Case series of 21 patients with extrahepatic metastatic lobular breast carcinoma to the gastrointestinal tract

Noah Switzer\textsuperscript{a,\*}, Andrew Lim\textsuperscript{a}, Lillian Du\textsuperscript{b}, Rani Al-Sairafi\textsuperscript{a}, Katia Tonkin\textsuperscript{c}, Dan Schiller\textsuperscript{a}

\textsuperscript{a}Department of Surgery, University of Alberta, Edmonton, Alberta, Canada
\textsuperscript{b}Department of Internal Medicine, University of Alberta, Edmonton, Alberta, Canada
\textsuperscript{c}Department of Oncology, University of Alberta, Edmonton, Alberta, Canada

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Invasive lobular breast cancer; Gastrointestinal metastasis; Epidemiology

\textbf{Abstract}
\textbf{Background:} Invasive lobular carcinoma (ILC) comprises 5-16\% of all breast cancers, with its incidence gradually increasing. ILC has a disproportionately higher incidence of spread to the gastrointestinal (GI) system.
\textbf{Methods:} This study is a retrospective chart review of all cases of ILC with gastrointestinal metastases seen at a university affiliated tertiary cancer institute between 2005 and 2010, examining demographic, epidemiological, medical, and treatment factors that may have an association with the risk of GI metastases.
\textbf{Results:} 343 consecutive cases of lobular breast cancer were reviewed, and 21(6\%) were found to have GI metastases. The mean age at initial diagnosis of primary tumor was 63 years. Stages at presentation of the breast primary were: Stages 1/2\%=73\% and stages 3/4\%=27\%. Receptor status of the primary breast cancer was as follows: HER2+\%=5\%, PR+\%=76\%, ER+\%=90\%. The mean age at time of diagnosis of metastatic disease was 67 years. The main presenting symptoms of GI metastatic disease were: incidental finding/asymptomatic (20\%), nausea (20\%), and abdominal pain (15\%). The major sites of extrahepatic gastrointestinal spread were the stomach (52\%), peritoneum (38\%), and omentum (19\%). Average five-year survival from initial diagnosis of ILC was 46\%. Five-year survival from diagnosis of gastrointestinal metastasis was 29\%.
\textbf{Conclusions:} Approximately 1 in 20 patients diagnosed with ILC will have spread to the GI tract, presenting 4 years after their initial primary diagnosis. Future research is needed in...
1. Introduction

Breast Cancer is the most common malignancy in women. Invasive lobular carcinoma (ILC) comprises 5–16% of all breast cancer cases, making it the second most common type of breast cancer [1–4]. While lung, brain, liver, and bone comprise the most common sites of metastatic spread, it is not uncommon for breast cancer to metastasize to the gastrointestinal (GI) system in comparison to other types of breast cancer [1]. On a review of 12,001 patients with metastatic breast cancer, ILC accounted for 58% of the GI metastasis compared to 38% due to invasive ductal carcinomas (IDC), although ILC comprised only 12% of the total breast cancers. Post-mortem studies comparing metastatic ILC versus IDC found a significant propensity for metastatic spread of ILC to the stomach, intestine, and peritoneum compared to IDC [2,6]. Still, the literature on extrahepatic gastrointestinal metastatic lobular carcinoma is comprised mostly of individual case reports, small case series, or autopsy series [1,5].

It is not uncommon for patients to first present with symptoms associated with their GI metastatic disease, like early satiety, epigastric pain, and weight loss, as their initial presentation of their breast cancer rather than from mammogram findings or physical exam of the breast [3]. Case reports have even described a presumed gastric cancer, Linitis Plastica, as the first indication of ILC, which is an important diagnostic distinction from a primary gastric cancer as the treatment regimen is significantly different [5,7].

The aim of this study is to describe quantitative demographic, epidemiological, medical, and treatment factors, that may have an association with the risk of GI metastases. Our case series of 21 patients is one of the larger case series in the literature exclusively reporting on ILC with GI metastasis. We also review the literature on clinical presentation, diagnosis, and outcomes in patients with ILC metastasis to the extrahepatic gastrointestinal tract.

