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Inflammatory breast cancer: a proposed conceptual shift in the UICC–AJCC TNM staging system

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Abstract

In the absence of histologic criteria that distinguish inflammatory breast cancer (IBC) from non-inflammatory breast cancer (non-IBC), the diagnosis of IBC relies entirely on the existence of clinical criteria as outlined by the Tumor-Node-Metastasis (TNM) classification of breast cancer. The current TNM classification of breast cancer restricts patients presenting with clinical IBC criteria to subcategory T4d. This has the immediate effect of relegating all patients with non-metastatic IBC to stage III regardless of tumor size or nodal spread. For patients presenting with metastatic disease, the TNM classification consigns them to stage IV and does not distinguish patients based on the presence of inflammatory criteria. Recent evidence by our group, as well as others, suggests that patients with IBC criteria have a significantly reduced overall survival among patients who present with distant metastasis at diagnosis (stage IV breast cancer). In light of these

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Contributors

TMF and NTU contributed to the original idea, writing, literature search, interpretation of the manuscript. GNH contributed to study design, data analysis, data interpretation, writing and approval of final manuscript. All other authors contributed equally data interpretation, revision of earlier drafts, and approval of the final manuscript

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results, this manuscript addresses whether the current TNM staging classification accurately represents the distinction between IBC and non-IBC.

Keywords

Breast cancer; IBC; Stage IV; metastasis; AJCC

Introduction

Breast cancer is the second most frequent cause of cancer related death among women.[1] Inflammatory breast cancer (IBC) is the most fatal form of breast cancer, and is responsible for a disproportionate number of deaths (up to 7% of all breast cancer-specific mortality) despite its relative rarity (2% of newly diagnosed breast cancers).[2]

In spite of sufficient evidence towards the aggressive nature of IBC, decades of research have failed to find a specific diagnostic marker that is specific for IBC at either the histologic or the molecular level.[3] In the absence of histologic criteria that distinguish IBC from non-inflammatory breast cancer (non-IBC), the diagnosis of IBC relies entirely on the existence of clinical criteria as outlined by the Tumor-Node-Metastasis (TNM) classification of breast cancer.

The current TNM classification of breast cancer restricts patients presenting with clinical IBC criteria to subcategory T4d.[4] This has the immediate effect of relegating all patients with non-metastatic IBC to stage III regardless of tumor size or nodal spread. This classification is based on available data from retrospective studies that demonstrated differences in outcome between IBC and non-IBC among patients presenting with locoregional disease (Table 1). For patients presenting with metastatic disease, the TNM classification consigns them to stage IV and does not distinguish patients based on the presence of inflammatory criteria.

Recent evidence by our group suggests that patients with inflammatory criteria have a significantly reduced overall survival among patients who present with distant metastasis at diagnosis (stage IV breast cancer).[5] In light of these results, this manuscript addresses whether the current TNM staging classification accurately represents the distinction between IBC and non-IBC.

Inflammatory breast cancer as a unique clinical entity

Despite the absence of a molecular marker to distinguish IBC and from non-IBC at the molecular level, both clinical entities are clearly different distinct in terms of their presentation, natural history and survival. Clinically, the characteristic skin changes have a rapid onset from the time of confirmed diagnosis.[6] While approximately 85% of patients with IBC present with metastasis to the regional lymph nodes, and almost 30% present with distant metastasis at the time of diagnosis.[7] As a result, IBC is associated with a 5-year overall survival rate of less than 55%.[8,9] Radiologically, one of the most striking features of IBC is the absence of a clinically dominant breast mass in about 50% of patients but instead patients frequently present with multicentric disease. Despite its name, inflammatory breast

cancer does not demonstrate the histologic characteristics that are typical of the inflammatory process.[10] The pathologic hallmark of IBC is the presence of microscopic lesions known as lymphovascular tumor emboli, which are composed of clumps of tumor cells within the lymphovascular spaces of the dermis. This histologic finding, while not specific, is a useful complement to the clinical diagnosis and may explain some of the clinical manifestations of the disease including its high propensity for spread.

