Int J Clin Oncol (2003) 8:67–71

ORIGINAL ARTICLE

Osamu Kobayashi · Yuka Sugiyama · Haruhiko Cho
Akira Tsuburaya · Motonori Sairenji
Hisahiko Motohashi · Takaki Yoshikawa

Clinical and pathological study of gastric cancer with ovarian metastasis

Received: August 5, 2002 / Accepted: January 14, 2003

Abstract
Background. The aim of this study was to determine the treatment strategy for ovarian metastases from gastric cancer, by a retrospective study of the treatment results.
Methods. We reviewed the records of patients with ovarian metastases from primary gastric cancer. Ovarian metastases were found in 24 of 897 female patients with gastric cancer. Of these, 21 patients with histologically proven disease were studied.
Results. Ovarian metastasis was detected before the primary gastric cancer in 1 patient, simultaneously in 6, and after in 14. Ovarian tumors were detected by computed tomography (CT) in a majority of patients (95%), while uterine tumors were detected in only 29%. Metastasis to the uterus was histologically examined in 14 tumors and confirmed in 11 tumors. All patients with positive endometrial cytology had uterine metastases. Total abdominal hysterectomy was performed with bilateral salpingo-oophorectomy in 12 patients and with unilateral resection in 2. In these 14 patients, 5 were curatively operated. In the clinical course, all patients developed multiple metastases, and patients suffered peritoneal dissemination. None survived for longer than 3 years. The median survival time after ovarian metastases (MST) was 10.3 months for all patients; 3.6 months in patients in their sixties, and 12.5 months in those in their fifties. Survival was significantly longer in patients who underwent curative resection (MST, 30.4 months) compared with those who had noncurative resection (MST, 10.3 months).
Conclusion. The prognosis for ovarian metastasis of gastric cancer was poor without curative resection. Because of frequent microscopic metastases to the uterus, total hysterectomy with bilateral oophorectomy is recommended if curative resection is possible.

Key words Gastric cancer · Ovarian metastasis · Recurrence · Prognosis · Survival

Introduction

Krukenberg[1] initially described an unusual type of ovarian tumor in 1896. In 1902, Schlagenhaufer[2] reported that these tumors were secondary, epithelial in origin, and metastatic to the ovaries. At present, the Krukenberg tumor is considered to be a metastatic carcinoma derived from a primary malignancy, usually from the gastrointestinal tract,[2–9] in which the stomach is the most frequent primary site. Krukenberg tumors were observed in 17.8% of all ovarian cancers.[4] The majority of metastatic gastric carcinomas to the ovaries are Krukenberg tumors, whereas metastatic ovarian tumors often do not fulfil the criteria of Krukenberg tumors.[5,8,10,11] Gastric cancer, the most common malignancy in Japan, frequently reveals lymph node, peritoneum, and liver metastases.[12] In contrast, ovarian metastasis is rare. There are only a few reports demonstrating the clinicopathologic characteristics of ovarian metastases from gastric cancer, including reports of autopsies,[10,13,14] a case report,[15] and a large series reported by gynecologists.[4] General surgeons rarely have experience with metastatic ovarian tumors.[7,16] Survival in patients with these tumors remains poor.[6] In the current study, we retrospectively investigated the clinicopathologic characteristics, treatment, and survival in patients with gastric cancer and ovarian metastasis.

O. Kobayashi (✉) · Y. Sugiyama · H. Cho · A. Tsuburaya · M. Sairenji · H. Motohashi
The Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0815, Japan
Tel. +81-45-391-5761; Fax +81-45-361-4692
e-mail: osamuski@olive.ocn.ne.jp

T. Yoshikawa
Department of Surgery, Yokohama Kowan Hospital, Yokohama, Japan

Patients and methods

From January 5, 1987 to December 25, 2000, 897 female patients with gastric cancer underwent gastrectomy or laparotomy at Kanagawa Cancer Center Hospital. All patients had measurements of serum tumor markers (TMs), chest radiography, ultrasonography, computed tomography (CT), and endoscopy. The patients underwent barium enema examination and laparoscopy when peritoneal metastasis was suspected. TMs included serum concentrations of carcinoembryonic antigen (CEA), carbohydrate antigen (CA)19-9, and CA125. The upper normal range for these TMs was 2.5 ng/ml, 37 U/ml, and 65 U/ml, respectively. When levels of one of these three markers was abnormal, the combination assay of the TMs was defined as positive.