2. Patients and methods

After receiving ethics approval by the Research Ethics Office at the University of Alberta, a retrospective chart review was conducted of all patients seen at the Cross Cancer Institute in Edmonton, Alberta, Canada between 2005 and 2010, with a diagnosis of lobular breast cancer.

Only patients with a final pathological tissue diagnosis of invasive lobular breast cancer or mixed invasive lobular/ductal and had extrahepatic gastrointestinal metastatic disease were included. Exclusion criteria were any other pathological breast cancer. Two independent reviewers analyzed all records.

The outcomes of interest included: age at diagnosis, site of primary breast cancer, stage at initial presentation, hormone receptor status, site of gastrointestinal metastasis, time from diagnosis of breast primary to gastrointestinal metastasis, time from gastrointestinal metastasis to death, and treatment regimen for both primary and metastatic disease.

3. Results

During the 5-year study period, 343 consecutive cases of lobular breast cancer were reviewed, and 21 (6%) were found to have GI metastases and were included in this study.

3.1. Primary tumor patient demographics

Basic patient demographics were collected (Table 1). The mean and median age at initial diagnosis of the primary tumor were 63 (40–74) years and 61 years respectively. Patient initial presentation varied; routine mammogram (38%), palpable breast mass (38%), nipple inversion (14%), fatigue (5%), and abdominal pain (5%). Cases were equally distributed between both breasts, with 10/21 presentations in the right breast, and 11/21 in the left breast. The site of primary breast cancer was most commonly in the outer...
upper quadrant; 40% for the right breast, and 54.5% for the left breast.

Stage at presentation of the breast primary was: Stage 1A = 17%, Stage 1B/2A = 17%, Stage 2B = 22%, Stage 3A = 11%, Stage 3B = 6%, Stage 3C = 17%, and Stage 4 = 11%. Receptor status of the primary breast cancer was as follows: Human epidermal growth factor receptor 2 (HER2) was positive in 5.3%, Progesterone receptor (PR) was positive in = 76.2%, and Estrogen receptor (ER) was positive 90.5%.

Five-year survival from initial diagnosis of lobular breast cancer was 46% (Figure 1).

3.2. Treatment of primary tumor

Treatment at the time of diagnosis reflected the standard of practice for breast cancer with 17 of the 21 (81%) primary tumors being treated surgically; 8-mastectomy with axillary node dissection, 4- lumpectomy with axillary node dissection, 2- lumpectomy with sentinel node biopsy, 2- mastectomy with sentinel node biopsy, and 1-mastectomy. 13 patients (62%) received adjuvant hormonal therapy, 8 patients (38%) received adjuvant chemotherapy, 6 patients (29%) received adjuvant radiotherapy and 1 patient refused all treatment (5%).

3.3. Gastrointestinal metastatic disease demographics

The mean age at time of diagnosis of metastatic disease was 67 years (Table 2). The mean interval from primary diagnosis to the GI metastatic presentation was 4 years. The main initial patient presentations included; Asymptomatic (20%), nausea (20%), abdominal pain (15%), small bowel obstruction (10%), dysphagia (5%), and GI bleed (5%). Sites of gastrointestinal spread included; Stomach (52%), peritoneum (38%), omentum (19%), esophagus (10%), duodenum (5%), jejunum (5%), transverse colon (5%), and pancreas (5%). Six patients had multiple GI sites of involvement.

Palliative treatment, including surgery, chemotherapy and radiation for metastatic disease was delivered in 17/21 (80%) patients. Five-year survival from diagnosis of gastrointestinal metastasis was 29% (Figure 2). While there was no statistical difference between survival time in the treatment versus non treatment group, there is a suggestive trend that treatment improves mean survival (10.8 months versus 1.4 months). Due to the limited number of patients in the no palliative treatment group, the survival analysis was incomplete and did not reach significance (Figure 3). Palliative surgery (n=2) versus no surgery (n=19) was also found to not statistically improve survival outcomes, however results are limited due to the small numbers in the palliative surgery group (Figure 4).

Location of GI metastases was also analyzed. Patients with metastatic disease involving the stomach (39%) and omentum (40%) have improved 5-year survivals compared to other sites (Figure 5).

