New Strategies in Breast Cancer: The Significance of Molecular Subtypes in Systemic Adjuvant Treatment for Small $T_{1a,b}N_0M_0$ Tumors

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Abstract

Awareness of breast cancer heterogeneity has strikingly increased in the past decade in parallel with the development of high-throughput molecular tests. Beyond the clear usefulness of antiestrogen 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-stage breast tumors smaller than 1 cm ($T_{1a,b}N_0M_0$) and suggest new strategies for future treatment recommendations for these patients. Clin Cancer Res; 20(24); 6242–6. ©2014 AACR.

Background

Screening and increased awareness have led to a rise in the detection of $T_1$ 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 behavior. This population suffers from low representation in clinical trials, which leads to a situation where medical oncologists lack high-level evidence that can guide them in the treatment of these patients. Tumor size and nodal involvement remain among the most important clinicopathologic prognostic factors in breast cancer, which puts $T_{1a,b}N_0$ (<1 cm) tumors in a group with a generally low risk of recurrence. Information on $T_{1a,b}N_0$ from large population databases of untreated patients demonstrates relatively low cancer-related mortality rates at 15 years (<10%), with much higher death rates from other causes in women older than 50 years (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 $T_{1a,b}N_0$ tumors, suggesting a potential benefit of more aggressive therapy in women diagnosed with tumors harboring any or all of these features (8–11). Furthermore, the classification of breast cancers into different subtypes (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 it was shown that the differences are also reflected by the mRNA expression profiles (14,15).

Is the threshold for offering adjuvant therapy in $T_{1a,b}N_0$ tumors dependent on the molecular subtype?

There is a lack of high-level evidence regarding the use of chemotherapy in women with $T_{1a,b}N_0$ tumors. However, it is possible to derive prognostic information based on tumor subtype. In a retrospective study conducted by Theriault and colleagues (16), 1,012 patients with $T_{1a,b}N_0$ breast cancer who did not receive chemotherapy or trastuzumab were evaluated. Compared with 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 risk of recurrence, respectively. Another study, conducted by Canellos and colleagues (17), exploring patterns of recurrence in 1,691 patients with $T_{1a,b}$ breast cancers confirmed the same findings. Multivariate analysis showed that women with HER2-positive and TNBC had an increased risk of loco-regional relapse by 3-fold and breast cancer–related events by 2-fold, 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 with only 8% in the luminal B patients. In another recent observational nonrandomized prospective study, included 4,113 women with $T_{1a,b}N_0$ breast cancer, patients with HR-positive...
Significance of Molecular Subtypes in T_{1a,b}N_{0}M_{0} Tumors

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 from the addition of adjuvant chemotherapy (19). The Oncotype DX 21-gene recurrence score 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, this system was endorsed by the National Comprehensive Cancer Network for ER-positive tumors >0.5 cm (T_{1b}) as a means to decide whether to give chemotherapy. In the National Surgical Adjuvant Breast and Bowel Project trials that evaluated the Oncotype DX, the distribution of the recurrence scores did not differ according to the size of the tumors and 15% to 16% of the T_{1a,b}N_{0} tumors were considered at high risk (20,23). In a population-based retrospective study, T_{1a,b}N_{0} tumors with a high recurrence score (>31) were associated with a 10.1% risk of breast cancer–related death at 10 years compared with 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 and colleagues (26) evaluated the accuracy of the 70-gene signature in T_{1} breast cancer irrespective of nodal involvement, and it was found to be an independent prognostic factor for breast cancer survival at 10 years. These data show that the 70-gene signature can also help to individualize adjuvant treatment recommendations in this population.

A more definitive proof of the utility of MammaPrint in the setting of T_{1a,b}N_{0} tumors might come from the MINDACT trial, which compares MammaPrint with the common clinicopathologic criteria in their respective abilities to select patients at high risk for adjuvant chemotherapy. MINDACT has enrolled 6,600 patients, of whom 14% (N = 919) have tumors less than 1 cm in size. The results of this trial are expected to be reported in 2015 to 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 approximately 2,000 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 drew specific attention, as it exhibited a steep mortality trajectory. This subgroup showed high frequencies of copy-number variance in the 1q region and amplification of the CCND1 and EWSY 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 in tailoring future chemotherapy in T_{1a,b}N_{0} cancers. For example, patients with amplification of the 11q13-14 amplicon could be recommended to receive chemotherapy, whereas luminal subgroups with copy-number alterations of favorable outcome (1q gain/16q loss) could 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 might be attributable to the different technologies used, their implementation, and the nature of the validation tools.

