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Tumour Review

Small breast cancers: When and how to treat

K. Tryfonidis [a,*], D. Zardavas [b], F. Cardoso [c]

[a] European Organization for Research and Treatment of Cancer (EORTC) Headquarters, Brussels, Belgium
[b] Breast International Group Headquarters (BIG Aisbl), Brussels, Belgium
[c] Breast Unit, Champalimaud Cancer Center, Lisbon, Portugal

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ABSTRACT

Small (T1a, b), lymph node negative breast tumors represent an entity diagnosed with increasing frequency due to the implementation of wide-scale screening programs. Patients bearing such tumors usually exhibit favorable long-term outcomes, with low breast cancer mortality rates at 10 years, even in the absence of adjuvant chemotherapy. However, most available data derive from retrospective studies. Additionally, a subset of patients with these tumors experience recurrence of the disease, indicating that early tumor stage itself is not a sufficient prognosticator. It is of paramount importance to refine the prognosis of this population, identifying patients with high risk of recurrence, for whom adjuvant treatment is needed. The underlying biology of the disease provides relevant information, such as grade and status of hormone receptors and HER-2 (human epidermal growth factor receptor 2), with high grade, triple negative and HER-2-positive tumors having worse prognosis. Additionally, multigene signatures may improve further the prognostication of patients with small, node negative breast cancers. Further research for this increasingly frequent group of patients is urgently needed, so that better informed clinical decision making, in particular regarding adjuvant chemotherapy, can occur.

Introduction

Tumor size is an important prognostic factor, positively correlated with axillary node infiltration at the time of diagnosis, tumor recurrence and mortality rates [1]. Although adjuvant systemic therapy is now routinely recommended for patients with node-positive breast cancer (BC) or node-negative tumors larger than 1 cm, its role in subcentimetric node-negative BC has to be better defined. Accumulating data from the use of biological markers and multi-gene prognosticators in treatment decision indicate that traditional clinical factors, such as size and nodal status, isolated are not enough to accurately prognosticate BC; additionally, these data raise the question whether patients with subcentimetric node-negative BC derive enough benefit from adjuvant chemotherapy (CT) to outweigh the risks of treatment [2,3].

The group of patients with node-negative tumors <1 cm has been traditionally excluded from adjuvant CT trials, due to their favorable prognosis, with a 10-year recurrence free survival (RFS) rate exceeding 90% [4]. Consequently, the benefits gained with newer adjuvant therapies have not been well defined for these BC patients. Recurrences and deaths do occur in some patients with T1N0M0 tumors [3]. Furthermore, accumulating evidence regarding the underlying biology of aggressive subtypes indicates that it has prognostic value independently from tumor burden (i.e. size and nodal status). For these reasons, the administration of adjuvant systemic treatment should be discussed with all these patients, taking into account additional prognostic parameters related to the biology of the disease, as well as patients' characteristics and preferences.

The implementation of screening programs has resulted in an increasing number of patients diagnosed with stage I BC, rendering this an important clinical dilemma [5–7]. Allgood et al. reported in 2011 that 31.6% of patients with T1a–b N0 tumors are diagnosed through screening programs, as opposed to clinical criteria (e.g. palpable mass) [8]. According to the SEER (Surveillance, Epidemiology, and End Results) database, for the years 2004–2008, 50% of the new BC cases were diagnosed with stage I disease and half of them (25%) had T1a, b tumors [9].

In this article we provide an overview of the literature and elaborate on some controversies between the existing consensuses guidelines in an attempt to better define the optimal management of the increasing population of women with small (<1 cm) node-negative breast tumors.

* Corresponding author at: EORTC, Clinical Research Physician, Breast Cancer Group, Av. E. Mounier 83/11, 1200 Brussels, Belgium. Tel.: +32 27741512; fax: +32 27741636.

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Clinical and pathological data from the SEER and NCCN programs

The SEER program is a network of cancer registries in the United States. Among 61,153 BC cases registered between 1998 and 2003, the 10-year mortality rate of T1a and T1b was 3.0% and 3.3% respectively, indicating that these groups have overall a good outcome, without major differences between these two categories. It was also shown that these smaller tumors are enriched with favorable biological aspects, such as ER-positivity and low grade [8].

A prospective cohort study within the National Comprehensive Cancer Network (NCCN) on clinical outcome of 4113 women with T1a, b N0M0 BC of all subtypes, treated between 2000 and 2009 (T1*a* = 1299 and T1*b* = 2815) was recently published [10]. Divergent results were reported among women with different subtypes, however these women had overall favorable prognosis, since recurrence rate (RR) or distant recurrence rate (DRR) did not exceed 10% in any of the subtypes, at a median follow-up of 5.5 years. The 5-year distant RFS (DRFS) for untreated patients with T1a tumors (n = 1197) ranged from 93% to 98%, and for patients with T1b tumors from 90% to 96%. Patients with hormone receptor (HR)-positive/HER-2-negative disease had the best DRFS rates, while patients with triple negative tumors had the lowest. The 5-year DRFS for treated patients with T1a tumors was 100% across all subgroups (total n = 102), and for patients with T1b tumors it ranged from 94% to 96% (total n = 609). These results substantiate that identification of patients with small tumors at risk of relapse is needed.

