The Effect of Biology in the Treatment of Small Breast Tumors

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OVERVIEW

Although the outcome of small (T1a/b) node-negative breast tumors is generally excellent, in the absence of prospective clinical trials, we are limited to data derived from retrospective analyses. Overall, the 10-year overall mortality rate is approximately 20%, while the 10-year breast cancer-specific mortality is in the range of 4% to 8% among this population in the absence of systemic therapy. This clearly reflects that many patients die of causes not related to breast cancer. Due in large part to breast cancer screening programs, the incidence of small tumors is increasing. There is consequently a growing interest in identifying factors that negatively affect the prognosis of these patients. Several studies have shown that patients with triple-negative and HER2+ tumors have a worse prognosis compared with hormone-receptor–positive, HER2- small breast cancers. However, the recent explosion of knowledge of the molecular characteristics of tumors is opening a new way to address cancer. Different genomic assays are currently available to help better predict the outcome of breast cancer patients. However, none of these techniques have been specifically evaluated in patients with small (T1a/b) node-negative tumors, and only a small number of patients with these tumors were included in those studies. In addition, very limited data are available about the role of these assays in patients with triple-negative or HER2-positive cancers. Although a chemotherapy-based strategy might be useful for triple-negative or HER2-positive T1b tumors, more information is urgently needed in order to optimize the treatment of our patients.

The incidence of small (T1a/b) node-negative breast tumors is steadily increasing due in part to the implementation of breast cancer screening programs.[1] Unfortunately, the role of adjuvant systemic therapy in this population remains unclear.

Classically, tumor size and axillary lymph node status have been considered the most important prognostic factors in patients with breast cancer.[2,3] For many years, small (T1a/b) node-negative breast tumors were believed to have such a good prognosis that systemic adjuvant therapy was not viewed to be necessary. However, more recent research on this issue has shown that certain subgroups of these patients have a significant risk of systemic recurrence. The challenge is therefore to identify patients most likely to benefit from systemic adjuvant therapy based on validated prognostic and predictive factors. Although clinical and pathologic features are currently the mainstay of clinical decision making for this population, a better knowledge of the molecular biology of breast cancer and the introduction of new prognostic tools into daily clinical practice, such as MammaPrint and Oncotype Dx (and most likely the PAM50 test in the upcoming months), are establishing a new and intriguing scenario in the adjuvant treatment of these patients.[4-8]

The best systemic strategies for small tumors vary across different guidelines and are a matter of current debate. For example, according to the National Comprehensive Cancer Network (NCCN) guidelines, the selection of the adjuvant systemic treatment for patients with breast cancer is based on hormone receptor and HER2 status, tumor size, and axillary lymph node status.[9] In brief, these guidelines do not recommend administration of adjuvant chemotherapy in breast tumors that are 0.5 centimeters (cm) or smaller without axillary lymph node involvement, irrespective of hormone receptor, and HER2 status. In addition, prognostic tools such as Oncotype Dx are recommended for HER2- and hormone-receptor–positive disease that is 0.5 cm or larger with negative axillary lymph nodes, whereas adjuvant systemic therapy is recommended for triple-negative and HER2+ breast cancers between 0.6 and 1.0 cm without axillary lymph node involvement. Therefore, considering these guidelines, a patient age 40 with a stage T1aN0 triple-negative breast cancer (0.5 cm of diameter, high tumor grade, and Ki-67 index of 80%) should not receive adjuvant chemotherapy. But, are we heading in the right direction under this or other guidelines?

Thus, we discuss the outcome of small (T1a/b) node-negative breast tumors; the factors that adversely affect the prognosis among this population; and how new prognostic tools and the molecular classification of breast cancer can help us to identify those patients that might benefit from adjuvant systemic therapy.

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OUTCOME OF SMALL (T1A/B) NODE-NEGATIVE BREAST CANCERS

Several authors have retrospectively analyzed the outcome of small (T1a/b) node-negative breast tumors. Overall, the 10-year breast cancer-specific mortality is in the range of 4% to 8%, while the 10-year overall mortality rate is approximately 20% among this population in the absence of systemic therapy. Most of these studies had a short follow-up and/or included a small number of patients. In addition, it is important to take into account that some of them recruited patients treated with adjuvant systemic therapy. This procedure can lead to an overestimation of the outcome that would be found in an entirely untreated population. For this reason, the studies summarized below have been selected either because they included a significant number of patients and/or because they had a longer follow-up. Moreover, only data from surgery-treated patients are reported.

