JBUON 2015; 20(2): 479-486
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Chemotherapy might not be beneficial in lymph node-negative, hormone-positive, and HER2-negative breast cancer patients: a long-term retrospective analysis

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Summary

Introduction: *In lymph node-negative, hormone-positive, and Her2-negative breast cancer patients, the benefits of adding adjuvant chemotherapy to hormonal therapy continue to be debated, especially for low to intermediate grade and small tumors.*

Methods: *Excluding patients with T4 disease, we retrospectively reviewed the records of patients with long-term follow-up at our center between 2003 and 2014. Among node-negative, hormone-positive and HER2-negative breast cancer patients, we compared two groups of patients: those given both chemotherapy (doxorubicin+cyclophosphamide) and hormonotherapy, and those prescribed hormonotherapy alone. The primary endpoints were progression-free (PFS) and overall survival (OS).*

Results: *Overall, no difference was observed between these two treatment groups in either DFS or OS. However, for both outcomes, there was a trend towards improved DFS and OS favoring the hormone-only group.*

Conclusions: *In selected subgroups of breast cancer patients, administering adjuvant hormonal therapy alone seems to be at least as good if not better than combining hormonotherapy and chemotherapy.*

Key words: *adjuvant, chemotherapy, ER positive, HER2 negative, hormonotherapy node-negative*

Introduction

Breast cancer is a worldwide health problem and the most common type of tumor among women. Based on USA statistics, one in eight women will develop breast cancer in her lifetime [1]. Breast cancer incidence has increased steadily since the 1970s, though it has stabilized to some extent over the last decade. In contrast, mortality rates have been decreasing steadily since the early 1990s [1,2]. This decrease in mortality rates is mainly due to the generalized use of screening techniques and improvements in adjuvant regimens [3].

Adjuvant treatments reduce mortality and recurrence rates, especially in lymph node positive breast cancer patients [4]. Adjuvant hormonotherapy has become the standard of care in hormone-positive breast cancer patients because of its associated reduced rates of mortality and tumor recurrence [5]. Adding chemotherapy to hormonal therapy has increased survival rates [6]. However, the benefits of adjuvant treatments are not the same across all subgroups of breast

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Received: 17/11/2014; Accepted: 02/12/2014

cancer. Another reality is that estrogen receptor (ER) positive tumors tend to be less responsive to chemotherapeutic agents than their ER negative counterparts [7].

In lymph node-negative, hormone-positive breast cancer, the likelihood of distant metastasis after adjuvant tamoxifen is roughly 15% at 10 years. As such, a large majority of such patients are likely over-treated if all patients are given chemotherapy [10]. For this reason, determining which node-negative, hormone-positive patients will not benefit from adjuvant chemotherapy is of considerable clinical importance. Currently, using multi-gene assays, several trials are ongoing attempting to determine which patient groups are likely to benefit or not from adjuvant chemotherapy, especially among node-negative, hormone-positive and HER2 negative breast cancer patients [9,10].

Given the above-mentioned evidence, we decided to perform a retrospective analysis of female breast cancer patients who were node-negative, hormone-positive, and HER2 negative. We analyzed our single-center records on the long-term follow-up of these patients, looking at risk factors like tumor grade, lymphovascular invasion, and tumor size.

Methods

Study design and subject recruitment

According to patient records at the Oncology Institute of Hacettepe University School of Medicine, out of 3541 breast cancer patients followed between 2003 and 2014, 634 were node-negative and both ER and/or progesterone receptor (PR)-positive. For the current study, these patients were analyzed retrospectively and stratified into two groups: (1) 170 patients who had received AC (doxorubicin and cyclophosphamide) plus hormonotherapy (tamoxifen and/or aromatase inhibitor); and (2) 464 who had received hormonal therapy alone. The demographic features of these patients are shown in Table 1. The mean patient age in the combined therapy group was 44.2±8.5 years, vs 54.5±10.5 in the hormone therapy-only group. Patients who had serious co-morbidities (including chronic kidney disease, functional congestive heart failure, recent myocardial infarction, uncontrolled diabetes mellitus and hypertension), and patients who had diseases that interfere with regular chemotherapy or hormonotherapy administration were excluded from analysis. In addition, patients with unknown or unconfirmed ER, PR or HER2 status were excluded. The same oncologists followed all patients periodically at recommended follow-up intervals. The study end-points were DFS and OS.

