

Lobular breast cancer: patterns of intraabdominal metastatic spread on imaging and prognostic significance

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Abstract

Objective: To retrospectively review the frequency, patterns and intra-abdominal sites of metastatic invasive lobular breast cancer, and to correlate the findings with overall survival.

Materials and methods: From a pathology database search revealing 327 patients with metastatic lobular breast cancer at our institution from January 2004 through August 2014, imaging was available in 116 patients (age range, 31–87 years, mean age, 55). Simple descriptive statistics were performed to record and tabulate the abdominal metastatic spread. Prognostic significance of abdominal metastases and individual abdominal metastatic sites was studied using the Log-rank test and construction of Kaplan–Meier curves.

Results: The most frequent sites of intra-abdominal metastatic invasive lobular breast cancer were peritoneum (55 patients, 47%), followed by liver (37 patients, 32%), bowel (34 patients, 29%), ovary (33 patients, 28%), retroperitoneum (16 patients, 14%), ureter (16 patients, 14%), and lymph nodes (15 patients, 13%). Bowel obstruction was noted in 15 patients (13%) and hydronephrosis in 25 patients (22%). The median abdominal metastasis-free survival was 76 months (interquartile range: 17–191). The overall survival (OS) was 86 months (interquartile range: 49–188). Patients with abdominal metastases had shorter OS. Patients with hepatic metastases had shorter overall survival than those patients without hepatic metastases ($p = 0.02$, Log-Rank test).

Conclusion: Invasive lobular breast cancer has a predilection for metastasizing to both typical (liver) and atypical intra-abdominal sites (peritoneum, GI tract, and adnexa). Presence of intra-abdominal disease and hepatic metastases in patients with ILC negatively affects overall survival.

Key words: Invasive lobular—Breast cancer—Metastases—CT

Breast cancer is the most common cancer among women, and the 2nd most common cause of cancer mortality in women in the US [1]. Invasive lobular carcinoma (ILC) is the second most common subtype of breast cancer after invasive ductal carcinoma (IDC), and represents approximately 10% of all invasive breast cancers [2]. IDC and ILC are histologically distinct diseases, and although both may metastasize to the liver and bone, ILC reportedly more frequently involves the peritoneum, GI tract and gynecologic organs [3–10]. Winston et al., in a retrospective study of 57 women with metastatic lobular carcinoma of the breast, described patterns of spread throughout the chest, abdomen and pelvis on CT [11]. In addition, there have been numerous case reports of gastric/bowel involvement from lobular breast cancer metastases [12–17]. However, a PubMed search revealed no radiologic studies that specifically correlated the incidence of abdominal metastases in ILC patients with overall survival. The purpose of this study was to retrospectively review the common sites of intra-abdominal metastases of ILC on CT scan in a large cohort of patients and to determine if specific sites have prognostic significance. In this era of precision oncology, knowledge of the predilection for spread and careful evaluation of

these sites is important in the imaging assessment of all patients with a history of ILC.

Materials and methods

Setting and subjects

In this institutional review board-approved, HIPAA-compliant, retrospective study performed at a tertiary cancer institute, our pathology electronic database search for “metastatic lobular” from January 2004 to August 2014 revealed 327 patients with metastatic lobular breast cancer. Electronic medical records were manually reviewed to confirm the diagnosis and record demographic data and date of diagnosis of breast cancer. Of the 327 identified patients, 164 patients underwent imaging at our institution, of which 48 were excluded due to inadequate imaging (imaging studies were incomplete or not available for review). The remaining 116 patients (age range, 31–87 years, mean age, 55) comprised the final study population.

Imaging parameters

The CT protocol for abdomen and pelvis in patients with breast cancer at our institute includes portal venous phase imaging (at 60–70 s) of the abdomen and pelvis. The CT scans were performed on multidetector scanners (four-slice (GE Healthcare, Barrington, IL, USA), 16-row (Siemens Medical Solutions, Forchheim, Germany), and 64-row (Toshiba America Medical Systems, Tustin, CA, USA)) with 0.5 mm collimation, 120 kVp, 500 mA (max), gantry rotation time 0.5 s, table speed of 26.5 mm/rotation). Intravenous contrast, 75–100 mL of iopromide (300 mg I/mL; Ultravist 300; Bayer HealthCare Pharmaceuticals, San Francisco, California) was administered with an automated injector (Stellant; Medrad, Warrendale, Pennsylvania) at a rate of 2–3 mL/s. Oral contrast, 500 mL of 2–4% gastrograffin or omni-paque 240, was administered 1.5–2 h prior to the CT scans. Axial and coronal images with 5 and 4 mm thickness, respectively, reconstructed with standard abdominal algorithm were available in all the patients.

