BJC

British Journal of Cancer (2015), 1–3 | doi: 10.1038/bjc.2015.115

Inflammatory breast cancer: time to standardise diagnosis assessment and management, and for the joining of forces to facilitate effective research

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Sir,

The term inflammatory breast cancer (IBC) was first used by Lee and Tannenbaum in 1924 (Lee and Tannenbaum, 1924). This uncommon form of breast cancer accounts for 2.5% of all breast cancer in the United States of America (Robertson *et al*, 2010), there are no published figures for incidence in the United Kingdom. IBC is widely acknowledged as an extremely aggressive form of locally advanced breast cancer with a very poor prognosis (Hance *et al*, 2005). In the past, progress of research into this condition has been limited by the lack of consistent, definitive and well-documented diagnostic criteria. The generation of evidence-based guidelines for the management of IBC is compromised by the paucity of data that is often of variable quality (e.g., due to small sample sizes). There have been only a few clinical trials designed exclusively for IBC with very few of these being randomised (Dawood and Cristofanilli, 2011). Data have primarily been comprised of small- to modest-sized cohorts of patients, often from trials where inflammatory cancers were included but not the primary target population for the trial. Statistical power to examine IBC cohorts in isolation within these trials is inevitably limited.

Recently, an International panel published a consensus statement for standardised diagnosis and management of IBC (Dawood *et al*, 2011). To date no effort has been made to co-ordinate or standardise UK practice and research endeavours regarding IBC.

The aims of the UK IBC working group are to establish a National mechanism for conducting research into IBC. It has thus far explored mechanisms for central collection of clinical, pathological and radiological data on diagnostic parameters, treatment and outcomes linked to tumour material that could serve as a clinical research resource. The initial outcome was to provide practical guidelines to encourage consistent definition, uniform collection of diagnostic information and standardisation of treatment approaches.

The International consensus statement remains an important contemporary blueprint for IBC management and the UK working group endorses it. The current paper seeks to provide a UK perspective on the diagnostic criteria, required documentation and commonly used treatments of IBC to give momentum and generate research interest into this disease in the United Kingdom. The UK group will separately identify key elements required to establish a collaborative research platform to enable the epidemiology and biology of this condition to be better understood and for specific research to be conducted aimed at improving outcomes for women afflicted by this challenging condition.

DEFINITION OF IBC

The first diagnostic criteria for IBC were published in 1956 by Haagensen (Haagensen, 1956). These criteria are the basis of the definition of IBC set forth by the American Joint Committee on Cancer (AJCC) as 'a clinicopathological entity characterised by diffuse erythema and oedema of the breast, often without an underlying palpable mass' (AJCC, 2002).

The diagnosis of IBC remains a clinical diagnosis with pathological confirmation of invasive disease with no specific additional pathological criteria and has therefore been open to subjectivity. The standardisation of diagnostic criteria is essential and will help minimise such subjectivity. Collection of good data sets in relationship to each case is also essential as is an accurate description of the individual features contributing to the diagnosis of each case of IBC.

CLINICAL PARAMETERS

One key diagnostic difficulty is the separation of the recognised feature of an aggressive rapidly appearing and progressive condition and a more indolent but long neglected locally advanced primary breast cancer. This has resulted in the requirement of a short history of less than 6 months as a diagnostic criterion. Although this is an arbitrary time cutoff, it will clearly separate the majority of slowly evolving locally advanced cancers.

PATHOLOGICAL CRITERIA

Importantly, IBC has no specific histological appearance and as such is not a recognised morphological subtype of invasive breast cancer. The current WHO definition (Lakhani *et al*, 2012) recognises that the diagnosis is based on clinical findings but emphasises that the clinical picture is a consequence of dermal lymphatic involvement and embolisation. The underlying invasive breast cancer is usually high grade and of no special type. There is evidence that tumours associated with an inflammatory clinical presentation are highly angiogenic, lymphangiogenic and vasculogenic (Vermeulen *et al*, 2010).

It is essential to acquire a tissue diagnosis of carcinoma, as infection, some inflammatory conditions and other tumours (notably some sarcomas) can mimic the inflammatory carcinoma clinical picture. Dermal lymphovascular tumour emboli present in a skin punch biopsy is a typical but not specific feature. Although multiple dermal punch biopsies are not required for a diagnosis, taking such biopsies can aid the diagnosis of IBC and provide a subclasification.

