New Strategies in Breast Cancer: The Significance of Molecular Subtypes in Systemic Adjuvant Treatment for Small T1a,bN0M0 Tumors

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Disclosure of Potential Conflicts of Interest

H.A. Azim is a consultant/advisory board member for Celgene, GlaxoSmithKline, Nanostring, and Novartis. M. Piccart is a board member for PharmaMar and a consultant/advisory board member for Amgen, Astellas, AstraZeneca, Bayer, Eli Lilly, Invivis, Merck, Novartis, Pfizer, Roche/Genentech, Sanofi-Aventis, Symphogen, Synthon, and Verastem. No potential conflicts of interest were disclosed by the other authors.
Abstract

Awareness of breast cancer heterogeneity strikingly increased in the last decade in parallel with the development of high throughput molecular tests. Beyond the clear usefulness of anti-estrogen treatment in luminal tumors and trastuzumab in HER2-positive tumors, breast cancer subtypes may have additional clinical and predictive roles that can be relevant to clinical practice. In this article, we discuss the significance of molecular subtypes in the systemic treatment of early staged breast tumors smaller than 1 cm (T1a,bN0M0) and suggest new strategies for future treatment recommendations for these patients.
**Background**

Screening and increased awareness have led to a rise in the detection of T1 breast tumors that are generally estimated to have a low risk of recurrence after loco-regional treatment (1–4). However, even small tumors can have an aggressive behaviour. This population of patients suffer from low representation in clinical trials which leads to a situation where medical oncologists lack high level evidence data that can guide them in the treatment of these patients. Tumor size and nodal involvement remain among the most important clinic-pathological prognostic factors in breast cancer, which puts T1a,bN0 (<1cm) tumors in a group of a generally low risk of recurrence population. Information on T1a,bN0 from large population databases of untreated patients demonstrates relatively low cancer mortality rates at 15 years (<10%), with much higher death rates from other causes in women older than 50y (5,6). However, it has been shown that about 25% of all relapses of small lobular/ductal cancers occur beyond 10 years (7). High grade, young age, high proliferation and vascular invasion are considered adverse prognostic signs even among T1a,bN0 tumors suggesting a potential benefit of more aggressive therapy in women diagnosed with tumors harboring any/all of these features (8–11). Furthermore, the classification of breast cancers into different sub-types (luminal A, Luminal B, triple negative, and HER2 positive), appears also to affect prognosis and treatment decisions in such early cases (10,12,13). This classification was first based only on histology features (estrogen receptor [ER], progesterone receptor and HER2) but later on it was shown that the differences are also reflected by the mRNA expression profiles (14,15).

**Is the threshold for offering adjuvant therapy in T1a,bN0 tumors dependent on the molecular subtype?**

There is lack of high level evidence regarding the use of chemotherapy in women with T1a,bN0 tumors. However, it is possible to derive prognostic information based on tumor
subtype. In a retrospective study conducted by Theriault et al., 1012 patients with T_{1a,b}N_{0} breast cancer who did not receive chemotherapy or trastuzumab were evaluated. Compared to patients with hormone receptor (HR)-positive disease, patients with HER2-positive and triple negative breast cancer (TNBC) had 4.9 and 2.7 times greater risks of recurrence, respectively (16). Another study conducted by Cancello et al exploring patterns of recurrence in 1691 patients with T_{1a,b} breast cancers confirmed the same findings (17). Multivariate analysis showed that women with HER2-positive and TNBC had an increased risk of loco-regional relapse by threefold and breast cancer related events by twofold, respectively. The luminal-B subtype was not associated with a statistically significant increased risk of recurrence when compared with Luminal A. The increased recurrence in HER2 patients was demonstrated despite the fact that 44% of HER2 positive patients were treated with chemotherapy compared to only 8% in the luminal B patients. In another recent observational nonrandomised prospective study that included 4,113 women with T_{1a,b}N_{0} breast cancer, patients with HR-positive disease had the lowest recurrence rates, while patients with HR-negative (TNBC or HER2 positive) tumors had the worse outcomes, again, despite the fact that only 8% of HR positive were treated with chemotherapy compared to more than 50% in the HR-negative group (18). Hence, based on the current data, it appears that women with small size, node-negative breast cancer are at higher risk of relapse if they have a HER2-positive or TNBC, while for luminal A and B cancers the risk is less clear.