A history of definitions

A variety of classification systems have been used to define IBC since the first publication of Haagsen's criteria in 1956.[11] These classification systems have been used both to identify IBC for daily practice and to select and report on patients for clinical research. The French PEV (Poussée Evolutive) breast cancer classification was devised in 1959 and is composed of four stages and classified tumors based on the extent of inflammatory skin changes as either PEV2 or PEV3.[12] Tumors classified as PEV2 and PEV3 were associated with inflammatory signs involving less than half, and more than half of the breast surface; respectively. Because this system did not include a minimum cut off for the extent of inflammatory skin involvement, it allowed for a much larger proportion of patients with breast cancer to be identified as IBC compared to the now widely adopted TNM system (see below). Many patients with minimal inflammatory signs were classified as IBC, who would otherwise be recognized to have secondary inflammatory skin changes under the standardized TNM system. To demonstrate this, researchers in Tunisia reassessed the incidence of IBC using the more stringent TNM criteria and reported a significant drop in the incidence of newly diagnosed IBC compared to historical reports of breast cancer in Tunisia using the PEV classification (5%−7% vs. 50%).[13]

In 1972, the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) collaborated to produce a standardized TNM classification of breast cancer. "Inflammatory carcinoma" was introduced after an initial trial period, and appeared in the first edition of the Manual of Staging of Cancer (1978) under subcategory T4d.[14] IBC is described as a "clinicopathologic entity" characterized by diffuse brawny induration of the skin of the breast with an erysipeloid edge, usually without an underlying palpable mass".[14] Pathologic evidence of dermal lymphatic invasion was required to make the diagnosis and the extent of skin involvement was not specified.

Since then, the TNM definition of IBC has undergone further modifications. In the 2nd edition (1983), category T4d was eliminated altogether, with the recommendation that the clinical criteria and staging of inflammatory carcinoma be reported separately from non-IBC.[15] The 3rd edition (1988), reintroduced category T4d, however, it was not until the 6th edition that IBC became recognized as "primarily a clinical diagnosis" with skin changes that "arise quickly" and "involve the majority of the breast".[16] The 7th edition brought more refinements by specifying the extent of skin involvement in IBC as encompassing a third or more of the skin overlying the breast.[4] Moreover, an international expert panel, which adopted the definition of IBC set forth by the AJCC, recommended a cut-off of 6 months from the onset of erythema after breast cancer diagnosis to differentiate between IBC (≤6 months) and locally advanced breast cancer with secondary erythema (>6 months).[6]

The heterogeneity of stage IV breast cancer

The AJCC defines stage IV disease as clinical evidence of distant metastasis discovered prior to the initiation of definitive treatment (surgery, systemic therapy, radiation therapy, active surveillance, or palliative care) or within 4 months after the date of diagnosis, whichever comes first, as long as the cancer has not clearly progressed during that time frame.[4]

One of the primary goals of the AJCC staging system is to stratify patients according to prognosis. As our knowledge of the clinical and biological complexity of breast cancer metastasis increases, so does our understanding of the prognostic heterogeneity of the subset of patients that are diagnosed with stage IV breast cancer. The role of immune-histological subtypes based on hormone-receptor and HER2 status was evaluated in a cohort of 815 patients diagnosed with metastatic breast cancer between 2007 and 2009. [17] Multivariate analysis revealed that subtype (HR+/HER2-, HR+/HER2+, HR-/HER2+, TN) was an independent prognostic factor, in addition to other established prognostic factors such as initial site of metastases (bone, visceral, brain, multiple) and age. As a result, there have been growing calls for the AJCC to consider the incorporation of these proven prognostic factors both for the early and late stages of breast cancer.[18–20] The new prognostic staging system for breast cancer introduced in the 8th edition of the AJCC cancer staging manual does not apply to stage 4 disease.

