Observational Study

Skin metastases in epithelial ovarian and fallopian tube carcinoma
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Abstract
This study aimed to investigate the clinical features and outcomes of skin metastasis in ovarian and fallopian tube carcinomas. We studied patients with epithelial ovarian or fallopian tube carcinoma who developed skin metastasis from 2001 through 2012, and were also treated with chemotherapy and/or surgery. Skin metastases were classified as umbilical metastasis (Sister Joseph nodule [SJN]) and nonumbilical metastasis. Patients who developed skin metastases at paracentesis sites were excluded. Of the 206 patients treated, 12 (5.8%) developed skin metastasis: 7 developed SJN, and 5 developed nonumbilical metastasis. Six patients had serous carcinoma, 3 had clear cell carcinoma, 2 had endometrioid carcinoma, and 1 had adenocarcinoma. Four patients out of the 7 who developed SJN had skin metastasis at initial diagnosis, and all 4 patients had SJN with concomitant peritoneal dissemination. Of the 4 patients, 3 received chemotherapy, and their survival ranged from 22 to 42 months. Of the 7 patients who developed SJN, 3 patients with stage IIIIC disease developed an SJN at recurrence and were treated with surgery and/or chemotherapy. Their survival duration after recurrence ranged from 26 to 43+ months. Five patients developed nonumbilical metastases 3 to 53 months (median 34 months) after initial diagnosis: 3 cases occurred in incisional scars of primary surgery, and 2 in subcutaneous metastasis in the other sites. Survival after recurrence ranged from 56 to 140+ months in 3 patients with incisional scar recurrence, and it was 5 months in 2 other patients. Sister Joseph nodule developed only in patients with peritoneal dissemination, and most patients with SJN survived for >24 months. Nonumbilical metastases occurring in incisional scars of primary surgery may carry a favorable prognosis.

Abbreviations: FDG = 18F-fluorodeoxyglucose, PET/CT = positron-emission tomography/computed tomography, SJN = Sister (Mary) Joseph nodule.

Keywords: ovarian carcinoma, fallopian tube carcinoma, skin metastasis, umbilical metastasis

1. Introduction
Ovarian carcinoma is a gynecologic malignancy with the highest mortality rate. It usually spreads directly to the peritoneal cavity, but may also metastasize through the lymphatic and hematogenous routes. Distant metastases may be noted at the time of ovarian cancer diagnosis or may occur during the course of the disease, and the most common sites are the pleura, liver, lungs, and lymph nodes. Skin metastases are rare, occurring in 0.9% to 4% of patients. Ovarian carcinomas were the primary tumors in 3.3% to 4% of women with skin metastasis.

Skin metastases are classified as metastatic umbilical tumors, which are known as Sister (Mary) Joseph nodule (SJN), and nonumbilical metastasis. The prognosis of patients with skin metastasis has been shown to be poor: in previous studies, the median survival of patients with skin metastasis from ovarian cancer was 12 months. However, in these studies, skin metastases at presentation and those developed after initial therapy were not analyzed separately. In addition, many patients did not appear to receive a current standard chemotherapy regimen, that is, platinum/taxane chemotherapy. Thus, survival data on patients with skin metastases who received platinum-based chemotherapy have not been sufficiently studied. In the present study, we retrospectively studied patients with epithelial ovarian or fallopian tube carcinoma to investigate the clinical features and outcomes of patients who developed skin metastases and were treated with platinum/taxane chemotherapy and/or surgery.

2. Patients and methods
A consecutive series of patients with epithelial ovarian or fallopian tube carcinoma treated at the Department of Gynecology, Kameda Medical Center, from January 2001 through December 2012, were identified from the tumor registry, and their medical records were reviewed to obtain clinical and pathological data. Of these patients, those who developed skin metastases at the time of diagnosis or during the course of the disease were included in this study. Patients with skin metastases found at autopsy, patients with borderline tumors, and patients who did not undergo treatment for cancer were excluded from this study. Patients who developed skin lesions at the site of
Clinical features of skin metastases at initial diagnosis.

