

Gastric Metastases Originating from Breast Cancer: Report of 8 Cases and Review of the Literature

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Abstract. *Background:* Breast cancer metastasis to the stomach is rare. It is very important to distinguish a breast cancer metastasis to the stomach from a primary gastric cancer on the basis of clinical, endoscopic, radiological and histopathological features, in order to administer the appropriate treatment. *Patients and Methods:* Eight patients with breast cancer metastasis to the stomach were identified in our database between 1995 and 2008. The clinico-pathological data and outcome from the medical records of these patients were then reviewed. *Results:* The median age at initial breast cancer diagnosis was 59.5 years (range 44-75 years), while the median interval between the primary breast cancer and the gastric involvement was 41 months (range 2-82 months). The primary breast cancer histological subtype was mostly lobular carcinoma. All the biopsy specimens were estrogen receptor (ER), cytokeratin (CK) 7 and gross cystic disease fluid protein-15 (GCDFFP-15) positive and CK-20 negative, while two of them (25%) were HER-2-neu positive. All the patients received chemotherapy and two of them were also treated with hormonal treatment. Two patients underwent surgical intervention, while one patient who had gastric involvement as the only metastatic site will proceed to surgical resection of the stomach. All these three patients were alive after 9, 39 and 44 months of follow-up, respectively. The response rate to chemotherapy was 50% (1 complete response [CR], 3 partial responses [PR]), and the median survival was 11 months (range, 1-44+

months). *Conclusion:* Breast cancer metastasis to the stomach can be differentiated from primary gastric cancer by comparing the biopsies from the gastric metastasis with the original histological slides from the primary breast tumor. Appropriate systemic treatment for metastatic breast carcinoma is the preferred treatment, whereas surgical intervention should be reserved for palliation or may be indicated in cases of solitary resectable gastrointestinal tract metastases.

Metastatic involvement of the gastrointestinal tract is rare. Breast cancer is one of the most frequent tumors implicated, but gastric metastasis is nevertheless an infrequent phenomenon in the natural history of breast cancer. The incidence of gastrointestinal tract metastasis has been estimated to be approximately 4-35% based on the results of autopsy series (1-5). Gastric metastases have been recognized in 0.3-18% of patients with generalized breast cancer and in some cases they may be the initial site of presentation (6-10). Metastatic spread to the stomach may occur many years after the initial treatment for breast cancer. The metastatic patterns of lobular and ductal carcinoma have been reported to differ significantly. Most series report a greater propensity for lobular carcinoma to metastasize to the gastrointestinal tract, the gynecological organs and the peritoneum (11, 12), while ductal carcinoma most frequently relapses in the liver, the lungs and the brain (13, 14). The clinical presentation of gastric metastases from breast cancer mimics a primary gastric tumor, as symptoms can be nonspecific and include dysphagia, dyspepsia, anorexia, abdominal pain, early satiety, nausea and vomiting, and bleeding. The radiological and endoscopic findings can also be similar to those of a primary gastrointestinal tumor. The discovery of a gastric tumor in a patient with a history of breast cancer is more likely to be a primary gastric lesion, but a metastasis from the breast cancer is possible and must be ruled out. The differential diagnosis between the two

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Table I. Patient characteristics.

Age (years)	Initial lesion	Other metastatic sites	Time elapsed* (mo)	Symptoms	Treatment	Survival (mo)
44	Lobular	Ovaries, bones	35	Dysphagia, vomiting, weight loss	FAC	11
52	Ductal	Bones, lung	18	Epigastric pain, vomiting, weight loss	FEC	23
63	Lobular	-	55	Abdominal pain, vomiting, anorexia	CMF, TAM	9+
67	Lobular	-	2	Epigastric pain, anorexia, vomiting	XELIRI, Letrozole	44+
58	Ductal	Skin, lung, bones	38	Dysphagia, weight loss, bleeding	FEC, 3M	4
61	Lobular	Peritoneum, bones	50	Pain, nausea, weight loss	EPI+ P	9
75	Lobular	Bones, ascites	82	Early satiety, weight loss, bleeding	CMF, TAM, Letrozole	1
49	Lobular	-	44	Pain, nausea	EPI + Tx	39+

mo: Months; FAC: 5-fluorouracil, doxorubicin, cyclophosphamide; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; CMF: 5-fluorouracil, methotrexate, cyclophosphamide; TAM: tamoxifen; XELIRI: camptothecin, xeloda; 3M: mitomycin-C, mitoxantrone, methotrexate; EPI: epirubicin; P: paclitaxel; Tx: taxotere. *Time elapsed from initial diagnosis of primary lesion.

tumors is very important in order to treat the patients properly and to avoid unnecessary surgery. Therefore, when faced with a patient who has a history of breast cancer, the physicians in collaboration with the pathologists should consider the possibility of gastric metastasis. In this study we to present eight cases of metastatic disease to the stomach from breast cancer.

