative serum CA-125 were not significantly higher among the 128 cases \( (p =0.454 \) (Table 3).

**Figure 1 and 2** shows patient survival rates. 5-year survival for ovarian metastases from gynecologic cancer group in the present study was 58%. The survival rate of gynecologic cancer group was significantly higher than non-gynecologic cancer group \( (p <0.001 \).

Extensive cytoreductive surgery did not improve the survival rates of metastatic ovarian cancer \( (p =0.169 \). The median survival period was 17 months after extensive cytoreductive surgery and 10 months after minimal palliative surgery.

Interestingly, in the current study, we found a significant difference in the level of CA 19-9 in each groups \( (p=0.005 \) (Table 4). Especially, the level of CA 19-9 of hepatobiliary cancer group was much higher than those of other groups. Median value of CA19-9 in hepatobiliary group was 830.5 and 88% of those increased more than 35 IU/mL. The median level of CA19-9 in hepatobiliary cancer group was the most highest among all subgroups (88%, \( p=0.001 \).

In univariate analysis, adverse prognostic factors were as follows: mass size, bilaterality, preoperative LN positive result, and metastasis from gynecologic origin were significantly
better prognosis than metastatic ovarian tumors (HR=1.029/p=0.05, HR=1.459/p=0.045, HR=1.679/p=0.011, and HR=0.324/p<0.001, respectively). In multivariate analysis, only two factors such as metastasis from gynecologic origin and preoperative lymph node positive result were significantly useful prognostic factors (HR=5.420/p<0.001, HR=1.675/p=0.013).

Discussion

1) Prognostic factors (gynecologic vs non-gynecologic)

In our study, patients with metastatic ovary tumors arising from non-gynecologic cancer groups (colorectal cancer group + stomach cancer group + hepatobiliary cancer group) showed significantly shorter survival compared to gynecologic cancer group. In previous studies, metastatic ovary tumors from non-gynecologic origin was the most significant factor for poor prognosis[1,2,5]. In a Japan report, Yada-Hashimoto et al. reported that the 5-year survival rates after resection of metastatic ovarian tumors from gynecologic and non-gynecologic origin were 47% and 19%, respectively, which showed significant shorter survival in non-gynecologic origin[1]. Also Webb et al. reported the overall 5-year survival rates of patients with metastatic ovarian cancer was 12% (gynecologic origin: 34%, breasts: 8.5%, stomach: 5.4%), and patients with non-gynecologic origin had a significantly poor prognosis[5].

This significant longer survival rates in gynecologic origin may be explained by different surgical methods and the pattern of disease spread[1]. In most cases of gynecologic origin cancers, bilateral salpingo-oophorectomy is performed with total hysterectomy, therefore, it is more likely that microscopic ovarian metastasis will be detected at primary surgery[1]. And compared with metastases from non-gynecologic cancer, gynecologic cancer shows intraabdominal carcinomatosis without distant metastasis and superficial spread patterns, therefore gynecologic origin metastases to ovary might show longer survival rates than non-
2) Prognostic factors (hepatobiliary group)

Among non-gynecologic groups based on primary tumor site, metastatic cancer of colorectal group showed favorable prognosis. In other words, especially, hepatobiliary cancer group is the most significant risk factor related with poor outcomes in metastatic ovary tumors.

3) CA19-9 (Preoperative diagnosis) & Importance of Preoperative diagnostic methods

Interestingly, the level of CA19-9 in hepatobiliary cancer group was much higher than the other groups (gynecologic, colorectal, stomach cancer groups). CA19-9 is a widely used diagnostic and prognostic biochemical marker in patients with pancreatic cancer. Christina RF. et al. reported that perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma[15]. And Cai et al. found that it is useful for predicting survival in cholangiocarcinoma if serum CA19-9 level is more than 150 U/mL[16]. The reason for this is probably that the CA19-9 in primary hepatobiliary cancer may be associated with higher CA19-9 level of metastatic ovary tumors from hepatobiliary cancer group. To our knowledge, it is the first published study to specifically investigate the preoperative CA19-9 values of metastatic tumors of the ovary. Therefore, it may be useful to check CA19-9 preoperatively to evaluate pelvic mass, and when preoperative CA19-9 is higher than 35U/mL, metastatic ovary tumors from hepatobiliary origin can be suspected.

In the current study, serum concentration of CA-125 was similar in all subgroups and not useful for the differential diagnosis of primary origin for metastatic ovary tumors. The efficacy of CA-125 for differential diagnosis of primary origin was in accordance with the report of Guerriero et al.[17], Lee et al.[3]. (Table 3)

4) Preoperative diagnostic image

In the current study, the preoperative detection rates of metastatic ovary tumors increased to 79.3% compared to 75% in previous study which was reported in 7 years ago[3]. This
increasing rates may be explained by new developing image modality.

In previous radiologic studies, the nature of an ovarian mass and size of mass may be useful for diagnosis[18,19]. In our study, multiloculation of metastatic ovarian tumors was more frequently observed in non-gynecologic cancer group than gynecologic cancer group. There were more smaller mass size in gynecologic group than that in non-gynecologic group. In cases of ovary tumors larger than 10cm in size, metastatic ovary tumors from non-gynecologic cancer group may be considered firstly.

5) Incidence & primary origin site

The prevalence of metastatic ovary tumors in Asia (14~30%) is higher than that of Western areas (7%)[1,3,20].

In present study, we divided into 4 time subgroups for the past 20 years as group 1 (1996-2000), group 2 (2001-2005), group 3 (2006-2010), and group 4 (2011-2015). Figure 1 showed that incidence of metastatic ovary tumors and changes of most common primary origin as time goes by. The overall incidence was a tendency to decrease, and the most common origin for metastatic ovary tumors was changed from stomach cancer to colorectal cancer. According to the 2005 Korean Cancer Registry, stomach, breast, and colorectal cancer, in that order, were the most common in Korean women. After about 10 years, the 2013 Korean Cancer Registry reported that thyroid, breast, colorecum, and stomach cancer were the most common cancer. Because of changes in primary cancer origin in Korean women, it makes change in the incidence rate of metastatic ovary tumor.

The most frequent primary origin in our study was colorectal origin and it is similar with reports in other countries. According to the Korean Cancer Registry, the prevalence of colorectal cancer increased higher than stomach cancer. Therefore, the primary origin for metastatic ovary tumors can be affected by the change of occurrence of other cancer.

6) Overview especially about survival & importance of distinguish both tumors
However, despite its apparent prevalence, it remains a diagnostic and management dilemma. Most patients die within 1 year of the diagnosis of ovarian metastasis from non-gynecologic origin[21,22]. Therefore, the ability to differentiate primary ovarian carcinoma from metastatic ovarian tumors before operation has significant therapeutic and prognostic implications. And when gynecologic surgeons encounter metastatic ovarian tumors before diagnosis of primary site is confirmed, an intensive search for the primary origin should be performed. Although it is easy to find the primary origin when pathologic confirm is clearly demonstrarated, there are many occasions in which histologic findings do not indicate the primary site.

**Conclusions**

Metastatic tumors from non-gynecologic cancer origin show poor prognosis more than non-gynecologic cancer origin. Hepatobiliary cancer group is the most significant risk factor related with poor outcomes in metastatic ovary tumors. Furthermore, CA19-9 may be used to detect hepatobiliary cancer group as an original tumor site for metastatic ovary tumors

<Reference>

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