

more difficult radiological visualisation preoperatively. As a consequence, a higher incidence of tumour-positive excision margins after lumpectomy and an increased risk of conversion to mastectomy are noted. This explains why breast conserving therapy (BCT) is selected less commonly for women with ILC, although the treatment results are independent of the histological subtype, as confirmed in the EORTC "boost no-boost trial". In a recent population based study on BCT for ILC including 416 patients, the 5 and 8 years local recurrence risk was 3.5% and 6.4%, respectively, despite margin involvement in 29% of the patients after lumpectomy and still 17% when the re-excision was taken into account. In both the univariate and the multivariate analyses, no influence of the surgical margins on the local recurrence risk was found.

A less commonly known and accepted indication for post mastectomy radiotherapy is the case of ILC, independent of the tumour stage. The combined analysis of the EORTC 10801 and DBCG 82TM trials in early stage breast cancer demonstrated that, for this patient category, the local recurrence rate after mastectomy without radiotherapy was 19% at 10 years, compared to only 10% for patients who were treated with a breast conserving approach (HR 2.7, range 1.2–6.3).

In this era where more attention is drawn to the importance of local control even in patients with metastatic disease, it could also be taken into consideration that patients with lobular carcinomas survive significantly longer than other breast cancer patients, particularly from the time of diagnosis of distant metastases.

So in summary, despite the higher risk of an incomplete tumour excision, patients with early stage lobular cancer do not have a higher local recurrence risk after BCT than patients with ductal cancer and could be offered this treatment even after a (focally) microscopically incomplete tumour excision. For patients after mastectomy, lobular histology should also be considered as a separate prognostic factor in favour of referral for radiotherapy.

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Invited

Risk for metastases and implications for systemic treatment

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Invasive lobular breast cancer (ILC) comprises approximately 5–15% of breast cancers. It appears to have a distinct biology and a different clinical behaviour than invasive ductal carcinoma (IDC).

Compared with IDC, ILC occurs more frequently in older patients, is larger in size and is more frequently oestrogen receptor and progesterone receptor positive. Moreover, ILC has a lower S-phase fraction, tends to be diploid, and is usually HER-2, p53 and epidermal growth factor receptor negative.

The pattern of metastatic dissemination is different for ILC and IDC. ILC is more likely to metastasize to the peritoneum, gastrointestinal tract and ovaries, whereas the lung, pleura, distant nodes and central nervous system are more frequently involved in IDC.

Despite having a more favourable biological profile, ILC is not associated with a better disease free or overall survival rate. In multivariate analyses, histologic type is not an independent prognostic factor for outcome.

However, there is evidence that the clinical and the pathological response to preoperative chemotherapy (PCT) are lower for ILC compared to IDC. This results in larger residual tumour volumes, more mastectomy rates and more positive resection margins after breast conservative surgery, leading to more "rescue" mastectomies. However, the low chemosensitivity to PCT of ILC can probably be explained by their biological profile, but this does not seem to result in a survival disadvantage. Since tumour downstaging is the main aim of PCT, patients with large ILC are probably not good candidates for PCT. In these patients, preoperative endocrine treatment should be further explored.

Recent data suggest that also in the adjuvant setting, adjuvant endocrine treatment results in better response for ILC compared to IDC. In elderly patients with medical comorbidities, who are poor candidates for cytotoxic chemotherapy, endocrine therapy can be a good alternative to improve patients' outcome with ILC.

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Proffered paper oral

Outcome of invasive lobular carcinoma compared to infiltrating ductal carcinoma: a population based study from British Columbia

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Background: Lobular carcinoma is the 2nd most common invasive breast cancer histology after ductal carcinoma. Though phenotypically they are different, the two histologies are often treated the same with presumed similar outcomes. We sought to compare the baseline demographics, standard pathologic factors and long term clinical outcomes between lobular and ductal carcinoma from a large population based breast cancer registry.

Methods: A retrospective cohort of referred patients to the BCCA with a diagnosis of stage I-III pure lobular or pure invasive ductal carcinoma from 1989–2000 was identified. Prior or synchronous breast cancers and cases with unknown grade were excluded. Standard demographic and pathologic factors was abstracted from the BCCA Breast Cancer Outcomes Unit database and compared between the two histologies. 10 year outcomes were calculated by Kaplan Meier method, with differences compared by log rank test. Median follow up for the entire cohort was 9.3 years.

Results: A total of 13,203 individual patients meeting identified inclusion criteria were identified: 11,911 invasive ductal and 1,292 invasive lobular cancers. Lobular carcinomas generally had a higher frequency of poor prognostic factors: older age (≥ 70 years old), larger tumour size, and greater frequency of N2 nodal involvement (all $p < 0.001$). However lobular carcinomas also had a higher frequency of better predictive factors; ER+ status and low grade tumours (both $p < 0.001$). There were differences in locoregional treatments and systemic therapies between the groups. No differences were seen at 10 year estimated relapse free survival (76% vs 74%), distant RFS (78% vs 77%), breast cancer specific survival (81% vs 81%) and overall survival (69% vs 70%) between lobular and ductal cancers respectively. Only 10 year locoregional RFS significantly favored lobular cancers (93% vs 89%; $p < 0.001$), though there was also a higher mastectomy rate (55% vs 39%) in this cohort.

