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EDITORIAL AND COMMENTARY

The TNM classification of breast cancer: need for change

Paolo Arnone · Stefano Zurrida · Giuseppe Viale · Silvia Dellapasqua · Emilia Montagna · Paola Arnaboldi · Mattia Intra · Umberto Veronesi

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Background

The need for a unified and internationally accepted cancer staging system was recognized in the first half of the twentieth century and led to the publication of the first International Union Against Cancer (UICC) [1] staging system in the 1950s. This was followed by the International Federation of Gynecology and Obstetrics (FIGO) classification of women's cancers [2] and the American Joint Committee for Cancer (AJCC) classification, the first edition of which was published in 1977 [3].

These manuals are based on clinical and pathological data and make it possible to assign a stage to a malignancy that indicates the extent of the disease, and also provides indications for treatment and prognosis. The UICC TNM classification (TNM_{UICC}) considers the size of the primary (T), regional lymph node status (N), and presence of distant metastases (M) as the fundamental disease characteristics.

Although the TNM classification has been regularly updated since its first edition in 1977 (new 7th edition published in December 2009), the TNM_{UICC} classification of breast cancer is, in our opinion, obsolete and requires radical overhaul, with the introduction of new information to produce a more modern and useful characterization of breast tumours.

Based on the experience of an interdisciplinary work group, which over the last 10 years examined over 30,000 breast cancer patients, the European Institute of Oncology has produced proposals for a revision of the TNM classification of breast cancers.

One of motives that inspired the new classification was the language of the existing TNM_{UICC} which often has a negative psychological impact on the patient receiving the diagnosis. Words like "malignancy", "carcinoma", and "infiltrating" are particularly at fault here. Psychological problems are present in around 20–40% of persons diagnosed with cancer [4] and the emotive terminology used by the physician or in the diagnostic report—which conjures up images of pain, suffering, and death—are likely to exacerbate these problems.

The fear and uncertainty that a cancer diagnosis generates may motivate the person to put her faith in the treating physician, ask questions about the illness, and find out more on the Internet. But the opposite reaction of

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P. Arnone (✉) · S. Zurrida · M. Intra
Senology Division, European Institute of Oncology,
Via Giuseppe Ripamonti 435, 20141 Milan, Italy
e-mail: paolo.arnone@ieo.it

S. Zurrida · U. Veronesi
European Institute of Oncology, Milan, Italy

S. Zurrida · G. Viale
Faculty of Medicine and Surgery,
University of Milan, Milan, Italy

G. Viale
Department of Pathology and Laboratory Medicine,
European Institute of Oncology, Milan, Italy

S. Dellapasqua · E. Montagna
Department of Medical Oncology,
European Institute of Oncology, Milan, Italy

P. Arnaboldi
Unit of Psychological Oncology,
European Institute of Oncology, Milan, Italy

withdrawing into oneself and experiencing the diagnosis is a death sentence, is common [5]. The way the diagnosis is communicated, by the physician or the diagnostic report, can markedly influence how the patient reacts. The terminology used by the TNM_{UICC} classification can exacerbate these problems and make it more difficult for the patient to come to terms with her disease [6].

When a patient is told she has "carcinoma in situ" she will usually become extremely anxious, thinking she has an incurable cancer. Consider a woman diagnosed with "infiltrating carcinoma". The already traumatic effect of the word "carcinoma" is worsened by its qualifier "infiltrating". The woman understands that, even though her illness may have been diagnosed at an early stage, it has already "infiltrated" her organs and will surely kill her. The result is that the patient has none of the hope necessary to face her treatment program, asks how long she has to live, and is beside herself with the thought she will not see her children grow up.

After an interview with the physician the patient with in situ carcinoma is reassured, learning she has ductal or lobular carcinoma in situ; that this type of lesion differs biologically from infiltrating carcinoma; and that she is likely to be completely cured. The second woman will also benefit from more information about the nature of her disease.

One of the important innovations of the European Institute of Oncology TNM classification (TNM_{IEO}) is to eliminate the terms "in situ carcinoma" and "infiltrating"—which are likely to be misconstrued by the patient—and replace them with a more logical and accurate terminology [7–9]. The new terminology also clearly indicates the difference between lesions that can metastasize and those which do not.