RADIOLOGICAL FEATURES

Although routine breast radiological investigations are recommended as part of staging work-up, the data are currently not sufficient to define any radiological signs specific for IBC. Radiological findings do not feature as part of the diagnostic criteria. Nonetheless, with full field digital mammography, skin and trabecular thickening are seen far more frequently than with conventional film/screen mammography, often with associated distortion and diffuse increase in breast density—a constellation of findings that is highly suggestive of the diagnosis (Gunhan-Bilgen *et al*, 2002; Le-Petross *et al*, 2008). High-resolution ultrasound demonstrates a focal abnormality in over 90% of cases, facilitating targeted biopsy (Gunhan-Bilgen *et al*, 2002; Le-Petross *et al*, 2008). Key diagnostic features on breast MRI are diffuse breast and prepectoral oedema, diffuse skin thickening and enhancement (present in over 90%, in contrast to neglected LABC) and either non-mass enhancement or multiple small masses throughout the breast (Le-Petross *et al*, 2011; Uematsu, 2012).

TREATMENT

Primary systemic therapy is the recommended first-line approach to treatment of IBC. A surgical opinion regarding feasibility of primary resection should be obtained prior to systemic therapy, and operable or successfully downstaged cancers should all be resected following primary

systemic therapy. Post-operative radiation therapy is almost always indicated (Yamauchi *et al*, 2012).

RECOMMENDATIONS FOR PROGRESS

We propose a series of recommendations for the diagnosis and management of IBC, which are summarised in Tables 1 and 2. These recommendations have many aspects in common with the International recommendations, but differ in certain respects. We discuss below the rationale for these differences.

Diagnostic criteria. The International guidelines and AJCC guidelines 7th edition state that erythema and oedema should be present in at least one-third of the breast. We have not specified criteria for the proportion of breast involvement or size criteria for erythema (or oedema), as this was considered too subjective to include as a useful specific criterion. It is particularly difficult to assess erythema inpigmented skin. We have instead recommended that the external appearance is documented by clinical photography, thus capturing much more detail than a narrative description alone.

Staging and response assessment. We have recommended a combination of mammography and ultrasound as minimum requirements for radiological imaging of the breast. MRI is also recommended, as this is the most accurate technique for characterisation and diagnosis of the primary lesion (Yang *et al*, 2008; Le-Petross *et al*, 2011). There are specific features that aid the differentiation from LABC (Le-Petross *et al*, 2011; Uematsu, 2012). In addition, it is accepted that in comparison with conventional imaging, MRI is the most accurate way of assessing both interim and final responses to treatment (Dall *et al*, 2011), which can help to guide therapy (for e.g., where breast conservation may be a possibility or to demonstrate persistent involvement of the chest wall musculature).

The presence of metastatic disease is common in women presenting with IBC, and staging clearly provides important information for prognosis and management and CT scanning is widely available and recommended as the primary staging modality. Bone scintigraphy is now recognised as adding little additional value over CT staging and is not recommended as a routine staging investigation in keeping with current UK practice. By contrast, PET-CT is a very effective investigation for identification of asymptomatic metastasis (Groheux *et al*, 2013) and where available, its use is encouraged.

Management. We have recommended concurrent use of primary cytotoxic therapy for HER-2-negative cancers and a combination of cytotoxic and anti-HER-2-based therapy for tumours overexpressing HER-2. There is now good evidence that pCR rates in HER-2-positive cancers can be significantly enhanced with chemotherapy and dual-targeted anti-HER-2 therapy using chemotherapy and trastuzumab with either pertuzumab or Lapatinib (Rea *et al*, 2013). Where dual-targeted therapy is available, we would endorse its use in treatment of IBC.

Breast surgery. Following neoadjuvant chemotherapy, excellent clinical responses may be achieved including a pathological complete response. In the absence of any data to suggest breast-conserving surgery (BCS) with clear margins is any less safe than in patients with non-IBC, there is no justification for the mandatory requirement for maintaining the convention of recommending mastectomy in all patients with IBC. Thus, attempted breast conservation after adequate downstaging can be considered based on multidisciplinary review of pre- and post-treatment clinical, radiological and pathological features.

Axillary management. There is no published evidence that suggests patients with IBC treated with neoadjuvant chemotherapy should have their axilla staged or treated any differently to any other patients with invasive breast cancer undergoing neoadjuvant chemotherapy.

