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Breast Cancer Management: Should We Treat Our Patients according to the TNM or the Molecular Classification?

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It is the merit of a French surgeon, Pierre Denoix, the former director of the Gustave Roussy Institute, to have created two major concepts in the breast cancer management: 1) the TNM classification and 2) the multidisciplinary "committees".

The TNM classification described four (in fact five) clinical T classes from T0 (non palpable tumor), T1 (0-2cm), T2 (2-5cm), T3 (over 5cm) and T4 (chest wall or cutaneous invasion). During the years, this initial classification improved separating the main classes in subclasses (T1a or T1b for example) and adding the post-operative classification (pTNM) according to the size in the permanent section of the operative specimen in pathology report.

This classification also included the clinical axillary nodal status N0, 1a, 1b, 2 and 3. The lymph node status in the TNM classification has also been recently upgraded by adding micro-metastatic and IHC characteristics of the lymph node according to post operative assessments. The M status is not any more clinical but is diagnosed on the workup on common metastatic sites. Initially, it was just according to the findings on the radiological analysis of the chest X-ray and the bone scan examination of the ribs, sternum, pelvis, and other common sites. Nowadays, it has become more and more sophisticated by searching the metastatic lesions in other organs, especially visceral organs, and PET scan is becoming a standard approach in some teams.

The immense merit of this classification was first to exist, in order to communicate between surgeons and other physicians about the patients. Moreover, it was useful particularly to schematically separate the operable breast cancer from the metastatic ones and to decide which patients were the best candidates for breast conserving therapy. As all classifications, TNM suffers from its own limitations. As an example, the significance of a small T1 in a large breast is quite different from a T2 lesion in a small breast. Actually, one can discuss the exact significance of a 1.9 cm versus a 2.1 cm lesion which are in different T status, but is there really a great difference between them (T1 or T2)?

Then, if we go back to the beginning of this paper, Pierre Denoix also created the concept of multi-disciplinary committees. In these meetings, next to the surgeons were sitting radiologists, pathologists, and radiation therapists. When he practiced, medical oncologists were not really concerned about breast cancer. Most of them were issued from hematology and used to consider breast cancer as a minor subject until papers by G. Bonadonna demonstrated the benefits of CMF adjuvant medical treatment on survival in the end of the 70's.[1] We all know the efficacy of medical oncology and the expected improvements in the coming years, since its immense development.

We have to emphasize two points: the discovery of hormonal receptors which led to the creation of Tamoxifen by ICI in England in the 60's, and the analysis of proliferation either by DNA analysis differentiating diploid from aneuploid tumors. Ploidy is associated with the S-phase analysis by flow cytometry as described by Remvikos *et al.* at Curie Institute in 1991 who demonstrated that the most proliferative tumor, the more efficient was the chemotherapy.[2] The proliferation index, whatever technique is used, allows deciding, if a patient is a candidate for an adjuvant hormonal therapy and/or chemotherapy according to its biological profile. Additionally, since 2004, HER2 profile has changed the management of breast cancer in case of the over-expression of the HER2 protein, and Trastuzumab

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has completely changed the prognosis of these tumors. All the biological information did not exist when Denoix practiced and the biological classification derived from Sorlie and Perou papers appeared only at the beginning of the 21st century.[3] The biological parameters have led to a molecular classification in which the tumors are separated as Luminal A-B, triple negative, HER2 positive, Claudine-low cancers. That was the initiation of "targeted" therapies, now called "precision" medicine, for the best benefits of our patients.

Let's go back again to the title of the paper and the question of what the best choice is for our patients; TNM or molecular classification.

This is a hard question for surgeons, since they are more familiar with TNM. However, the word "operable breast cancer" does not mean that the surgeon must operate before any other treatments. This is the concept of neoadjuvant treatment.

Due to the biological profile of the tumor, a patient with a small tumor with negative receptors and a high proliferative index could be a good candidate for a primary chemotherapy (neoadjuvant treatment), while a large tumor with a low proliferative index and high hormonal receptors would be a good candidate for a locoregional treatment first and a chemotherapy, if given, will be administered only in the post operative course. The initial purpose of neoadjuvant treatment was to permit a conservative treatment where a mastectomy was initially impossible due to the tumor-breast size ratio, or permit surgery where it was initially technically impossible. In addition, neo adjuvant treatment realizes an in vivo test for the efficacy of the medical treatment, and the ultimate benefit is when a complete response is obtained on the surgical specimen. On the other hand, the lack of response or the progression under chemotherapy is the proof of a really aggressive disease and necessitates a protocol modification. Furthermore, the benefits of neoadjuvant treatment versus locoregional benefits have been clearly demonstrated and its impact on the overall survival has been recently demonstrated; the pathologic response has become the "surrogate marker" of the neoadjuvant treatment efficacy.

When the surgery has been realized, adjuvant chemotherapy is mainly administered to prevent distant recurrences and contra-lateral cancers. It can even be given to patients with low proliferative, hormone receptors positive (HR+) cancers according with the size of the tumor and invasion to axillary nodes.

What does that it all mean? How should or can we decide between the two classifications?

Ideally, we should have a good preoperative biopsy specimen before deciding the best treatment choices for a given patient. In a very near future, we will have the whole genome in one week for three hundred Euros! In addition, every classification is always disputable and the exact significance of different parameters can be unclear. For instance, are the prognostic and predictive significance of positive hormonal receptors at the level of 10 identical to 100%? Do positivity of estrogen receptors and negativity of progesterone receptors have the same significance as compared to the time when both hormonal receptors are positive? The cut off point of KI67 is another good example. Clearly, a Ki67 at 5% is associated with a good prognosis and at 60% is associated with an aggressive cancer. However, is the cut off between good and bad 14-20% or more than 20%? The recent introduction of TIL does not simplify our ideas.

Does that mean that we have to rely on biological parameters subjects to variations between laboratories and pathologists and should we all send our specimens to highly sophisticated centralized platforms? certainly not!

More recently, commercial molecular signatures have demonstrated their ability to separate low risk from high risk patients. Unfortunately, there is always an intermediate group in which making a medical decision remains difficult.

The only solution for surgeons to survive in this new era is to know the biology and medical treatments similar to the medical oncologists. Ideally, medical oncologists should also know surgical procedures and learn the radiation techniques. Cancer is a continuous disease in which physicians define virtual categories to help them with their medical decisions and to enable them to communicate both with their colleagues and their patients.

From the multidisciplinary teams, will emerge the best treatment options for the patients in which the surgeons should keep their place as long as they know how and when to operate.

Finally, it seems that the old Heraclite sentence "the only thing which does not change is that everything is always changing" remains also true for breast cancer management.

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