Image review

All available CT images of these patients were retrospectively reviewed by a senior radiologist specializing in cancer imaging, with 23 years experience, to record the sites and imaging features of intra-abdominal metastatic lesions. The radiologically detected metastatic lesions were confirmed with pathologic correlation of at least one metastatic site wherever possible ($n = 60$). However, in routine practice metastatic disease is often not pathologically confirmed, in which case metastatic disease was confirmed using correlation with clinic notes, presence of new lesions, elevation of tumor

markers, and/or displayed changes in accordance with any known metastatic lesions.

The radiologist recorded the distribution of metastatic sites in the abdomen, as well as presence or absence of hydronephrosis and bowel obstruction. For peritoneal carcinomatosis, presence of omental or peritoneal nodules, omental thickening/mass, diffuse or focal peritoneal thickening was recorded. The presence and volume of ascites (mild-moderate or large) was recorded; however, simple ascites without any of the other features of peritoneal disease was not considered peritoneal carcinomatosis. Sites and extent of bowel involvement were recorded, including presence of bowel wall thickening, and if present, length of thickened segment (short arbitrarily determined as being < 10 cm and long arbitrarily determined as being > 10 cm), presence of discrete serosal nodules, and whether disease occurred at a single site or was multifocal. When present, date and site of 1st bowel obstruction, as well as presence/absence of a clear transition point at the time of bowel obstruction were recorded. The presence of upper abdominal, mesenteric, retroperitoneal, and pelvic lymphadenopathy was noted. Lymph nodes that measured greater than 1 cm in short axis were considered abnormal. The presence/absence of retroperitoneal infiltrative tissue and ureteric wall thickening were noted. Finally, the presence of ovarian masses, whether unilateral or bilateral, the size of the largest ovarian mass, and composition (solid, cystic or mixed) were recorded. Presence or absence of hepatic metastases was also recorded; however, given the similar incidence of hepatic metastases in both IDC and ILC [3–7], we did not focus on the specific number or appearance of hepatic metastases.

The date of the first abdominal metastasis was recorded. The survival information was recorded from the electronic medical records. Patients who were lost to follow-up were right censored at the time of the last known follow-up. The median follow-up duration was 146 months (interquartile range: 86–320).

Statistical analysis

Simple descriptive statistics were performed to record and tabulate the abdominal metastatic spread. The prognostic significance of abdominal metastases and individual abdominal metastatic sites was studied using the Log-rank test and construction of Kaplan–Meier curves.

Results

Frequency of metastatic disease

Of total 116 patients included in this study, 72 (62%) patients (age range, 36–80 years, mean age, 54) had radiographic evidence of intra-abdominal metastases.

The remaining 44 patients had distant metastases, but at sites outside the abdomen.

The most frequent first site of abdominal metastasis was liver (28/116, 24%), followed by peritoneum (27/116, 23%), ovary (23/116, 20%), bowel (13/116, 11%), ureter (6/116, 5%), retroperitoneum (4/116, 3%), and lymph nodes (2/116, 2%). 30/116 patients (26%) presented with two or more synchronous metastatic sites at presentation.

During the follow-up period of median 146 months, the most common abdominal metastatic sites were peritoneum (55/116 patients, 47%), followed by liver (37/116 patients, 32%), bowel (34/116 patients, 29%), ovary (33/116 patients, 28%), retroperitoneum (16/116 patients, 14%), ureter (16/116 patients, 14%), and lymph nodes (15/116 patients, 13%) (Table 1).

Bowel involvement

Of the 34 patients with bowel involvement, the disease was distributed throughout the gastrointestinal tract, with slight colonic predominance: colon/rectum (26 patients, 76%), small bowel (21 patients, 62%), stomach (21 patients, 62%), and appendix (1 patient, 3%) (Table 2). Bowel was involved at multiple sites in 25 patients (74%), and at a single site in 9 patients (26%). Of those patients involving a single gastrointestinal site, 5 involved the stomach, 2 involved colon, 1 small bowel, and 1 appendix. Metastases typically presented as bowel wall thickening ($n = 34$), with short segment (< 10 cm) involvement in 8 patients and long segment (> 10 cm) involvement in 3 patients; 23 patients had both short and long segments detected radiographically (Fig. 1). A discrete serosal nodule was seen in only 1 patient. 15 patients developed bowel obstruction, with a clear transition point evident in 13 patients (87%), including the ileum (6), colon (3), gastric outlet (2), duodenum (1), and jejunum (1).

