The Assisi think tank focus on postoperative radiation for lobular breast cancer

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RUNNING TITLE: postoperative radiation for breast lobular carcinoma

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Abstract

The "Assisi Think Tank Meeting" (ATTM) on Breast Cancer, endorsed by the European Society for Radiotherapy & Oncology (ESTRO) and the Italian Association of Radiotherapy and Clinical Oncology (AIRO), and conducted under the auspices of the European Society of Breast Cancer Specialists (EUSOMA), is a bi-annual meeting aiming to identify major clinical challenges in breast cancer radiation therapy (RT) and proposing clinical trials to address them. The topics discussed at the meeting are pre-selected by the steering committee. At the meeting, these topics are discussed in different working groups (WG), after preparation of the meeting by performing a systematic review of existing data and of ongoing trials. Prior to the meeting, each WG designs a survey on the topic to be discussed to reflect current clinical practice and to identify areas requiring further research. Herein, we present the work done by the Assisi WG focusing on lobular carcinoma and the RT perspectives in its

treatment, including providing recommendations for locoregional therapy, mainly RT for patients with non-metastatic lobular breast cancer.

Introduction

In breast cancer, invasive ductal carcinoma (IDC) is the most common histological type, with invasive lobular carcinoma (ILC) being the second most common type (~ 10-15%)[1]. Since the 1970s, numerous variants of ILC have also been described based on histochemical studies of carcinomas showing an overall lobular histopathology, but with varying cytological or architectural features when compared to classical ILC[2,3]. Even though ILC is not a rare disease, there are few evidence-based recommendations concerning management. In 1989, Schnitt et al.,[4] were concerned about the safety of BCS with radiation therapy (RT) (BCT – Breast Conserving Therapy) compared to mastectomy due to the frequent presence of multifocal and multicentric disease. More than two decades ago, Poortmans et al.,[5] suggested that ILC be considered a different entity, compared to other breast cancer types, requiring a different approach to RT decision-making (mainly postmastectomy RT) based on the limited data that were available.

At present, we know that ILC has distinct pathological, biological and clinical features, yet there are limited data to guide systemic and locoregional therapies. The lack of knowledge about the most appropriate management of ILC is because it is less prevalent than IDC, is disproportionally underrepresented in clinical trials, but mostly because specific histological type was not reported [6-12].

The "Assisi Think Tank Meeting" (ATTM) on Breast Cancer, endorsed by the European Society for Radiotherapy & Oncology (ESTRO) is a bi-annual meeting, aiming to identify major clinical challenges in breast cancer RT and to propose clinical trials to address them.

The 2024 Assisi Think Tank steering committee selected locoregional management of ILC as a topic to be discussed.

Methods

This work is presented according to the predefined WG tasks:

Section 1) A general summary of the systematic literature search and the presentation that was made to the WG on current evidence about ILC, including risk factors, histology, genetics, and management.. [**APOLOGIES 'COMMENTS' ARE NOT WORKING FOR ME ON MY LAPTOP! AS YOU KNOW I THOUGHT SECTION 1 WAS UNNECESSARY AND HAS BEEN COVERED IN MULTIPLE PREVIOUS REVIEWS (GOOGLE SCHOLAR SAYS >1000 IN 2024 ALONE!). BUT IF THE CONSENSUS IS TO KEEP IT THEN IT SHOULD BE INCLUDED IN THE TITLE OF THE MANUSCRIPT.**

Section 2) A summary of the systematic review focusing on the effect of RT for ILC, mainly on local (LR) or regional recurrence (RR), and if not available, survival outcomes.

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I think it's clearer.

