

BRIEF REPORT

# Gastric metastasis of breast cancer: A frequent mimicker of primary gastric cancer in breast cancer patients

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## Key words

breast cancer, gastric cancer, gastric metastasis, invasive lobular carcinoma.

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## Introduction

In the Netherlands, like in many western countries, the incidence of breast cancer is high. Thanks to a well-organized screening program and effective therapies, survival is good, resulting in a high prevalence of breast cancer (10-year prevalence of 118 000 women in 2019).<sup>1</sup> Survivors are at risk of developing metastatic disease, even after many years; metastases have been documented after 20 years.<sup>2</sup> In addition, these patients are at risk of getting secondary primary cancer a risk that is usually in line with the risk in the general population.<sup>3</sup>

Metastatic breast cancer will rarely present as metastasis to the stomach, however, when it does, it presents a diagnostic challenge. In many case reports and several small series, it has been documented that the clinical presentation, the radiological and endoscopic picture, and even the pathology of gastric metastasis can mimic primary gastric cancer.<sup>4–8</sup> Awareness of this possibility is pivotal and immunohistochemical staining for estrogen receptors and GATA Binding Protein 3 (GATA-3) can be of additional help to resolve the issue.<sup>9,10</sup>

The incidence of gastric cancer in the Netherlands is low (1000 men and women in 2019), so a breast cancer survivor rarely gets gastric cancer.<sup>11</sup> This means that in the case of cancer of the stomach in a breast cancer survivor, there is a serious differential diagnosis between primary gastric cancer and metastasis of breast cancer to the stomach.

Another issue to consider in patients with a history of breast cancer and primary gastric cancer is the possibility of a familial cancer syndrome with a mutation of the CDH1 gene.<sup>12,13</sup> In patients with this syndrome, breast cancer present as lobular cancer and gastric cancer has a diffuse growth pattern.<sup>12,13</sup>

Recently, it has been suggested that a large proportion of these familial cancer syndromes are overlooked in patients with breast cancer and gastric cancer.<sup>14</sup>

We retrospectively studied cancers of the stomach in patients with breast cancer from our institution over the last 32 years. The aim was to see how often cancer of the stomach in these patients is metastatic breast cancer and which clinical and pathological factors can be helpful in distinguishing this from primary gastric cancer. A second objective was to assess how many patients with breast cancer and primary gastric cancer fulfill the criteria for considering familial cancer syndrome.

## Materials and methods

The study was a single-center retrospective review of gastric biopsies in patients with a history of breast cancer from 1988 to 2020. The study is in accordance with the Dutch guidelines on the use of residual tissue and patient data. Patients with a history of ductal carcinoma in situ of the breast were excluded. Clinical data were retrieved from electronic medical records or microfilms, including patient characteristics, clinical presentation, and treatment.

Slides from gastric biopsies and resection specimens were retrieved from the pathology files and reviewed. Additional immunohistochemical staining for estrogen receptors and GATA-3 were performed if not already available. Slides from the breast cancers were also retrieved from the pathology files and reviewed. A diagnosis of gastric metastasis was made when the morphology of the cancer was compatible with the morphology of the breast cancer and estrogen receptor and/or GATA-3

