Thieme

Distinct Pattern of Metastases in Patients with Invasive Lobular Carcinoma of the Breast

Typische Metastasierungsmuster bei Patientinnen mit invasiv-lobulärem Mammakarzinom

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ABSTRACT

Background Invasive lobular carcinoma (ILC) comprises around 10–15% of invasive breast cancers. Few prior studies have demonstrated a unique pattern of metastases between ILC and the more common invasive ductal carcinoma (IDC). To our knowledge, such data is limited to first sites of distant recurrence. We aimed to perform a comparison of the metastatic pattern of ILC and IDC at first distant recurrence as well as over the entire course of metastatic disease.

Methods We used a prospectively collated database of patients with metastatic breast cancer. Breast cancer recurrence or metastases were classified into various sites and a descriptive analysis was performed.

Results Among 761 patients, 88 (11.6%) were diagnosed with ILC and 673 (88.4%) with IDC. Patients with ILC showed more frequent metastases to the bone (56.8 vs. 37.7%, $p = 0.001$) and gastrointestinal (GI) tract (5.7 vs. 0.3%, $p < 0.001$) as first site of distant recurrence, and less to organs such as lung (5.7 vs. 24.2%, $p < 0.001$) and liver (4.6 vs. 11.4%, $p = 0.049$). Over the entire course of metastatic disease, more patients with ILC had ovarian (5.7 vs. 2.1%, $p = 0.042$) and GI tract metastases (8.0 vs. 0.6%, $p < 0.001$), also demonstrating reduced tendency to metastasize to the liver (20.5 vs. 49.0%, $p < 0.001$) and lung (23.9 vs. 51.9%, $p < 0.001$). All associations but bone held after sensitivity analysis on hormonal status. Although patients presenting with ILC were noted to have more advanced stage at presentation, recurrence-free survival in these patients was increased (4.8 years vs. 3.2 years, $p = 0.017$). However, overall survival was not (2.5 vs. 2.0 years, $p = 0.75$).

Conclusion After accounting for hormone receptor status, patients with IDC had greater lung/pleura and liver involvement, while patients with ILC had a greater propensity to develop ovarian and GI metastases both at first site and overall. Clinicians can use this information to provide more directed screening for metastases; it also adds to the argument that these two variants of breast cancer should be managed as unique diseases.

ZUSAMMENFASSUNG

Einleitung Invasiv-lobuläre Karzinome (ILC) machen rund 10–15% aller invasiven Brustkrebserkrankungen aus. Einige frühere Studien haben gezeigt, dass das ILC und das häufiger anzutreffende invasiv-duktale Karzinom (IDC) jeweils eigene Metastasierungsmuster aufweisen. Soweit uns bekannt ist, beschränken sich diese Daten auf die Lokalisation der ersten Fernrezidive. Ziel dieser Studie war es, die Metastasierungsmuster von ILC und IDC bei den ersten Fernrezidiven sowie über den gesamten Verlauf der Metastasierung zu vergleichen.

Methoden Grundlage der Studie war eine prospektiv zusammengestellte Datenbank von Patientinnen mit metastasiertem Brustkrebs. Brustkrebsrezidive bzw. Metastasen wurden nach deren Lokalisation klassifiziert, und die Daten wurden einer deskriptiven Analyse unterzogen.