The systematic review criteria of exclusion were: publications not in English, full text not available, purely LCIS, metastatic ILC, reports that grouped ILC with IDC or other histology without providing separate outcomes, or not indicating outcomes of RT. Search engine was PubMed. The search terms were as follows: [(radiation [Title/Abstract]) OR (radiotherapy [Title/Abstract])) OR (radiation therapy [Title/Abstract])) AND (lobular [Title/Abstract])) AND (breast cancer [Title/Abstract]). The full search resulted in 409 titles. Selected based on titles n=199, selected based on abstract/full text for further review n=118. Four publications that appeared relevant via abstract were excluded as full text was not available (year of publication: 1981; 1991; 1996; 2002). Five additional relevant publications were identified by the reference list of the full texts reviewed and quoted. Large, randomized radiation trials

evaluating dose and fractionation, partial breast irradiation, and regional node irradiation were evaluated separately as most did not appear in the above search. The summary is presented in section 2 and in tables 1 - 3.

Section 3) A discussion of the data, and recommendations according to the level of evidence using a short version of the US Agency for Healthcare Research and Quality (AHRQ, www.ahrq.gov), that was used by EUSOMA to define the quality indicators. [18]

Results

Section 1: Outline of current data about ILC

ILC is almost exclusively found in women, accounting for 10-15% of female breast cancers but less than 1% of male breast carcinomas[19-23]. Generally, patients diagnosed with ILC tend to be older than patients with IDC. *CDH1* pathogenic germline mutation has been reported to be associated with the development of gastric and breast cancer, including ILC[24]. In contrast ILC is, not commonly associated with *BRCA* 1 or 2 pathogenic germline mutations,. Less common pathogenic germline mutations associated with ILC are *ATM, CHEK2*, and *PALB2*[25], but most patients with ILC don't have known pathogenic mutations in any of the high penetrance breast cancer predisposition genes. Exceptions included very young women and the Ashkenazi Jewish population. Such patients should be tested using a panel of genes that includes *BRCA2, CHEK2, PALB2*, and *CDH1* according to national or international guidance. [25,26].

The classical morphological appearance of ILC is often easily recognizable and a diagnosis may be made without supplementary immunohistochemical or molecular analysis (Figure 1). Subtypes of ILC eg pleomorphic, solid, alveolar, and tubulo-lobular) may present greater

diagnostic challenges, further complicated by the fact that they often exist alongside classical ILC . Furthermore, carcinomas with mixed lobular and ductal histology are common[1,27].

The majority of ILCs exhibit a unique genetic alteration with 16q loss, and since the *CDH1* gene - encoding for the adhesion molecule E-cadherin - is located at 16q22.1, this may lead to loss of E-cadherin protein expression (Figure 1). E-cadherin is under normal circumstances important for cell-cell adhesion between epithelial cells, and the loss of this membrane-bound protein contributes to the diffuse infiltrative pattern of ILC[1,27]. E-cadherin loss is, however, not mandatory for the diagnosis of ILC and presence of E-cadherin does not exclude ILC[1,27-29].

Around 95% of ILCs express estrogen (ER) and progesterone receptors (PR). HER2 overexpression is relatively rare (3-13%)[1,7,30] and triple negative ILC accounts for less than 2% [31]. ILC is most frequently reported as malignancy grade II due to the single cell infiltration without tubular formation, whereas otherwise it expresses characteristics that are more associated with grade I disease. Moreover, ILC has previously been reported to have more undetermined grade compared with IDC. Thereby, ILC classical type is typically histological grade 2, expresses ER and PR, without overexpression of HER2 and has a low Ki67 index[28,32,33]. The pleomorphic variant is considered to be associated with more aggressive disease, exhibiting marked cellular atypia, nuclear pleomorphism, increased mitotic rate, higher proliferation index, with low rates of ER positivity, and with HER2 amplification in 35–80% of cases[34]. Classical ILC has lower levels of stromal tumour-infiltrating lymphocytes (TILs)[35] and less programmed death-ligand 1 (PD-L1) expression[36], which may be associated with the more sparse stromal reaction ("desmoplastic reaction"). A cohort of 459 ILC cases suggested that a high level of TILs was associated with younger age, larger tumours, lymph node involvement, poor differentiation, HER2 amplification and poor overall survival (OS)[37].

Limited data are available concerning multi-gene classifiers in ILC but one study including patients within 15 prospective trials reported a 3-fold lower prevalence of high oncotype recurrence scores (RS >26 in 8% - ILC vs 24% - IDC)[33].

