Characteristics and clinical outcome of T1 breast cancer: a multicenter retrospective cohort study


introduction

The frequency of small breast cancers (BCs) has increased over time, due to the development of screening strategies [1]. T1 tumors became the most frequently diagnosed invasive BC in developed countries [2], including T1a (≤5 mm), T1b (>0.5 but ≤1 cm) and T1c (>1 but ≤2 cm) tumors. These small tumors carry good prognosis with cancer-specific survival rates after 5–10 years as high as 90% or 95% [3–7]. It was generally acknowledged that most of these tumors do not require adjuvant systemic therapy (AST), notably T1a,b. However, they constitute a heterogeneous group and many studies identified biologically defined at-risk patients within T1 BC [3, 4, 8]. Studies with long follow-up have shown that relapse occurs in up to 20% of cases at 10–20 years [9]. In tumors above 2 cm and/or node-positive, AST has shown survival benefits [10, 11]. The question of whether patients with T1a,b tumors should receive AST remains debated since the benefit/risk ratio has not been clearly demonstrated [12]. No definitive guidelines have been published for this subgroup, despite consistent trends in clinical practice toward more aggressive treatment in patients with well-known risk factors (high-grade, lymphovascular peritumoral invasion (LVI), HER2 overexpression). The objectives of our study were to describe the main characteristics of T1a, b and c (11–15 mm only) BC and to identify prognostic factors for survival in each of the three subgroups.

patients and methods

We retrospectively collected the medical files of all patients diagnosed with BC who were eligible for sentinel lymph node biopsy (SLNB) between January 1999 and December 2008 in 13 French sites. Patients were eligible if they had invasive BC, stage T0, T1 or T2 ≤3 cm, clinically negative axillary lymph nodes (LNs), absence of neoadjuvant therapy and evaluation of LN status determined upon SLNB or completion axillary LN dissection whenever carried out. From this cohort, we selected those with T1 tumors and analyzed the following parameters: age, Scarff Bloom Richardson (SBR) grade, hormonal receptors status (HR) (ER and/or PR expression, with a 10% threshold of positivity), HER2 status, LVI, histological type, LN status and AST (hormone therapy, chemotherapy and/or trastuzumab), which was not standardized among sites. Five molecular subtypes were defined according to clinic-pathologic criteria [13]. Because information on Ki-67 was not available, we used grade to capture cell proliferation, as described by Von minckwitz et al. [14]. The following definitions were used: triple-negative (basal-like, HER2−/HR−), HER2 positive (nonluminal, HER2+/HR−), luminal (HR+) which can be divided in luminal A (HR+/HER2−/grade1 or 2), luminal B-HER2-negative like (HR+/HER2+/grade 3), luminal B-HER2-positive like (HR+/HER2+ all grades). Five categories of LN status were defined: negative LN (pN0i−), isolated tumor cells [pN0(i+)], micrometastases (pN1mi) and macrometastases (>2 mm), divided into single and multiple macrometastases.

statistics

Categorical and quantitative variables were described using descriptive statistics (mean, standard deviation [SD], median and ranges or counts and frequency). Patients and tumors characteristics were compared (T1a versus T1b and T1a,b versus T1c) with \( \chi^2 \) tests for discrete variables and rank Wilcoxon or student tests for continuous variables.

Overall survival (OS) was defined as the time from SLNB to death from any cause. Recurrence-free survival (RFS) was defined as the time from SLNB to breast, node, distant relapse or death. OS and RFS rates were estimated using the Kaplan–Meier method and compared with the log-rank tests. Cumulative incidences of axillary and metastatic recurrences were estimated using the Prentice method and compared with the Gray test [15, 16].

The prognostic value of tumor stage was adjusted on the following variables: tumor grade, LN status, LVI and AST, using a multivariate Cox’s proportional hazards regression model. The effect of clinical characteristics was estimated with the hazard ratio and compared between the three tumor size subgroups with the following Wald statistic:

\[
\frac{(\beta_1 - \beta_2)^2}{\text{var}(\beta_1) + \text{var}(\beta_2) - 2\text{Cov}(\beta_1, \beta_2)}
\]

Because of the high number of comparisons, P-values were adjusted for the multiplicity with the Hommel’s method [17].