Ergebnisse Unter 761 Patientinnen wurde bei 88 (11,6 %) die Diagnose ILC gestellt und bei 673 (88,4 %) die Diagnose IDC. Bei Patientinnen mit ILC traten die ersten Fernrezidive häufiger in Form von Knochenmetastasen (56,8 vs. 37,7 %, p = 0,001) und Metastasen des Magen-Darm-Trakts auf (5,7 vs. 0,3 %, p < 0,001) und nicht in Organen wie Lunge (5,7 vs. 24,2 %, p < 0,001) oder Leber (4,6 vs. 11,4 %, p = 0,049). Über den gesamten Verlauf der metastatischen Erkrankung waren Ovarialkarzinome (5,7 vs. 2,1 %, p = 0,042) und Metastasen des Magen-Darm-Trakts (8,0 vs. 0,6 %, p < 0,001) häufiger bei Patientinnen mit ILC anzutreffen, wohingegen Metastasen in der Leber (20,5 vs. 49,0 %, p < 0,001) und der Lunge (23,9 vs. 51,9 %, p < 0,001) weniger häufig vorkamen. Nach Beachtung des Hormonstatus wurden alle Zusammenhänge außer Knochenmetastasen in der Sensitivitätsanalyse bestätigt. Obwohl das Erkrankungsstadium bei der Erstvorstellung von Patientinnen mit ILC fortgeschrittener war, hatten diese Patientinnen ein höheres rezidivfreies Überleben (4,8 Jahre vs. 3,2 Jahre, p = 0,017). Trotzdem hatten diese Patientinnen kein längeres Gesamtüberleben (2,5 vs. 2,0 Jahre, p = 0,75).

Schlussfolgerung Nach Berücksichtigung des Hormonrezeptorstatus wiesen Patientinnen mit IDC eher Metastasen in der Lunge/der Pleura und in der Leber auf, wohingegen Patientinnen mit ILC stärker dazu neigten, Ovarialmetastasen sowie Metastasen des Magen-Darm-Trakts zu entwickeln. Diese Information erlaubt den Klinikärzten, beim Screening gezielter nach Metastasen zu suchen; es verstärkt auch das Argument, dass diese 2 Brustkrebsvarianten als separate Erkrankungseinheiten zu behandeln sind.

Introduction

Invasive lobular carcinoma (ILC) is the second most common histologic type of breast cancer with an incidence of 10–15 %. Data from the Surveillance, Epidemiology, and End Results (SEER) registry have shown that the incidence of ILC has been increasing, while the incidence of invasive ductal carcinoma (IDC), the most common histology in breast cancer, has remained essentially constant [1]. ILC is more than just a histologic variant of breast cancer; it has distinct molecular, morphologic, biologic and epidemiologic characteristics, which have clinical and prognostic implications [2–6]. In ILC, small cells tend to infiltrate the stroma in long, single-file sheets. E-cadherin loss, present in 90 % of ILC cases, is considered the hallmark lesion of ILC. Patients with ILC have a higher frequency of multifocal and bilateral tumors [3, 7]. Mammography in the setting of ILC is challenging due to its infiltrative growth pattern, which frequently delays the diagnosis [8, 9]. ILC is associated with older patient age, and ILC tumors are often larger size, better differentiated, and exhibit higher levels of estrogen receptor (ER) positivity [2, 5]. In a genome-wide analysis of predisposition polymorphisms specific to invasive lobular carcinoma, there was a notable overlap with susceptibility polymorphisms to ER-positive tumors [10]. ILC tumors also tend to have lower Ki-67 expression and be HER-2 and p53 negative [11]. Of all breast cancer subtypes, mutations targeting PTEN, TBX3, and FOXA1 with resulting increased AKT phosphorylation have been found to be enriched in ILC tumors [4, 12, 13].

In comparison to patients with IDC, patients with ILC have been described to have significantly improved disease free survival (DFS) and overall survival (OS) in the initial years following the diagnosis of early-stage breast cancer. However, some studies have shown that this initial advantage is tempered by a higher risk for late recurrence for patients with ILC [5, 14]. Studies reviewing overall survival have not seen consistently significant differences between ILC and IDC [15, 16].

Patients with ILC have been observed to have a different pattern of initial metastatic spread compared to patients with IDC [3, 5, 17]. They have been reported to have a higher likelihood of bone, GI and ovarian metastasis as the first site of distant disease recurrence and to be less likely to have CNS, regional lymph nodes and lung metastasis as their first site of metastatic recurrence [3, 5]. Studies have also reported a predilection for ILC tumors to metastasize to the gastrointestinal tract and ovaries [3, 17–19]. However, to our knowledge, patterns of metastases over the entire disease course of patients with ILC have been poorly described. A study by Inoue et al. of 330 patients included only 19 patients with ILC and followed them over an average of 9 years [20]. This study found that lung metastases were significantly less likely to occur overall in ILC patients than in IDC patients, and that peritoneal metastases were significantly more likely.