ILC is challenging to detect on clinical examination and mammographically or on ultrasound[38]. Axillary ultrasound commonly shows diffuse cortical thickening with no hilar mass effect, making the diagnosis of nodal involvement challenging, (Figure 2) [38,39]. Therefore, ILC is often diagnosed in a more advanced stage with larger tumour size and more extensive nodal involvement compared to IDC[38].

Due to difficulties in assessing the extent of the primary tumour, a tendency for multifocality, and margin involvement after BCS, proportionally more patients with ILC are treated with mastectomy[31,33,40-44] . Contrast-enhanced mammogram (CEM) may improve the ability to evaluate the extent and focality of ILC [45], but magnetic resonance imaging (MRI) is the recommended modality to assess disease extent, including evaluation of nodal involvement[46]. Preoperative MRI in patients with ILC has been suggested to reduce re-excision rates after BCS without necessary increasing the rate of mastectomy [47]. MRI was also found to be most sensitive for the evaluation of the extent of nodal involvement and is routinely recommended as part of routine breast and axillary evaluation in ILC[38,48].

Distant metastatic pattern of ILC often differs from IDC[33,49]. ILC has a tendency for metastasis to bone, peritoneum and retroperitoneum, ovaries, stomach, skin and leptomeningeal disease with a lower incidence of metastases in lung and intracranial parenchyma compared to IDC[33,49]. It is also known for a propensity for uncommon metastatic sites.

The pattern of spread and pathophysiology of ILC challenge the ability to detect distant dissemination by imaging[50]. ILC is hypometabolic, has lower cell density, a lack of TILs

(inflammatory reaction), and a lack of Glut-1 transporter expression, thus is often much less avid on 18F-FDG (fluorodeoxyglucose) in positron emission tomography (PET)[51]. New tracers such as 68Ga-labeled fibroblast activation protein inhibitor (68Ga-FAPI) which target cancer-associated fibroblasts in the tumour microenvironment of many cancers and are currently being evaluated in clinical trials[52].

Whether or not ILC is associated with contralateral breast cancer is controversial. Some authors indicated that ILC is associated with contralateral breast cancer unrelated to patient factors, breast cancer stage, or therapy (chemotherapy or radiation)[40,53-56], while some did not note a higher rate of contralateral breast cancer with ILC compared to IDC[33,57,58].

[https://www.sciencedirect.com/science/article/abs/pii/S0009926015004377 **(THE MOST IMPORTANT PAPER ON THIS!!]**

Section 2: Should ILC influence the choice of local therapy to the breast?

BCT (BCS + RT) vs. Mastectomy (+/- RT)

Breast conserving therapy

Studies reporting the outcomes of BCT are listed in Tables 1&2, and partially in Table 3 (if mastectomy patients were included in the study). Table 1 shows the rates of LR, and Table 2 shows the localization of the LRs[4,40,55,57,59-63].

Weiss et al.,[61] included several breast cancer histologies, including ILC. The significant differences in tumour related features and breast cancer stage at diagnosis limit evaluation. Patients with tubular and colloid (non-lobular) cancers tended to have smaller tumours and node negative disease, whereas ILC patients were older, had more advanced T and N stage, and higher rates of ER positivity. However, tubular IDC, compared to ILC, had higher LR

rates (Table 1). Overall, all cohort studies in Table 1, but one[59], showed similar LR outcomes for ILC and IDC after BCT. These include a case control study evaluating factors related to LR that did not find that ILC was associated with higher LR compared to IDC [64]. **?**

An extensive intraductal component (EIC) (defined as 25% or more of the tumour area containing ductal carcinoma in situ, DCIS), was associated with higher LR rates after BCT compared to ILC[4,64], and the highest risk of LR was noted for patients younger than 35 years[64].