All statistical tests were two-sided. The level of statistical significance was set at a P-value of 0.05. Statistical analyses were carried out with the R software version 2.15.2

results

Among 8100 eligible women, 5423 had T1 tumors, including 708 T1a, 2207 T1b and 2508 T1c (11–15 mm). Main patients and tumors characteristics are summarized in Table 1 (supplementary file S1, available at Annals of Oncology online). T1a tumors differed from T1b tumors with respect to age (lower), LVI (less frequent), HR (more frequently negative), HER2 status (more frequently positive), molecular subtype (less luminal A and more triple-negative, HER2 and luminal HER2-positive like tumors), LN status (more frequently negative) and histological type (less frequently lobular). T1c tumors were different from T1b tumors with respect to age, SBR grade (higher frequency of grade 3), LVI (more frequent), subtype (more luminal B HER2-negative like), LN status (more frequently positive) and histological type.

Trastuzumab was almost never prescribed, due to the study period (90% of patients included before 2006). As expected, the higher the tumor stage, the more frequently AST was used. Even in the positive HR population, patients with T1a tumors received hormone therapy less often than T1b or T1c patients: 84.7%, 91.2% and 95.3%, respectively, for T1a, T1b and T1c (P < 0.0001) (supplementary file S2, available at Annals of Oncology online).

After a median follow-up of 60.5 months, OS rate was 97.6% [95% confidence interval (95% CI) 97.1–98] at 60 months, 95.4% (94.5–96.4) at 84 months and 90.7% (85.2–96.4) at the estimated 10-year outcome. No significant difference was observed between T1a, T1b and T1c tumors (P = 0.335). In multivariate analysis, factors significantly associated with improved survival were age, hormone therapy and SBR grade 1 (supplementary file S3, available at Annals of Oncology online).

In the whole population, RFS rates were 94% (95% CI 93.8–95.2), 92.1% (91.1–93.2) and 83.8% (77.6–90.5) at 60, 84 and
120 months, respectively. RFS was significantly higher in T1b tumors (95.9%, 95% CI 95–96.9) when compared with T1a (93.2%, 91–95.4) or T1c tumors (93.8%, 92.8–94.9), $P = 0.01$ (Figure 1). The 5-year RFS was 90% without AST, 90% with adjuvant chemotherapy only, 96% with hormonal therapy only and 94% with both. The 5-year RFS rate according to tumor subtype is shown in Table 2 (and supplementary file S4, available at *Annals of Oncology* online). In multivariate analysis, hormone therapy was associated with longer RFS, while younger age, LVI and grade 2 and 3 were associated with shorter RFS (Table 2). In the subgroup of patients with T1a tumors, hormonal status, LVI, and grade 2 and 3 were associated with shorter RFS, while younger age was significantly associated with longer RFS (HR: 0.5, 0.25–0.99, $P = 0.024$) (supplementary file S5, available at *Annals of Oncology* online). Similar results were obtained by excluding trastuzumab-treated HER2-positive patients ($n = 75$; data not shown).

Cumulative incidence of metastases was 1.7% (95% CI 1.3–2.1) at 60 months and 2% (1.5–2.5) at 84 months. It was significantly higher in T1a than in T1b tumors (84-month rate: 3% and 1%, respectively, HR: 0.5, 0.25–0.99, $P = 0.024$) (supplementary file S5, available at *Annals of Oncology* online). In multivariate analysis, grade 3 was the only factor significantly associated with a higher incidence of metastases (HR: 3.61, 1.686–7.74, $P < 0.001$).

**discussion**

In this cohort of 5423 patients with T1 BC, the overall prognosis was excellent, with 5- and 10-year OS rates of 97.6% and 90.7%, respectively. Data from literature are consistent with these findings, although most studies focus on infracentimetric tumors, excluding T1c [4, 5, 18]. However, relapse is not infrequent after a long period. In our study, recurrence rate was only 6% at 5 years but 16.2% at 10 years. This is also consistent with literature. In the study of Joensuu et al., in which patients did not receive AST, median follow-up was 17 years. All T1 tumors were included and the 20-year BC-specific survival rate was 81%, showing that a significant percentage of patients died of the disease [19]. Another study included all T1 tumors (38 T1a, 256 T1b and 1045 T1c) treated between 1967 and 1995 [20]. Disease-free survival (DFS) rates were 91.9%, 86.1% and 82.4% at 10 years, respectively, and 70.7%, 76.7% and 69.1% at 20 years. These results show that there is a continuous risk of late relapses in these so-called ‘good prognosis’ tumors.

