Bone metastasis from ovarian cancer

Clinical analysis of 26 cases

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ABSTRACT

الأهداف: دراسة الخصائص السريرية لنقيلة العظم من سرطان المبيض ومساعدة الأطباء على عمل استرتيجية العلاج.

الطريقة: أجريت دراسة استعادية في المستشفى الاقليمي التابع لجامعة شاندونغ، شاندونغ، الصين. تم مراجعة 26 حالة لنقيلة العظم من سرطان المبيض خلال الفترة من يناير 2002م حتى مايو 2008م وجمع البيانات السريرية.

النتايج: في هذه الدراسة، بلغت نسبة ظهور نقيلة العظم حوالي 0.82%. تم مراجعة 26 حالة مصابة بنقيلة العظم ظهرت في الفقرة العنقية، و 10 في الفقرة القطنية، و8 في الحوض، و7 في القفرة الصدرية، و5 في الأطراف و1 في الضلوع و 2 في القص. كما ظهرت نقيلة الرئة بصورة متزامنة في 9 حالات، ونقيلة الكبد في 5 حالات، ونقيلة الدماغ في 4 حالات، ونقيلة الطحال في 3 حالات، ونقيلة الغدة الكظرية في حالتين والنقيلة اللمفاوية في 12 حالة. تم اكتشاف 12 حالة 88.5% من نقيلة الدماغ في المرحلة الثالثة والرابعة و 3 حالات 11.5% في المرحلة الثانية. كانت مدة البقاء في الحالات التي تم علاجها بالعلاج الشامل أطول من الحالات التي استخدم فيها العلاج الكيمياوي والإشعاعي لوحده.

خاتمة: أن نقيلة العظم من سرطان المبيض نادر بينما ارتفاع المرحلة النسيجية لسرطان المبيض يزيد من مخاطر نقيلة العظم خصوصاً في الحالات المصاحبة للرئة أو النقيلة اللمفاوية. ويعد العظم الفقري والحوض من الأماكن المنتشرة لنقيلة العظم كما أن العلاج الشامل يساعد في تحسين وقت مدة البقاء للمرضى.

Objectives: To study the clinical characteristics of bone metastasis from ovarian cancer, and facilitate physicians to develop treatment strategies.

Methods: This retrospective study was carried out in the Provincial Hospital Affiliated to Shandong University, Shandong, China. Twenty-six cases of bone metastasis from ovarian cancer treated between January 2002 and May 2008 were reviewed, and the clinical data were collected.

Results: In the current study, the incidence of bone metastasis is 0.82%. Twelve cases of bone metastasis occurred in the cervical vertebra, 10 in the lumbar vertebra, 8 in the pelvis, 7 in the thoracic vertebra, 5 in the limbs, one in the ribs, and 2 in the sternum. Lung metastasis occurred concomitantly in 9 cases, liver metastasis in 5 cases, brain metastasis in 4 cases, splenic metastasis in 3 cases, adrenal metastasis in 2 cases, and lymphatic metastasis in 12 cases. Twenty-three cases (88.5%) of bone metastasis were detected in stage III-IV, and 3 (11.5%) in stage II (p=0.000). The survival time in cases treated using comprehensive therapy was longer than those using radiotherapy or chemotherapy alone (p=0.047).

Conclusion: Bone metastasis from ovarian cancer is rare, however, the increasing pathological stage of ovarian cancer may add to the risk of bone metastasis, especially in the cases with lung or lymphatic metastasis. The pelvis and vertebral bone are the most common location of bone metastasis, and comprehensive treatment may improve the survival time of patients.

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Ovarian cancer is a common gynecological cancer, and the most common cause of death among women with gynecologic cancer in the world,[1] which accounts for 4% of all female cancers with over 190,000 new cases diagnosed each year.[2] The end point of most ovarian cancers is death by intra-abdominal metastasis or intestinal obstruction, but rarely hematogenous

or lymphatic spread to other organs such as the liver, pleura, lungs, skin, brain, and spleen have been reported, while bone metastasis is extremely rare.[3] In a retrospective study of 225 patients with ovarian cancer, Dauplat et al found bone metastasis was developed in only 4 patients with an incidence of 1.6%.[4] In another study of 90 cases with ovarian cancer, only one case of bone metastasis was detected and the incidence of bone metastasis was 1.1%.[5] In the current English literatures, most cases of bone metastasis from ovarian cancer were published as case reports and few systematic clinical observations have been performed. Subsequently, the clinical characteristics of bone metastasis from ovarian cancer such as survival time, optimal treatment, and prognosis were kept unclear. Most of physicians may not be familiar with the bone metastasis from ovarian cancer due to its rarity. However, the bone metastasis from ovarian cancer can result in severe pain, pathological fracture, or paraplegia, which may affect the life quality of patients seriously. Consequently, it is critical for physicians to better understand the clinical characteristics of the malignant lesions. Therefore, we reviewed retrospectively the 2189 cases of ovarian cancer treated in our hospital. The objective of this study is to review the clinical characteristics of bone metastasis from ovarian cancer, and facilitate the physicians to make treatment strategies.