**On the Horizon**

**Luminal tumors**

In the past decade, several genomic signatures emerged as useful tools to define patients at high risk of recurrence who might benefit more of the addition of adjuvant chemotherapy (19). The Oncotype DX® 21-gene recurrence score (RS) assay is able to predict risk for distant recurrence among ER positive breast cancers treated with tamoxifen (20). Except
from being prognostic, in two retrospective studies involving both node-negative and node-positive patients, Oncotype DX® was found to be predictive for the chemotherapy benefit (21,22). Therefore it was endorsed by the NCCN for ER positive tumors with a tumor size >0.5 cm (T1b) in order to decide whether to give chemotherapy. In the NSABP trials that evaluated the Oncotype DX®, the distribution of the recurrence scores did not differ according to the size of the tumors and 15-16% of the T1a,bN0 tumors were considered at high risk (20,23). In a population-based retrospective study, T1a,bN0 tumors with high RS (>31) were associated with a 10.1% risk of breast cancer death at 10 years compared to 1.3% in the low risk group (24).

The MammaPrint® 70-gene signature has been previously validated as an independent prognostic factor in node-negative and node-positive breast cancer (25). Mook et al. evaluated the accuracy of the 70-gene signature in T1 breast cancer irrespective of nodal involvement, and it was found to be an independent prognostic factor for breast cancer survival at 10 years (26). These data show that the 70-gene signature can also help to individualise the adjuvant treatment recommendations in this population.

A more definite proof of the utility of Mammaprint® in the setting of T1a,bN0 tumors might come from the MINDACT trial that compares Mammaprint® with the common clinico-pathological criteria in their respective abilities to select patients at high risk for adjuvant chemotherapy. MINDACT has enrolled 6600 patients of whom 14% (N=919) have tumors less than 1cm. The results of this trial are expected to be reported in 2015-2016 and will provide high level evidence about the clinical relevance of applying gene expression predictors in this setting.

In one of the largest efforts in the field, the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) group has performed an integrated genomic analysis of around 2000 breast cancer primary samples (27). New breast cancer clusters were
identified of which an ER-positive subgroup composed of 11q13/14 cis-acting luminal tumors draw specific attention as it exhibited a steep mortality trajectory. This subgroup showed high frequencies of copy number variance (CNV) in the 11q region and amplification of the CCND1 and EMSY genes that reside in the amplicon. Although the predictive role of 11q13-14 amplicon is not clear, the dismal prognosis of these patients may help tailoring future use of chemotherapy in T1a,bN0 cancers. For example, patients with amplification of the 11q13-14 amplicon could be recommended to receive chemotherapy, while luminal subgroups with copy number alterations of favorable outcome (1q gain/16q loss) may be spared adjuvant chemotherapy. This concept remains speculative and requires further validation. The fact that different prognostic/predictive gene sets were developed by different groups, but nonetheless do similar jobs as prognostic tools is attributed to the different technologies used, their implementations, and to the nature of the validation tools.