Surprisingly, we found that T1a tumors had a worse prognosis than T1b, or even T1c tumors with respect to RFS or distant RFS. Multivariate analysis identified AST, LVI and grade but not tumor size as major determinants of relapse events. Yet, this poorer outcome of T1a is against all previous publications. In the series of Mann et al., the 6-year distant DFS rate was not different between 95 T1a (95%) and 196 T1b (91%) tumors [21]. In another cohort of 214 T1N0M0 tumors [22], no difference was observed between T1a,b and T1c tumors. In the study by Lee et al. (88 T1a,b N0M0) [7], 5-year DFS rates were not statistically different in T1a (100%) and T1b (92%) tumors ($P = 0.27$) nor was distant DFS (100% and 96%, respectively, $P = 0.4$). The study published by Chia et al. included 430 patients with T1a,b tumors and 507 T1c tumors, who did not receive AST. Ten-year RFS rates were 82% and 75%, respectively, BC-specific survival was 92% and 90% and OS was 79% and 78% [23]. Other studies showed better outcomes in smaller tumors. In the SEER cohort, OS was longer in T1a tumors compared with T1b, while BC-related death rates were similar in both subgroups [4].

### Table 1. Patients and tumors characteristics at baseline (percentages are calculated in relation to the number of available data)

<table>
<thead>
<tr>
<th></th>
<th>T1a ($n = 708$)</th>
<th>T1b ($n = 2207$)</th>
<th>T1c ($n = 2508$)</th>
<th>Adjusted $P^*$ T1a versus T1b</th>
<th>Adjusted $P^*$ T1ab versus T1c</th>
</tr>
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<tbody>
<tr>
<td><strong>SBR grade, n (%)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>285 (51)</td>
<td>1157 (53)</td>
<td>917 (37)</td>
<td>0.128</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>217 (39)</td>
<td>867 (40)</td>
<td>1205 (48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>54 (10)</td>
<td>156 (7)</td>
<td>378 (15)</td>
<td></td>
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<tr>
<td><strong>LVI, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>470 (96)</td>
<td>1662 (92)</td>
<td>1676 (82)</td>
<td>0.015</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>21 (4)</td>
<td>143 (8)</td>
<td>359 (18)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Hormonal status, n (%)</strong></td>
<td></td>
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<tr>
<td>Negative</td>
<td>112 (18)</td>
<td>175 (8)</td>
<td>222 (9)</td>
<td>&lt;0.001</td>
<td>0.262</td>
</tr>
<tr>
<td>Positive</td>
<td>502 (82)</td>
<td>222 (92)</td>
<td>2280 (91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HER2 status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Negative</td>
<td>329 (85)</td>
<td>1262 (94)</td>
<td>1429 (93)</td>
<td>&lt;0.001</td>
<td>0.302</td>
</tr>
<tr>
<td>Positive</td>
<td>60 (15)</td>
<td>84 (6)</td>
<td>112 (7)</td>
<td></td>
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<tr>
<td><strong>Lymph node, n (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>pN0</td>
<td>643 (92)</td>
<td>1864 (87)</td>
<td>1863 (78)</td>
<td>0.004</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pN1</td>
<td>56 (8)</td>
<td>290 (14)</td>
<td>535 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adjuvant therapy, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>81 (14)</td>
<td>362 (17)</td>
<td>810 (34)</td>
<td>0.066</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hormonetherapy</td>
<td>434 (62)</td>
<td>1859 (84)</td>
<td>2186 (87)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>14 (2)</td>
<td>22 (1)</td>
<td>38 (2)</td>
<td>0.066</td>
<td>0.425</td>
</tr>
</tbody>
</table>
Finnish study (49 pT1a, 264 pT1b, 539 pT1c) [24], the smaller the tumor size, the higher the 9-year DFS was ($P = 0.009$). Patients from the National Cancer Database with T1a,b N0M0 BC ($n = 123212$) had longer 5-year survival rates with T1a (94.3%) than with T1b tumors (93.1%), $P = 0.04$ [6]. In the study of Joensuu et al., a significant difference was observed between T1a,b and T1c tumors at 20 years with BC-specific OS rates of 92% and 75%, respectively [19]. Survival curves started to separate at ~12 years. In the Japanese study, the difference between T1b and T1c tumors was statistically significant and the authors concluded that T1c tumors constitute a high-risk group within T1 tumors [20]. However, in the NSABP-B21, the only randomized trial reported to date specifically focused on T1a-b, a greater risk of ipsilateral BC recurrence was unexpectedly observed in pT1a compared with pT1b [25].