Fisher et al. retrospectively evaluated the outcome and treatment of patients with breast tumors smaller than 1 cm without axillary lymph node involvement from five National Surgical Adjuvant Breast and Bowel Project (NSABP) randomized clinical trials.[10] Two hundred and thirty-five patients with estrogen receptor (ER)-negative tumors and 1,024 patients with ER+ tumors were identified in these trials. Median follow-up was 8 years. Patients with ER+ tumors received surgery alone (26%); surgery and tamoxifen (53%); or surgery, tamoxifen, and chemotherapy (21%). Patients with ER- tumors received surgery alone (26%) or surgery and chemotherapy (74%). The 8-year recurrence-free survival (RFS) rates for women with ER- and ER+ tumors who received surgery alone were 81% and 86%, respectively. The 8-year overall survival (OS) rates for surgery-treated patients with ER- and ER+ tumors were 93% and 90%, respectively, and the 8-year OS rate for all patients was 92%, regardless of treatment and ER status. However, only half of these patients died from breast cancer.

Rosen et al. retrospectively assessed the prognosis of 767 patients with stage T1/2 node-negative breast cancer treated with surgery alone.[11] A total of 171 patients with small (T1a/b) node-negative breast tumors were included in the analysis. Median follow-up was 18 years. This subgroup had RFS rates of 91% and 88% at 10 and 20 years, respectively. Additionally, there were 178 (23.2%) deaths caused by breast cancer among all patients included in the study. In this regard, it is important to note that the probability of death from breast cancer did not exceed the probability of death caused by other causes among women with small (T1a/b) node-negative breast tumors.

Finally, Chia et al. retrospectively evaluated the 10-year outcomes in a population-based cohort of node-negative, lymphatic, and vascular invasion–negative early breast cancers without adjuvant systemic therapy.[12] The 430 tumors included in this analysis were smaller than 1 cm. Median follow-up of the entire series was 10.4 years. The 10-year OS rate was 79%, and the 10-year breast cancer-specific survival was 92%.

It is necessary to emphasize that one of the major weaknesses of these studies, apart from their retrospective nature, is the fact that the effect of HER2 status in the outcome of these patients was not analyzed.

In summary, the outcome of small (T1a/b) node-negative breast cancers is generally excellent. However, the breast cancer-specific mortality, probably the most appropriate end point for this particular subgroup, varies between 4% and 8% among these patients, warranting an optimization of the adjuvant systemic therapy for this population.

KEY POINTS

- Due to the increase in breast cancer screening programs, the incidence of small, node-negative tumors is increasing, which leads to a growing interest in identifying factors that negatively impact the prognosis of patients with breast cancer.
- The recent explosion of knowledge about the molecular characteristics of tumors is opening a new way to tackle cancer. In breast cancer, different genomic assays are available to better predict the outcome of patients with breast cancer. However, none of them has been specifically evaluated in patients with T1a/b node-negative tumors and the number of patients with these tumors included in these studies was very small.
- Although clinical and pathologic features are currently the mainstay of clinical decision making for this population, a better knowledge of the molecular biology of breast cancer and the introduction of new prognostic tools into daily clinical practice, such as MammaPrint and Oncotype Dx (and most likely the PAM50 test in the upcoming months), are establishing a new and intriguing scenario in the adjuvant treatment of these patients.
- The breast cancer intrinsic subtypes may represent a relevant prognostic factor regardless of tumor size. Overall, triple-negative and HER2+ breast cancers by immunohistochemistry are associated with a higher risk of recurrence among small (T1a/b) node-negative tumors.
- Although the outcome of small (T1a/b) node-negative breast tumors is generally excellent, in the absence of prospective clinical trials, we are limited to clinical data derived from retrospective analyses.