These studies suggest a tendency for more distant recurrences in patients with IDC [57,61,65] whereas the combined data from 15 International Breast Cancer Study Group (IBCSG) trials reported that there were more distant recurrences in patients with ILC[33] . However, these studies were not primarily designed to compare outcomes between ILC and IDC and confounding factors such as disease stage and other histopathologic features may have led to these findings. Several authors attributed the overall better prognosis of ILC compared to IDC to the molecular and biological features of the tumour rather than the locoregional therapy approach.[40,66].

An analysis of LR rates after BCT according to the different ILC subtypes and other characteristics such as classical, pleomorphic, signet cell and mixed histologies, presence of lobular carcinoma in situ (LCIS), multifocality and lymph node involvement, did not find any association of these features with higher rates of LR. Receptor status was not reported and neither was the correlation of LR with systemic therapy [4].

Mastectomy

Table 3 lists studies that include mastectomy, with/without postmastectomy RT[31,41,42,44,67-70]. These were either retrospective or registry-based studies (such as Surveillance, Epidemiology, and End Results database, SEER; National Cancer Database, NCDB),

therefore, patients who underwent mastectomy and postmastectomy RT probably had higher risk disease eg higher disease stage, more often received chemotherapy and so worse breast cancer outcomes[44,69]. Nevertheless, several reports suggest that ILC patients who underwent postmastectomy RT had a more than 3 times lower risk of LR compared to the ILC patients without postmastectomy RT (Hazard Ratio, HR 0.30; 95% Confidence Interval, CI 0.10-0.89). This was after adjustment for age at diagnosis, tumour stage and use of postoperative systemic treatment. [68]

A pooled analysis of the DBCG – 82TM and EORTC 10801 [67], two prospective randomized trials comparing BCT with mastectomy, with postoperative chest wall irradiation showed that patients with ILC without postmastectomy RT had a 2.69-times higher risk of LR (95% CI, 1.17 to 6.21) compared to IDC without postmastectomy RT. In contrast to BCT, young age and EIC, were not associated with LR after mastectomy. Although ILC was not a significant factor for LR after BCT in the pooled analysis, the risk of LR was significantly higher after modified radical mastectomy without RT[67].

Truong et al.,[42] reported the outcomes of patients with early stage breast cancer undergoing mastectomy without RT. A multivariable analysis of factors associated with increased (LRR) found that a tumour size >2 cm, ILC, and close/positive surgical margins were significant.

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The different ILC subtypes or receptor status were rarely reported in studies related to LR rates or other breast cancer outcomes[33]. Patients with ER-negative ILC had worse survival outcomes compared to ER-negative IDC; however, the analysis did not report the ILC type, or the outcomes according to BCS (with or without RT) [33]. An analysis from the National Cancer Database (NCDB) of women with ILC breast cancer stage cT1-4N1-3M0 included a total of 114,859 (99.6%) with classical ILC, and 401 (0.4%) with pleomorphic ILC. A greater proportion of patients with pleomorphic ILC had T3-4 and node-positive disease and were

more likely to have ER negative and HER2 positive disease. Overall, pleomorphic ILC was associated with poorer OS compared to classical ILC. Comparison of OS according to subgroups with pleomorphic versus classical ILC demonstrated that in T3-4/N1-3 disease pleomorphic morphology had inferior survival outcomes. No differences were noted by HER2 status[72].

A large registry study comparing the outcomes of 125,780 patients with triple negative -ILC and triple negative -IDC (1.3% ILC, 98.7% IDC), reported breast cancer outcomes at a median follow up of 49.7 months[31]. The ILC patients were significantly older than the IDC (median age 67 versus 58 years, $p < 0.001$), were less likely to present with high-grade tumours and to receive chemotherapy or RT. ILC patients were more likely to have a higher stage at presentation and undergo mastectomy ($p < 0.05$). In univariate analysis, triple negative ILC patients had worse OS compared to those with triple negative IDC. However, after adjusting for age at diagnosis, grade, breast cancer stage, and treatment, there were no significant differences in OS.[31]

Relation between overall survival and LR after BCT versus mastectomy

Unsurprisingly, isolated LR after BCT was associated with better survival outcomes compared to isolated chest wall LR after mastectomy (Relative Risk, 2.65; $p = 0.0089$)[69].