The second major innovation proposed by the TNM_{IEO} classification is to specify T and N more precisely, with the advantages of furnishing a more exact and useful indication of "disease stage", and at the same time retaining compatibility with the older T and N categories and hence permitting statistical comparisons between older data and new data.

An important aim of previous TNM_{UICC} classifications was to provide some indication of prognosis and hence also a rough guide to treatment. Ductal carcinoma in situ (DCIS) and lobular carcinoma (LCIS) are included within the T classification. However, as noted above, these neoplasms are non-invasive by definition and are incapable of metastasizing to distant sites. They should not, therefore, be considered either malignant or carcinoma, and should be excluded from the TNM classification. We propose adopting the classification of Tavassoli [10] which drops the terms DCIS and LCIS, and instead uses ductal intraepithelial neoplasia (DIN) and lobular intraepithelial neoplasia (LIN) (Table 1), and further divides these entities according to the grade of the neoplasia.

Furthermore, since the word "infiltrating" in "infiltrating carcinoma" is redundant as carcinoma is by definition infiltrating (or invasive), we also propose removing "infiltrating" from the TNM classification.

Tumour size (T)

In the TNM_{UICC} classification, cancers are classified into categories (T1, T2, etc.) according to size, but with no real logic to the categories. This approach was reasonable 60 years ago when the first TNM classification was developed. At that time it was only possible to diagnose a breast cancer large enough to be palpated. Today, however, the lack of logic in the T categories is evident. First, because they do not make full use of the information provided by modern diagnostic methods which allow the identification of ever smaller tumours. Thus, the T1 category ranges from a few millimetres to 2 cm, with a large difference in prognosis between the extremes. These differences in prognosis are in part acknowledged by the T1 subcategories (T1a, 1–5 mm; T1b, 6–10 mm; and T1c 11–20 mm), but these are essentially arbitrary and needlessly complex.

The prognostic variation within T2, which includes cancers from 2.1 to 5 cm, is even more marked, and further illustrates the arbitrariness of T categories which consider diameter rather than volume. Thus, a tumour of diameter 2.1 cm would have a volume 4.5 ml (assuming it were spherical) while a 5 cm cancer would have volume of about 60 ml. The difference in prognosis between the two masses is marked.

We therefore propose abolishing the T categories of the TNM_{UICC} classification and replacing them by the exact specification of tumour size in centimetres (Table 2). The result is a more intuitively comprehensible and information-rich classification.

Regional lymph nodes (N)

The classification of locoregional lymph node involvement proposed by the TNM_{IEO} follows the logic of the new T classification: it specifies the exact number of lymph nodes found to be metastatic over the total number removed and examined. For example $pN_{(5/21)}$ states that 5 out of the 21 lymph nodes examined were metastatic. Consider the utility of this: if 3 nodes were positive of the 28 axillary lymph nodes removed and examined the N stage would be N1b by TNM_{UICC}, but simply pN+(3/28) by TNM_{IEO}.

Table 1 TNM breast staging comparison guide: sixth UICC versus Tavassoli classification (Primary Tumour (T))

TNM_{uicc} 6th version (2002)		Tavassoli Classification	
Primary Tumour (T)			
pTis	**pTis (DCIS)** - Ductal Carcinoma In Situ.		
	DCIS grade 1	⇒	Ductal Intraepithelial Neoplasia grade 1c (DIN1c)
	DCIS grade 2	⇒	Ductal Intraepithelial Neoplasia grade 2 (DIN2)
	DCIS grade 3	⇒	Ductal Intraepithelial Neoplasia grade 3 (DIN3)
	pTis (LCIS) - Lobular Carcinoma In Situ.		
	LCIS (classic)	⇒	Lobular Intraepithelial Neoplasia grade 2 (LIN2)
	LCIS (High grade –pleiomorphic)	⇒	Lobular Intraepithelial Neoplasia grade 3 (LIN3)

Table 2 TNM breast staging comparison guide: sixth UICC versus TNM_{IEO} (Primary Tumour (T))