Staging and immunohistochemistry

Pathological and clinical staging at the time of diagnosis was defined according to the American Joint Commission on Cancer (7th Edn) [11]. Tumor grade was defined as per the Bloom-Richardson criteria: I, II, III, or other/unknown [12]. ER and PR status were determined by immunohistochemistry (IHC) [as positive when 1% of the tumor cells stained positive during IHC testing and otherwise as negative]. The HER2 score was derived from the IHC score (negative: 0 and 1+, positive: 3+) and the ratio of HER2 to chromosome 17 signaling, as per American Society of Clinical Oncology-College of American Pathologists (ASCO-CEP) guidelines. Specimens scored 2+ were further evaluated by means of a fluorescence *in situ* hybridization (FISH) technique. HER2 amplification was defined as a ratio of HER2 to chromosome 17 signaling greater than 2.2 [13].

Statistics

All analyses were two-tailed. Differences between categorical variables were identified by Pearson's x^2 analysis, and differences between continuous variables using either independent Student's t-test or one-way analysis of variance (ANOVA), as suitable. Kaplan-Meier analysis was used to construct life table plots. Statistical differences between groups were analyzed with log-rank test and stratified for co-variates. Cox regression analysis was used to determine the effects of co-variates and hazard ratios. Comparing treatment regimens in terms of DFS and OS, risk ratios associated with events were calculated, along with 95% confidence intervals (95% CI) from Cox proportional-hazards models. All analyses were conducted using the Statistical Package for Social Sciences (SPSS Inc, Chicago, Ill, version 22) software. Statistical significance was set at at $p<0.05$.

Results

Lymphovascular invasion (LVI)

Log-rank analysis showed no difference in DFS among patients with T1-T3 disease stage who were node-negative, hormone-positive, and HER2-negative, in relation to positive vs negative LVI (p=0.84) (Figure 1a). The same was true for OS (p=0.80) (Figure 1b). On the other hand, when log-rank analysis was repeated, stratified by LVI (present/absent), the DFS in LVI-absent patients treated only with hormonal therapy was significantly superior to that of those in the combined therapy group (p=0.028) (Figure 1c). In patients with LVI, these two groups were no different (p=0.43) (Figure 1d).