COMMONLY USED FACTORS THAT ADVERSELY AFFECT THE PROGNOSIS OF SMALL (T1A/B) NODE-NEGATIVE BREAST CANCERS

Although the risk of relapse of small (T1a/b) node-negative breast tumors is low, there is a growing interest in identifying factors that negatively affect the prognosis of these patients, to recognize which patients might benefit from adjuvant systemic therapy as well as to avoid unnecessary side effects.

In the study of Fisher et al. the risk of recurrence was greater in women who had tumors of 1 cm in size than for those women who had tumors of less than 1 cm; in women age 49 or younger compared with women age 50 or older; and in women with ductal or lobular carcinoma compared

with women who had other histologic tumor types, irrespective of ER status.[10] In the analysis of Rosen et al., patients with infiltrating ductal carcinoma had a worse RFS rate than patients with special tumor types (medullary, mucinous, tubular, adenocystic, and papillary) and infiltrating lobular carcinoma.[11]

In the study of Chia et al. tumor grade appeared to be an important predictor of risk of breast cancer death, regardless of tumor size.[12] Finally, Hanrahan et al. also retrospectively analyzed the OS and cause-specific mortality of patients with stage T1a/bN0 breast cancer registered in the Surveillance, Epidemiology, and End Results (SEER) Program from 1988 to 2001.[13] The main limitation of this analysis was that the proportion of patients who received adjuvant chemotherapy or hormonal therapy was unknown. A total of 51,246 patients were identified. Median follow-up was 64 months. In this study, a trend toward higher probability of death was found in patients younger than age 50 at diagnosis; in patients with adverse pathologic features such as high tumor grade, ER- status, and progesterone-receptor–negative status; and in patients with an inadequate axillary lymph node assessment (fewer than six nodes removed at axillary dissection).[13]

Although none of these studies evaluated the influence of HER2 status in the prognosis of these small (T1a/b) node-negative tumors, other series have appropriately assessed this issue.

Gonzalez-Angulo et al. reviewed the risk of recurrence in women diagnosed with stage T1a/b, node-negative breast cancer taking HER2 status into account.[14] A total of 965 patients were identified at the MD Anderson Cancer Center between 1990 and 2002. Patients who received adjuvant chemotherapy or trastuzumab were excluded. Median follow-up was 74 months. Ten percent of patients had HER2+ tumors, and the 5-year RFS rates were 77.1% and 93.7% in patients with HER2+ and HER2- tumors, respectively ($p = 0.001$). The 5-year distant RFS rates were 86.4% and 97.2% in patients with HER2+ and HER2- tumors, respectively ($p = 0.001$). Among HER2+ tumors, the risk of recurrence was similar to independent of hormone-receptor status, although the fact that up to 55% of hormone-receptor–positive patients received adjuvant hormone therapy should be taken into consideration to avoid misinterpretations. Unfortunately, the authors did not analyze the outcome of HER2+ patients according to tumor stage (T1a vs. T1b).

Curigliano et al. also identified 150 consecutive patients with HER2+ tumors among a population of 2,130 patients with stage T1a/b, node-negative breast cancers at the European Institute of Oncology between 1999 and 2006.[15] A matched cohort was selected by using variables of hormone-receptor status, age, and year of surgery. No patient received adjuvant trastuzumab, but up to 50% of patients received adjuvant chemotherapy in the hormone-receptor–negative group, and more than 90% of patients received adjuvant hormone therapy, alone or in combination with chemotherapy, in the hormone-receptor–positive group. Median follow-up was 4.6 years. In the hormone-receptor–positive group, the 5-year disease-free survival (DFS) rates were 99% (95% CI, 96% to 100%) for HER2- disease and 92% (95% CI, 86% to 99%) for HER2+ disease. In the hormone receptor–negative group, the 5-year DFS rates were 92% (95% CI, 84% to 100%) for HER2- disease and 91% (95% CI, 84% to 99%) for HER2+ disease. It is important to emphasize that in the hormone-receptor–negative group, the authors compared HER2+ with patients with triple-negative breast cancer. Moreover, the DFS rates according to tumor stage (T1a vs. T1b) and hormone receptor status were adequately assessed. Among HER2+ and hormone-receptor–positive tumors, the 5-year DFS rates were 88% (95% CI, 67% to 96%) in patients with stage T1a and 95% (95% CI, 82% to 99%) in patients with stage T1b. Among HER2+ and hormone-receptor–negative tumors, the 5-year DFS rates were 93% (95% CI, 72% to 98%) in patients with stage T1a and 85% (95% CI, 60% to 95%) in patients with stage T1b. However, considering the limited number of patients and the treatment heterogeneity, definitive conclusions cannot be drawn from this subgroup analysis.