TNM_{uicc} 6th version (2002)		TNM_{IEO}	
Primary Tumour (T)		**Primary Tumour (T)**	
Tx	Primary tumour cannot be assessed	⇒	IDEM
pT0	No evidence of primary tumour	⇒	IDEM
pTis	**pTis - Carcinoma in situ.** • **pTis (DCIS)** - Ductal carcinoma in situ. • **pTis (LCIS)** - Lobular carcinoma in situ. • **pTis (Paget's)** - Paget's disease of the nipple with no tumour	⇒	EXCLUDED (see Table 1 Tavassoli Classification)
pT1	Tumour 2.0 cm or less in greatest dimension		
T1 Mic	Microinvasion 0.1 cm or less in greatest dimension[a]	⇒	**pTmic**
T1a	Tumour more than 0.1 but not more than 0.5 cm in greatest dimension	⇒	**T (with size in cm)** Add the following suffixes: **m**: if multifocality or multicentricity present **eic**: if extensive DIN present (≥ 25% of tumour) **pvi**: if peritumoural vascular invasion present **infl**: if lymphangitic or Inflammatory carcinoma present **eg:** pT 1,9 (m)
T1b	Tumour more than 0.5 cm but not more than 1.0 cm in greatest dimension		
T1c	Tumour more than 1.0 cm but not more than 2.0 cm in greatest dimension		
pT2	Tumour more than 2.0 cm but not more than 5.0 cm in greatest dimension		
pT3	Tumour more than 5.0 cm in greatest dimension		
pT4	Tumour of any size with direct extension to:		
T4a	chest wall (Chest wall includes ribs, intercostal muscles, and serratus anterior muscle but not pectoral muscle)		
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast		
T4c	Both of the above (T4a and T4b)		
T4d	Inflammatory carcinoma[b]		

[a] T1 Mic is defined as microinvasion 0.1 cm or less in greatest dimension. The presence of multiple tumour foci of microinvasion should be noted in parentheses. Microinvasion is infiltration of neoplastic cell beyond the basal membrane of adjacent tissue without foci greater than 0.1 cm in max diam. In the presence of multiple micro-invasive foci, classification is based on largest size (not the sum of diameters of several foci). Presence of multiple foci must be noted, as for multiple larger size carcinomas

[b] Inflammatory carcinoma is a clinicopathologic entity characterized by diffuse brawny induration of the skin of the breast with an erysipeloid edge, usually without an underlying palpable mass. If the skin biopsy is negative and there is no clinically apparent primary tumour, when the clinical diagnosis is inflammatory carcinoma (T4d), the pathological staging should be pTX. Skin depression, nipple retraction or other skin alterations (except those for T4b and T4d) can also be present in T1, T2, and T3 disease and do not change the T category. Radiologically there may be a detectable mass and characteristic thickening of the skin over the breast. This clinical presentation is due to tumour embolization of dermal lymphatics with engorgement of superficial capillaries

Over the last decade sentinel node biopsy has completely revolutionized the surgical approach to the axilla in breast cancer [11]. This revolution has been felt in the TNM_{UICC} classification, but the modification proposed by the TNM_{IEO} is to simply add the suffix (sn) (Table 3). For a lymph node with extracapsular, invasion the suffix ExCp is added.

Sentinel node biopsy combined with intra-operative examination of 50 μm serial sections [12] has led to the frequent finding of micrometastases (<2 mm) or even of

Table 3 TNM breast staging comparison guide: sixth UICC versus TNM_{IEO} (Regional Lymph Nodes (N))

TNM_{uicc} 6th version (2002)		TNM_{IEO}	
Regional Lymph Nodes (N)[a, b]		Regional Lymph Nodes (N)[a]	
pN		pN	
pNx	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)	⇨	IDEM
pN0	No regional lymph node metastasis histologically, no additional examination for isolated tumour cells (ITC)[d]		
pN0(i-)	No regional lymph node metastasis histologically, negative IHC		
pN0(i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2mm[e]		
pN0(mol–)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)[e]		
pN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)[e]		
pN1	Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[f]		
pN1mii	Micrometastasis (greater than 0.2mm, none greater than 2.0mm)		
pN1a	Metastasis in 1 to 3 axillary lymph nodes		
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[f]		
pN1c	Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[f,g]		
pN2	Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent[c] internal mammary lymph nodes in the *absence* of axillarylymph node metastasis		
pN2a	Metastasis in 4 to 9 axillary lymph nodes (at least one tumour deposit greater than 2.0mm)		
PN2b	Metastasis in clinically apparent[c] internal mammary lymph nodes in the *absence* of axillary lymph node metastasis		
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent[c] ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes		
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumour deposit greater than 2.0mm), or metastasis to the infraclavicular lymph nodes		
pN3b	Metastasis in clinically apparent[c] ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[f]		
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes		