Peritoneal involvement

Peritoneal disease was the most common site of metastatic disease overall, seen in 55 of 116 patients (47%). Of these 55 patients, 40 patients (73%) had peritoneal thickening, 12 patients (22%) had discrete peritoneal

Table 1. Sites of intra-abdominal metastatic disease in 72 patients

Site	No. (%) of patients
Peritoneum	55 (47)
Liver	37 (32)
Bowel	34 (29)
Ovary	33 (28)
Retroperitoneum	16 (14)
Ureter	16 (14)
Lymph nodes	15 (13)
Total	72*

*63 Patients (88%) had more than one site of intraabdominal disease

Table 2. Sites of gastrointestinal involvement in 34 patients

Site	No. (%) of patients
Colon/rectum	26 (76)
Small bowel	21 (62)
Stomach	21 (62)
Appendix	1 (3)
Total	34*

*Bowel was involved at multiple sites in 25 patients (74%)

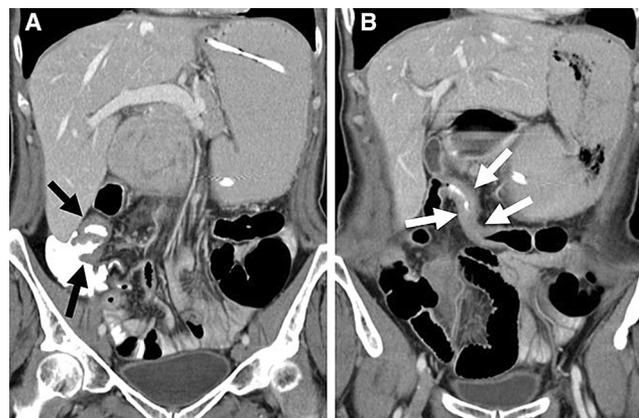


Fig. 1. 68-year-old female with history of invasive lobular breast carcinoma presents with abdominal pain, nausea and vomiting. Coronal reconstructed abdominopelvic CT obtained following NG-tube placement reveals short (A) and long (B) areas of bowel wall thickening involving the ileocecal region (black arrows) and transverse colon (white arrows), respectively.

nodules, 36 patients (65%) had omental involvement, presenting as discrete nodules in 6 patients (11%), omental “cake” in 6 patients (11%), and ill-defined nodularity/thickening in 24 (44%) patients (Fig. 2). Peritoneal thickening along the superior bladder wall was detected in 18/55 patients (33%) (Fig. 3).