We aimed to evaluate the development of a metastatic disease pattern in patients with ILC, in comparison to those with IDC, both with respect to the entire course of metastatic disease as well as to validate the previously described data on site of first distant recurrence.

Methods

Study population

We used a prospectively collated database of consecutive patients with metastatic breast cancer who were treated at the outpatient clinic in Magee-Womens hospital of UPMC and the University of Pittsburgh Cancer Institute to identify patients diagnosed with distant metastatic disease between January 1, 1998 and December 31, 2012. Only patients with complete and reliable information were included in the analysis. IDC or ILC histology was defined by H & E staining as well as E-cadherin/p120 catenin dual staining. We did not collect information on the various types of ILC histology or the expression pattern of E-cadherin or p120 catenin stains. Patients with any other breast cancer histology, including mixed ILC/IDC, were excluded from the analysis. Hormone recep-

▶ **Table 1** Baseline characteristics in the study.

Factor	IDC (n = 673)		ILC (n = 88)		Total (n = 761)		p value
	n/years	%/range	n/years	%/range	n/years	%/range	
Age at primary diagnosis (median and range)	50	21–89	54.5	33–84	51	21–89	0.004
Age at metastatic diagnosis (median and range)	54	23–90	59	33–89	55	23–90	< 0.001
Race (Caucasian)	618	91.8	79	89.8	697	91.6	0.51
Stage at diagnosis	n = 597		n = 73		n = 670		0.01
▪ I	89	14.9	5	6.9	94	14.0	
▪ II	219	36.7	18	24.7	237	35.6	
▪ III	141	23.6	23	31.5	164	24.5	
▪ IV	148	24.8	27	37.0	175	26.1	
Hormone receptor status (positive) (n = 757)	465	69.3	69	80.2	534	70.5	0.036
HER2 status (positive) (n = 635)	188	33.1	12	17.6	200	31.5	0.009
Number of metastatic sites (median and range)	3	1–8	2	1–6	2	1–8	0.16
Number of chemotherapy lines (median and range)	3	1–10	2	1–7	2	1–10	0.37

tor status is considered positive if at least 1% of tumor cells stain for either estrogen or progesterone receptor by immunohistochemistry. Demographic information, tumor characteristics, and survival data were obtained from the patients' medical records in a prospective manner. Breast cancer recurrence or metastases were classified as follows: bone, central nervous system (CNS), lung and/or pleura, liver, skin, soft tissue, distant lymph nodes, ovary and gastrointestinal (GI) tract. Sites of metastasis were identified either radiologically or through histopathological examination and were collated into the database based on the treating oncologist's assessment. Locoregional recurrences were not included.

Outcome variables

We performed a descriptive analysis by various sites of distant metastasis after patients were categorized according to the tumor histology into ILC and IDC. Recurrence-free survival was defined as time from primary diagnosis to the onset of distant metastatic disease (excluding those patients who had de novo metastatic disease). Overall survival was defined as time from onset of distant metastatic disease to death or last follow-up.