HER2-enriched tumors

Five major randomized studies have shown that trastuzumab improves disease-free survival (DFS) and overall survival in the adjuvant setting when added to backbone chemotherapy in HER2-positive breast cancer (28–31); however, none of these studies recruited patients with T_{1a,b}N_{0} except the BCIRG006 trial, which randomly assigned 3,222 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 T_{1b} 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 overtreating 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). The records of 97 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). The recurrence-free survival rate 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 nonrandomized prospective study performed at Dana-Farber Cancer Institute (Boston, MA; Adjuvant Paclitaxel/Trastuzumab study), 406 women with HER2-positive, node-negative tumors smaller than 3 cm were treated with a regimen that included paclitaxel, 80 mg/m², 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 T₁a,bN₀ HER2-positive breast cancer in terms of balancing benefits versus risks. The same group is currently planning another clinical trial (ATEMPT), comparing TDM1 with trastuzumab plus paclitaxel in T₁ HER2-positive patients, which may provide alternative future regimens for these patients. The Aphinity trial, which is evaluating the usefulness of pertuzumab in addition to trastuzumab and chemotherapy also enrolled a limited number of T₁a,bN₀ 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 (TIL). TILs were found to be in greater numbers in the HER2 and TNBC compared with the luminal subtypes (35). In the FinHER trial, which randomized 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). These data support the role of antitumor 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 T₁a,bN₀ that would derive the highest benefit of trastuzumab and chemotherapy in the adjuvant setting.

**Triple-negative breast cancer**

TNBCs, which account for 15% to 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 a heterogeneous group of diseases with different biologies and clinical behaviors (38–40). Current guidelines suggest adjuvant chemotherapy for patients with tumor size >0.5 cm (T₁a,b) (ref. 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 (TNBC type) was developed to determine the TNBC molecular subtype from gene-expression profiles (42). This tool was further validated in the Tumor Cancer Genome Atlas data. TNBC subtype-specific differences in survival were demonstrated; for instance, although the immune-modulator subtype had a median DFS duration 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 receptor-targeted therapies (43). The METABRIC consortium has also identified a large subgroup among 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 T₁a,bN₀ 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 T₁a-T₁b cutoff**

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 relatively no impact on rate of breast cancer–related deaths (24). As it becomes clearer that the aggressiveness of tumors is biology driven rather than influenced by tumor size alone, it may not be advisable to artificially dichotomize patients using the 0.5-cm cutoff 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 preoperative biopsies, the effect of paraffin temperature, the pathologic observer discrepancies, and the 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 T₁a and T₁b in HER2-positive tumors (18, 47). Therefore, oncologists should be cautious when making decisions solely based on whether the tumor is T₁a or T₁b. It is possible that in the near future assays such as Oncotype DX or MammaPrint and newer prognostic tools such as TNBCtype will be helpful in defining the best treatment strategy for small tumors.

**Concluding Remarks**

The frequency of T₁a,bN₀ tumors is increasing sharply, especially in the Western world as a result of mammographic screening. The need to balance risks and benefits when establishing a 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 facilitate more accurate tailoring of treatment recommendations for this population of breast cancer patients (Table 1). Instead of differentially dichotomizing treatment decisions based on tumor size (>0.5 cm), it is hoped that the future will bring more individualized treatment strategies that will take into account the biologic aggressiveness of the tumor, the clinical parameters (age and comorbidities) of the patient, and the patient's preferences.

**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>
</thead>
<tbody>
<tr>
<td>Luminal</td>
<td>( T_{1a} \rightarrow \text{No chemotherapy} )</td>
<td>( T_{1a,b} \rightarrow \text{Oncotype DX MammaPrint} )</td>
</tr>
<tr>
<td></td>
<td>( T_{1b} \rightarrow \text{Oncotype DX} )</td>
<td>( 11q13/14, 1q \text{gain/1q6 loss} )</td>
</tr>
<tr>
<td></td>
<td>( T_{1a} \rightarrow \text{No adjuvant therapy} )</td>
<td>( T_{1a,b} \rightarrow \text{Tolerable regimens} )</td>
</tr>
<tr>
<td></td>
<td>( T_{1b} \rightarrow \text{Trastuzumab + aggressive chemotherapy} )</td>
<td>New drugs, TILs</td>
</tr>
<tr>
<td>HER2 positive</td>
<td>( T_{1a} \rightarrow \text{No chemotherapy} )</td>
<td>( T_{1a,b} \rightarrow \text{TNBCtype, 5 loss/8q gain/10p gain/12p gain} )</td>
</tr>
<tr>
<td>TNBC</td>
<td>( T_{1a} \rightarrow \text{No chemotherapy} )</td>
<td>TILs</td>
</tr>
<tr>
<td></td>
<td>( T_{1b} \rightarrow \text{Adjuvant chemotherapy} )</td>
<td>TILs</td>
</tr>
</tbody>
</table>

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