| Case no. | Type of skin met | Age at diagnosis, y | Stage | Histotype | Symptoms related to skin met | Metastases concomitant to skin met | Treatment for skin met | Survival after skin met, mos | Status |
|----------|-----------------|---------------------|-------|-----------|-----------------------------|-----------------------------------|-----------------------|-----------------------------|--------|
| 1        | SJN             | 72                  | IVB   | Serous, G1| None                         | PeriD                             | Surgery, Chemo (TC)       | 27 DOD                      |        |
| 2        | SJN             | 70                  | IVB   | Serous, G3| None                         | PeriD                             | Chemo (E, TC)            | 42 DOD                      |        |
| 3        | SJN             | 79                  | IVB   | Endometrioid, G3 | None                           | PeriD, LN (paraortic)          | Surgery*                                                                 | 7 DOD |
| 4        | SJN             | 61                  | IVB   | Clear cell | None                         | PeriD                             | Surgery, Chemo (TC)       | 22 DOD                      |        |

DOD = dead of disease, E = ectopic, LN = lymph nodes, PeriD = peritoneal dissemination, SJN = Sister Joseph nodule, skin met = skin metastasis, TC = paclitaxel/carboplatin.

* Case 3 did not receive chemotherapy because of medical comorbidities and older age.

Table 1

paracentesis and colostomy were also excluded. This retrospective study was approved by the Institutional Review Board.

In this study, skin metastasis was diagnosed pathologically and radiologically. New skin lesions with an abnormal uptake of 18F-fluorodeoxyglucose (FDG) on integrated positron-emission tomography/computed tomography (PET/CT), and also skin lesions that increased in size during the clinical course, were diagnosed as skin metastases. Clinical and pathological factors examined included age, stage, histotype, the site of metastasis at initial diagnosis, initial treatment, time to skin recurrence, treatment for skin metastasis, and overall survival. We examined skin metastases separately by the site (SJN vs nonumbilical metastasis) and the time at which skin metastasis was noted (skin metastasis at presentation vs skin metastasis as a recurrent or a progressive disease). Differences in age were compared using Student t test.

3. Results

During the study period, 206 patients with epithelial ovarian or fallopian tube carcinoma were treated: 191 patients underwent surgery with or without chemotherapy and 15 patients received chemotherapy alone. These 15 patients had pelvic tumors with peritoneal dissemination on imaging studies and elevated serum CA-125 levels (range 127–3851 U/mL), and ovarian cancer was diagnosed with histologic examination of tissue biopsies or cytological examination of ascites fluid.

Of the 206 patients, 12 patients (5.8%) developed skin metastasis. All patients were initially treated at our institution. None of the patients received bevacizumab treatment, partly because bevacizumab use for ovarian cancer was approved in November 2013 in Japan. An SJN developed in 7 patients and nonumbilical metastases developed in 5 patients. Skin metastasis developed at initial diagnosis in 4 patients (1.9%) and as a recurrent or progressive disease in 8 patients. Patients with skin metastasis at initial diagnosis were significantly older compared with those with skin metastasis as a recurrent or progressive disease (mean age at diagnosis of skin metastasis 71 years vs 57 years; P = .015). No significant difference in age was observed between the patients with SJN and those with nonumbilical metastasis (64 vs 58 years; P = .28). Six patients had serous carcinoma, 3 had clear cell carcinoma, 2 had endometrioid carcinoma, and 1 had adenocarcinoma.

3.1. SJN

Four patients developed an SJN at initial diagnosis (Table 1), occurring in 17% of the patients with stage IV disease (n = 23). These patients’ symptoms were not associated with umbilical tumors. All 4 patients had peritoneal dissemination. Survival time of the 3 patients who received platinum/taxane chemotherapy ranged from 22 to 42 months.

Three patients developed an SJN as a recurrent disease (Fig. 1), and all the 3 patients had stage IIIIC disease at initial diagnosis (Table 2). They developed an SJN after more than 2 years of being progression-free, and were treated with surgery and/or chemotherapy. Their survival after recurrence ranged from 26 to more than 43 months.

3.2. Nonumbilical metastasis

Five patients developed nonumbilical metastasis as a recurrent or a progressive disease (Table 2). The time from initial diagnosis to the development of skin metastasis ranged from 3 to 53 months. Nonumbilical metastases developed after abdominal peritoneal dissemination at presentation in 2 patients; however, metastases developed in 3 other patients who did not experience abdominal dissemination. Three patients developed nonumbilical metastases at abdominal incisional scars of primary surgery; these 3 patients survived more than 4 years after skin metastasis. Two other patients developed a subcutaneous nodule as a progressive disease during chemotherapy; both patients died of disease 5 months after the diagnosis of skin metastasis.