Statistical analysis

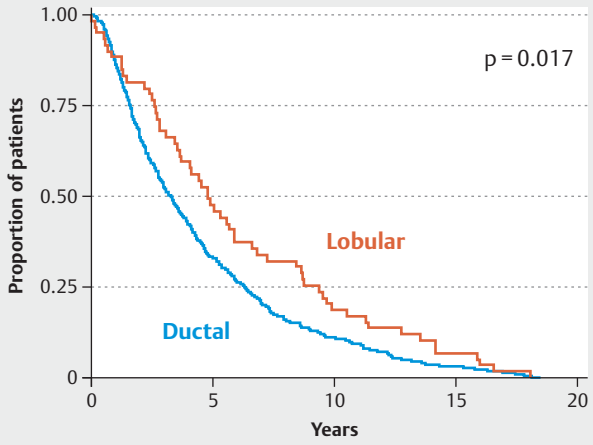
Means and standard deviations were used to summarize continuous variables with normal distribution. Categorical variables were summarized as percentage of total. Univariate analysis used standard statistical methods such as Chi-square test, Fisher's exact test, ANOVA or Wilcoxon rank sum test, as appropriate, to test for significant associations between patient's baseline characteristics and the ILC and IDC categories. Survival curves were estimated using the Kaplan-Meier method. All statistical analysis was performed using Stata statistical software release 11, StataCorp, College Station, TX. The study was reviewed and approved by the Institutional Review Board of University of Pittsburgh.

Results

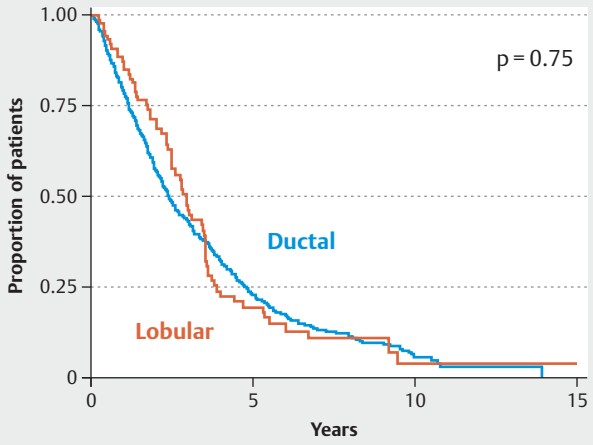
From among 960 patients identified in the database during the study time period, we found 761 patients with metastatic breast cancer with either IDC or ILC histology. Of these, 88 (11.5%) had ILC and 673 (88.4%) had IDC. Patients with ILC were significantly older at diagnosis of primary breast cancer and metastatic disease (▶ **Table 1**). The median age at primary diagnosis for patients with ILC was 54.5 (range 33–84) compared to 50 (21–89) in the IDC group, p = 0.004. Similarly, median age at diagnosis of distant metastatic disease was 59 (33–89) for patients with ILC compared to 54 (23–90) for those with IDC, p < 0.001. Patients with ILC had more advanced disease at the time of primary diagnosis (31.5% stage III and 37% stage IV or de novo metastatic disease in the ILC group, compared with 23.6% stage III and 24.8% stage IV in the IDC group, p = 0.01). In addition, patients with ILC had more hormone receptor-positive disease (80.2% in the ILC group compared to 69.3% for the IDC group, p = 0.036). HER2-positive disease was more frequent in patients with IDC (33.1% in the IDC group compared to 17.6% for the ILC group, p = 0.009).

Recurrence-free survival and overall survival

After excluding 175 patients with de novo metastatic disease, recurrence-free survival from primary diagnosis to initial metastasis was significantly different between the two groups (median RFS was 3.2 years for IDC vs. 4.8 years for ILC, p = 0.017) (▶ **Fig. 1**).



▶ **Fig. 1** Kaplan-Meier curve showing recurrence-free survival from primary breast cancer to onset of distant metastatic disease (excluding patients who had de novo metastatic disease).



▶ **Fig. 2** Kaplan-Meier curve showing overall survival from diagnosis of distant metastatic disease to death or last follow-up.

There was no significant difference in overall survival (time from first metastasis to death or last follow-up) between the two groups (OS was 2.0 years for IDC vs. 2.5 years for ILC, p = 0.75) (▶ **Fig. 2**).

Pattern of metastatic disease

With respect to the first site of distant metastatic disease, patients with ILC had greater involvement of the bones (56.8% in ILC compared to 37.7% in IDC, p = 0.001) and GI tract (0.3% in IDC vs. 5.7% in ILC, p < 0.001) (▶ **Table 2**). More patients with IDC had lung and/or pleura involvement (24.2% in IDC compared to 5.7% in ILC, p < 0.001) and liver involvement (11.4% in IDC compared to 4.6% in ILC, p = 0.049). We found no statistically significant difference between patients with IDC and ILC in the frequency of CNS, skin, soft tissue, distant lymph node or ovarian metastatic involvement as the site of first metastatic disease.