Methods. We reviewed retrospectively 2189 cases of ovarian cancer treated in Shandong provincial hospital affiliated to Shandong University between January 2002 and May 2008. Among 2189 cases, 26 were diagnosed with bone metastasis during the treatment or in the follow-up period. The clinical data of 26 cases, such as age, pathological stage, site of bone metastasis, treatment methods and survival time, were collected and analyzed. The study was approved by the ethical committee of our hospital and performed according to the principles of Helsinki Declaration. The diagnosis of bone metastasis was confirmed using the following criteria: 1) gradually aggravated bone pain, tenderness, percussion pain, compression symptoms of adjacent tissues; 2) x-radiographs (Soredex, Helsinki, Finland), computed tomography (Siemens AG, Erlangen, Germany) or magnetic resonance (GE 1.5-T MRI, Milwaukee, WI, USA) reveal osteolytic destruction or pathological fracture; 3) Emission computed tomography (Infinia Hawkeye 4, GE healthcare, Milwaukee, USA) shows radionuclide concentration in tumor foci; and 4) histological confirmation.

The inclusion criteria of the current study were clinically identifiable bone metastatic lesions resulted from ovarian cancers, while the bone metastasis from other cancers was excluded.

To find prior related research, a comprehensive, computerized literature search was performed in MEDLINE from January 1, 1960 through June 30, 2013, by 2 independent investigators. We searched the related studies with the following text words: "ovarian cancer," or "oophoroma," or "carcinoma of ovary" or "malignant tumor of ovary" and "bone metastasis". Only articles written in English were included in the current study.

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The comparison of incidence of bone metastasis between patients in stage II and stage III-IV was performed using Fisher exact test. The association between survival time and treatment methods was determined with univariate logistic regression analysis. The comparison of time interval of the occurrence of bone metastasis and the diagnosis of ovarian cancer between lower and higher stage cases was performed using one-way analysis of variance. A probability value of <0.05 was considered to indicate statistical significance.

Results. In the current study, 26 cases were diagnosed with bone metastasis from ovarian cancer, the incidence is 0.82%. The age of 26 cases ranged from 24-75 years old, with a mean of 46.7 years old. All the cases were staged using the International Federation of Gynecology and Obstetrics (FIGO) surgical pathological staging system.[7] In 26 cases, 22 were diagnosed with ovarian cancer after surgery, among which one was in stage I-c, 2 in stage II-b, 5 in stage III-b, 8 in stage IV-c and 6 in stage IV. The other 4 cases with stage IV were diagnosed using needle aspiration. In 26 cases, 19 were ovarian epithelial cancer, including 13 cases of serous papillary adenocarcinoma and 6 cases of clear cell carcinoma, 7 cases were ovarian germ cell tumor, including 3 cases of dysgerminoma and 4 cases of yolk sac tumor. In terms of the treatment of ovarian cancer, comprehensive staging surgery was performed in 3 cases of stage II and postoperatively, no visible tumor available. The cytoreductive surgery was performed in 13 cases of stage III and the diameter of residual tumor was less than 1cm. Cytoreductive surgery was also performed in 10 cases of stage IV, but the diameter of residual tumor was more than 2 cm. The clinical characteristics of 26 cases of bone

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metastases including the sites, symptoms and the time to develop bone metastasis were listed in **Table 1**. In the current study, the most common site of bone metastasis is cervical vertebra (n=12), followed by lumbar vertebra (n=10), pelvis (n=8) and thoracic vertebra (n=7). The time interval between the occurrence of bone metastasis and the diagnosis of ovarian cancer is shorter in higher stage cases than that in lower stage cases, but there is no significant difference (p=0.069). In addition, 23 cases (88.5%) of bone metastasis were detected in stage II-IV, and only 3 cases (11.5%) occurred in stage I-II there is significant difference between the 2 rates (p=0.000).

In addition to bone metastasis, concomitant lung metastasis occurred in 9 cases, liver metastasis in 5 cases, brain metastasis in 4 cases, splenic metastasis in 3 cases, adrenal metastasis in 2 cases, and 12 cases suffered from lymphatic metastasis. In terms of the treatment of the bone metastasis, 2 cases gave up treatment, and the other 24 cases were treated using chemotherapy, radiotherapy, and disodium pamidronate or radionuclide therapy. The treatment and survival time for all patients were listed in **Table 2**. In terms of the survival time, the cases who gave up treatment have shorter survival time than those treated actively (p=0.038); The cases treated using comprehensive therapy, including both chemotherapy and radiotherapy, had significantly longer survival time, when compared to those treated using radiotherapy or chemotherapy alone (p=0.047).

Table 1 - Clinical characteristics of 26 cases of bone metastases.

Classification	Number of cases
Site of bone metastasis	
Cervical vertebra	12
Lumbar vertebra	10
Thoracic vertebra	7
Pelvis	8
Limbs	5
Ribs	1
Sternum	2
Time to develop bone metastasis	
Stage I	
Three years	1
Stage II	
Two years	2
Stage III	
One year	5
One to two years	6
Five years	2
Stage IV	
After the diagnosis of ovarian cancer	8
One years	2
Symptoms of bone metastasis	
No obvious pain	4
Low back pain	8
Thoracodynia	6
Difficulty in walking	9

Table 2 - The treatment and survival time of 26 cases with bone metastasis.