IBC with de novo distant metastasis

IBC is 3 times as likely to present with stage IV disease compared to non-IBC. Approximately 20% to 30% of patients with IBC present with stage IV disease,[21–23] compared to 6% to 10% in non-IBC.[24,25] However, owing to the rarity of IBC, whether the outcome of IBC is worse than the outcome of non-IBC among patients with stage IV disease was not known. Our group reported on the largest cohort to date of patients with stage IV (*de novo* metastatic) breast cancer diagnosed at a single institution: 1504 patients, 206 with IBC and 1298 with non-IBC.[5] Our findings show that patients with stage IV IBC at diagnosis have worse survival outcomes than patients with stage IV non-IBC.[5] At a median follow-up period of 4.7 years, IBC was associated with shorter median OS time than non-IBC: 2.27 years (95% CI, 1.92–2.88) versus 3.40 years (95% CI, 3.20–3.68) (P=0.0128, log-rank test). This was also reflected in the lower 2-year and 5-year OS rates as well as across subgroups defined on the basis of age, ethnicity, HER2 status, and receipt of surgery or HER2-targeting therapy. In a multicovariate Cox model that included 1389 patients, the diagnosis of IBC was a significant independent predictor of worse OS (hazard ratio = 1.431, P=0.0011). Other significant predictors of worse OS included ethnicity (Black), younger age at diagnosis, negative HER2 status, and visceral site of metastasis. The results of a propensity-score matched analysis further confirmed this conclusion: HR (IBC vs. non-IBC) = 1.342 (P = .0275).

These results are consistent with shorter breast cancer-specific survival rates associated with stage IV IBC that were observed by Schlichting et al. using data from the Surveillance, Epidemiology and End-Results (SEER) registry.[26] The median breast cancer-specific survival (BCS) was found to be significantly lower for stage IV IBC compared to stage IV

non-IBC (1.75 years, range: 0–15.7 versus 2.3 years, range: 0–18.9, respectively; $P<0.0001$). These results are also in line with non-comparative studies and confirm what has been suspected from clinical practice.[27,28]

Taken together with previous retrospective studies that have directly compared IBC to non-IBC among patients with stage III breast cancer, these studies (Table 1) have clearly shown that IBC is associated with worse overall survival (OS) than non-IBC stage for stage.[29–31]

Discussion

The UICC/AJCC TNM classification system relies heavily on prognostic evaluation of both anatomical and increasingly on non-anatomical prognostic factors.[32] In the context of IBC, the TNM system is used both for the purpose of diagnosis and the purpose of disease staging. For diagnosis, there has been significant progress in refining the diagnostic criteria for IBC. In contrast, the staging of IBC is less clear and the TNM system does not accurately reflect the differences in outcome between IBC and non-IBC. In this case, the current TNM classification for IBC is based on prognostic evidence from retrospective studies in the non-metastatic setting (Table 1), and does not take into account the clear and statistically significant differences in survival between IBC and non-IBC in stage IV disease.[29–31]

While there have been increasing calls for the incorporation of clinically relevant and proven prognostic factors (ER/PR receptor status, HER2/neu, site of metastasis) into the AJCC staging system, IBC status is already included albeit not in stage IV. The lack of clarity regarding the staging of IBC directly impacts our ability to make scientific progress and improve disease outcome. A systematic review by Kim et al has attributed a discrepancy in the criteria used to define and select IBC as the leading factor contributing to differences in IBC outcome reported across different studies.[33] This uncertainty also contributes to the frequent exclusion of patients with IBC from the majority of breast cancer trials and has blunted the pharmaceutical industry's enthusiasm to develop new drugs that are specific to IBC. Consequently, there are currently no approved IBC-specific treatments, and patients with IBC are treated on the basis of the results of prospective breast cancer trials that in most cases exclude patients with IBC.