**Table 1** Demographics and characteristics of disease

	Primary gastric cancer (n = 21)	Gastric metastasis (n = 23)	P-value
Age at the time of diagnosis of breast cancer			0.290
Mean ± SD	65.8 ± 12.8	61.2 ± 13.7	
Median [min, max]	67.0 [44, 84]	61.0 [37, 83]	
Palpable tumor			0.941
No	2 (10%)	3 (13%)	
Yes, discretely	10 (48%)	13 (57%)	
Yes, vaguely	1 (5%)	2 (9%)	
Missing	8 (38%)	5 (22%)	
Side breast cancer			0.361
Left	9 (43%)	8 (35%)	
Right	12 (57%)	12 (52%)	
Both sides	0	2 (9%)	
Missing		1 (4%)	
Size breast cancer (mm)			0.235
Mean ± SD	24.8 ± 11.2	33.5 ± 20.4	
Median [min, max]	20.0 [13, 50]	30.5 [8, 80]	
Missing	2 (10%)	9 (39%)	
Surgical treatment of the breast			0.071
No surgery	0	5 (22%)	
Breast conservative therapy	7 (33%)	5 (22%)	
Mastectomy	15 (67%)	13 (57%)	
Histology breast cancer			<b>0.001</b>
Invasive ductal carcinoma	15 (71%)	5 (22%)	
Invasive lobular carcinoma	2 (10%)	13 (57%)	
Other	3 (14%)	4 (17%)	
Missing	1 (5%)	1 (4%)	
Estrogen receptor status breast cancer			0.718
Negative	1 (5%)	2 (9%)	
Positive	15 (71%)	19 (83%)	
Missing	5 (24%)	2 (9%)	
Adjuvant therapy			0.217
No	5 (24%)	3 (13%)	
Yes	9 (43%)	15 (65%)	
Missing	7 (33%)	7 (30%)	
Age at the time of diagnosis of gastric cancer			<b>0.037</b>
Mean ± SD	76.3 ± 11.3	67.0 ± 14.5	
Median [min, max]	76.0 [48, 92]	70.0 [39, 90]	
Interval between diagnosis of breast cancer and presentation of gastric neoplasm (months)			0.110
Mean ± SD	115.1 ± 86.8	92.2 ± 105.7	
Median [min, max]	91.5 [11, 334]	40.5 [0, 413]	
Missing	1 (5%)	1 (4%)	
Presenting GI-symptoms			0.544
No	2 (10%)	1 (4%)	
Yes	14 (67%)	15 (65%)	
Missing	7 (33%)	7 (30%)	
Known metastatic disease at the time of presentation with gastric complains			0.097
No	13 (62%)	8 (35%)	
Yes	3 (14%)	7 (30%)	
Missing	5 (24%)	8 (35%)	
Endoscopy			<b>0.041</b>
No specification	6 (29%)	6 (26%)	
Linitis plastica	1 (5%)	8 (35%)	
Stenosis	2 (10%)	1 (4%)	
(Cured) ulcer	10 (48%)	2 (9%)	
Tumor/polyp	2 (10%)	2 (9%)	

(Continues)

**Table 1** (Continued)

	Primary gastric cancer ( <i>n</i> = 21)	Gastric metastasis ( <i>n</i> = 23)	<i>P</i> -value
Multiple anomalies (suspect for malignancy)	0	1 (4%)	
Missing		3 (13%)	
Growth pattern gastric tumor			<b>&lt;0.001</b>
Diffuse	7 (33%)	23 (100%)	
Intestinal	14 (67%)	0	

The *p*-value of < 0.05 as significant.

were positive. If not, a diagnosis of primary gastric cancer was made.

Patient, disease, and treatment characteristics were analyzed using descriptive statistics. Differences in outcomes between the two groups were analyzed with the Mann–Whitney *U* test and the Fisher's exact test. All statistical analyses were performed using the statistical software IBM SPSS version 23.

## Results

A total of 44 patients were identified from the pathology files, including 23 patients with gastric metastasis of breast cancer and 21 patients with primary gastric cancer. In three patients, a diagnosis of gastric metastasis was made after revision of the slides and additional staining, and in two of these patients, unfortunately, gastrectomy was performed. Patient characteristics are summarized in Table 1. Patients with gastric metastasis more often had a history of invasive lobular carcinoma (*P* 0.001). There were no differences in age at presentation with breast cancer, palpability, and side of the involved breast, tumor size, estrogen receptor expression, or adjuvant systemic therapy. Also, no statistically significant differences were found in the type of surgery—breast conserving or mastectomy—although, in five patients with gastric metastasis, no surgery was performed because of the synchronous occurrence of breast cancer and gastric metastasis. At presentation with gastrointestinal symptoms, patients with gastric metastasis were statistically significantly younger, although there was no statistically significant difference in the interval since the diagnosis of breast cancer between patients with gastric metastasis or primary gastric cancer. Patients with gastric metastasis significantly more often presented with linitis plastica on endoscopy and had a diffuse growth pattern of the tumor in the biopsy. Almost all patients presented with gastrointestinal symptoms. There were no differences in distant breast cancer metastasis between patients with primary gastric cancer or gastric metastasis.

The overlap in the interval time between the diagnosis of breast cancer and the diagnosis of gastric metastasis or primary gastric cancer is shown in Figure 1. The median interval between the diagnosis of breast cancer and primary gastric cancer was 91.5 months (range 11–334 months) and for gastric metastasis, 92.2 months (range 0–413 months). None of the patients with lobular breast cancer and primary diffuse gastric cancer presented with gastric cancer at an age below 40. We were unable to assess the family history due to lack of data in the patient records.