Ovarian and uterine tumors were diagnosed by surgical resection with pathological examinations after CT or laparoscopic observation. Histologic type, the depth of wall invasion, the extent of lymph node metastasis, and the stage of primary tumors were determined according to the classification of gastric carcinoma made by the Japanese Gastric Cancer Association.[17] The ovarian metastasis-free interval was defined as the period between the gastrectomy and the occurrence of the ovarian metastasis, while the survival time after metastasis was defined as that between the occurrence of the ovarian metastasis and death or the last follow-up. No-one failed to be followed up in the study period.

Data values are presented as means ± standard deviation (SD). Comparisons between two groups were analyzed by the χ^2 method. Survival after ovarian metastasis was analyzed by the Kaplan-Meier method and compared by the log-rank test. The Cox regression test was used to analyze multiple variables. The SPSS 6.1 Medical Pack program (SPSS, Chicago, IL, USA) was used for all the statistical analyses.

In this report, the term "curative" was defined as no residual tumor macroscopically, and "Krukenberg tumor" was defined as a tumor fulfilling the following criteria of Woodruff and Novak:[3] (1) the tumor is in the ovaries; (2) there is demonstrated evidence of intracellular mucin secretion by the formation of signet-ring cells; and (3) the diffuse infiltration of the stroma shows the general appearance of a sarcoma-like picture.

Results

Ovarian metastases were found clinically, in 24 of the 897 (2.7%) patients with gastric carcinoma. Of these 24 patients, 3 did not undergo oophorectomy because of severe peritoneal metastases at laparoscopy ($n = 2$) or simultaneous multiple distant metastases ($n = 1$). Twenty-one patients diagnosed pathologically by surgical resection of the ovarian tumors were studied, including 14 patients who underwent simultaneous hysterectomy with intent to cure or for optimal debulking. The characteristics of the primary tumors are as shown in Table 1. Histologically, signet-ring cell was the most common component (17 of 21; 81%). Most cases were advanced; for example, T3, N2, and stage IV.

Table 1. Characteristics of primary gastric tumor

Category	No. of patients
Macroscopic type	
Type 2	3
Type 3	4
Type 4	5
Type 5	9
Dominant histology	
Signet ring cell	4
Poorly differentiated[a]	13
Tubular	4
Depth of tumor (T)	
T2	1
T3	15
T4	5
Lymph node metastases	
N0	1
N1	4
N2	13
N3	3
Peritoneal dissemination	
Yes	10
No	11
Stage	
II	1
IIIa	4
IIIb	6
IV	10
Gastrectomy	
Curative	17
Noncurative	4

[a] With a signet ring cell component

The patients were diagnosed by CT, TMs, and endometrial cytology. CT was sensitive for detecting ovarian tumor, but not for uterine metastasis. All patients with positive endometrial cytology had uterine metastases (Table 2).

The mean ovarian metastasis-free interval was 27 months. The patients' ages ranged from 34 to 63 years, with a mean of 48.1 ± 7.9 years, and 71% were premenopausal. Seventeen of the 21 patients (81%) had metastases consistent with Krukenberg tumors, and all of the primary tumors contained a component of signet ring cells. Krukenberg tumors were more frequent in the premenopausal patients (14/15; 93%) than in postmenopausal patients (3/6; 50%). The size of the ovarian tumors ranged from 3.0 to 17.0 cm in diameter, with a mean of 9.4 ± 4.6 cm. Abdominal hysterectomy confirmed metastasis to the uterus in 6 patients histologically (43%). Simultaneous metastatic sites besides the ovaries and uterus were present in 17 patients. Of these, 15 patients had peritoneal metastases. The median survival time after the detection of the ovarian tumors (MST) was 10.3 months. The MST in patients aged under 60 was significantly longer when compared with that in those aged 60 or over (Table 3).