pN (x/y)
(***X= number of pathological lymph nodes***
Y= number of lymph nodes removed)

Add the following suffixes:

sn: sentinel lymph node
excp: extracapsular invasion
bln: bunched lymph nodes
ITCs: Isolated tumour cells

eg: pN(4/28) **excp**

pN(0/2)**(sn-ITCs)**

[a] The regional lymph nodes are: (1) *Axillary* (ipsilateral): interpectoral lymph nodes (Rotter's node) and lymph nodes along the axillary vein and its tributaries, which may be divided into the following three levels: Level 1(lower axilla): lymph nodes lateral to the lateral margin of the pectoralis minor; Level 2 (middle axilla): lymph nodes between the medial and lateral margins pectoralis minor and interpectoral lymph nodes (Rotter's nodes); Level 2 (apex of the axilla): lymph nodes medial to the medial margin of pectoralis minor including those known as subclavicular, infraclavicular or apical Note: intramammary lymph nodes are considered axillary lymph nodes; (2) *ipsilateral infraclavicular* (subclavicular); (3) *mammary internal* (ipsilateral): are situated in the intercostal space along the lateral edge of the sternum on the endothoracic fascia; (4) *supraclavicular* (ipsilateral)

[b] Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node", e.g., pN0(i+)(sn)

[c] Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically

[d] Cases with only isolated tumour cells (ITC) in regional lymph nodes are classified pN0. Isolated tumour cells (ITC) are defined as individual tumour cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but which may be verified on H&E stains. ITCs do not usually show evidence of metastatic activity (e.g., proliferation or stromal reaction)

[e] RT-PCR: reverse transcriptase/polymerase chain reaction

[f] Not clinically apparent is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination

[g] If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumour burden

small clusters of cancer cells (isolated tumour cells). The TNM_{UICC} classification was forced to change and the categories N_{mic} and N_{itc} were introduced and are used for example in the trial 23/01 [13].

Distant metastases (M)

The TNM_{UICC} classification uses M1 to indicate the presence of distant metastasis. We suggest specifying the site

Table 4 TNM breast staging comparison guide: sixth UICC versus TNM_{IEO} (Distant Metastasis (M))

TNM_{uicc} 6th version (2002)		TNM_{IEO}		
Distant Metastases (M)		**Distant Metastases (M)**		
pM		pM		
pMx	Distant metastasis cannot be assessed			Distant metastasis cannot be assessed
pM0	No distant metastasis	⇨		No distant metastasis
			pM1 PUL	Lung
			pM1 OSS	Bone
			pM1 HEP	Liver
			pM1 BRA	Brain
			pM1 LYM	Extraregional lymph nodes
pM1	Distant metastasis present (site may be specified)	⇨	**pM1 MAR**	Bone Marrow
			pM1 PLE	Pleura
			pM1 PER	Peritoneum
			pM1 ADR	Adrenal
			pM1 SKI	Skin
			pM1 OTH	Other organs
			pM1susp	Clinical suspicious of metastases requiring verification

of distant disease spread, since different sites can be treated with different possibilities of success using new treatment modalities, such as radiofrequency thermoablation [14], stereotactic radiosurgery (gamma knife) [15], high-intensity focused ultrasound [16], and monoclonal antibodies [17, 18]. We propose using suffixes to indicate the metastatic sites. Table 4 illustrates the use of M suffixes proposed by the TNM_{IEO} in comparison with the current TNM_{UICC} system.

