Pathology: is it still necessary?

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introduction

One may wonder what may be the reasons to ask this apparently odd question. Undoubtedly, the main concern is that we are still far away from being able to precisely identify the target population of patients for tailored interventions. It has been repeatedly shown by the results of large clinical trials that the benefit of new therapeutic approaches is relatively small, and that it is most likely confined to defined subgroups of patients, which should be properly identified for the adoption of the new treatment to be truly rewarding in clinical practice [1–4]. What is needed is an accurate assessment of the likelihood of individual patients to benefit from the different therapeutic options that are currently available.

Traditionally, we have relied on the morphological and biological features of the tumor to identify patients at different risk of disease progression and for predicting the efficacy of different therapeutic approaches [5]. It is undisputable that this approach is not entirely satisfactory, because it only allows identification of a very limited number of subgroups of patients, characterized by a different risk of tumor progression (low, intermediate and high) and a different responsiveness to endocrine treatments (highly responsive, non-responsive and incompletely responsive) or to targeted interventions (HER2 positive and negative) [6]. Accordingly, we are still very far from a truly individualized therapeutic approach, most likely due to the relative paucity of the available prognostic and predictive parameters, which do not allow a more specific portrait of the individual patient to be drafted. Furthermore, we must admit that the pathological evaluation of breast cancer has shown additional drawbacks, mainly related to the lack of consistency and reproducibility in the assessment of at least some of the prognostic/predictive parameters. This is particularly true for the evaluation of hormone receptor status [4] and of the overexpression/amplification of the HER2 gene [7], where the rate of false-negative and false-positive results is exceedingly high. As a result, a growing sense of distrust towards the role of the traditional pathological characterization of breast cancer has emerged, and pathology is now viewed as a finite and possibly exhausted source of clinically important pieces of information.

molecular biology assays

The development of novel molecular biology assays, mainly based on gene expression profiling, has run into this scenario with a profound impact on the expectations of both clinicians and patients [8, 9]. The potential usefulness of these techniques is indeed very remarkable, and they have been immediately granted an enthusiastic acceptance and have raised extraordinary expectations (as always happens with newly discovered technical approaches), as the ultimate answer to all the clinical questions. Interestingly, these sophisticated techniques have been initially used not to add original pieces of information—thus complementing the traditional pathological evaluation of breast cancer—but instead they have been proposed as an alternative approach to replace the one already available. The actual usefulness of a new assay over an existing one should be weighed against the additional amount of information provided and—if additional pieces of information are not provided—against the accuracy and cost-effectiveness of the results obtained. Ad hoc designed clinical trials will document whether molecular assays actually provide clinically useful additional information and/or more accurate and reproducible results than the traditional histopathological approach.

For the time being, however, pathology cannot be safely replaced by molecular assays. Take for instance the emphasis placed in the new molecular classification of breast cancer [10], with the luminal types, the basal-like type and the HER2-positive type, and its prognostic and predictive implications. Does this classification add new pieces of information as compared with the traditional World Health Organization (WHO) classification of breast carcinoma complemented by the assessment of hormone receptor and HER2 status? It has already been known for decades that the lack of hormone receptors and the overexpression of HER2 protein correlate with a worse prognosis.

Is running a gene expression profile assay for a luminal type breast cancer more accurate or more cost-effective than histopathology in identifying an invasive lobular carcinoma with extensive immunoreactivity for estrogen receptor (ER) and progesterone receptor (PgR)? Will this modify our expectations of high responsiveness of this tumor to endocrine therapy? Furthermore, the basal-like group of breast cancer likely encompasses a large variety of tumors (high-grade invasive ductal carcinomas not otherwise specified, medullary carcinomas, adenoid cystic carcinomas, some apocrine carcinomas) with distinct prognostic and predictive implications that escape molecular identification. Are we ready to accommodate all these different tumor types in a unique molecular class, and to treat all of them in a similar manner?
Will the new era see patients with an indolent adenoid cystic carcinoma treated with aggressive chemotherapy because it belongs to the basal-like class?

It has been shown that gene expression profiling allows identification of patients most likely to undergo pathological complete response (pCR) after neo-adjuvant chemotherapy. But ER status and histological grade are as predictive of pCR. Therefore, molecular class alone can replace histopathologic characteristics for prediction of pCR, but provides little additional information when these characteristics are included [11]. Should we refrain from grading breast cancers and assessing ER status to take full advantage of the introduction of the novel molecular assays?

**molecular assays or traditional pathological evaluation?**

It is unwise to claim that the new molecular assays should replace the traditional pathological evaluation of breast cancer, when we could take the greatest advantage by combining the two approaches for the maximum benefit of the patients. In my view, to get closer to a truly tailored treatment of breast carcinoma patients we should first take the most from the traditional morphological and immuno-phenotypical evaluation of the tumors and improve with all means the accuracy and reproducibility of the collected data. This will allow a first allocation of the patients in different prognostic and predictive subgroups. It is within these pathologically defined subgroups of patients that the molecular assays should prove useful in identifying further subsets including a more and more homogeneous population of patients. We do not need any new assay for selecting the candidate patients to anti-HER2 interventions, provided that we improve the accuracy and reproducibility of the current immuno-histochemical or in situ hybridization assays [12]. What is surely needed is a novel assay to identify among the candidate patients those who will actually benefit from the anti-HER2 therapies, and who will take the greatest benefit from one therapy or the other.

**conclusion**

The extraordinary power of the new techniques is that they allow us to explore the whole universe of gene expression in the tumor cells. We will have the opportunity to identify new genes, whose deregulation is important in the neoplastic transformation, in tumor progression and in the susceptibility to different therapeutic approaches. Once these newly identified genes have been hierarchically ranked according to their prognostic or predictive power, and a reasonably low number of them have proved to be informative enough, then we will have the opportunity of raising antibodies to the encoded proteins and of developing immuno-histochemical assays accordingly. This will eventually lead to molecular characterization of breast cancer suitable for daily clinical practice, at a reasonably low cost and easily offered to the entire population of patients.

In conclusion, I am convinced that pathology is indeed even more necessary in this molecular era than it used to be, first to precisely identify the subgroups of tumors deserving additional molecular investigations to address very specific questions, and second to bring to the bedside the discoveries of the new molecular assays.

**disclosure**

No significant relationships.

**references**