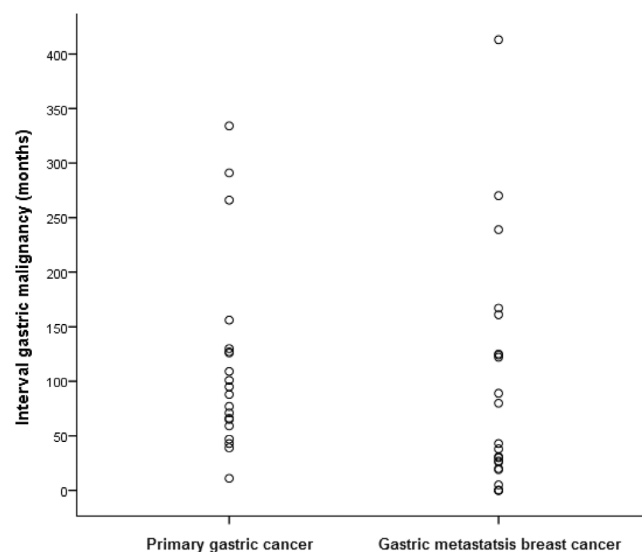
The pathology of a gastric biopsy with metastatic invasive lobular breast cancer is illustrated in Figure 2. The metastasis is indistinguishable from diffuse gastric cancer on an H&E slide, but

since the tumor is positive for estrogen receptors and GATA-3, a diagnosis of gastric metastasis of breast cancer was made.

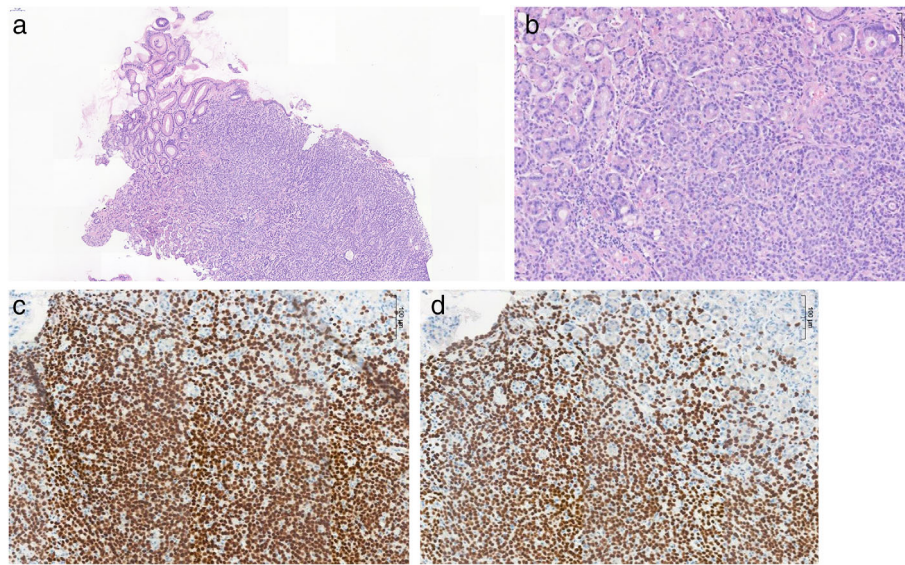
Once a diagnosis of gastric or primary gastric cancer was made, survival in both groups did not differ, as illustrated in Figure 3.

## Discussion

This study confirms previous studies on gastric metastasis of breast cancer in that we also found that more patients than usual had lobular breast cancer and that gastric metastasis usually presented as diffuse gastric cancer. Clinically, gastric metastasis was indistinguishable from primary gastric cancer. In addition to previous studies, we also studied patients with a history of breast cancer and primary gastric cancer, which also showed that patients with metastatic gastric cancer more often had lobular cancer and a diffuse growth pattern on biopsy. Further, we could demonstrate that there is a large overlap between both groups in age at which breast cancer was presented and the interval between breast cancer and gastric metastasis or primary gastric cancer. We found that in more than half of the patients, cancer of the stomach was in fact metastatic disease. These findings highlight the importance of awareness of the possibility of gastric metastasis and performing the right immunohistochemical stains.



**Figure 1** Interval between the diagnosis of breast cancer and gastric metastatic disease / primary gastric cancer (months).



**Figure 2** (a) Photomicrograph demonstrating a gastric biopsy with gastric metastasis of breast cancer (H&E stain). (b) Detail (H&E stain). (c) Same biopsy stained for estrogen receptor highlighting the tumor cells. (d) Same biopsy stained for GATA-3.