Total abdominal hysterectomy was performed with bilateral salpingo-oophorectomy in 12 patients and unilateral resection in 2, and, of the 14 patients, 5 had curative surgery. On the other hand, 5 bilateral and 2 unilateral oophorectomies without hysterectomy were noncurative. Only the

Table 2. Sensitivity (positive cases/overall cases) of diagnostic tools in ovarian tumor and uterine metastases

Diagnostic tool	Ovarian tumor (n = 21)	Uterine tumor (n = 14)
CT	95.2% (20/21)	28.6% (4/14)
Endometrial cytology	29.4% (5/17)	45.5% (5/11)
TMs		
CEA	35% (6/17)	27% (3/11)
CA19-9	47% (8/17)	27% (3/11)
CA125	31% (5/16)	40% (4/10)
Combination assay	76% (13/17)	58% (7/12)

CT, Computed tomography; TM, tumor marker; CEA, carcinoembryonic antigen; CA, carbohydrate antigen

Table 3. Characteristics at detection of ovarian tumor, and median survival time after the detection of the ovarian tumors (MST)

Category	No of patients	MST (months)	P
Overall	21	10.3	
Age at appearance of ovarian tumor			
Thirties, forties	3,10	10.3	0.0008
Fifties	5	12.5	0.0042
Sixties	3	3.6	
Menopause			0.4768
Pre	15	11.7	
Post	6	5.8	
Appearance of ovarian tumor			0.1345
Pre, simultaneous	1,6	8.7	
Postgastrectomy	14	12.5	
Metastatic site of ovary			0.9453
Unilateral	5	12.5	
Bilateral	16	9.5	
Histologic type of ovarian tumor			0.7966
Krukenberg type	17	10.3	
Other	4	12.5	
Size of ovarian tumor			0.4673
Smaller than 9 cm	9	11.7	
9 cm or larger	12	10.3	
Metastases to uterus			0.7772
Yes	14 (6[a])	10.3	
No	3	30.4	
N/A	4		
Simultaneous metastatic site			0.9664
No	4	9.5	
Yes	17	10.3	

The MST was 10.3 months for all patients; 3.6 months for those in their sixties, 12.5 months for those in their fifties (P = 0.0042 vs sixties), and 10.3 months for those in their thirties or forties (P = 0.0008 vs sixties)
N/A, not applicable
[a] Metastases to the uterus were confirmed histologically after hysterectomy

patients who underwent curative resection of the ovaries and uterus survived longer than the rest ($P < 0.04$; Fig. 1). Multivariate analysis demonstrated that the significant independent factors for survival were age (P = 0.0034) and curability (P = 0.0057; Table 4).

Discussion

Ovarian metastases from gastric cancer are commonly derived from advanced gastric cancer,[10,13,18] and are associated with peritoneal metastasis.[3,6–8,13] In our series of patients, peritoneal metastases were found simultaneously in 15 (71%) and afterward in 20 (95%) patients. Early gastric cancer is unlikely to spread to ovaries.[13,18] We experienced one patient who developed multiple metastases involving bilateral ovaries and bone, found at autopsy 9 years after curative gastrectomy for mucosal carcinoma that contained signet ring cells. The incidence of ovarian metastases from gastric cancer was more than 19% in autopsy series,[10,14] and 6.7% clinically.[18] Diagnosis of ovarian tumors by abdominal mass or pain is usually straightforward.[4,6–8,19] Krukenberg tumors are not infrequent with gastric cancer and swell to a large mass, with a mean size of 9 cm,[6,14,19] whereas non-Krukenberg tumors tend to be small and their diagnosis is complicated.[10] In our series, the sensitivity of CT for

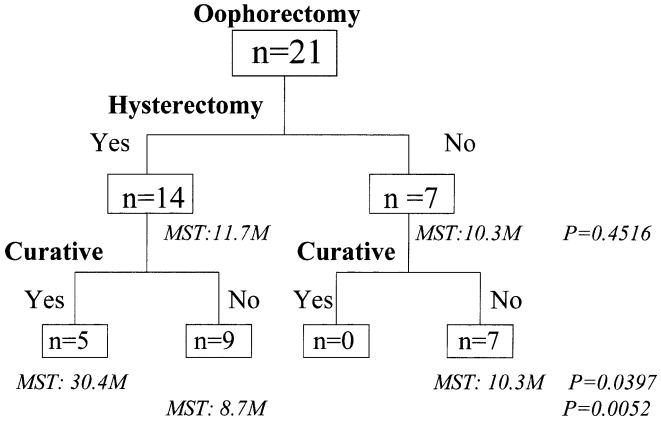

Fig. 1. Operative factors and survival. Survival was significantly longer in patients who underwent curative resection (30.4 months [*M*] median survival time [*MST*]) compared with those who had a noncurative resection ($P < 0.04$)