With respect to the pattern of metastatic spread during the entire course of metastatic disease, patients with IDC had greater lung and/or pleura (51.9% in IDC compared to 23.9% in ILC, p < 0.001) and liver involvement (49% in IDC compared to 20.5% in ILC patients, p < 0.001) (▶ **Table 2**). Ovarian and GI metastases were more frequent in patients with ILC (ovarian: 5.7% in ILC compared to 2.1% in IDC, p = 0.042; GI tract: 8% in ILC vs. 0.6% in IDC, p < 0.001). There was no difference in frequency with regard to CNS, skin, soft tissue or distant lymph node spread.

In order to investigate if there are differences in patterns of metastases between IDC and ILC within similar tumor subtype (hormone receptor-positive and HER2-negative disease), a sensitivity analysis was performed – 85% of patients had IDC and 15% had ILC (▶ **Table 3**). Similar to the above results, over the entire course of metastatic disease, patients with IDC had greater lung and/or pleura (46% in IDC compared to 17.7% in ILC, p < 0.001) and liver involvement (49.1% in IDC compared to 21% in ILC patients, p < 0.001) and patients with ILC had greater ovarian and GI metastases (ovarian: 8.1% in ILC compared to 2.8% in IDC, p = 0.042; GI tract: 9.7% in ILC vs. 0.3% in IDC, p < 0.001). Controlling for tumor subtype eliminated the association between ILC and bone metastases. There was no difference in frequency with regard to CNS, skin or soft tissue spread. Interestingly, distant lymphatic involvement was more frequent in patients with IDC (25.6 compared to 9.7%; p = 0.006).

Discussion

Our study has one of the largest groups of ILC patients with metastatic disease in the literature with 88 patients, and we are among the first to differentiate between first metastasis and metastatic sites throughout the course of disease. Our study also incorporates known data regarding hormone receptor status in these two tumor types to evaluate a large possible confounder of metastatic tendency. Our patient population is consistent with the existing literature on ILC patients. Our patients were older at diagnosis as well as initial metastasis and had more advanced disease at time of primary diagnosis. Patients in our ILC population also demonstrated increased tendency towards hormone receptor positivity.

At both the initial point of metastatic disease as well as the entire course we found more ovarian and GI tract metastasis in patients with ILC and more lung and/or pleura and liver disease in patients with IDC. This is consistent with the case reports in the prior literature as well as the data by Inoue [3, 5, 20]. Hormone positive tumors have an increased tendency to metastasize to the bone, while HER2/neu and basal-like are more likely to metastasize to the viscera. Our sensitivity analysis suggests that the increased tendency towards bone metastasis in ILC patients reported in prior literature may be a factor of their hormone status and less a characteristic of the histologic type.

The distinct metastatic spread of ILC tumors to the ovary and GI tract could be related to their unique biology. ILC is believed

▶ **Table 2** Patterns of metastases in invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) of the breast.

Site	IDC		ILC		Total		p value
	n	%	n	%	n	%	
Patterns of metastases as first site of distant recurrence							
Bone	254	37.7	50	56.8	304	40.0	0.001
CNS	41	6.1	2	2.3	43	5.7	0.14
Lung and pleura	163	24.2	5	5.7	168	22.1	< 0.001
Liver	77	11.4	4	4.6	81	10.6	0.049
Skin	18	2.7	1	1.1	19	2.5	0.38
Soft tissue	6	0.9	2	2.3	8	1.1	0.23
Distant lymph nodes	59	8.8	5	5.7	64	8.4	0.33
Ovary	4	0.6	2	2.3	6	0.8	0.094
GI	2	0.3	5	5.7	7	0.9	< 0.001
Patterns of metastases during the course of metastatic disease							
Bone disease	447	66.4	68	77.3	515	67.7	0.041
CNS disease	214	31.8	21	23.9	235	30.9	0.130
Lung and pleura	349	51.9	21	23.9	370	48.6	< 0.001
Liver	330	49.0	18	20.5	348	45.7	< 0.001
Skin	45	6.7	5	5.7	50	6.6	0.72
Soft tissue	26	3.9	5	5.7	31	4.1	0.42
Distant lymph nodes	180	26.8	18	20.5	198	26.0	0.21
Ovary	14	2.1	5	5.7	19	2.5	0.042
GI	4	0.6	7	8.0	11	1.5	< 0.001