Table 2  Demographic of patients with extrahepatic gastrointestinal metastasis from primary invasive lobular carcinoma of the breast.

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Age at metastatic diagnosis (years)</th>
<th>Symptoms of GI disease (%)</th>
<th>Location of GI disease (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Asymptomatic</td>
<td>Stomach</td>
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<td></td>
<td>Median</td>
<td>Nausea</td>
<td>Peritoneum</td>
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<td></td>
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<td>Abdominal Pain</td>
<td>Omentum</td>
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<td></td>
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<td>Small Bowel obstruction</td>
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<td>Dysphagia</td>
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<td>GI bleed</td>
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<td>Transverse colon</td>
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<td>Pancreas</td>
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*6 patients had multiple site involvement

Figure 1  Kaplan Meier curve of overall survival of patients from diagnosis of primary invasive lobular carcinoma of the breast.
Figure 2  Kaplan Meier curve of overall survival of patients from diagnosis of extrahepatic gastrointestinal tract metastasis from invasive lobular carcinoma of the breast.

Figure 3  Overall survival benefit of combined palliative treatment versus no treatment upon initial diagnosis of extrahepatic gastrointestinal metastasis from invasive lobular breast cancer.

Figure 4  Overall survival benefit of palliative surgery versus no palliative surgery upon initial diagnosis of extrahepatic gastrointestinal metastasis from invasive lobular breast cancer.
4. Discussion

4.1. Invasive lobular carcinoma: a distinct entity

Invasive lobular carcinoma is a distinct tumor biology subgroup of breast cancer, a histologically heterogeneous disease [8]. Compared often to IDC, it has significantly different pathologic behavior that has marked clinical and treatment consequences. ILC is characterized by a unique growth pattern that displays an increased frequency for contralateral breast involvement and is often multifocal and multicentric [4,9]. Clinically, there is often a delay in diagnosis. The primary tumor is often missed on breast examination and screening mammogram, as it is less demarcated on physical examination and has more subtle mammographic features. For treatment, it is more difficult to achieve negative surgical margins in ILC tumors and an associated increased local recurrence rate has been described although this is debated in the literature [4,10]. It is therefore not surprising that the pattern of metastatic spread is also unique, as ILC has a disproportionate tendency for spread to the gastrointestinal tract [2,4]. Therefore, it is important to treat ILC as a distinct pathologic entity compared to the ductal variant of breast cancer.

Our study reported a GI metastasis rate of 6% of patients with ILC, which is within the 4-18% range quoted in the literature [11]. The explanation behind the tropism of ILC for the gastrointestinal tract remains to be clearly elicited, but e-cadherins and the unique microenvironment of the GI tract have been implicated. E-Cadherins are epithelial specific cell-to-cell adhesion molecules that are responsible for the maintenance of differentiation and prevention of invasion. In normal glands, these molecules are well expressed at the borders of epithelial cells and the loss of these molecules have been implicated in lobular breast carcinomas [12]. Studies looking at E-Cadherin expression found that ILCs, in contrast to IDCs, stained negative for E-Cadherins [12,13]. Therefore, ILCs form irregularly bordered tumors with diffuse infiltration, are more invasive and dedifferentiated, contrary to IDCs, which form cohesive tumor groups [14]. While this does not explain why ILC spreads specifically to the GI system, but it confirms the fact that it has a distinct method of cellular invasion. Other genes involved in lipid/fatty acid metabolism, immune defense, stress responses, electron transport and nucleosome assembly have also been implicated in the dissimilar metastatic dissemination between the groups [15]. Other theories on the predilection for the GI tract postulate that potentially the unique microenvironment of the gastrointestinal tract allows for proliferation of the tumor cell by providing the necessary building blocks for survival or the morphology of tumor cell shape might favor being trapped in the microanatomy of the GI tract [8].