**HER2-enriched tumors**

Five major randomised studies have shown that trastuzumab improves disease-free survival (DFS) and overall survival (OS) in the adjuvant setting when added to backbone chemotherapy in HER2 positive breast cancer (28–31); however, none of them recruited patients with T1a,bN0 except the BCIRG006 trial that randomly assigned 3222 women with HER2-positive early-stage breast cancer to receive doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks, the same regimen plus trastuzumab or docetaxel and carboplatin plus trastuzumab (29). Despite this fact, most clinical guidelines and most clinicians, as demonstrated in practice surveys, recommend giving trastuzumab for these small tumors, particularly T1b tumors (32). This is influenced by the significantly higher risk of relapse in HER2-positive patients (13,16). Nevertheless, it is also true that medical oncologists might be over treating a large fraction of these patients by offering the classic chemotherapy (anthracycline-taxane) plus trastuzumab combination. The REMAGUS French
breast cancer group retrospectively reviewed the medical charts of patients who had presented with invasive $T_{1a,b}N_0$, HER2-positive breast cancers (33). Ninety-seven node-negative patients were retrieved. Forty-one (42%) had been treated with adjuvant trastuzumab. During a median overall follow-up of 29 months, all patients who had received a trastuzumab-based therapy were free of recurrence, even though they generally had more adverse prognostic factors (HR negative and higher grade). Recurrence-free survival at 29 months for the 56 patients who had not received an adjuvant trastuzumab-based therapy was estimated at 93.6%. Four of the five recurrences observed in this group were distant metastases and occurred in HR-negative patients, suggesting the poorer outcome of this subgroup. In another recent non-randomized prospective study performed at Dana-Farber (APT study), 406 women with HER2-positive, node-negative tumors smaller than 3 cm were treated with a regimen that included: paclitaxel 80 mg/m$^2$ plus trastuzumab 2 mg/kg for 12 weeks, followed by 9 months of trastuzumab alone at a dose of 6 mg/kg every 3 weeks (34). After a median follow-up of 3.6 years, only four recurrences (0.9%) were observed (34). About 20% of the trial patients had T1a tumors. This suggests that paclitaxel plus trastuzumab can be considered an attractive approach for $T_{1a,b}N_0$ HER2-positive breast cancer in terms of balancing benefits versus risks. The same group is currently planning another clinical trial (ATEMPT), comparing TDM1 to trastuzumab plus paclitaxel in $T_1$ HER2 positive patients, a study which may provide alternative future regimes to these patients. The Aphinity trial, which evaluates the usefulness of pertuzumab in addition to trastuzumab and chemotherapy, also enrolled a limited number of $T_{1a,b}N_0$ patients at high risk (ER negative or grade 3). The results of this trial are expected to be reported in 2016 and will provide high-level evidence for the treatment of this subgroup of patients.

The role that the immune system plays in the development and clinical behavior of breast cancer can differ according to the subtypes. A way to define the immune response
against cancer is the quantification of tumor-infiltrating lymphocytes (TILs). TILs were found to be in greater numbers in the HER2 and TNBC compared to the luminal subtypes (35). In the FinHER trial, which randomised patients with HER2 positive breast cancers to 9 weeks of trastuzumab or no trastuzumab in the adjuvant setting, each 10% increase in lymphocytic infiltration was significantly associated with decreased distant recurrence in patients randomized to trastuzumab arm (36). This data supports the role of anti-tumor immunity in the efficacy of trastuzumab. In addition, patients with HER2 positive disease and high TILs were found to benefit more from adjuvant anthracycline-based chemotherapy as observed in the BIG02-98 randomized phase III trial (35). This suggests that TILs may be used to define patients with $T_{1a,b}N_0$ that would derive the highest benefit of trastuzumab and chemotherapy in the adjuvant setting.

**Triple negative**

TNBCs, which account for 15-20% of all invasive breast cancers, have an aggressive nature and increased risk of relapse and breast cancer related deaths compared with other subtypes (37). Although from a clinical point of view, TNBCs are managed as one group, recent studies have shown that TNBCs are composed of an heterogeneous group of diseases with different biologies and clinical behaviors (38–40). Current guidelines suggest adjuvant chemotherapy for patients with tumor size > 0.5cm ($T_{1b}$) (41). As no targeted therapy is currently available for the treatment of TNBCs, chemotherapy remains the only option. Using gene expression profiling, seven distinct TNBC subtypes were identified and later on, a bioinformatics tool (TNBCtype) was developed to determine the TNBC molecular subtype from gene expression profiles (42). This tool was further validated in the Tumor Cancer Genome Atlas (TCGA) data. TNBC subtype-specific differences in survival were demonstrated; for instance, while the immune-modulator subtype had a median DFS of 20.1 months, the luminal-androgen-receptor subtype (not to be confused with luminal ER positive
tumors) had a median DFS of 4.4 months. This may also have clinical relevance as there is progress in the development of androgen receptors targeted therapies (43). The METABRIC consortium has also identified a large subgroup in the TNBC- basal-like tumors characterized by high-genomic instability (5 loss/8q gain/10p gain/12p gain) and relatively good long-term outcomes (27). These molecular findings may guide future differential use of chemotherapy in $T_{1a,b}N_0$ cancers.