Omission of RT after BCS

For patients undergoing BCS without RT, the presence of ILC had a higher LR rate compared to IDC.[60,67,69,73-76] The median time to LR in women undergoing BCT (including RT) was longer compared to those who had BCS without RT (Tables 1&3). Prospective trials, including randomized controlled trials that established the potential approach of omission of radiation in low-risk breast cancer patients, did not indicate if patients with ILC were included, nor did they report outcomes according to histological type.[12,77] The LUMINA

prospective cohort allowed for only ductal, tubular, or mucinous histology. Two percent of the patients (n=12) were regarded as "other" histology [78]. At this time there exists no clear data about the impact of histopathological features on outcomes after omission of RT.

Partial breast irradiation after BCS

Randomized control trials evaluating partial breast irradiation (PBI), either explicitly indicated that only ductal histology be allowed[79,80] or accepted all histological types as long as other low risk features apply (based on grade, ER/PR, unifocality, size and resection margins),[81-86] resulting in proportions of ILC patients in these trials varying from 0-13%. However, none of these trials reported the outcomes of ILC as a distinct population, most probably due to the limited number of patients included. In the ELIOT trial[84], 11% of the trial population had lobular or mixed lobular and ductal histology (n = 148), with the 15 years analysis according to histology, showing no significant impact on LR according to (ILC vs IDC) morphology [HR 2.13 95%CI (0.62–7.28]. The overall LR rates were high in the PBI arm at 15 years and similar among the different histologies: IDC 13.6% (10.2–17.5), ILC 12.6% (4.9–24.2) and mixed 11.8% (1.8–32).

Strnad et al.,[87] reported the 5-year results of the German-Austrian multicenter phase II trial using interstitial multicatheter brachytherapy for PBI for low-risk breast cancer. ILC constituted 16.4% of the trial population and the investigators indicated that there was no significant association with LR, disease free-survival and OS for ILC [87]. Nonetheless, the trial population had low-risk disease and the mean surgical margin in the trial was 10 mm[87]. Another study reported the outcomes of 821 consecutive patients who underwent intracavitary brachytherapy partial breast irradiation including 7% ILC cases. The authors reported that the 10-year LR was 2.5% for IDC and 14% for ILC and recommended the exclusion of ILC from PBI due to the high LR.[88] Galimberti et al.,[58] recommended to avoid

PBI for patients with ILC who tend to have more extensive disease than estimated on imaging. Breast MRI was recommended to assess the possibility of remote tumour foci if PBI is considered.

Should ILC change the approach to the regional nodes?

There are no data about how recommendations for regional node irradiation should be modified in ILC, as leading trials did not record sufficiently detailed morphological information. [89]. Currently, there are no differences in the surgical approach to axillary staging in cN0 disease, and sentinel lymph node biopsy (SLNB) is the standard approach independent of histology [90,91]. The recent SENOMAC trial[92], a phase III prospective randomized noninferiority trial, evaluated the role of ALND versus omission of ALND (with breast and regional RT given according to local or national policy) in patients with cN0, T1 to T3 disease with 1-2 macrometastatically involved sentinel lymph nodes. ILC represented ~ 20% of the patients in each treatment arm (278 vs 226 patients). The median follow-up was 46.8 months (range, 1.5 to 94.5). In subgroup analysis of there was no significant difference for recurrence or death (HR 0.91, 95% CI (0.47–1.76)) comparing ILC vs IDC. This provides no support for a different approach in ILC although small numbers and short follow-up provide significant limitations to interpretation. Additionally there were no differences in the number of nodal? metastases in the ILC group compared to IDC in patients who underwent ALND[92]. This observation was also made in an earlier publication by Voogd et al.,[93] evaluating node positivity among patients with clinically negative lymph nodes.