Patients and Methods

Eight patients diagnosed as having gastric metastases from breast cancer were treated in our department from 1995 to 2008. The medical records of these patients were retrieved from our registry and their clinicopathological characteristics (age, stage, histological type, grade, hormone receptor status, HER-2-*neu* status, Ki-67 expression by immunohistochemistry, previous therapies, presenting symptoms, presence of other metastatic sites and endoscopic findings), treatment and outcome were analyzed. The histology of the endoscopic biopsies and the primary tumor were reviewed by an expert pathologist. Specimens were considered to be HER-2-*neu* positive when they scored +3 by immunohistochemistry or positive by fluorescent (FISH) or colorimetric (CISH) *in situ* hybridization. The patients were evaluated after the diagnosis of gastric metastasis by endoscopy and computed tomography (CT) scans every 3 cycles of treatment and bone scan every 6 months. Responses were assessed using the World Health Organization (WHO) criteria. Overall survival (OS) was defined as the time from the date of diagnosis of gastric metastasis until the date of death from any cause. Surviving patients were censored at the date of last follow-up. Kaplan-Meier curves were used to calculate the median OS. Informed consent was obtained from all the patients.

Results

The patient characteristics are shown in Table I. In one patient, gastric involvement was revealed during initial staging evaluation (two months after breast cancer diagnosis), whereas in 7 patients, gastric metastasis was developed during the course of their disease. The median age was 59.5 years (range 44-75 years) and the median time

between primary breast cancer diagnosis and metastasis to the stomach was 41 months (range 2-82 months). Five patients had been treated for primary breast cancer with modified radical mastectomy and three patients with partial mastectomy and lymph node dissection. Seven patients had received adjuvant chemotherapy with or without adjuvant hormonal therapy. Two patients, who were positive for HER-2-*neu*, had been treated with trastuzumab for one year.

All the patients with gastric involvement had nonspecific gastrointestinal symptoms, such as abdominal pain, bloating, dyspepsia, dysphagia, early satiety, vomiting, weight loss and anemia. The vast majority of patients had lobular breast carcinoma (6/8), while in three patients gastric involvement was the only metastatic site. Endoscopic biopsies initially confirmed the endoscopic diagnosis in seven patients, while in one patient repeated endoscopies with biopsies were needed. In this patient, the diagnosis was suspected after CT scan and double contrast barium meal. All the biopsy specimens were estrogen receptor (ER), cytokeratin (CK) 7 and gross cystic disease fluid protein-15 (GCDPF-15) positive and CK 20 negative, while two of the patients were HER-2-*neu* positive. One patient treated with chemotherapy achieved a complete response, which was histologically confirmed (no tumor detected after surgical resection of the stomach). Three patients achieved a partial response (histologically confirmed after surgical resection of the stomach in one patient, Figures 1, 2), yielding an overall response rate of 50%. The median survival following the detection of gastric involvement was 11 months (range, 1-44+ months). The Kaplan-Meier survival curve is shown in Figure 3.

Discussion

In the current series, 5/8 patients had concurrent metastatic disease to sites other than the stomach. Similar pattern of metastases was reported by Taal *et al.* (10). In the three cases

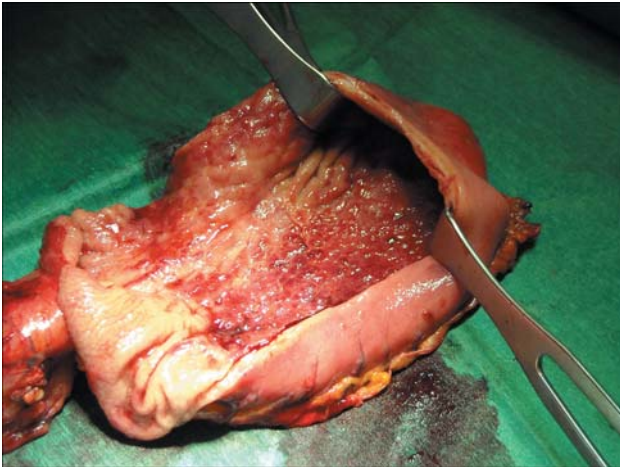


Figure 1. Surgical specimen, with a “strawberry-like” infiltration of the gastric mucosa from a patient with lobular carcinoma metastatic to the stomach as the only site of metastasis. Notice that the cancer spares the gastroesophageal junction and pylorus.