4. Discussion

This study indicates that survival of patients with skin metastases may not be as poor as previously reported.[1,6] Patients with SJN at presentation who received current standard chemotherapy survived more than 20 months. Even patients who developed skin metastases as recurrent disease survived more than 4 years when the recurrence developed at incisional scars of primary surgery.

Skin metastasis from epithelial ovarian carcinoma is rare. The incidence of skin metastasis in ovarian carcinoma patients ranged
from 0.9% to 4% in previous studies in which skin metastases were confirmed by cytology or histology. Its incidence was influenced by the chemotherapeutic regimens administered; autopsy data showed that the incidence of skin metastasis in patients who received the current standard chemotherapeutic regimens, such as platinum and taxane, was lower than that in patients who received older chemotherapeutic regimens that are not as effective as current standard regimens (4.3% vs 17.9%).

In our study, pathological examination and imaging studies revealed that 5.8% of patients with epithelial ovarian or fallopian tube carcinomas were diagnosed to have skin metastases, although skin metastases at presentation were not included. Skin metastases at the stage IV disease site occurred in 17% of patients in our study, which was a higher percentage than that found in previous studies (0.91%–3.7%). Reasons for this difference are unclear, but may include that Japanese populations are aging, as older women appear to be more likely to develop skin metastasis at presentation. The high rate in our study appears to reflect the high rate of older women living in our medical service area.

In women, ovarian carcinoma is the most common origin of SJN: 42% to 47.7% of women with SJNs had ovarian carcinoma. The most significant risk factor of developing an SJN is peritoneal dissemination. In our 7 patients with SJNs, all had peritoneal dissemination before or concomitant with their SJN. A review of the literature showed that 21 of 22 (95%) patients with SJNs at presentation experienced peritoneal dissemination (Table 3). Thus, the vast majority of SJNs appear to develop by direct invasion from the underlying intraperitoneal metastatic tumors. However, lymphatic or hematogenous spread may also contribute to their development.

| Case no. | Type of skin metastasis | Age at initial diagnosis, y | Stage | Histotype | Initial therapy | Time to skin rec, mos | Symptoms related to skin rec | Metastases before/concomitant with skin rec | Treatment for skin rec | Survival after skin rec, mos | Status |
|----------|-------------------------|----------------------------|-------|-----------|-----------------|-----------------------|-----------------------------|---------------------------------|---------------------|---------------------------|--------|
| 5        | SJN                     | 49                         | IBC   | Endometrioid, G2 | Chemo (TC), Surgery | 115                   | Umbilical tumor | Pelvic tumor/none | Surgery              | 43+                  | AWD       |
| 6        | SJN                     | 58                         | IBC   | Serous, G1   | Chemo (TC), Surgery | 28                    | Umbilical tumor | Pelvic tumor/none | Chemotherapy (DTX, LPD) | 33                  | DOD       |
| 7        | SJN                     | 45                         | IBC   | Serous, G1   | Chemo (TC), Surgery | 38                    | Umbilical tumor | Pelvic tumor/none | Chemotherapy (TC, CPT-11) | 26                  | DOD       |
| 8        | Nonumbilical            | 48                         | IC1   | Clear cell  | Surgery, Chemo   | 8                     | None            | None/None         | Surgery, RT           | 140+                 | NED       |
| 9        | Nonumbilical (incision scar) | 53                 | IBC   | Serous, G1   | Surgery, Chemo (TC) | 16                   | None            | LN (saphenous, sacralsuperior, paraaortic) | RT, immunotherapy | 56+                 | NED     |
| 10       | Nonumbilical (incision scar) | 54                 | IBC   | Serous, G2   | Surgery, Chemo (TC) | 53                   | None            | Skin tumor        | Chemotherapy (DTX, LPD) | 56                  | DOD       |
| 11       | Nonumbilical (non-umbilical) | 49                | IBC   | Serous, G3   | Surgery, Chemo (TC) | 40                   | None            | Pelvic tumor/none | Chemotherapy (TC, CPT-11, LPD) | 5                  | DOD       |
| 12       | Nonumbilical (non-umbilical anterior abdomen) | 72 | NB       | Adenoca, G3 | Laparotomy, Chemo (TC, DTX) | 3                    | None            | Pelvic tumor/none | Chemotherapy (primary therapy continued) | 5                  | DOD       |

Table 2
Clinical features of skin recurrences.