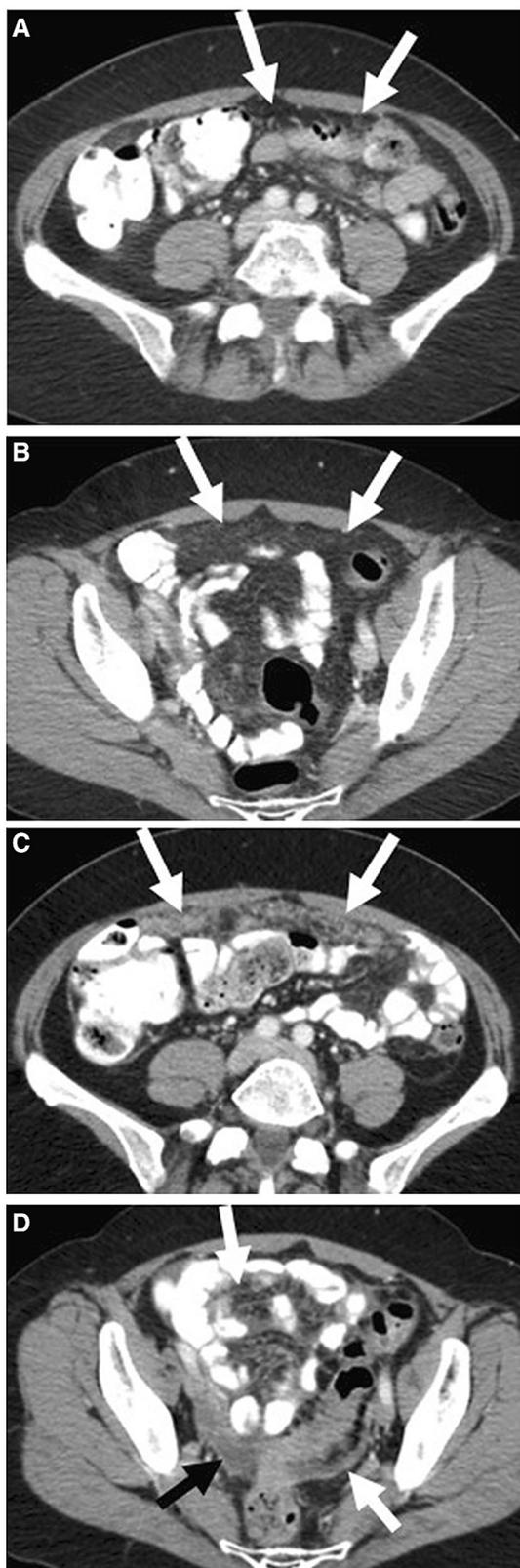
Ascites was noted in 51/116 patients (44%), mild to moderate in 42 patients and large in 9 patients. Of the 51 patients with ascites, other signs of peritoneal disease were evident in 49 patients; the remaining 2 patients had hepatic metastases.

Adnexal involvement

Of 33 patients with ovarian involvement, 28 (85%) had bilateral disease (Fig. 4), and 5 (15%) had unilateral ovarian involvement. The mean size of ovarian masses was 4.4 cm (range, 2.5–8 cm). Ovarian masses were mixed cystic and solid in 20 patients (61%) and solid in 13 (39%).

Nodal involvement

Lymphadenopathy was the least common intra-abdominal manifestation of metastatic lobular breast cancer. Of



◀**Fig. 2.** 57-year-old female with ILC and rising tumor markers. Axial contrast enhanced abdominopelvic CT scan reveals subtle nodularity in the omentum (**A**, arrows) and pelvic peritoneum (**B**, arrows). Four months later, abdominopelvic CT scan shows marked progression, with omental “cake” (**C**, arrows), marked pelvic peritoneal thickening (**D**, white arrows), and new ascites (d, black arrow).

15 patients with nodal involvement, upper abdominal nodes were involved in 9 patients (60%), retroperitoneal nodes in 9 patients (60%), pelvic nodes in 3 patients (20%), and mesenteric nodes in 2 patients (13%).

Retroperitoneal and ureteric involvement

Infiltrative retroperitoneal tissue and/or ureteric thickening were noted in 25/116 patients (22%). Hydronephrosis was also present in 25 patients (22%) (Fig. 3).

Hepatic metastases

The liver was the most common first site of abdominal metastasis, seen in 28 patients (24%). During the follow-up period, hepatic involvement was seen in 37 patients (32%), the second most common intra-abdominal site after peritoneum.

Correlation of metastasis with survival

The median abdominal metastasis-free survival was 76 months (interquartile range: 17–191). The overall survival (OS) for the 116 patients in our study was 86 months (interquartile range: 49–188 months). Patients with abdominal metastases were associated with a shorter OS (median 78 months, interquartile range 46–173 vs. median 175 months, interquartile range 73–337; $p = 0.02$) (Fig. 5). The median overall survival for patients with hepatic metastases was 73 months (interquartile range, 45–114 months), and for patients without hepatic metastases was 135 months (interquartile range 63–227 months). Patients with hepatic metastases had shorter overall survival than those patients without hepatic metastases ($p = 0.02$, Log-Rank test) (Fig. 6). No other specific site of intra-abdominal disease, nor the presence of bowel obstruction or hydronephrosis had a statistically significant effect on overall survival.



Fig. 3. 48-year-old women who first presented with metastatic invasive lobular breast cancer to adnexa, subsequently developed infiltrative retroperitoneal soft tissue (**A**, black arrows) and hydronephrosis (**A**, white arrows), as well as serosal encasement of the bladder (**B**, arrows).

Discussion

Multiple prior studies have compared the patterns of metastatic disease of IDC and ILC, noting similar incidence and appearance of hepatic metastases [3–7].