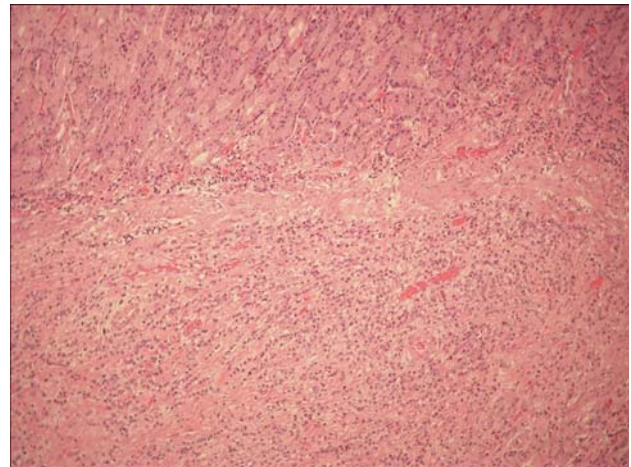


Figure 2. Hematoxylin and eosin staining of a lobular breast carcinoma metastatic to the stomach, magnification $\times 200$.

with gastric involvement alone, the diagnosis was confirmed by comparison of the gastric biopsies with the primary breast carcinoma.

A high index of suspicion for metastatic breast cancer should be maintained when a patient has a history of breast cancer and develops gastric symptoms. Endoscopic, radiological and histological evaluation is essential to discriminate primary gastric cancer from breast cancer metastasis to the stomach. Radiological and endoscopic findings are nonspecific, and may be hard to distinguish from primary gastric cancer and non-Hodgkin’s lymphoma. The most common pattern of breast cancer metastasis to the stomach is linitis plastica with diffuse infiltration of the submucosa and muscularis propria, while the pattern of discrete nodules or external compression is less common (5, 10, 15). Radiological evidence of linitis plastica has been reported to be consistent with the metastatic involvement of the stomach by lobular breast cancer. Taal *et al.* (10) reported that 83% of patients with gastric involvement had lobular breast cancer as a primary histological subtype. In the current series 5/8 patients had the lobular type of breast carcinoma. Because the lesion is often limited to the submucosal and seromuscular layers of the stomach, the endoscopic evaluation may be normal in 50% of cases or may show only discrete mucosal abnormalities indistinguishable from other tumors or benign disease (16). Radiological findings on CT scan or barium meal include encasement of the whole stomach as seen in linitis plastica, multiple lesions of the stomach or extrinsic lesions of the gastric wall. Deep biopsies are needed to obtain representative material and the histological features should be compared with those of the primary breast tumor in order

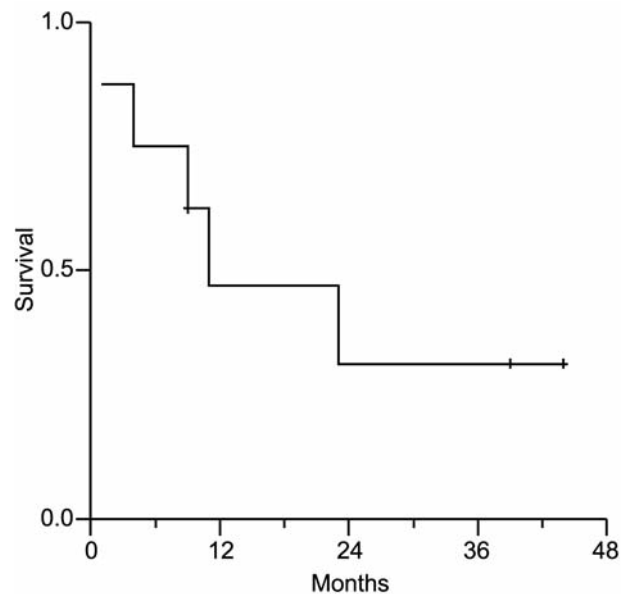


Figure 3. Survival after the diagnosis of gastric metastasis.

to confirm the diagnosis. Occasionally, lobular breast carcinoma may produce a signet ring morphology which can be confused with a primary gastric adenocarcinoma (10). The large number of signet-ring cells combined with a gastric mucosal spreading pattern can mean that metastatic disease to the stomach is almost indistinguishable from primary gastric linitis plastica (9). However, breast signet-ring cell carcinoma may show some morphological differences from gastric and colonic signet-ring cell carcinoma, such as a

single, well-circumscribed univacuolated intracytoplasmic lumina, with a central eosinophilic inclusion, whereas other signet-ring cell carcinomas have the extended, globoid, and optically clear cytoplasmic acid mucin that pushes the nuclei against the cell membrane (17).