Table 4. Multivariate analysis by Cox's proportional hazard model in patients who underwent oophorectomy

Category	Factor	Significance (P value)	Odds ratio
Age	Under sixties/sixties	0.0034	0.0056
Curability	Yes/no	0.0057	0.0306
Menopause	Pre/post	0.0508	0.0906
Ovarian metastasis	Simultaneous/metachronous	0.0723	0.1767
Size of ovarian tumor	<9.5/≥9.5 cm	0.1121	1.2096
Simultaneous metastases	Yes/no	0.4107	1.9464
Krukenberg type	Yes/no	0.5971	0.5954

detecting ovarian tumor was 95% (20 of 21 cases), with a minimum size of 3.0 cm. We also demonstrated the usefulness of laparoscopy, TMs, and endometorial cytology in diagnosing ovarian metastases. We performed laparoscopy in 3 patients, 2 of whom did not undergo oophorectomy because of severe peritoneal metastases. These findings suggest that laparoscopy benefits patients with ovarian metastases, because they frequently involve the peritoneum. The predictive value of a single TM for ovarian metastases was low, and combination assays should be used. Endometrial cytology has been one of the diagnostic tools for the early detection of Krukenberg tumors.[20]

Gastric cancer metastasized to the ovaries has the poorest prognosis among secondary ovarian cancers, with a median survival time of less than 10 months.[19,8] Patients who survived for longer than 5 years were uncommon.[6,7] Petru et al.[11] demonstrated that the 5-year survival rate was significantly higher in patients with the disease confined to a single ovary and the pelvis than in those with bilateral ovarian metastases and abdominal spread. Prognostic factors for Krukenberg's tumors were curative treatment and limited disease extent.[21] Our data were similar to those of previous reports in terms of the median survival time (10.3 months), but poor prognosis depended on neither extraovarian metastases nor laterality. In our uni- and multivariate analyses, age and curability were the only prognostic factors. All patients aged in their sixties had severe peritoneal dissemination consistent with ovarian metastases. Curative resection and residual tumor volume would be the most important prognostic parameters,[11,21] as shown in the current study.

The overall response rate to chemotherapy in patients with ovarian metastasis was reported to be lower than that in those with extraovarian metastasis (14% vs 31%). Because of the low response to chemotherapy, surgical resection should be considered.[22] Demopoulous et al.[19] suggested that pelvic resection offered little hope of eradicating the disease in ovarian metastases, particularly those from gastric cancer. We decided on total hysterectomy in patients without peritoneal metastases beyond the pelvic cavity. In our series, 14 of 17 patients (82%) had simultaneous metastases to the uterus. Metastasis to the uterus was confirmed in 11 of 14 cases (79%) pathologically, including 5 cases of such metastases diagnosed preoperatively by endometrial cytology. This result suggests not only the important role of accurate diagnosis in detecting uterine involvement but also the significant therapeutic role of hysterectomy combined with oophorectomy in patients with ovarian metastases. In contrast, the role of chemotherapy is to control the frequent peritoneal metastasis, for which new drugs, such as a novel tegafur-combination drug (S1), may be active.[23]

Mrad et al.[6] reported a series of eight patients with Krukenberg tumors from gastric cancer, five of whom were treated with oophorectomy and the remaining three by chemotherapy alone. They concluded that, as neither surgery nor chemotherapy was efficient for ovarian metastases, prophylactic resection would be important. They recommended bilateral oophorectomy combined with gastrectomy in postmenopausal women with gastric cancer. Prophylactic oophorectomy combined with gastrectomy was also recommended,[16] in particular for tumor invading multiple lymph nodes, or in women younger than 50 with primary gastric cancer.[18] However, because of the low incidence of ovarian metastases from gastric cancer, prophylactic oophorectomy may not be justified in women under 50. The role of prophylactic oophorectomy in women affected with adenocarcinoma of the gastrointestinal tract is still debatable.[24] Prospective studies are needed to evaluate the role of prophylactic oophorectomy in patients with gastric cancer.

This report has documented the impact on survival of surgical treatment for patients with ovarian metastases from gastric cancer. We recommend that oophorectomy be employed for the treatment of patients with ovarian metastases. Total hysterectomy with bilateral oophorectomy should be the choice of treatment if curative resection is possible. In order to perform curative surgery for the metastasis, early detection would be important.

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