Conclusion: Though invasive lobular carcinomas are epidemiologically and phenotypically different from ductal carcinomas, clinical outcomes are comparable between these two common histologies.

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Proffered paper oral

Preventing reoperation in invasive lobular breast cancer

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Background: Invasive lobular breast cancer (ILC), the 2nd most common breast malignancy, has an increasing incidence, higher failure rates of breast-conserving surgery (BCS) and higher reoperation rates compared to invasive ductal carcinoma (IDC). The value of MRI and associated ultrasound (US) in the workup of ILC has been established. Can reoperation and recurrence be decreased by implementing a clinical algorithm?

Methods: A clinical algorithm was designed with the purpose of lowering reoperation rates and recurrence. Biopsy-proven ILC patients underwent an MRI to estimate extension and feasibility of BCS. Abnormal MRI findings were followed by an US to confirm suspicious lesions and biopsy of these. Positive findings add up points (table 1). Patients ≤ 9 points underwent BCS, those ≥ 10 points underwent mastectomy. Consecutive patients were included in a 38 month period since 2006 and compared with 195 historical controls. Indication for reoperation: positive margins. Descriptive statistics and exact Fisher's test for p .

Results: Biopsy-proven ILC patients ($n = 126$) were included; 78 (61.9%) underwent BCS, 48 (38.09%) underwent mastectomy, 7 were reoperated. Reasons included close margins on final pathologic evaluation ($n = 5$), underestimation during intraoperative evaluation ($n = 1$), and lack of adherence to the clinical algorithm ($n = 1$). The reoperation rate was lowered to 5.55% compared to 16.92% ($p = 0.0029$). With a mean follow-up of 19.34 months (2–44, SD: 11.61), 4 patients died (2 of advanced second malignancies, 1 catheter-related sepsis in the context of lung cancer, and 1 initially metastatic breast cancer).

Discussion: The importance of one-time surgery must be underscored, as it is associated with less psychological burden and better cosmetic results. MRI and secondary US are invaluable adjuncts in the preoperative work-up of ILC. Reoperation rate is decreased by implementing a clinical algorithm. Follow-up of patients will be presented in the future, to evaluate the impact of the clinical tool on recurrence.

Table 1. Invasive lobular carcinoma – Clinical tool

(1) Tumor/breast index (favoring or not BCS) (IRM > US > clinical > mammography)	1 – BCS uncertain 10 – Mastectomy
(2) MRI findings	0 – Unique lesion 1 – Other lesions
(a) US confirms other lesions	0 – Unique lesion 1 – Other lesions
(b) Biopsy of other lesion(s) (preoperative OR intraoperative biopsy of wire-guide marked lesions)	0 – Unique lesion 1 – Suspect lesion 2 – Malignant
(c) Multicentric	1 – Uncertain 5 – Certain
(d) Multifocal	1 – Uncertain 3 – Certain
(3) Intraoperative assessment of margins	1 – Negative 8 – Positive
(4) Excision of margins possible	0 – Yes 1 – No
Score	>10: Mastectomy <9: BCS possible
Final pathologic assessment	Negative margins: One-time surgery possible Positive margins: Reoperation

*In decreasing order of sensitivity, diagnostic tools to determine extent of lesion.

219 Proffered paper oral Lobular cancer is different, but its surgical management is changing over time: analysis of an institutional database over a 10-year period

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Background: Lobular carcinoma is a common form of breast cancer, and is known to be more often multicentric and bilateral, leading surgeons to pursue a more aggressive approach. Aim of the present report is to compare patients with invasive ductal (DC) and lobular carcinoma (LC) to study clinical differences over a recent time interval.

Materials and Methods: A retrospective review of 1417 breast cancer patients operated at one Institution from October 1999 to October 2009 was performed. Patients with particular types of histology other than ductal or lobular (n=38), with stage IV at presentation or in the immediate post-operative work-up (n=95), enrolled in neo-adjuvant chemotherapy protocols (n=46), or patients with no information on initial stage of disease (n=56) were excluded, leaving 1182 patients for analysis. Patients were thereafter analysed according to two study intervals (1999–2004 and 2004–2009) to report differences in surgical trends. Median follow-up was 4 years.