▶ **Table 3** Patterns of metastases in hormone receptor-positive, HER2-negative invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) of the breast.

Site	IDC (n = 352)		ILC (n = 62)		Total (n = 414)		p value
	n	%	n	%	n	%	
Patterns of metastases during the course of metastatic disease							
Bone disease	268	76.1	47	75.8	315	76.1	0.95
CNS disease	85	24.1	9	14.5	93	22.5	0.1
Lung and pleura	162	46.0	11	17.7	173	41.8	< 0.001
Liver	173	49.1	13	21.0	186	44.9	< 0.001
Skin	25	7.1	4	6.5	29	7.0	0.85
Soft tissue	11	3.1	5	8.1	16	3.9	0.06
Distant lymph nodes	90	25.6	6	9.7	96	23.2	0.006
Ovary	10	2.8	5	8.1	15	3.6	0.042
GI	1	0.3	6	9.7	7	1.7	< 0.001

to have an independent association with exposure to hormone therapy, even when factoring in hormone receptor status [21, 22]. Endogenous areas of hormone production such as the ovary may create a favorable environment for ILC to metastasize. Additionally, E-cadherin downregulation has previously been reported to be associated with incidence of ovary-specific metastases [23]. Germline CDH1 mutations and E-cadherin loss have also been associated with gastric cancer in the literature, which may explain the tendency of ILC towards this site [24].

In terms of survival outcomes, our study noted a significant difference in DFS, but not OS, between ILC and IDC. The survival curves suggest a favorable risk profile for ILC early on in the disease course, but at the expense of greater risk for death later on in the disease course. The lack of difference in overall survival is

consistent with most prior studies, and Rakha et al. and Pestalozzi et al. reported similar findings regarding disease-free survival in their studies as well [5, 14]. A recent study from Japan looked at luminal cancers (hormone receptor-positive and HER2-negative) and found that luminal ILC had inferior survival outcomes compared to luminal IDC, worsening over time [25]. It is possible that the favorable biologic profile of ILC assists with improvement in initial disease-free survival, but that the combination of later onset, increased tumor burden and age lead to a worse survival tendency of ILC patients over time. It may also be possible that GI or ovarian metastases are generally more difficult to detect on routine imaging, leading to worse overall outcomes once metastases are identified.

There are a few notable limitations to this study that can supply the course for future research. This paper did not collect data on subtypes of ILC, which may have an effect modification on our findings. Our population is also predominantly Caucasian, and findings, especially about survival, may be modified in another ethnic distribution. At this stage of data collection, we are not able to explore other possible confounders regarding metastatic site distribution, such as effect of treatment.

In conclusion, this study clearly ties together prior case reports and limited-population studies in its metastatic distribution of ILC vs. IDC disease. It not only explores first site and overall sites for disease, but also takes into account hormone receptor status for its results. Our study ultimately demonstrates distinct differences in both the sites of first metastatic disease and the subsequent course of subsequent metastatic disease in patients with ILC compared to those with IDC. This study lays the groundwork for future studies investigating the reasons for the differing metastatic patterns.

Compliance with Ethical Standards

Funding

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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.

The study was reviewed and approved by the Institutional Review Board of University of Pittsburgh.

Informed consent

Informed consent was waived, as per approval from IRB, from all individual participants included in the study.

Conflict of Interest

The authors declare that they have no conflict of interest.

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