In sum, a younger age at diagnosis, ER- status, HER2+ status, and high tumor grade adversely affect the prognosis of node-negative breast cancers smaller than 1 cm. These factors should be taken into account to define the best adjuvant systemic therapy for these patients.

HOW CAN NEW PROGNOSTIC TOOLS HELP TO BETTER IDENTIFY WHICH PATIENTS WITH SMALL (T1A/B) NODE-NEGATIVE TUMORS MIGHT BENEFIT FROM ADJUVANT SYSTEMIC THERAPY?

MammaPrint and Oncotype Dx are two prognostic tests based on retrospective analyses that are currently used in clinical practice. These tools can help physicians to determine whether or not a patient with breast cancer will benefit from adjuvant chemotherapy.

MammaPrint was initially evaluated in a series of 295 consecutive women diagnosed with stage T1/2, ER- or ER+ breast cancer, with or without axillary lymph node involvement.[6] Up to 40% of patients had received adjuvant chemotherapy. At 10 years, the probability of remaining free of distant metastases was lower in the group with a poor-prognosis signature than in the group with a good-prognosis signature (HR for distant metastases = 5.1; $p < 0.001$). The prognosis profile was significantly associated with tumor grade, ER status, tumor diameter, and age at diagnosis, but not with the number of axillary positive nodes. The authors did not specifically analyze these findings among small (T1a/b) node-negative breast cancers. Subsequently, MammaPrint was validated with the same results in a series of 307 patients with stage T1/2, node-negative, ER- or ER+ breast cancer.[8] No patient received adjuvant systemic therapy. Only 11 patients with small (T1a/b) tumors were included in the analysis. Of these tumors, six had a poor-prognosis signature. The authors did not evaluate in detail the characteristics of these patients, although ER- status and high tumor grade were associated with a poor-prognosis

signature again. Finally, MammaPrint was assessed in 965 patients with stage T1 breast cancer irrespective of node status, age, and ER, PR, and HER2 status.[16] Only 10% of patients had received adjuvant chemotherapy. The results were consistent with those reported in previous studies. A total of 140 small (T1a/b) tumors were included in the analysis. However, given the heterogeneity of these patients, solid conclusions should not be drawn.

MammaPrint is not only an independent prognostic factor for patients with early stage breast cancer, but it may also be predictive for the benefit of chemotherapy. Knauer et al. analyzed a pooled database from six prior studies.[17] Five hundred and forty-one women diagnosed with stage T1–3, ER- or ER+ breast cancer, with or without axillary lymph node involvement were included. Only patients with a poor-prognosis signature had a significant benefit from chemotherapy (distant disease-free survival, 76% vs. 88%; $p = 0.01$), whereas patients with a good-prognosis signature did not benefit from chemotherapy treatment (distant disease-free survival, 93% vs. 99%; $p = 0.2$). The chemotherapy benefit among small (T1a/b) node-negative breast cancers was not assessed in this study.