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial including 793 patients, of which 71 (9%) had ILC and of these 55 ILC were in the SLNB-only group. The study intended to evaluate no axillary therapy (including RT)Outcomes were not reported according to morphology. ILC but the 5-year event-free survival for the SLNB-only group

was 93% (95CI, 89%–94%) and there were no isolated axillary recurrences [94]. Therefore, for low risk ILC patients who are 'Z0011 eligible', the omission of axillary node irradiation may be reasonable.

Radiation dose and boost

The studies listed in Tables 1 and 3 report dose/fractionation ranges for whole breast or chest wall (described at depth in most cases for regional RT). A recent small phase 2 trial that evaluated two dose fractionations for the whole breast 28.5 or 30 Gy (5 fractions, once weekly) with no elective coverage of lymph nodes suggested that ILC histology (10% of the patients in the trial) was associated with better local control[95]. **I CAN'T ACCESS THIS PAPER IN SAN FRANCISCO! BUT THERE WERE 158 PTS AND ONLY 6 LRS SO I CAN'T BELIEVE THIS WAS ANYWHERE NEAR STATISTICALLY SIGNIFICANT!**

~~In addition, the recent SENOMAC trial[92] allowed for different RT protocols according to the participating site, including a total dose of 50 Gy in 25 fractions and moderate hypofractionation to a total of 40.05-42.5 Gy in 15-16 fractions; while a slightly lower total dose to the nodes was accepted. Limited by the small number of ILC patients and events, the SENOMAC trial suggests that ILC axillary disease can be controlled with RT, without additional (boost) dose.~~ **NOT SURE THIS STACKS UP SEEMS COMPLICATED TO INTRODUCE THE POSSIBILITY OF AN AXILLARY 'BOOST' DOSE WHICH WOULD BE VERY UNUSUAL PRACTICE (CERTAINLY IN THE UK! MAYBE OMIT?**

Tumour bed boost dose as a component of BCT was reported as a range or as a total dose (including whole breast dose). The RT techniques for boost varied between and within studies and included electrons, brachytherapy, and photon radiation. The indications for a boost were

also not clearly stated. Limited by the small number of patients, Schnitt et al.,[4] indicated no correlation between radiation dose and use of a boost with LR rates in ILC?. In a univariate analysis of 1603 patients from the EORTC boost/no-boost trial, ILC was found to have a non-significant lower HR for LR of 0.70 (95% CI 0.31-1.60) compared to IDC [96]. Therefore, it was impossible to conclude if there is an advantage for an additional boost dose for ILC, and which adverse features, including grade, triple negative status, pleomorphic subtype, and close or involved margins are important for applying a boost.

Discussion

It is not possible to draw definitive conclusions or provide treatment recommendations concerning locoregional therapy specifically for ILC based on currently published data.

The literature describes several small studies, with designs that cannot exclude confounding factors which seriously limit interpretation.

Treatment recommendations ideally should be based on level I evidence, of which there is very little[97]. Nevertheless observational data from cohorts and case-controls studies can provide some insights[98] and, whilst recognizing the caveats described above, allow tentative recommendations to guide care and inform future research. These are summarized in table 4 and reflect consensus among ATTM participants.

Overall, BCT for ILC showed similar outcomes compared BCT for IDC, therefore ILC as such is *not* an indication for mastectomy. High rates of LR were observed after BCS without postoperative RT or with PBI compared to IDC. The criteria for PBI eligibility from the American Brachytherapy Society (ABS)[99], American Society for Radiation Oncology (ASTRO)[100], The Groupe Européen de Curiethérapie of European SocieTy for Radiotherapy & Oncology (GEC-ESTRO)[101], ESTRO Intraoperative radiation therapy guidelines, and The ESTRO and Oncology Advisory Committee in Radiation Oncology Practice (ACROP)[102]

differ in some aspects but for histology subtype, all guidelines, but one[103], indicate that ILC histology is *not* recommended for PBI. This is most probably related to ILC being highly challenging to assess the local extent of ILC and the absence of multifocality via imaging.