This point is also illustrated by the fact that in two patients, a diagnosis of gastric metastasis was only made after gastric resection. Both patients were treated before the year 2000. Around this time, we became more focused on the possibility of gastric metastasis masquerading as gastric cancer in patients with a history of breast cancer.

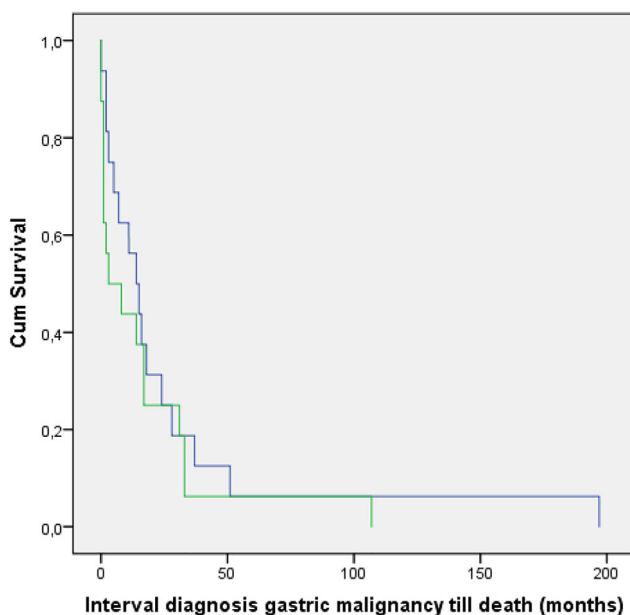
Gastric metastasis is an example of the metastatic pattern of lobular breast cancer, which more often than other histological types

has intestinal metastasis.<sup>4,15</sup> The median interval between the diagnosis of breast cancer and gastric metastasis in our series was 92 months, which is comparable to that of El-Hage *et al.*<sup>4</sup> Nevertheless, some of our patients presented with gastric metastasis synchronous with breast cancer, and in others, there was an interval of more than 30 years. Of course, certainly in patients with a very long interval, the possibility of a metastasis from a second primary breast cancer has to be entertained. We did not perform molecular studies in these cases. However, long intervals between the diagnosis of breast cancer and metastasis have been reported previously.<sup>2</sup>

In some of our patients, a diagnosis of gastric metastasis was only made after revision of the slides and in two patients after gastric resection. All these patients were treated before the year 2000, which attests to the importance of awareness of this possibility and the importance of the use of immunohistochemical markers, one of which (GATA-3) was not available at that time.

The possibility of a familial cancer syndrome with breast and gastric cancer has to be considered in the group of patients with primary gastric cancer. According to international recommendations, this has to be considered in patients with lobular breast cancer and diffuse gastric cancer if (i) two or more patients of any age in one family have gastric cancer with one diffuse gastric cancer, (ii) individual patients have diffuse gastric cancer before the age of 40, and (iii) in families with a diagnosis of lobular cancer and diffuse gastric cancer, one of which before the age of 50.<sup>13</sup> Unfortunately, we did not have data on the family history of our patients, but none of our patients had gastric cancer before the age of 40. In addition, familial gastric cancer is rare in the Netherlands.<sup>16</sup> We, therefore, think that the vast majority of our patients with breast cancer and gastric cancer had sporadic gastric cancer. This is in contrast to what Mahar *et al.* surmised,<sup>14</sup> but they seemed to have overlooked the possibility of gastric metastasis of breast cancer.<sup>17</sup>

Because our study spans a period of more than 30 years, we were not able to recover all the clinical data. Also, not all the slides



**Figure 3** Survival functions of metastatic disease or primary tumor. —, Primary gastric cancer; —, gastric metastasis breast cancer.

or paraffin blocks of the breast cancers were available, so we could not always compare the morphology of the primary tumor with the gastric specimen. We considered estrogen receptor-positive and/or GATA-3-positive gastric tumors as metastatic breast cancer, but estrogen receptor positivity has rarely been found in primary gastric cancer.<sup>18</sup> Also, we could not review all breast cancers and receptor expression does not always correspond to the primary breast tumor and the metastasis.<sup>19</sup> Nevertheless, we feel confident that combining both markers and comparing the gastric tumor with the available breast cancer allowed us to make a reliable classification.

We conclude that in patients with gastric cancer and a history of breast cancer, gastric metastasis of breast cancer is a serious possibility, and this differential diagnosis can only be reliably resolved by immunohistochemistry. In most cases, primary gastric cancer is sporadic, but the possibility of familial cancer has to be entertained.

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