The first hypothesis to explain the relatively less favorable outcome of T1a tumors in our dataset is that they exhibited several unfavorable prognostic factors and expected differences with T1b or T1c tumors, in particular a higher frequency of negative HR status, HER2 overexpression and triple-negative subtype, even though the high number of missing data for ER, PR and HER2 may limit interpretation of this result. The higher percentage of negative HR status might be partly explained by the higher percentage of undetermined cases (13.3% versus <0.5% in other subgroups). The more than twice higher percentage of HER2-positive status might be explained by an erroneous HER2 testing on the intraductal rather than on the invasive component and by the relatively high number of missing data that may carried a bias. Alternatively, HER2 overexpression could be truly more frequent in T1a, due to yet to elucidate biological reasons. A similar pattern of more-frequent HER2 positivity in T1a compared with T1b was also found in other series [26, 27]. This difference in HER2 status could be particularly relevant since HER2 overexpression is now widely recognized as a poor prognosis factor in small tumors, as it is in larger ones [24, 26, 28]. A recent meta-analysis (764 patients) in T1a,bN0M0 tumors showed a detrimental effect of HER2-positive status on RFS (HR: 4.68), distant RFS (HR: 5.6) and BC-specific mortality (HR: 2.6) [29]. These studies did not differentiate between T1a, b and c tumors. Nevertheless, there is now sufficient evidence to state the poor prognosis of HER2 status even in infiltrating micrometastases and consider anti-HER2 therapy in these patients. Although retrospective, the study of Rodrigues et al. showed that patients with T1a,bN0 HER2-positive tumors treated with adjuvant trastuzumab-based chemotherapies ($n = 149$) had a significant survival benefit (40-month DFS rates of 99% versus 93% for patients who did not receive this regimen, $P = 0.018$) [30]. Of note, a US study (APT trial) will prospectively evaluate a combination of adjuvant weekly paclitaxel–trastuzumab (12 weeks) followed by trastuzumab for 40 weeks in patients with low-risk, node-negative, HER2-positive, <3 cm tumors. Although not comparative, this study should provide important data about toxicity, recurrence and survival.

Thus, and this is our second hypothesis, the lack of adjuvant trastuzumab-based treatment in small HER2-positive tumors could have contributed to a less favorable outcome in the more frequently HER2-positive pT1a. Similarly, we believe that patients with T1a tumors received insufficient chemotherapy and hormone therapy. Even in the HR-positive subgroup, endocrine therapy was prescribed less often in T1a tumors. In multivariate analysis, hormone therapy was significantly associated with lower overall mortality and lower recurrence rates. In the subgroup of T1a tumors, hormone therapy was also significantly associated with improved OS. AST in small tumors remains debated, in particular in very small (i.e. T1a) BC. In the NSABP-B21 (1009 patients with pT1a,b) [25], tamoxifen had no significant impact on distant metastases and OS. However, some studies suggest benefits. For example the analysis of 1259 patients with T1a,b BC included in the NSABP trials [5] showed that patients with negative ER had nonstatistically different 8-year RFS rates and OS when treated with surgery alone or surgery plus chemotherapy. However, in ER-positive tumors, the outcome was significantly better when tamoxifen was added to surgery (8-year RFS of 93% and 86%, respectively, $P = 0.01$).

Apart from endocrine therapy, other factors independently associated with outcome in our study were SBR grade for OS, LVI and grade for RFS and grade for distant metastases. We did not find prognostic value for LN involvement.