There are two key points to be considered for PBI after BCS for ILC: the use of MRI and other more sensitive imaging such as contrast-enhanced mammography, and the selection of the most appropriate PBI technique as they differ in their dosimetric coverage and consequently the breast volume receiving a therapeutic dose[104]. Therefore, proper imaging and planning for PBI, similar to that conducted in the IMPORT-LOW trial using mini-tangential fields to reduce RT-related toxicity due to the volume effect, might be a safe option for postoperative RT in these patients and should be further explored [81]. As for omission of RT after BCS, we encourage the investigators of the prospective trials that included ILC to report the outcomes according to histological type.

As for mastectomy, studies reported higher LR rates for ILC without RT compared to IDC without RT, and higher LR rates when compared to BCT for ILC[67,68]. The absolute contribution of postmastectomy RT to reduce LRs in ILC is suggested to be higher compared to postmastectomy RT for IDC but this could relate to the greater TN stage in patients with lobular histology[67]. Nevertheless concerns about reducing the extent of mastectomy, including skin sparing and nipple sparing approaches without RT in ILC remain valid [105-107].

Regional control with regional node irradiation was suggested to be similar, or even in some reports, possibly better for ILC compared to IDC[33,92]. Regional node irradiation can replace ALND in patients with limited nodal burden based on the SENOMAC and AMAROS trials[92]. and studies of avoidance of axillary surgery or RT in minimally node positive disease after SLNB irrespective of ILC vs IDC histology are needed.

Commented [CA3]: In **Should ILC change the approach to the regional nodes?** it is written: Therefore, for low risk ILC patients who are 'Z0011 eligible', the omission of axillary node irradiation may be reasonable.
Are the 2 statements a bit contradictory?

[AMAROS REF - Bartels SA, Donker M, Poncet C, Sauvé N, Straver ME, van de Velde CJ, Mansel RE, Blanken C, Orzalesi L, Klinkenbijl JH, van der Mijle HC. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer: 10-year results of the randomized controlled EORTC 10981-22023 AMAROS trial. Journal of Clinical Oncology. 2023 Apr 20;41(12):2159-65.]

ILC is present in ~10-15 % of patients with breast cancer, therefore annually there are a considerable number of patients diagnosed with ILC worldwide. It will be challenging to perform prospective randomized trials specifically on this population for each therapeutic question, but initiatives such the Lobular Breast Cancer Alliance (LBCA) (https://lobularbreastcancer.org/) and multiLCIS study [NCT06133465] that aim to provide input and improve management deserve strong support. For other future studies, we strongly recommend reporting the outcomes of breast cancer types separately, including ILC and its subtypes. In any prospective or retrospective studies assessing treatments (including systemic therapy) we advise referring to the essential requirements endorsed by ESTRO [108] and to the PRECEDENT project recommendations[109] to allow future analysis of the benefit of different locoregional therapies.

Conclusion

There are limited data to justify different locoregional management practices in patients with ILC compared to IDC, and in most circumstances management changes on this basis should be avoided. The reasonable exception to this general principle is the recommendation for PBI or RT omission after BCS. Recording of histological type in prospective trials and observational studies is needed to address the limited evidence base that exists and improve future patient care.

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Figure 1: (A) Examples of invasive ductal carcinoma (IDC)/carcinoma of no special type (NST) and (B) Invasive lobular carcinoma (ILC) on HE sections (19x original magnification) accompanied by corresponding immunohistochemical stains for E-cadherin (C, D). Presence of E-cadherin on the cell membranes will in the immunohistochemical stains show as a brown color, whereas loss of E-cadherin will fail to produce a brown reaction in the tissue.

A shows a highly differentiated IDC with retained E-cadherin expression (brown coloring) (C). B shows a classical ILC with tumor cells growing in single filing (arrow) with no expression of E-cadherin (no brown color) (D).

Figure 2: Examples of small lymph nodes completely involved with metastasis from invasive lobular carcinomas. (A) Macrometastasis in a lymph node measuring 3,78 mm and as such potentially not visible on imaging. (B) A 1 mm lymph node with micrometastasis (HE sections, 4x original magnification)