Grade

In T1-3, node-negative, hormone-positive and

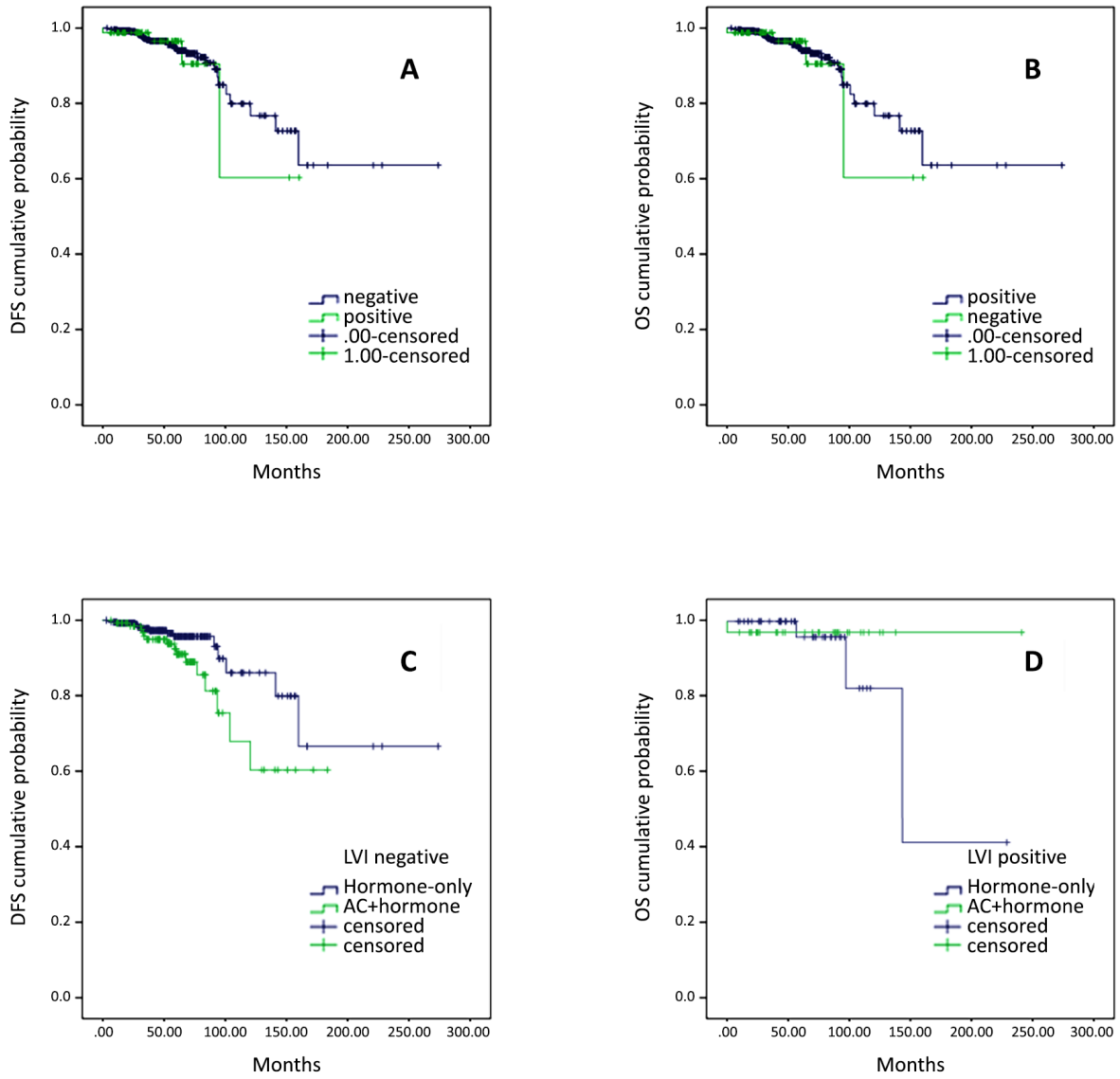

Figure 1. A: DFS plots of LVI positive and negative patients (p=0.84); **B:** OS plots of LVI positive and negative patients (p=0.80); **C:** DFS plots of adriamycin+ cyclophosphamide+hormone and hormone-only groups in LVI negative patients. (p=0.028); **D:** OS plots of adriamycin+ cyclophosphamide +hormone and hormone-only groups in LVI negative patients (p=0.043).

HER2-negative patients, no difference was shown by log-rank test in DFS between tumor grades (p=0.29) (Figure 2a), and the same was true for OS (p=0.51) (Figure 2b). When stratified by tumor grade, we also identified no difference between combined therapy and hormone-only therapy patients among grade 1 and grade 3 tumors (p=0.25 and p=0.39, respectively). However, in patients with grade 2 tumors, DFS was significantly superior in the hormone treatment-only subgroup (p=0.038). No difference in OR was identified between the two treatment groups across the three tumor grades (p=0.33, p=0.44 and p=033, respectively).

T stage

DFS was better among T1 node-negative, hormone-positive and HER2-negative patients than their T2 counterparts (log-rank, p=0.026; Figure 3a). Since the number of T3 patients was low, T3 patients were excluded from these analyses as either a factor or stratified factor. No differences by T stage were noted in OS in the same group of patients (p=0.24; Figure 3b). When stratified by T stage, no difference between the two treatment groups was noted in either DFS or OS among T1 and T2 patients (p=0.25 and p=0.63, and p=0.36