As described for HER2 positive patients, TILs were also found to be high in the TNBC breast cancer group (35). Increasing 10% increments of infiltration were in fact associated with better prognosis, supporting a possible prognostic role of TILs in patients with small tumors.

**The $T_{1a}$–$T_{1b}$ cut-off**

The classical staging system discriminates between T1a and T1b tumors (below or above 0.5 cm) based on large longitudinal cohorts that demonstrated minimal differences in prognosis between these groups with relative no impact on rate of breast cancer deaths (24). As it is becoming clearer that the aggressiveness of the tumors is biology-driven rather than just influenced by tumor size, it is not obvious to artificially dichotomize patients using the 0.5 cm cut-off for diagnostic tests and treatment decisions. Moreover, there is evidence that tissue fixation and handling may affect tumor size (44,45). This includes the impact of pre-operative biopsies, the effect of paraffin temperature, the pathological observer discrepancies and tendency for rounding results that have been shown to influence the correct estimation of tumor size (46). In two recent reports there were no clear differences in outcomes between patients with $T_{1a}$ and $T_{1b}$ in HER2 positive tumors (18,47). Therefore oncologists should be cautious when making decision solely based on the distinction of whether the tumor is $T_{1a}$ or $T_{1b}$. It is possible that in the near future assays such as Oncotype DX® or MammaPrint® and
newer prognostic tools such TNBCtype will be of great help in defining the best treatment strategy for small tumors.

Concluding Remarks

The frequency of T_{1abN0} tumors is increasing sharply, especially in the western world as a result of mammography screening. The need to balance risks and benefits when deciding the treatment strategy in this relatively good prognostic group of patients is not trivial. The recent molecular classification of breast cancers, together with the development of new prognostic tools and omics-based clinical trials, may tailor more adequately the treatment recommendations for this population of breast cancers (Table 1). Instead of differentially dichotomising treatment decisions based on tumor size (>0.5cm), it is desirable that in the near future more individualized treatment strategies are applied which will take into account the biological aggressiveness of the tumor, the patient’s clinical parameters (age, comorbidities) and preferences.

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Table 1. Diagnostic and treatment options for T1a,b breast cancer

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Current recommendations</th>
<th>Future possible recommendations</th>
</tr>
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<tbody>
<tr>
<td>Luminal</td>
<td>T1a- No chemotherapy</td>
<td>T1a,b- Oncotype DX®</td>
</tr>
<tr>
<td></td>
<td>T1b- Oncotype DX®</td>
<td>MammaPrint®                                       11q13/14, 1q gain/16q loss</td>
</tr>
<tr>
<td>HER2 positive</td>
<td>T1a- No adjuvant therapy</td>
<td>T1a,b- tolerable regimens</td>
</tr>
<tr>
<td></td>
<td>T1b- Trastuzumab+ aggressive chemotherapy</td>
<td>New drugs TILs</td>
</tr>
<tr>
<td>TNBC</td>
<td>T1a- No chemotherapy</td>
<td>T1a,b- TNBCtype, 5 loss/8q gain/10p gain/12p gain TILs</td>
</tr>
<tr>
<td></td>
<td>T1b- Adjuvant chemotherapy</td>
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Abbreviation: TILs: tumor-infiltrating lymphocytes.
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