In contrast, Oncotype DX was retrospectively evaluated in the NSABP trial B14, a clinical trial that analyzed the treatment with tamoxifen in node-negative, ER+ patients.[7] The levels of expression of 21 genes were used to calculate a recurrence score (RS). The rates of distant recurrence at 10 years in the low-risk (≤ 18), intermediate-risk, and high-risk groups (≥ 31) were 6.8%, 14.3%, and 30.5%, respectively. The rate in the low-risk group was significantly lower than that in the high-risk group ($p < 0.001$). A total of 109 patients with small (T1a/b) tumors were included in the analysis. Of these patients, 59.5% had a low RS, 25% had an intermediate RS, and 15.5% had a high RS. A high RS was also associated with a higher rate of distant recurrence at 10 years among these patients, although the differences with respect to the patients with intermediate and low RS tumors were not as significant as observed in larger tumors. Later, Oncotype DX was assessed in the NSABP trial B20 that tested the effect of adding cyclophosphamide, methotrexate, and fluorouracil or methotrexate and fluorouracil chemotherapy to 5 years of tamoxifen in the treatment of patients with node-negative, ER+ breast cancer.[5] Patients with high RS tumors had a large benefit from chemotherapy (relative risk for distant recurrence, 0.26; 95% CI, 0.13 to 0.53), although patients with low RS tumors did not benefit from chemotherapy treatment (relative risk for distant recurrence, 1.31; 95% CI, 0.46 to 3.78). The chemotherapy benefit in patients with intermediate RS tumors remains controversial. A total of 110 patients with small (T1a/b) tumors were included in the analysis. Of these patients, 64% had a low RS, 20% had an intermediate RS, and 16% had a high RS. Unfortunately, the chemotherapy benefit according to tumor stage (T1a vs. T1b vs. others) was not evaluated in this study.

Finally, neither MammaPrint nor Oncotype Dx have been assessed among small (T1a/b) node-negative HER2+ and triple-negative breast cancers, and their use in clinical practice is not recommended in these patients.

In summary, some small (T1a/b) node-negative breast cancers are considered high-risk tumors by MammaPrint or Oncotype Dx, in particular high-grade ER+ and ER- tumors, and might benefit from adjuvant systemic therapy. However, the effect of tumor stage (T1a vs. T1b vs. others) in this benefit, its influence in the selection of the adjuvant treatment, and the optimal chemotherapy regimen merit further investigation.

IS THE MOLECULAR CLASSIFICATION OF BREAST CANCER RELEVANT FOR DEFINING THE BEST ADJUVANT SYSTEMIC TREATMENT FOR PATIENTS WITH SMALL (T1A/B) NODE-NEGATIVE BREAST CANCERS?

Breast cancer is an extremely heterogeneous disease with multiple clinical presentations and tumor characteristics. Gene-expression profiling studies have classified breast tumors into a number of distinct biological and intrinsic subtypes with prognostic and therapeutic implications, thus providing a new molecular classification of breast cancer. According to this classification, at least four different molecular subtypes have been identified: luminal A, luminal B, HER2-enriched, and basal-like.[18]

Molecular profiling is not currently ready for use in clinical decision making. Therefore, a combination of immunohistochemical surrogate markers (using ER and PR status, HER2 status, tumor grade, and KI-67 index) have been validated for molecular subtyping. However, as previously mentioned, neither HER2 status nor Ki-67 index were analyzed in some of the studies discussed above. Surrogate definitions of intrinsic subtypes of breast cancer are summarized in Table 1.[19,20]

The PAM50 gene-expression assay is one of the tools in current development to classify breast cancers into intrinsic subtypes.[4] Recently, Bastien et al. evaluated the concordance between PAM50 breast cancer subtyping and immunohistochemistry, concluding that a standard immunohistochemical panel for breast cancer does not adequately identify the PAM50 gene-expression subtypes.[21]

Theriault et al. analyzed the outcome of patients with stage T1a/b, node-negative breast tumors according to breast can-

TABLE 1. Surrogate Definitions of Intrinsic Subtypes of Breast Cancer

Subtype	ER and/or PR	HER2	Ki67 Index
Luminal A	Positive (PR > 20%)	Negative	< 14%
Luminal B	Positive	Negative	≥ 14%
Luminal B/HER2	Positive	Positive	
HER2-overexpression	Negative	Positive	
Basal-like	Negative	Negative	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