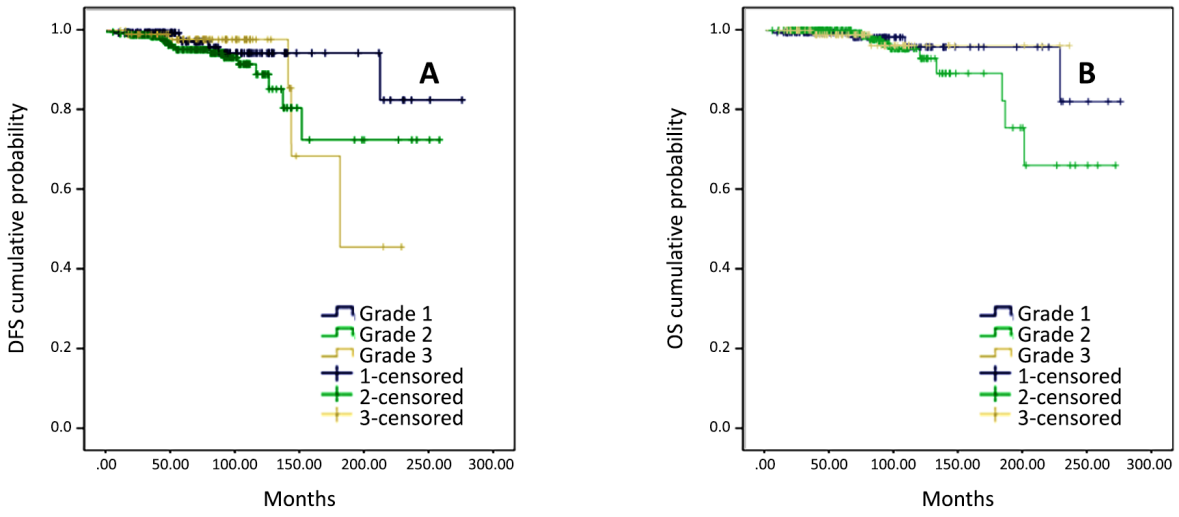

Figure 2. A: DFS plots as per grades (p=0.029); **B:** OS plots as per grades (p=0.51).

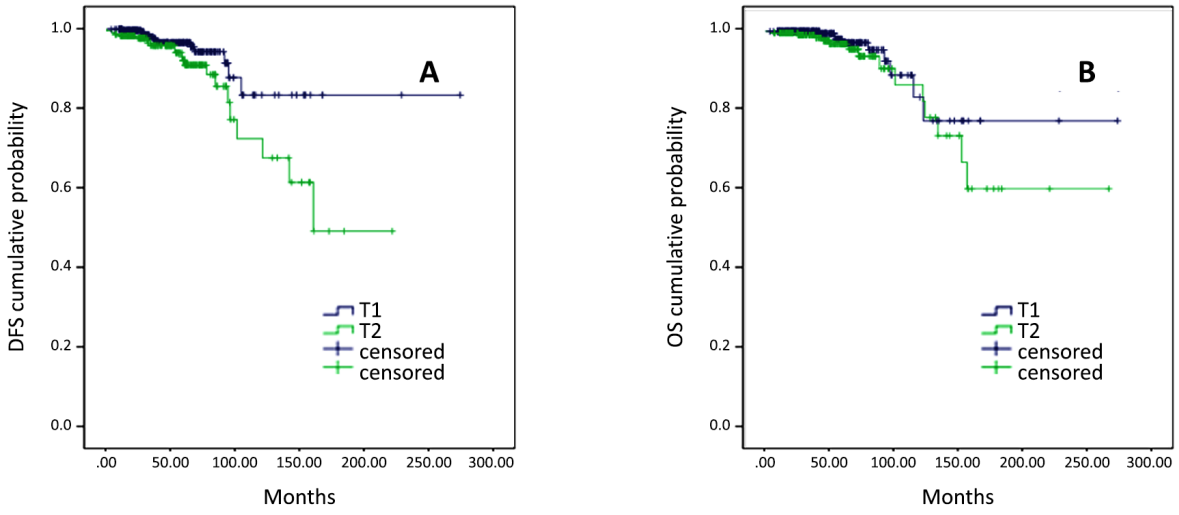

Figure 3. A: DFS plots as per T stages (p=0.026); **B:** OS plots as per T stages (p=0.024).

and p=0.67, respectively).

T 1-3 hormone-positive, HER2-negative and node-negative patients

In these patients, there was no difference in DFS between the two treatment groups (p=0.079), though there was a trend favoring those who had received hormone therapy alone (Figure 4a). No difference in OS was noted (p=0.56;Figure 4b). However, the two groups were dissimilar in age, menopausal status, tumor grade, and T-stage distribution (Table 1). For this reason, the results were adjusted for these co-variates by proportional Cox regression analysis. When adjusted for age, T stage, grade and menopause, there was still no difference in DFS between the two treatment groups (p=0.208, HR: 0.530), though a non-significant trend favoring hormonotherapy-only patients was noted (Figure 4c). The results for OS were similar, either non-adjusted (p=0.56) or adjusted for age, menopausal status, T stage and grade (p=0.658, HR: 0.754; Figure 4d), though a trend again was noted favoring hormone treatment-only.