4.2. Diagnostic uncertainty

Patients presenting with GI metastasis can be challenging diagnostically. Symptoms range widely from patients being relatively asymptomatic to complaining of vague, non specific GI symptoms of nausea, abdominal pain, and dysphagia to more alarming symptoms of bowel obstruction and GI bleed. Clinicians need to maintain a high index of suspicion in patients with a history of breast cancer presenting with gastrointestinal complaints, regardless of how remote the breast cancer. Our study reported a 4 year mean interval time from diagnosis of primary breast cancer to the development of GI metastasis, but there are literature case reports published about patient presentations with GI metastasis as long as 30 years later [11]. The disease free interval can be so markedly prolonged that case reports have commented that the patient will often forget to even report their history of breast cancer on the initial surgical consult [5,16].

To make a challenging clinical situation even more difficult, lobular breast cancer metastases can mimic several forms of primary gastric cancer: diffuse gastric infiltration can appear similar to limitis plastica type infiltration and localized infiltration can be confused with small polyps that can appear like a gastrointestinal stromal tumor (GIST) [17]. Comparisons using immunohistochemistry, including estrogen/progesterone receptor status, gross cystic disease fluid protein (GCDFP) and cytokeratin expression, should be performed on/between the primary breast cancer (if possible) and the gastrointestinal specimen in all patients with a
history of previous breast cancer with a new diagnosis of a GI neoplasm [16]. Unlike gastric cancers, metastatic lobular cancers show strong estrogen receptor positivity (72%), moderate progesterone positivity (33%), GCDFP reactivity (78%), and cytokeratin 5 and 6 reactivity (61%). Another confounding factor is that there are reports of lobular breast cancers containing signet rings cells, which could confuse the pathologist in incorrectly diagnosing a gastric primary [18].

4.3. Survival comparisons

It appears that there could be a survival benefit with the addition of palliative intervention upon the presentation of metastatic gastrointestinal disease. However, due to this study’s small sample size, significant conclusions are limited. Palliative therapy for metastatic breast cancer is supported by the literature and is generally associated with a survival benefit [19-21]. Localization of extrahepatic GI metastasis to the stomach and omentum are observed to be associated with more favorable outcomes, although not statistically significant. This could be due to the earlier presentation of these patients’ symptoms with more proximal GI obstruction.

Five-year survival from diagnosis of ILC gastrointestinal metastasis was 29%. This is similar to the reported 5-year survival rate of 25% reported in 2013 by the National Cancer Institute for metastatic breast cancer of all ages [22]. Reported survival rates from metastatic breast cancer are improving in the literature with the advent of newer chemotherapy and targeted therapeutic agents, advances in imaging technology and improved understanding of new cancer pathways [23]. Compared to IDC, ILC has more favorable histopathologic markers, increased ER receptor positivity (76% versus 59.5%), low nuclear grade and reduced HER-2 positivity [9,10]. HER-2 is associated with a more aggressive form of breast cancer with decreased overall survival, therefore, intuitively lower expression of this growth factor receptor gene should translate with survival benefits but this is debated [9,10,24]. Studies have shown mixed evidence that ILC is associated with a similar [25], worse [10,26] or better [8,27] prognosis compared to IDC.

4.4. Treatment of ILC

Interestingly, in our data set, mastectomy was used in 11 of 21 patients, while breast-conserving therapy was only performed in 6 of 21 patients. This likely speaks to the difficulty in establishing tumor margins more than the surgeon worrying about the risk of local recurrence, as this point is debated in the literature. A mini review of the literature in 2008 found 7 studies that reported on 5-year local recurrence rates comparing ILC and IDC, and found mixed results [10]. However one study found that ILC treated by lumpectomy is 2 times more likely to be intraoperatively converted to a mastectomy [28].

Palliative systemic hormone therapy is the primary treatment modality of patients with progression of disease to other organs including the GI tract [29]. Surgery is usually only reserved for the complications of disease, including obstruction, bleeding and perforation [29].

5. Conclusions

Approximately 1 in 20 patients diagnosed with a primary breast cancer of lobular histology will have metastatic spread to the GI tract, presenting approximately 4 years after their initial primary diagnosis. The most common presentation of metastatic disease is nausea and abdominal pain, with the most common site of spread being the stomach. There remains a paucity of data in the literature and our project is one of the first to further characterize these patients. Future research is needed in developing treatment regimens for these patients, as the 5-year survival is only approximately 1 in 4.

Conflicts of interest

The authors have no conflicts of interests to declare.

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None.

References