cer subtype determined by immunohistochemistry.[22] One thousand and twelve patients diagnosed between 1990 and 2002 at the MD Anderson Cancer Center who did not receive chemotherapy or trastuzumab were included. Median follow-up was around 60 months. There were 771 hormone-receptor–positive, 98 HER2+, and 143 triple-negative breast cancers. Compared with patients with hormone-receptor–positive disease, patients with HER2+ breast cancer had 4.98 -times (95% CI, 2.91–8.53) the risk of worse RFS, and patients with triple-negative breast cancer had 2.71-times (95% CI, 1.59–4.59) the risk of worse RFS. Amar et al. also evaluated the outcome of small (T1a/b) node-negative breast cancers according to hormone receptor and HER2 status.[23] Of the 421 tumors identified, 364 (86.5%) were HER2-, 28 (6.7%) were HER2+, and 29 (6.9%) were triple-negative breast cancers. The median follow-up time was only 1,015 days. Unlike the previous study, 3%, 25%, and 27.6% of HER2-, HER2+, and triple-negative patients with breast cancer received adjuvant chemotherapy, respectively, and 17.8% of HER2+ patients received trastuzumab-based adjuvant therapy. During the follow-up, the tumor recurred in nine patients: four were HER2- tumors (1.1%), two were HER2+ tumors (7.1%), and three were triple-negative tumors (10.7%). Unfortunately, no correlation between immunohistochemistry and PAM50 test was performed in this both studies.

Among ER+ tumors, there is evident tumor heterogeneity by gene-expression assays. In this way, luminal B tumors are associated with poor breast cancer-specific survival than luminal A tumors.[24] Both are usually ER+ tumors. However, luminal B tumors are associated with increased expression of proliferative genes resulting in higher tumor grade and Ki-67 index. In addition, up to 20% of luminal B tumors are HER2+.[25] As stated above, ER- status, HER2+ status, and high tumor grade adversely affect the prognosis of small (T1a/b) node-negative breast cancers. These characteristics are very infrequent in luminal A tumors. Therefore, it could indirectly be concluded that luminal A small (T1a/b) node-negative tumors are associated with the best outcome. Nevertheless, it would have been interesting to analyze in the previously mentioned studies the outcome of ER+ patients taking into account Ki-67 index and tumor grade. In this manner, we would have been able to identify a well-defined subgroup of patients with ER+, small (T1a/b) node-negative breast cancers with an excellent prognosis, essentially composed of luminal A tumors, who might not benefit from adjuvant chemotherapy without the need to use MammaPrint, Oncotype Dx, or even PAM50 recurrence test. Additionally, the risk of relapse of luminal B small (T1a/b) node-negative tumors would have also been reported.

Unfortunately, there is no data about the prognostic effect of PAM50 intrinsic subtyping among small (T1a/b) node-negative breast cancers. For this reason, it would be interesting to evaluate the outcome of these patients according to molecular subtyping. Despite this, the breast cancer intrinsic subtypes have shown prognostic significance, remaining more significant in multivariate analyses than other standard parameters (ER status, histologic grade, tumor size, and node status), and have also been used to generate a risk of recurrence score.[4] Therefore, the breast cancer intrinsic subtypes may represent an important prognostic factor despite the tumor size. Considering that only the luminal A subtype contains low-risk patients, whereas the luminal B, HER2-enriched, and basal-like subtypes include intermediate- and high-risk tumors, the PAM50-based, low-risk luminal A tumors among small (T1a/b) node-negative breast cancers could constitute a subgroup with a favorable prognosis that would not benefit from adjuvant chemotherapy. In regards to the management of PAM50-based high-risk small (T1a/b) node-negative tumors, including all the intrinsic subtypes, would tumor stage (T1a vs. T1b vs. others) have an effect in the benefit derived from adjuvant systemic therapy? Should cancer staging guide the choice of the adjuvant systemic therapy, or should we rely only on the biologic behavior? What is the breast cancer-specific mortality among the different molecular subtypes without adjuvant systemic therapy? These questions remain open and most of them will probably never be fully answered.

In sum, the breast cancer intrinsic subtypes may represent a relevant prognostic factor regardless of tumor size. Overall, triple-negative and HER2+ breast cancers by immunohistochemistry are associated with a higher risk of recurrence among small (T1a/b) node-negative tumors.

CONCLUSION

Although the outcome of small (T1a/b) node-negative breast tumors is generally excellent, in the absence of prospective clinical trials, we are limited to clinical data derived from retrospective analyses. Different studies have shown that a younger age at diagnosis, ER- status, HER2+ status, and high tumor grade adversely affect the prognosis of these patients and should be taken into consideration in order to define the best adjuvant systemic therapy for this population.