Table 1. Demographic features of the treatment groups

	AC+hormone N (%)	*Hormone only N (%)*	*p value*
Age (years)*	44.2±8.5	54.5±10.5	<0.05
T1	57 (14.9)	325 (85.1)W	<0.05
T2	100 (42.9)	133 (57.1)	<0.05
T3	13 (7.1)	6 (3.5)	<0.05
Pre-menopause	130 (41.7)	182 (58.3)	<0.05
Post-menopause	39 (12.3)	278 (87.7)	<0.05
Grade 1	18 (10.7)	150 (89.3)	<0.05
Grade 2	85 (29.7)	201 (80.3)	<0.05
Grade 3	60 (54.1)	51 (45.9)	<0.05
Histology (IDC)	135 (82.8)	295 (76.8)	ns
Histology (ILC)	30 (6.1)	31 (8.1)	ns
Histology (mix)	18 (11)	58 (15.1)	ns
LVI (+)	34 (20)	47 (10.1)	
Smoking	43 (25.3)	95 (20.5)	

*mean±standard deviation, ns: non significant, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, LVI: lymphovascular invasion, A: adriamycin,C: cyclophosphamide

T2/T1+T2, node-negative, hormone-positive, grade 2 and HER2-negative patients

In this subset of patients there was no difference between the two treatment groups for either DFS (p=0.16; Figure 5a) or OS (p=0.78; Figure 5b). When only patients with T1 tumors were analyzed, a difference in DFS was detected, once again favoring hormonal therapy-only (p=0.031; Figure 5c); however, this benefit failed to affect OS (p=0.42; Figure 5d).

Discussion

In lymph node-negative, hormone-positive patients, it is not yet clear which therapeutic approach is the best option for certain breast cancer subtypes. To aid in this decision, certain predictive pathological factors have been used to estimate the risk of tumor recurrence. Clinically, nodal involvement, ER, PR and HER2 status, tumor grade, Ki-67 level, and the presence vs absence of LVI have been used to assist such decisions [14-17].

Despite the limitations of its retrospective design, the current study yielded several important observations. The first is that, although not statistically significant, a trend was identified favoring patients who had received hormone therapy alone over those receiving combined chemo- and hormone therapy. In our sample, the majority of patients had either a T1 or T2 tumor stage. To avoid performing underpowered analyses, we excluded certain patients during some analyses (e.g., T3 stage patients were excluded during our analysis of the effects of T stage on DFS and OS). However, we included T3 stage patients during multivariate analyses. We found that the two treatment groups were inhomogeneous in several co-variates. However, when adjusted for several known risk factors, the hormone-only group tended to experience prolonged survival.

A second important point is that we analyzed a specific subgroup of T2/T1-2, node-negative, grade 2, hormone-positive patients separately, since such patients are the most difficult to make decisions. Although in T1-2N0M0 patients, DFS was significantly better in hormone-only treated patients, no such benefit was observed for OS. As a result, we at least can say that chemotherapy did not add benefit over hormonotherapy alone in this patient population.

Third, on Cox regression analysis LVI, tumor grade, menopausal status, T stage (T4 not included) and patient age failed to exert any significant influence on either DFS or OS. The prognostic value of LVI continues to be an issue of debate, but its presence seems to indicate a poor prognosis [17]. However, the presence of LVI was insufficient to place patients in a high-risk category, possibly because adjuvant treatments were used [18,19]. Even though our patient sample was not large, LVI did not seem to affect either tumor recurrence or OS in hormone-positive patients.

There is no doubt that tumor size, tumor grade, and whether a patient has or has not nodal involvement are important determinants of a