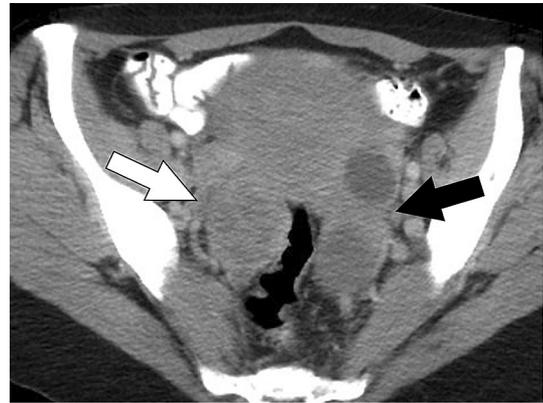


Fig. 4. 51-year-old female presented with denovo metastatic invasive lobular breast cancer to bones, endometrium, and bilateral ovaries (arrows). Abdominopelvic CT reveals predominantly cystic left ovarian metastasis with thick septation (black arrow) and heterogeneous, solid right ovarian metastasis.

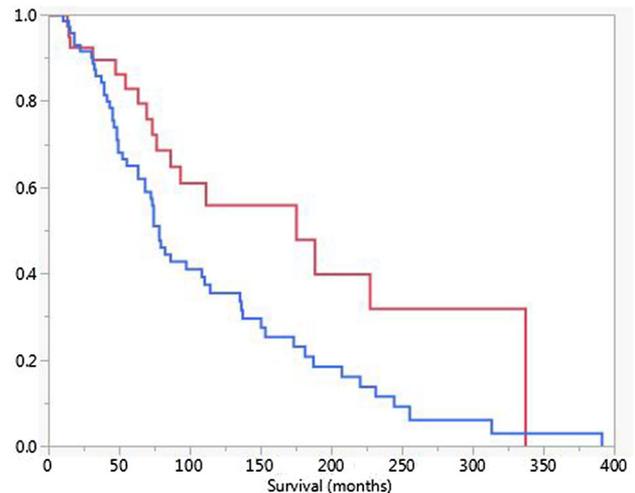


Fig. 5. Kaplan–Meier survival curves showing a statistically significant difference in the overall survival between ILC patients with (blue line) and without (red line) abdominal metastatic disease.

However, atypical sites of abdominal spread have been reported to occur much more commonly in patients with ILC [3–10]. In this study, we retrospectively reviewed metastatic patterns of invasive lobular breast carcinoma within the abdomen and pelvis, including sites that are atypical for IDC metastases, but known to occur in ILC. Familiarity with the manifestations of lobular breast cancer metastases to the abdomen, which can develop remote from diagnosis and present as a first sign of recurrent disease [6, 9], is important. Given their propensity for bowel, ovaries, and the peritoneum/retroperitoneum, metastases may be radiographically indistinguishable from sites of primary disease. However, knowledge of the clinical history of invasive lobular

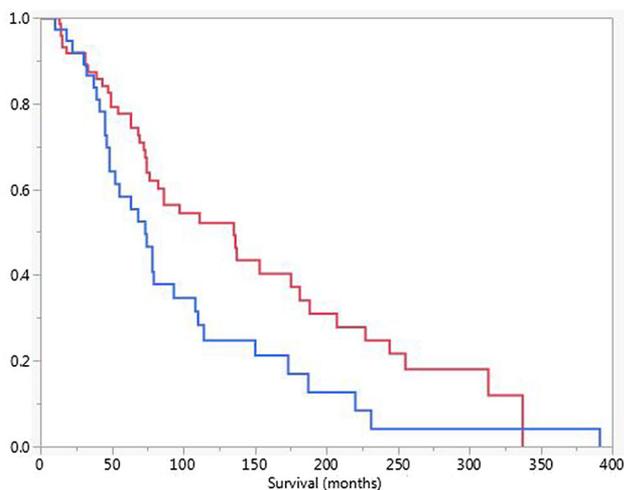


Fig. 6. Kaplan–Meier survival curves showing a statistically significant difference in the overall survival between patients with (blue line) and without (red line) hepatic metastatic disease from ILC.

breast cancer and awareness of its tendency for metastasizing to these specific sites can direct appropriate immunohistochemical staining, which may help to distinguish between metastatic ILC and a new primary malignancy, thus affecting therapeutic decisions [10].