Radiotherapy. Adjuvant radiotherapy is the recognised standard of care following surgery for IBC and should only be omitted where there are clear contraindications. Supraclavicular radiotherapy is therefore recommended in all patients with documented or suspected axillary node involvement at diagnosis. Internal mammary chain radiation should be considered if there is any radiological suspicion of internal mammary node involvement, but the evidence for internal mammary node involvement as routine practice for all women with IBC and axillary node involvement is not considered strong enough for a recommendation for this to be applied in all cases.

Endocrine therapy. We have included a recommendation that all hormone receptor-positive patients receive post-operative adjuvant endocrine therapy as would be standard therapy after surgery for all early breast cancers.

Ultimately, by establishing clear national guidelines in IBC we aim to develop future IBC-specific clinical trials and foster long-term clinical and academic collaborative projects with international partners.

A mechanism for central registration of IBC would supply essential data to progress the study of this disease. Associated tissue collections will allow application of emerging new '-omics' and next-generation sequencing technologies to help uncover more about the biology of IBC, potentially leading to new strategies to improve patient outcomes.

Table 1. UK recommendations for the diagnosis of IBC

Diagnosis	Diagnostic procedures	Imaging and staging	Pathology
✓ Rapid and progressive onset of breast erythema or peau d'orange ± underlying mass with maximum symptomatic duration of 6 months ✓ Histopathological or cytological confirmation of breast cancer on perioperative biopsy	✓ Duration and nature of symptoms ✓ Description of breast appearance and physical examination including proportion of breast involved by erythema ✓ Degree of extension beyond the breast if present ✓ Size and location of any breast mass and presence of palpable axillary and supraclavicular fossa nodes ✓ Presence of any symptoms or signs of metastatic cancer. ✓ A clear statement that the condition fulfils the diagnostic and is considered an inflammatory breast cancer	✓ Bilateral diagnostic mammography with ultrasound of the breast and axilla and image-guided biopsy of suspicious lymph nodes as well as of any focal ultrasonographic abnormality in the breast ✓ Clinical photographs of the breast at diagnosis and if there is any interval progression immediately before commencing systemic therapy ✓ MRI in instances where breast parenchymal lesions are not detected by mammography or breast ultrasound ✓ Baseline and subsequent MRI to monitor response to therapy ✓ Whole-body staging either with contrast enhanced CT or PET/CT	✓ Biopsy to confirm invasive carcinoma ✓ Measure of hormone receptor expression and HER-2 status ✓ Skin punch biopsy of at least two representative areas of erythema/peau d'orange

Abbreviations: CT = computed tomography; IBC = inflammatory breast cancer; PET = positron emission tomography.

Table 2. UK recommendations for the management of IBC

MDT	Surgery	Chemotherapy	Endocrine therapy	Radiotherapy
✓ Case discussion with all clinical, imaging and pathology, including biomarker status, available	✓ Mastectomy ✓ In selected cases responding well to primary systemic therapy, a breast conservation approach may be considered ✓ Immediate reconstruction is not recommended. Delayed breast reconstruction is an appropriate option following mastectomy ✓ Axillary clearance recommended for patients with histologically (or cytologically) proven lymph node involvement identified by fine-needle aspiration core biopsy or sentinel lymph node biopsy	✓ Assess fitness to receive primary systemic chemotherapy (a full-dose anthracycline- and taxane-containing chemotherapy regimen such as sequential docetaxel-FEC) ✓ Anti-HER2 therapy in HER-2-positive IBC should be administered concurrently with chemotherapy with co-administration of anthracycline and anti-HER2 therapy considered in patients with no cardiac risk factors ✓ Assessment of response to primary systemic chemotherapy should include a combination of physical examination and radiological assessment. MRI is recommended for baseline evaluation and response assessment	✓ All hormone receptor-positive cancers	✓ Post mastectomy, chest wall radiotherapy is currently recommended irrespective of response to systemic therapy ✓ Supraclavicular fossa radiotherapy should be given where there is clinical pathological or radiological documentation, or suspected axillary node involvement according standard treatment protocols

Abbreviations: IBC = inflammatory breast cancer; MDT = Multi-Disciplinary Team; MRI = magnetic resonance imaging.

ACKNOWLEDGEMENTS

We are grateful to the input of participants at both the first and second UK Inflammatory Breast Cancer Symposium, held in 2011 and 2013, respectively, and to Breast Cancer Campaign for sponsoring the second of these symposia. This document has been endorsed by the members of the NCRI Translational, Pathology and Functional Imaging subgroup.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Published online 31 March 2015