Treatment	Number of cases	Survival time mean (range)
Giving up treatment	2	3.0 (2-4)
Disodium pamidronate	2	7.0 (5-9)
Chemotherapy	6	8.4 (4-16)
Radionuclide therapy	2	11.0 (6-16)
Chemotherapy+ radiotherapy	8	14.2 (7-32)
Chemotherapy + radiotherapy + disodium pamidronate	3	17.3 (9-35)
Chemotherapy + radiotherapy + radionuclide therapy	3	21.5 (10-37)

Discussion. In the current study, we focused on the clinical characteristics of bone metastasis from ovarian cancer, to facilitate physicians in diagnosing and making treatment strategies. Up to now, few studies have been published on the issues in English literatures. In the current study, 26 cases were diagnosed with bone metastasis from ovarian cancer and the incidence is 0.82%, which is lower than the results of autopsy studies. In English literatures, the autopsy studies presented with a relatively high incidence of bone metastasis from ovarian cancer.[6] In clinics, some cases of ovarian cancer may give up treatment and following-up, and the examination for bone metastasis in ovarian cancer cases was not performed regularly. In addition, approximately 50% of metastases sites were asymptomatic and unknown during the lifetime,[6,8] which result in a relatively lower incidence of the bone metastasis from ovarian cancer in clinical study than autopsy study. Ovarian malignancies usually spread to bone by direct extension, transperitoneal seeding, hematogenous dissemination or lymphatic spread,[5] among which the vertebral venous system may play an important role in the spreading of the ovarian cancer to the bone. Some authors suggest that the pelvis and vertebral bone are the most common location of bone metastasis from ovarian cancer.[9] Baize et al[6] presented a case of the bone metastasis from ovarian cancer occurred in the left iliac ramus. Tiwari et al reported one case of bone metastasis from ovarian cancer occurred in lumbar spine.[10] In an autopsy study of 305 patients performed by Abdul-Karim et al[9] bone metastasis was detected in 7 cases; the most common site was thoracic vertebra, followed by clavicle and axial skeleton.[9] In the current study, 26 cases were diagnosed with bone metastasis, among which 29 metastasis sites occurred in spine, 8 in pelvis, the others in limbs, ribs or sternum. Spine and

pelvis presented a higher incidence of bone metastasis than other site, confirming the above viewpoints.

Moreover, we found the time interval between the occurrence of bone metastasis and the diagnosis of ovarian cancer is closely correlated to the pathological stages of ovarian cancer. In the 10 cases of stage IV, 8 were diagnosed with bone metastasis just as the ovarian cancer were diagnosed, and in 13 cases of stage III, 11 were diagnosed one year or 1-2 years after the ovarian cancer was diagnosed. While, in terms of the 3 cases of stage I-II, 2 or 3 years passed after the ovarian cancer was diagnosed. Although, no statistical significance was detected and we attributed it to the small sample size. In addition, 23 cases of bone metastasis occurred in patients of stage III-IV, while only 3 cases occurred in those of stage I-II and there is a significant difference between the 2 groups. The current data indicate the increasing pathological stage of ovarian cancer, and the risk of bone metastasis may increase sharply. In the report of 225 patients with ovarian cancers, Dauplat et al[4] found the bone metastasis from ovarian cancer usually occurred after the concomitant liver metastasis, and the initial bone metastasis was very rare. Previous study[11] also suggested that the lung or lymphatic metastasis was the risk factors of bone metastasis. In the current study, among 26 cases of bone metastasis cases, the concomitant lung metastasis occurred in 9 cases, liver metastasis in 5 cases, lymphatic metastasis in 12 cases, which confirmed the viewpoint of the above authors, namely, in the cases of lung or lymphatic metastasis from ovarian cancers, more attention should be paid for the possibility of the bone metastasis.

In terms of the treatment of bone metastasis from ovarian cancers, chemotherapy, radiotherapy, radionuclide therapy, disodium pamidronate or comprehensive therapy can be used. Although the prognosis is poor, the active treatment play an important role in improving the quality of life and the survival time of patients. In the current study, 2 cases gave up treatment and their survival time were significantly shorter than those treated actively. In addition, we found that comprehensive treatment may be more effective than chemotherapy or radiotherapy alone, which resulted in a longer survival time, in 26 cases.

Study limitations. Due to the rarity of the bone metastasis cases from ovarian cancer, a large-sample randomized controlled trial cannot be performed to confirm these viewpoints. According to the current data, we suggest that comprehensive treatment should be performed for the cases of bone metastasis from ovarian cancer. This may be helpful for physicians in making treatment strategies and improve the survival time of patients in the future.

In conclusion, bone metastasis from ovarian cancer is rare. The increasing pathological stage of ovarian cancer may increase the risk of bone metastasis, especially in cases with lung or lymphatic metastasis. The pelvis and vertebral bone are the most common locations of bone metastasis, and comprehensive treatment may improve the survival time of patients.

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