Conclusion & recommendations

Among patients with stage IV breast cancer, individuals diagnosed with IBC have significantly worse survival outcomes. It is important for the TNM system to accurately distinguish between IBC and non-IBC and acknowledge the worse prognosis of IBC and non-IBC stage for stage. Because the TNM system is used to distinguish between IBC and non-IBC, inaccurate representation leads to widespread uncertainty in terms of selection criteria for clinical research. The current TNM system does not take into account the clear and statistically significant differences in survival between the two groups presenting with metastatic disease (stage IV).

We therefore propose a simple stratification for the prognostic grouping of patients with stage IV disease based on the presence of inflammatory criteria characteristic of IBC at diagnosis (Stage IV_{IBC}). Given the rarity of IBC, and stage IV IBC in particular, this is

based on the highest level of evidence currently possible.[5,26] In preparing the next edition of the AJCC staging system, consideration should be given to incorporating an IBC as a prognostic factor within stage IV disease. This modification will allow the UICC/AJCC staging system to more accurately reflect the heterogeneous nature of metastatic breast cancer. In our stride towards personalized medicine these changes could lead to more accurate representation of IBC patients in breast cancer trials and herald the beginning of much needed drug development specific to patients with IBC.

Search strategy and selection criteria

Referenced articles were selected manually at the discretion of the authors based on their relevance to the original published findings by our group as well as the authors' own knowledge of the medical literature. Where appropriate, we reference review articles to provide more detailed information on specific topics.

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Table 1

Survival in selected IBC studies

Study	Date	Stage & study design	Sample size	Survival IBC vs. non-IBC (%)
Low JA, et al. 2004 [31]	1980 – 1988	Prospective (NCI) Stage III (IBC vs. non-IBC)	Total: 107 IBC: 46 Non-IBC: 61	OS at 15 years: IBC vs. non-IBC (IIIB): 20.0% vs. 23.1%
Cristofanilli M, et al. 2007 [29]	1974 – 2000	Retrospective (single institution) Stage III (IBC vs. non-IBC)	Total: 1,071 IBC: 240 Non-IBC: 831	OS at 5 years: IBC vs non-IBC: 40.5 vs. 63.2 (P < .0001)
Dawood S, et al. 2011 [30]	2004 – 2007	Retrospective (SEER) Stage III (IBC vs. non-IBC)	Total: 4,304 IBC: 828 Non-IBC: 3,476	BCSS at 2-years: IBC vs. non-IBC: 84% vs. 91% (P = .008)
Sutherland S, et al, 2010 [27]	1990 – 2007	Retrospective (single institution) IBC only (Stage III vs IV)	Total: 155 Stage III: 127 Stage IV: 28	Median OS: IBC, stage III vs stage IV: 3.9 vs. 1.7 years (P = .002)
Dawood S, et al. 2012 [28]	2004 – 2007	Retrospective (SEER) IBC only (Stage III vs IV)	Total: 2,384 III: 1,662 IV: 722	2-year IBCSS IBC, stage IIIB, IIIC and IV: 81%, 67% and 42% (P < 0.0001)
Schlichting JA, 2012 [26]	1990 – 2008	Retrospective (SEER) Stage III (IBC vs. non-IBC) Stage IV (IBC vs. non-IBC)	Stage III: 37,308 IBC: 4,441 Non-IBC: 32,867 Stage IV: 14,365 IBC: 1,085 non-IBC: 13,280	Median BCSS Stage III, IBC vs. non-IBC: 4.75 years vs. 13.4 years (P < 0.0001). Median BCSS Stage IV, IBC vs. non-IBC: 1.75 years, vs. 2.3 years (P < 0.0001)
Fouad TM, et al. 2015 [5]	1987 – 2012	Retrospective (single institution) Stage IV (IBC vs. non-IBC)	Total: 1,504 IBC: 206; non-IBC: 1,298	Median OS Stage IV, IBC vs. non-IBC: 2.27 vs . 3.40 years; (P = 0.0128)

T	N	M	G	HER2	ER	PR	Stage group
T1-T4c	Any N	M1	1–3	Any	Any	Any	IV-nIBC
T4d	Any N	M1	1–3	Any	Any	Any	IV-IBC