In our series, the most common first sites of abdominal metastases were to the liver (24%) and peritoneum (23%). Overall, peritoneal involvement was most common (47%), followed by liver (32%), bowel (29%), and ovarian (28%) involvement. Peritoneal disease was reported in 30% of patients in Winston’s study [11], with similar rates of hepatic (32%) and bowel (32%), though less adnexal involvement (21%). In their autopsy series, Lamovec et al. reported incidences of 60% peritoneal involvement, 68% hepatic, 60% bowel, and 52.2% ovarian metastases [5]. Harris et al. reported 93% peritoneal/retroperitoneal involvement in their post-mortem series (though did not separate retroperitoneum from peritoneum), 43% hepatic involvement and 36% ovarian metastases [3]. Although less than autopsy studies, our higher detection of peritoneal involvement when compared to Winston may, in part, relate to improvements in radiologic techniques and increased frequency of imaging follow-up, with improved sensitivity of subtle peritoneal stranding/nodularity. Of note, in the largest study, Borst et al. included patients diagnosed with metastatic breast cancer from 1973–1990 with “clinically evident disease”, diagnosed via “histologic examination, radiologic studies and physician surveys”, and reported significantly lower incidences of gastrointestinal (4.5%), gynecologic (4.5%), and peritoneal-retroperitoneal (3.1%) involvement [4]. Given the less sensitive radiologic techniques available, the non-clinically evident or early metastatic disease may have been missed or not evaluated radiographically. In

addition, the continually improving therapies available for breast cancer patients allow them to live longer, and potentially develop new and/or more disease sites, which we may have captured in our more recent study.

Although Winston did not further describe the radiographic appearance of peritoneal involvement, in our study, peritoneal disease most commonly presented as diffuse or focal peritoneal and/or omental thickening (51 patients, 93%). Discrete peritoneal or omental nodules or omental cake were less commonly seen. Bladder wall thickening was noted in 33% of those patients with peritoneal involvement (Fig. 3). Harris et al. described autopsy findings of “tiny nodules, tending to become confluent” [3] which would explain the typical radiographic appearance that we noted. As metastatic lobular breast cancer most commonly involved the peritoneum, and may often present as very subtle peritoneal thickening/nodularity (Fig. 2), it is imperative that radiologists be cognizant of this potential site of early metastatic disease.

The incidence and prevalence of different gastrointestinal sites varies slightly in our cohort when compared to earlier studies. Overall, bowel metastases were seen in 29% of patients with intrabdominal disease, with slight colonic predominance (76%) over stomach and small bowel (62% each), and appendix (1 patient, 3%). Of the 4.5% of patients with GI involvement in Borst’s study of 359 ILC patients, 50% involved small bowel, 19% involved stomach, and 13% effected colon/rectum [4]. In their autopsy series, Lamovec reported 40% intestinal involvement and 20% gastric involvement [5], while Harris reported 43% gastric and 29% intestinal involvement [3], neither further specifying intestinal sites nor size/appearance of metastases. Winston reported a much lower incidence of GI metastases, including 26% colonic, 16% gastric, and 11% small bowel metastases [11]. They attributed this to the lack of tailoring their CT protocols for specific GI tract evaluation. In both our study and Winston’s, a single case of appendiceal involvement was included; in our series, this was first detected on CT, and corresponded with increased tumor markers.

Bowel wall thickening was the most common appearance of gastrointestinal involvement in our series, more commonly involving a short segment (< 10 cm) than long segment (> 10 cm), and 2× more likely to involve multiple sites than a single site (Fig. 1). A single patient was noted to have a discrete serosal nodule, however, this was in conjunction with other sites of bowel disease, including both long and short segments of wall thickening. Harris described a distinctive pathologic appearance, with diffuse infiltration of carcinoma cells into the serosa, muscularis propria, submucosa and mucosa, causing a linitus-plastica type appearance when involving the stomach, with associated deep ulcers in a single case [3]. On CT, Winston et al. described all metastases as areas of bowel wall thickening, specifically noting the absence of

any isolated mural masses [11]. El-Hage et al., in their study of 74 patients with metastatic ILC with an emphasis on gastric metastases, described three types: diffuse (including linitis plastica with thickened folds and diffuse invasion), ulcerated nodular invasion, and external compression, noting the diffuse type was the most common, seen in 80% of their patients with gastric metastases [18]. Metastatic lobular breast cancer is a particular pitfall for pathologists, as it can be histologically identical to signet ring cell carcinoma of the stomach, and proper immunohistochemistry must be performed to differentiate the two [19]. Thus, when a biopsy is performed, clinical history or suspicion for lobular breast cancer metastasis should be conveyed to the pathologist.