Outcome reports from retrospective studies

Several retrospective studies have investigated the outcome of patients with subcentimetric tumors. Rosen et al. reported in 1981 a 10-year RFS of 91% among 171 patients that received no adjuvant systemic treatment [4,2]. Moon et al. later reported a lower 10-year RFS of 83%, among 154 patients [11]. Most other retrospective series had shorter follow-up (Table 1). Interestingly, it has been reported that although many cancer recurrences occur in the first decade, patients with these small tumors and less aggressive subtypes may relapse during the second decade of their follow-up or later [12]. Chia et al. reported in 2004 the 10-year clinical outcome for 1187 cases of pT1–2 N0, no lymphovascular invasion (LVI) BC without adjuvant systemic treatment [13]. Of note, different results were reported for women with T1a and T1b tumors in terms of RFS (82% and 75% respectively), and breast cancer specific survival (BCSS) (92% and 90% respectively), but similar results in terms of overall survival (OS) (79% and 78% respectively), implying that BCSS might capture more accurately the natural course of BC than RFS. Additionally, this study revealed that high grade was associated with increased recurrence rates among women with T1a tumors, since a 10-year RFS of 74% was reported as compared to 88% for T1a tumors with low grade. Recently, a multicenter, retrospective study reported the clinical outcomes and characteristics of 5423 patients with T1 tumors (708 T1a and 2208 T1b). OS was not different between T1a, b or c tumors, but RFS was significantly higher in T1b than in T1a tumors (P = 0.001). In multivariate analysis, tumor grade, ET and LVI were found to be independent prognostic factors. OS rate was 97.6% at 60 months, 95.4% at 84 months and 90.7% at the estimated 10 year outcome. Also in the whole population, RFS rates were 94%, 92.1% and 83.8% at 60, 84 and 120 months respectively. RFS was significantly higher in T1b when compared with T1a or T1c tumors (95.9% vs 93.2% vs 93.8%) [14].

The conclusion of these studies is that, despite the favorable prognosis of patients with small breast tumors, there is a subset experiencing recurrence of the disease. However, these retrospective studies did not take into account HER-2 status, and the majority did not report if and which type of adjuvant treatment was administered.

Table 1
Retrospective studies assessing the outcomes of T1a, b tumors.

Author	No pts with T1a–b tumors	Year	Result according HR status	Median follow-up	Outcome
Rosen et al. [68]	171	1981	NR	18 years	91% – 10 years RFS 88% – 20 years RFS
Moon et al. [11]	154	1987	NR	15 years	83% – 10 years RFS 87% – 5years RFS
Stierer et al. [69]	121	1992			84% – 15 years RFS
Arnesson et al. [70]	254	1994	NR	7 years	98.7% – 7 years DDFS
Leitner et al. [71]	218	1995	NR	6.9 years	93% – 7 years RFS overall 67% – 7 years RFS with poor risk factors 99% – 7 years RFS with neither risk factors
Mann et al. [72]	257	1999	NR	6 years	93% – 6 years DDFS 81% – 6 years DDFS with LVI
Wood et al. [73]	282	2002	NR	7 years	98.7% – 10 years DDFS
Chia et al. [13]	430	2004	84% – 5 years RFS (ER +)* 80% – 5 years RFS (ER−) 76% – 10 years RFS for ER+ and ER neg**	10.4 years	74% – 10 years (grade 3)
Colleoni et al. [15]	401	2004	Reported***	43 months	97% – 4 years DFS for T1a 97.6% – 4 years DFS for T1b 93.3% – 4 years DFS for Ki-67
Houvenaeghel et al. [14]	2,916	2013	Reported****	60.5 months	93.2% – 60 month for T1a 95.9% – 60 month for T1b 93.8% – 60 month for T1c

Abbreviations: DDFS, distant disease-free survival; DFS, disease-free survival; ER, estrogen receptor; HR, hormone receptors; LVI, lymphovascular invasion; NR, not reported; RFS, recurrence-free survival; HR, hormonal receptors.

* In this series, 113 tumors with size smaller than 1 cm were included in a total of 826 analyzed patients. ER status was known in 226 patients and 33 had a borderline defined HR status. Information was not given on how many patients with subcentimetric tumors had known ER status and its impact on outcome was not reported.

** These results were for the entire cohort of ER positive and ER negative tumors regardless of tumor size.

*** In this report out of 358 patients with sub-centimetric tumors, 275 received ET, 43 received chemo endocrine treatment and 40 did not receive any treatment. In a median follow-up of 43 months, 6 events were reported overall, 5 in the endocrine treated cohort and 1 in the non-treatment cohort.

**** The 5-year RFS rate was 96% in patients that received ET only and 94% for patients that received both ET and CT adjuvant treatments.