Table 3
Ovarian or fallopian tube carcinoma patients with Sister Joseph nodule at presentation who received chemotherapy.
hematogenous spread is also involved in the development of SJNs, as SJNs can develop as a recurrent disease in patients without peritoneal dissemination.[24] Patients with an SJN at initial diagnosis often present with umbilical symptoms including an umbilical mass, umbilical bleeding, and pruritus.[10,13–16,18–25] Sometimes they have only umbilical symptoms without typical ovarian cancer symptoms. In a previous report, a patient with SJN who did not have abdominopelvic abnormalities on computed tomography (CT) scan at presentation developed an ovarian tumor 10 months later.[20]

Patients with SJN at presentation are expected to have similar survival as patients with other distant metastases (stage IV disease), if they receive platinum/taxane chemotherapy. In this study, 3 patients received paclitaxel/carboplatin chemotherapy and survived more than 22 months. Review of the studies in which treatment and survival data are provided shows that the median survival of patients with SJN at presentation, who received platinum and/or taxane chemotherapy, is 26 months,[1,2,10–12,25] which compares favorably with the 25-month survival of patients with stage IV disease who underwent primary debulking surgery.[22] Therefore, patients with SJN should be treated with the current standard treatment for an advanced ovarian carcinoma, that is, a combination of cytoreductive surgery including SJN resection and adjuvant platinum/taxane chemotherapy. On the contrary, patient survival with SJN developing as a recurrent disease may not be favorable; it is influenced by the time to recurrence and coexisting recurrent diseases.

Nonumbilical metastases in ovarian carcinoma are less likely to occur compared with SJN, and develop as a recurrent or progressive disease in almost all cases. In addition to hematogenous and lymphatic spread, nonumbilical metastases develop by contiguous spread and implantation. Skin metastasis after laparoscopy and paracentesis has been a well-known phenomenon in patients with advanced or recurrent ovarian cancer[11,2,22,28]; this type of metastasis is developed by implantation of cancer cells at the site of the procedures. Nonumbilical metastasis often develops in previous incisional scars.[9,30] Isolated incisional metastases occur by cancer cells contaminating surgical wounds.[21] Another explanation is “oncotaxis” in which otherwise dormant tumor cells may be distantly attracted to sites of tissue inflammation, such as surgical wounds, thus initiating local recurrence.[31] Scalp and limb metastases, both very rare, have been reported.[12,33]

Since almost all nonumbilical metastases occur as a recurrent disease, prognosis of patients with these metastases is poor. However, patients who develop skin metastases in previous incisional scars without coexisting metastatic diseases may have a long-term survival after developing this disease.[22,30] In our study, these 3 patients survived more than 4 years. Treatments for nonumbilical metastasis depend on the site of disease, presence or absence of coexisting diseases, and time to recurrence. Resection may be considered if the skin lesion is an incisional metastasis without coexisting diseases. Radiation therapy is effective in improving pruritus associated with skin lesions,[34,35] and may prolong survival in some patients.[36] Also, in endometrial carcinoma, patients with isolated incisional recurrence had better survival than patients with nonisolated incisional recurrence.[37] Prognosis of patients with skin lesion outside previous surgical incision is poor, as this type of skin metastasis is a late manifestation associated with multiple metastases.[32,33,35,38]

The limitations of this study include the exclusion of patients with skin metastases developed at the site of paracentesis and colostomy, which resulted in the small number of the patients. These types of skin metastases were not necessarily evaluated fully, because they usually occurred in patients with refractory disease who required repeat paracentesis and whose survival time was inevitably short. Thus, survival time after diagnosis in patients with nonumbilical metastasis in the present study may be longer than that observed in previous studies. Another limitation is the diagnostic method for skin metastases. Skin metastases are traditionally diagnosed histologically or cytologically. However, in the present study, PET/CT was used to confirm the diagnosis of skin metastasis, because PET/CT has a higher diagnostic reliability compared with conventional imaging techniques, such as magnetic resonance imaging and CT.[39] Using PET/CT, skin ulceration sometimes occurring after biopsy of subcutaneous lesions can be avoided. Moreover, PET/CT can reveal unusual disease spread and be helpful for treatment planning.[39]

5. Conclusions

In conclusion, patients with SJN at presentation from epithelial ovarian or fallopian tube carcinoma may have a relatively long survival if they receive current standard chemotherapies. Therefore, these patients, including older women, may be referred to a cancer center and treated adequately. Recent studies have suggested that molecular targeted therapy using an antiangiogenetic agent (bevacizumab) may alter the patterns of recurrence and increase the incidence of brain and skin metastasis.[40,41] It is important for physicians to recognize symptoms or signs that would suggest skin metastasis.

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