Harris et al. described hydronephrosis as a common secondary phenomenon [3], though Winston et al. specifically attribute hydronephrosis to “metastatic infiltrate of the retroperitoneum” in 11% of their patients [11]. We noted hydronephrosis in 22% of patients, but directly related to retroperitoneal stranding in only 24% of these patients (Fig. 3), and attributable to ureteral wall involvement in 36%; in 24%, both retroperitoneal stranding and ureteral wall thickening were evident. Of note, 4 patients (16%) with hydronephrosis had no radiographically apparent retroperitoneal stranding nor ureteral wall thickening. Geller et al. noted ureteral involvement in 8.3% of 181 patients with metastatic breast cancer; but did not specify the breast cancer subtype [20]. Merino and Livolsi reported hydronephrosis in 5 of 24 patients (21%) with signet ring cell carcinoma (all of invasive lobular breast origin), noting histologic confirmation of tumor cells infiltrating the ureters in all cases [21].

In a retrospective study of 96 patients with metastatic ILC compared to 2749 patients with metastatic IDC, Ferlicot et al. noted a significantly wider distribution of metastases in cases of ILC than IDC. They reported synchronous secondary visceral sites at the first diagnosis of metastases in 25% of ILC patients vs. 15.8% of those with IDC, attributing the finding potentially to the phenotypic trait of discohesive small cells related to E-cadherin loss seen in the majority of ILC cases [22]. We noted the presence of radiographically detectable synchronous metastases in 42% of our study population, though included the peritoneum in addition to viscera.

The data from our study suggest that the presence of abdominal disease in patients with ILC has a statistically significant negative effect on OS, decreasing from 175 months (range, 73–337 months) in patients without radiographic evidence of abdominal disease, to 78 months (range, 46–173 months) in patients with radiologic evidence of abdominopelvic metastases (Fig. 5). In further evaluating this group, with respect to common sites of disease, and presence or absence of bowel obstruction or hydronephrosis, the only statistically significant variable was the presence of hepatic

involvement by ILC (Fig. 6). In this subgroup, overall survival decreased from 135 months (range, 63–227) to 73 months (range, 45–114).

Limitations of our study include its retrospective design, as well as our selection of patients from a tertiary cancer center, where the patient population includes referral of often complex cases, that might not reflect tumor behavior in the general population. Although imaging parameters were constant, CT scans were performed on different model scanners, with minor differences in resolution, a limitation of a retrospective study. In addition, imaging studies were at variable intervals, based on clinical parameters, and the number of available studies per patient differed. Over the course of our study, both diagnostic and therapeutic regimens evolved, thus patients received various treatment regimens. Finally, a single radiologist performing the interpretations did not allow for concordance validation.

In conclusion, we found the predilection of ILC to metastasize to both typical (liver) and atypical intra-abdominal sites (peritoneum, GI tract, and adnexa). The incidence of involvement of various sites was higher in our cohort than in prior imaging studies, likely due to a combination of improved imaging techniques, more regular imaging follow-up and improved management leading to longevity of patients with metastatic disease. In addition, we noted that the presence of intra-abdominal disease and hepatic metastases in patients with invasive lobular breast cancer negatively affects overall survival. Early metastases to the abdomen may be indistinct and overlooked, and may occur years after primary disease. In the era of precision oncology, knowledge of the predilection for spread and careful evaluation of these sites is important in all patients with a history of ILC. Subtle changes should be noted, and their potential indication of early abdominal recurrence conveyed to the referring clinician.

Compliance with ethical standards

Conflict of interest Pamela J. DiPiro declares that she has no conflict of interest. Sree Harsha Tirumani declares that he has no conflict of interest. Gisele P Cruz declares that she has no conflict of interest. Nikhil H Ramaiya declares that he has no conflict of interest. Susan C Lester declares that she has no conflict of interest. Atul B. Shinagare is a consultant for Arog Pharmaceuticals and has received research funding from GTx, Inc.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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