Biological factors

As molecular and genetic understanding of breast cancer pathology has increased, new biological characteristics have been identified as prognostic indicators, and new adjuvant treatments have been developed. This has resulted in an increasingly personalized approach to breast cancer treatment that takes into account the diverse biological characteristics of the individual patient and her disease.

Examples include the expression by cancer cells of nuclear receptors for estrogens (ER) and for progesterone; expression of the Ki-67 marker of cell proliferation [19] present in active phases of cell cycle (G1, S, G2, and mitosis), but absent from resting cells (GO) [20]; and more recently expression of human epidermal growth factor receptor 2 (HER2).

HER2 (also known as neu or erbB2) is overexpressed in approximately 20–30% of breast cancers, usually because gene duplication events increase the number of copies of the HER2 gene in each cancer cell. HER2 overexpression indicates an aggressive type of breast cancer, and the relatively new monoclonal antibody drug trastuzumab is able to inactivate HER2 and improve the prognosis for this type of breast cancer.

There is some evidence that the way HER2 expression is measured in breast cancer samples can influence the indication for trastuzumab use [21]. HER2 expression is most often assessed immunohistochemically (IHC), assigning a score of 0 to +3 according to the intensity and completeness of staining on the cancer cell membrane [22, 23]. The second method, typically used if the IHC result is uncertain, employs fluorescent in situ hybridization (FISH) to estimate the number of copies of the HER2 gene per cancer cell. The HER2 gene is present on the long arm of chromosome 17 (17q21-q22) [24] and HER2 gene copy number is usually expressed relative to chromosome 17. Unfortunately, notwithstanding efforts to introduce a standardized and reliable HER2 assay method, the result may sometimes be uncertain, introducing uncertainties in the indication for trastuzumab use.

We propose introducing HER2 into the TNM_{IEO} classification, specifying not only the ICH score (indication of percentage of cancer cells with highly positive staining), but also the result of the FISH analysis, if performed, specifying the amplification/non-amplification/polysomy of chromosome 17, and including the absolute or relative number of copies of the HER2 gene.

Another important consideration regarding the role of cancer stem cells in cancer spread. According to the cancer stem cell theory a small number of cancer stems cells are present in most tumours. These are relatively slow growing and divide asymmetrically to produce more self-renewing stem cells, but mainly the quickly dividing cells that form the mass of the tumour. Although these latter cells are variably differentiated they do not possess metastatic

potential. According to this view, the cells in a cancer are hierarchically organized, as in normal tissue, and the carcinogenetic process can be regarded as organogenesis gone wrong. The quantity of stems cells and their detailed properties are likely to vary between one cancer and another accounting for differences in expansion kinetics. It has been suggested for example that the "basal-like type" of breast cancer has an evaluated number of cancer stem cells [25, 26].

A cancer with a high proportion of cancer stem cells might have greater more metastatic potential, since cells shed from the primary tumour would be more likely to be stem cells.

These considerations indicate that tumour size is a rather rough-and-ready indicator and that more refined molecular characterization of the cancer is likely to provide much more precise prognostic information.

We therefore propose that adding prognostically important suffixes, such as EIC (extensive intraductal component), PVI (perivascular invasion), M (multifocal), and inf (inflammatory) to the new T specification, which provide new information without compromising comprehensibility to either patient or clinician (e.g. $pT1.5_{EIC}$; $pT0.7_{PVI}$).

We believe that a TNM workable classification should also be flexible enough to accommodate new information about prognostic indicators for breast cancer, including gene expression profiles. It is now possible to analyse the expression of thousands of genes simultaneously, using microarray techniques, and this has resulted in the identification of various sub-types of breast cancers, based on gene expression profile, that also show distinct clinical and prognostic features.

The two main breast cancer groups are defined by the presence or absence of ER. ER+ cancers are divided into luminal A and luminal B types according to gene expression profile, while ER− cancers are divided into normal breast-like, HER2+ and "basal-like".

The luminal B type has poorer prognosis than the luminal A type, but better prognosis than ER− cancers. ER− cancers have gene expression profiles (particularly basal epithelial-like cancers) similar to those of the basal epithelial cells or myoepithelial cells of healthy breast tissue, which express neither hormone receptors nor HER2 and have poor prognoses.

Conflict of interest None.

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