![Figure 1. Recurrence-free survival according to tumor stage.](https://academic.oup.com/annonc/article-abstract/25/3/623/148804/figure-1)
Our study has limitations, mainly its retrospective methodology that may carry bias, although we collected data from all consecutive patients presenting with early-stage BC. A potential bias may also rely upon the lack of central revision of ER, PR and HER2 status, as well as the possible effect of tissue fixation and processing on reliability of size measurements. However, patient population was collected from reference centers and tumor features were analyzed by highly trained and national-expert pathologists. Because our study started in 1999, we did not study global gene expression and molecular signatures, and we have no data on proliferation index. However, molecular subtypes were approximated using IHC and pathological surrogates, including ER, PR, HER2 and grade. Information on circumstances of BC diagnosis was also lacking although it might impact on tumor characteristics. Interval cancers are known to be more aggressive, to have more rapid growth than screening cancers and to overexpress HER2 in higher percentages of cases. Our study also has strengths, such as the large size of the cohort, and in particular the high number of T1a tumors that are very scarce in most studies. It also distinguished subgroups of T1 tumors according to size, which is also rarely done.

In conclusion, our results suggest that within the group of T1N0M0 BCs, tumor size is not the major determinant of prognosis and that biological characteristics of the tumor might be more relevant prognostic factors, although median follow-up is limited. Consequently, therapeutic strategy should give a larger place to these histological and biological characteristics (grade, LVI, HR and HER2 status). Even though the anticipation of a minimal benefit may still justify AST for some patients, consensus guidelines do not recommend adjuvant therapy in T1a pN0 tumors. This attitude might be questioned if additional risk factors are associated and consequently, AST should be discussed with patients based on the event rates reported in this and other studies.

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disclosure
The authors have declared no conflicts of interest.

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The impact of adjuvant radiotherapy on the survival of primary breast cancer patients: a retrospective multicenter cohort study of 8935 subjects†

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Background: Radiotherapy (RT) is proven to be an important backbone for adjuvant therapy in randomized, controlled trials, but it is unclear if these effects are provable in a daily routine cohort of breast cancer patients. This study sought to answer the following questions in a daily routine cohort of breast cancer patients:
1. Does guideline-adherent RT improve primary breast cancer patient survival?
2. Is breast-conserving surgery (BCS) followed by RT equal to a mastectomy (MA) with regard to outcome parameters?
3. Does adjuvant RT compensate for an incomplete tumor resection (R1)?

Patients and methods: In this retrospective, multicenter cohort study, we investigated data from 8935 primary breast cancer patients recruited from 17 participating certified breast cancer centers in Germany between 1992 and 2008. Guideline adherence based on internationally validated guidelines.

Results: The patients who received guideline-adherent RT for primary breast cancer were associated with significantly improved survival parameters [recurrence-free survival (RFS): \( P < 0.001 \); overall survival (OS): \( P < 0.001 \)] compared with patients who did not receive guideline-adherent adjuvant RT. Furthermore, the results demonstrated that there were no significant differences in RFS and OS between BCS followed by RT and MA [RFS: \( P = 0.293 \); OS: \( P = 0.104 \)]. Adjuvant RT did not improve the outcome of patients receiving nonguideline-adherent incomplete tumor resection via BCS (R1); these patients showed a significantly impaired RFS \( [P < 0.001] \) and OS \( [P < 0.001] \) compared with patients who underwent guideline-adherent complete tumor resection via BCS (R0). In addition, non-guideline-adherent RT after MA (over-therapy) did not significantly influence survival [RFS: \( P = 0.838 \); OS: \( P = 0.613 \)].

Conclusion: Our study confirms the importance of guideline-adherent adjuvant RT. It shows highly significant associations between RFS or OS and guideline adherent RT. Nevertheless, inadequate (R1-) surgical resection in a daily routine cohort of patients increases the risk of local recurrence and appears not to be compensated by the following RT.

Key words: radiotherapy, breast cancer, guideline adherence, survival, cohort

†This work was presented at San Antonio Breast Cancer Symposium (SABCS) 2013.
‡These authors contributed equally to this work.

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