Results: There were 171 LC (14.5%) and 1011 DC patients in the study period. Median age was 63 years for DC and 65 years for LC patients. Median diameter was 1.7 cm for both groups. Diagnoses of LC were more frequent in the second half of the study period (55/465 vs. 116/662, p<0.01). Tumors were diagnosed at an early T stage (<2 cm in diameter) in 670/1011 DC and 105/171 LC (p=NS). Multicentricity was reported in 108/1011 (10.6%) DC and in 31/171 (18.1%) LC patients (p<0.01). A positive margin of resection at initial surgery was documented in 71/1011 (7%) DC and in 21/171 (12.3%) LC patients, respectively (p<0.001). Mastectomy was performed in 72/171 (42%) LC patients, and in 401/1011 (39.7%) DC patients, respectively (p=NS). Although the rate of mastectomy decreased over time in both groups, this was more pronounced for LC patients (from 31/55 in the period 1999–2004 to 43/116 in the period 2004–2009, p<0.05). There was a trend for more contralateral cancer surgery in the LC group (38/1011 vs 11/171, p=0.1). An ipsilateral relapse was diagnosed in 19 (1.8%) DC and 2 (1.2%) LC patients (p=NS). Systemic relapses (14/171 vs. 40/1011) or deaths (13/171 vs. 48/1011) were not significantly different in both groups.

Conclusions: Although LC is more often multicentric, associated with a positive margin of resection and a trend for bilaterality, it is not associated with a higher incidence of local recurrence. LC is diagnosed more frequently in recent years, and it is now treated by surgeons similarly to its DC counterpart, with of a more significant reduction of the mastectomy rate in this group.

Thursday, 25 March 2010

15:30–17:00

CLINICAL SCIENCE SYMPOSIUM

Bone microenvironment and bone disease

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Invited

Bone targeted therapy for early breast cancer

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Background: Bisphosphonates (BPs) and denosumab (an antibody to RANK-ligand) are potent inhibitors of bone resorption that reduce the risk of skeletal complications and prevent treatment induced bone loss. However, their use in cancer may provide more than just supportive care and modify the course of the disease by disrupting the metastatic process, and reduce the risks of disease recurrence. Whether this reflects just the indirect inhibitory effects on the vicious cycle within the bone marrow microenvironment or directs effects on the cancer is an area of debate and uncertainty.

Pre-clinical evidence: *In vitro* studies have shown that BPs induce tumour cell apoptosis and inhibit tumour cell adhesion, invasion, proliferation, and angiogenesis. *In vivo* animal studies have shown that bone targeted therapies can prevent establishment of bone metastases and inhibit progression of established lesions. BPs appear to enhance the anti-tumour activity of cytotoxic drugs in a sequence dependent manner.

Clinical evidence: In the early disease setting, improvements in disease free survival have been seen in some, although not all clinical trials of adjuvant bisphosphonates. Additionally, supportive exploratory clinical data have been reported from the cohort of patients who received neoadjuvant chemotherapy +/- zoledronic acid in the ongoing AZURE trial. A smaller residual invasive tumour size and a higher rate of pathological complete response was observed in those patients receiving zoledronic acid in addition to chemotherapy. A neoadjuvant biomarker study, ANZAC is evaluating the effects of chemotherapy followed by zoledronic acid on proliferation, angiogenesis markers and apoptosis. Studies to evaluate the potential for denosumab to prevent metastasis are also in progress.

Conclusions: The potential anti-tumour and disease-modifying role of adjuvant bone targeted therapies holds great promise. Bone targeted agents may have anticancer activity but results from recently completed large adjuvant studies must be awaited before their routine use in metastasis can be recommended.

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Invited

New developments in the treatment of metastatic bone disease

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Classical "skeletal-related events" (SREs) include need for radiotherapy, pathologic fractures, need for bone surgery and spinal cord compression. Complications of bone metastases (BM) also include hypercalcemia, severe pain and deterioration of quality of life for which specific monitoring tools have just been developed. Taken from data in placebo groups of randomized bisphosphonates (BPs) trials, the mean skeletal morbidity rate in breast cancer, i.e. the mean number of objective SREs per year, varies between 2.2 and 4.0. It is lower nowadays because of an earlier use of BPs. BPs are able to interrupt the vicious circle typical of tumor osteolysis by acting directly on osteoclasts and maybe also on tumor cells. BPs reduce the skeletal morbidity rate by 25% to 40%. It has been shown in a 2-year controlled comparative trial between pamidronate and zoledronic acid (ZA) that this latter compound has a superior efficacy as the likelihood of getting a SRE during therapy is reduced by a further 20%. The administration of a high "loading" dose of ibandronate could be especially useful in patients with severe bone pain but this concept should be tested in controlled trials. ZA 8 mg is not more effective than the 4 mg dose level which suggests that we have reached some form of a ceiling effect with classical BP schemes to reduce SRE incidence. Recently presented data (Body et al., CABS 2009) in patients with highly aggressive or advanced disease indicate that ZA not only prevents SREs, but has also a positive effect on survival. Denosumab is a fully human monoclonal antibody that inhibits RANK Ligand, a key factor that mediates the increased osteoclast activity typical of BM. The effects of denosumab (120 mg sc q4 weeks) and ZA (4 mg q4 weeks adjusted for Creat. Clear.) on the incidence of SREs in patients with BM from breast cancer have been compared in a double-blind double-dummy phase III trial. Denosumab significantly delayed the time to first on-study SRE compared with ZA (hazard ratio [HR] 0.82; 95% CI: 0.71–0.95; P=0.01) in this 34-month study. Denosumab also significantly delayed the time to first and subsequent on-study SRE (multiple event analysis)