Detailed immunohistochemical analysis may be the only reliable method to differentiate between metastatic and primary gastric carcinoma. Metastatic breast carcinoma is usually positive for CK7, GCDFP-15, carcinoembryonic antigen (CEA), ER and progesterone receptor (PgR), and negative for CK20. CK20 proves to be particularly positive in gastric, colorectal, pancreatic and in transitional cell carcinomas, while it is not observed in any carcinomas of the breast (18). CK7 in contrast is extensively expressed in 90% of breast carcinomas and its expression was also observed in 50-64% of primary gastric adenocarcinoma (19). Although ER and PgR positivity in gastric biopsies suggest breast cancer metastasis to the stomach, it is worth noting that ER and PgR positivity with weak to moderate staining intensity has been reported in 32% and 12%, respectively, of patients with gastric cancer (5). ER α can be used to diagnose gastric metastasis from breast cancer as van Velthuysen *et al.* (20) reported that no primary gastric tumor expressed ER α . They also observed that the absence of E-cadherin staining was significantly related to metastatic breast carcinoma (20). Furthermore, cytoplasmic positivity for GCDFP-15 may also function to confirm mammary origin. Positive staining with GCDFP-15 has been found to be a sensitive (55-76%) and specific (95-100%) marker for correctly identifying a malignant lesion as metastatic breast carcinoma (21). An excellent correlation between GCDFP-15 positivity and the origin of a metastatic breast adenocarcinoma has been demonstrated (5). The positivity for CK7 and GCDFP-15 including hormone receptor expression, and in contrast, the negativity for CK20 and CA19-9 were of great value in differentiating an unsuspected lobular breast carcinoma from a gastric carcinoma in the present cases.

Data on treatment are scarce. Breast cancer metastasis to the stomach represents evidence of systemic disease and systemic therapy, such as chemotherapy and/or hormonal therapy, rather than surgical resection is indicated (5, 10, 22, 23). Only after a correct diagnosis can the treatment of generalized breast cancer be initiated. Surgical treatment should be reserved only for patients who develop complications such as obstruction or bleeding (7, 8, 10, 15, 22, 23). In most cases, surgical resection is not possible due to local invasion (10). McLemore *et al.* (22) reported that surgical intervention did not have a significant effect on survival (28 vs. 26 months). However, patients with metastasis only to the gastrointestinal tract who underwent palliative surgical resection tended to have a more prolonged median survival (44 vs. 9 months). This difference was not statistically significant. The decision-making process for surgical

intervention should be based on the clinical presentation and symptoms, the availability of chemotherapeutic options and a quality of life discussion (22). In the current study, surgery was of benefit in two patients in whom gastric involvement was the only site of metastases. Both these patients were ER and/or PgR positive and were treated with hormonal therapy post-surgically. Another patient will proceed to surgical intervention as the stomach is the only metastatic site. Interestingly, these three patients were alive after 9-44 months of follow-up, whereas all the rest succumbed after a median time of 9 months. This difference was statistically significant ($p=0.024$), which would justify the use of surgical intervention in cases of operable solitary breast cancer metastasis to the gastrointestinal tract.

The choice of systemic treatment is based on age, presenting symptoms, performance status, ER status and previous treatment. All the present patients had received prior chemotherapy and two of them were treated with hormonal therapy (tamoxifen, letrozole). The response rate in this small series was 50%, similar to that reported by Taal *et al.* (10) (46%) but higher than that reported by Schwarz *et al.* (7) (30%). The median survival of the present patients from the time of diagnosis of gastric metastases was 11 months, similar to that reported by Taal *et al.* (10) (10 months) but shorter than that reported by McLemore *et al.* (22) (28 months) and by Ayantunde *et al.* (13) (20 months). In three patients, survival exceeded 2 years, while in the series of Taal *et al.* (10), 22% of the patients survived for more than 2 years.

In conclusion, primary gastric cancer can be distinguished from metastasis from a breast carcinoma by means of immunohistochemical analysis. Complete histopathological and immunohistochemical analysis of the gastric biopsies in comparison with the original breast cancer histology is essential to support the diagnosis of metastatic breast cancer. Surgical intervention should be reserved for palliation or may be a reasonable choice in cases of solitary resectable gastrointestinal tract metastases. Appropriate systemic treatment for metastatic breast carcinoma is the preferred treatment.

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