Additionally, several genomic assays are currently available to help better predict the outcome of breast cancer patients. In this way, some small (T1a/b) node-negative breast cancers are classified as high-risk tumors by MammaPrint or OncotypeDx, in particular high-grade ER+ and ER- tumors, and might benefit from adjuvant systemic therapy. However, the effect of tumor stage (T1a vs. T1b vs. others) in this benefit, its influence in the selection of the adjuvant treatment, and the optimal chemotherapy regimen merit further evaluation.

Finally, triple-negative and HER2+ breast cancers by immunohistochemistry have been associated with a higher risk of recurrence among small (T1a/b) node-negative tumors. Unfortunately, there is no data about the prognostic impact of PAM50 intrinsic subtyping. For this reason, it would be interesting to evaluate the outcome of these patients according to molecular subtyping in the absence of systemic therapy in order to optimize the management of these tumors.

APPENDIX 1: TREATMENT ALGORITHM FOR SMALL (T1A/B) NODE-NEGATIVE BREAST TUMORS

ER-Positive/HER2-Negative

1. T1a→adjuvant endocrine therapy
2. T1b
   - Adjuvant endocrine therapy in postmenopausal patients with low-grade/intermediate-grade tumors (PR positive > 20% and Ki67 < 14% are typically associated with luminal A subtype and can help to better identify those patients that are unlikely to benefit from adjuvant chemotherapy).
   - Consider MammaPrint or Oncotype Dx mainly in premenopausal women, and/or in patients with high-grade tumors:
     - High risk/high recurrence score→adjuvant chemotherapy + adjuvant endocrine therapy
     - Low risk/low recurrence score→adjuvant endocrine therapy
     - Intermediate recurrence score→adjuvant endocrine therapy

Triple-Negative Breast Cancer

1. T1a→consider adjuvant chemotherapy in very young women (age ≤ 40), and/or in patients with high-grade tumors
2. T1b→consider adjuvant chemotherapy

ER-Positive/HER2-Positive

1. T1a→adjuvant endocrine therapy. Consider adjuvant chemotherapy plus trastuzumab in very young patients (age ≤ 40), and/or in patients with high-grade tumors.
2. T1b→adjuvant endocrine therapy. Consider adjuvant chemotherapy plus trastuzumab.

ER-Negative/HER2-Positive

1. T1a→consider adjuvant chemotherapy plus trastuzumab in very young patients (age ≤ 40), and/or in patients with high-grade tumors.
2. T1b→consider adjuvant chemotherapy plus trastuzumab

Following these proposed guidelines, our recommendation for a 40-year-old patient with a stage T1aN0 triple-negative breast cancer (0.5 cm of diameter, high tumor grade, and Ki67 index of 80%) would be chemotherapy with taxanes-based therapy.

This recommendation is based on the following:

1. ER-negative status, younger age at diagnosis, and high tumor grade are independent adverse prognostic factors among small (T1a/b) node-negative breast cancers.[10,12,13]
2. Triple-negative breast cancers by immunohistochemistry are associated with a higher risk of recurrence among small (T1a/b) node-negative tumors.[22,23]
3. Most basal-like tumors are triple-negative by immunohistochemistry.[25]
4. Basal-like tumors show a high chemosensitivity.[26]
5. Basal-like tumors have a significantly worse clinical outcome.[26]

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Relationships marked "U" are uncompensated.

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The treatment effect of systemic therapy in HER2-enriched tumors remained significant even after adjustment of other prognostic factors (HR 0.43, CI 0.19â€“0.98; p = 0.047). Notably, tumor size was not associated with patientsâ€™ survival and treatment decision.ConclusionThe treatment decision of small breast cancer should be made by biological subtype and not by tumor size or lymph node status.Â BackgroundThe treatment of patients with small (T1a/b) breast cancer is based on retrospective analysis. The influence of intrinsic tumor subtypes on patientsâ€™ outcome and treatment decision remains unclear.Patients and methodsThis is a prospective cohort register study including 1008 patients with small T1a/b breast cancer treated between 2003 and 2011.