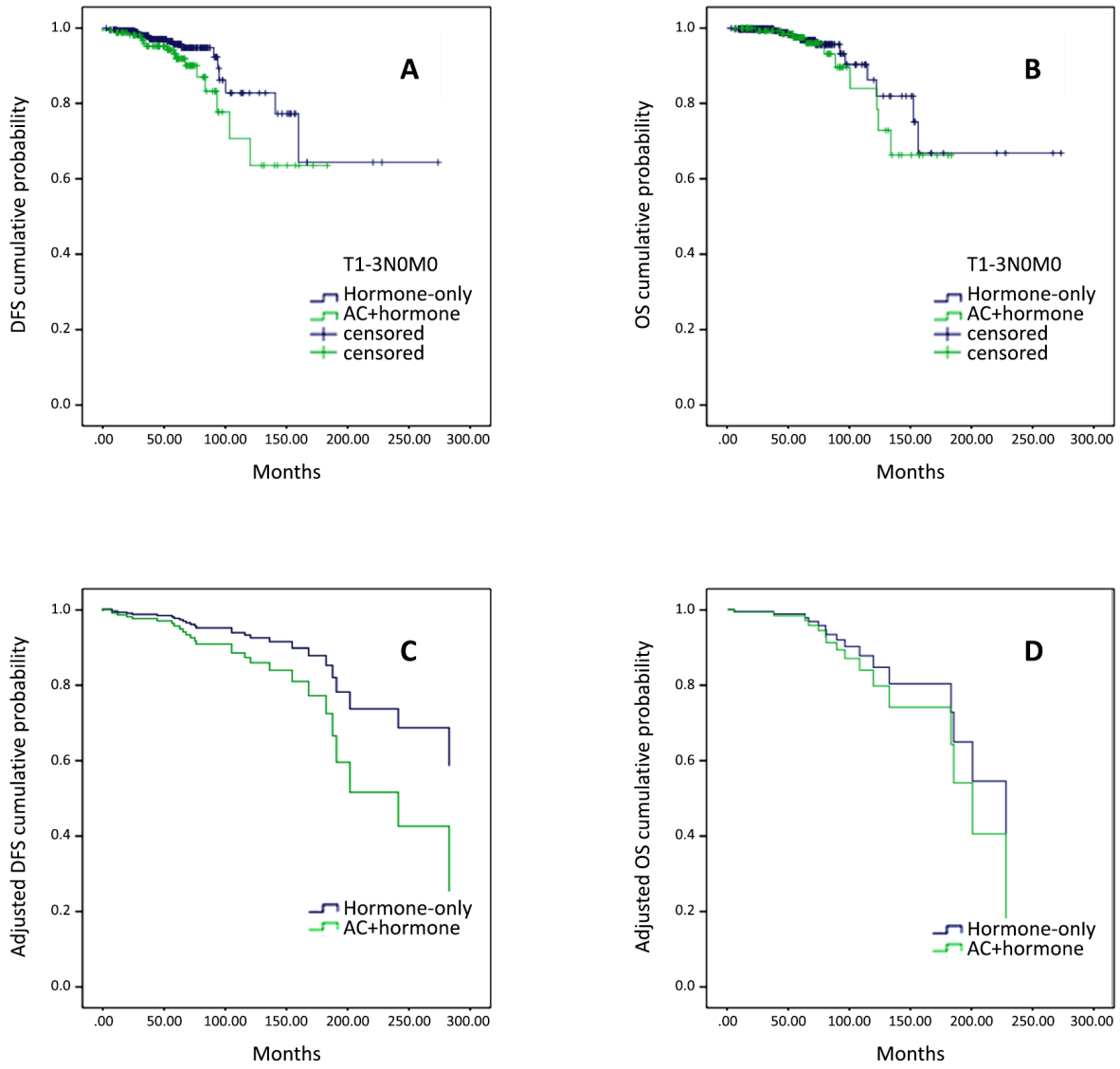

Figure 4. A: DFS plots of adriamycin+ cyclophosphamide +hormone and hormone-only groups in T1-3N0M0 subgroup (p=0.079); **B:** OS plots of adriamycin+ cyclophosphamide +hormone and hormone-only groups in T1-3N0M0 subgroup (p=0.56); **C:** Cox-regression DFS plots of adriamycin+ cyclophosphamide +hormone and hormone-only groups as adjusted for co-variates (p=0.208); **D:** Cox-regression OS plots of adriamycin+ cyclophosphamide +hormone and hormone-only groups as adjusted for co-variates (p=0.658).

patient's prognosis. The most important among them, with respect to tumor recurrence and metastasis, is nodal involvement [20,21]. However, in our sample, we identified no significant influence of either tumor grade or tumor size on disease recurrence or survival. This does not mean that grade and tumor size do not influence prognosis. We especially highlight how, in our population, these two variables failed to affect OS and DFS, especially in T1 and T2 patients.

Our results might be interpreted in light of two facts. First, hormone-positive tumors tend to be less responsive to chemotherapy; therefore, in selected hormone-positive populations, chemotherapy might be detrimental rather than beneficial [7]. Second, after having surgery to resect breast cancer, women can be placed on hormonal therapy immediately. On the other hand, it is generally 4-6 weeks after surgery that chemotherapy is initiated, with hormone therapy typically starting several months after chemotherapy is completed. In hormone-sensitive tumors, this delay prevents patients from the immediate benefits of hormonotherapy. Third, chemotherapy itself may adversely affect survival by disturbing bodily functions in a way that introduces life-threatening situations over the long-term.

In conclusion, in this retrospective analysis of breast cancer patients, we found that combining chemotherapy and hormone therapy was no bet-

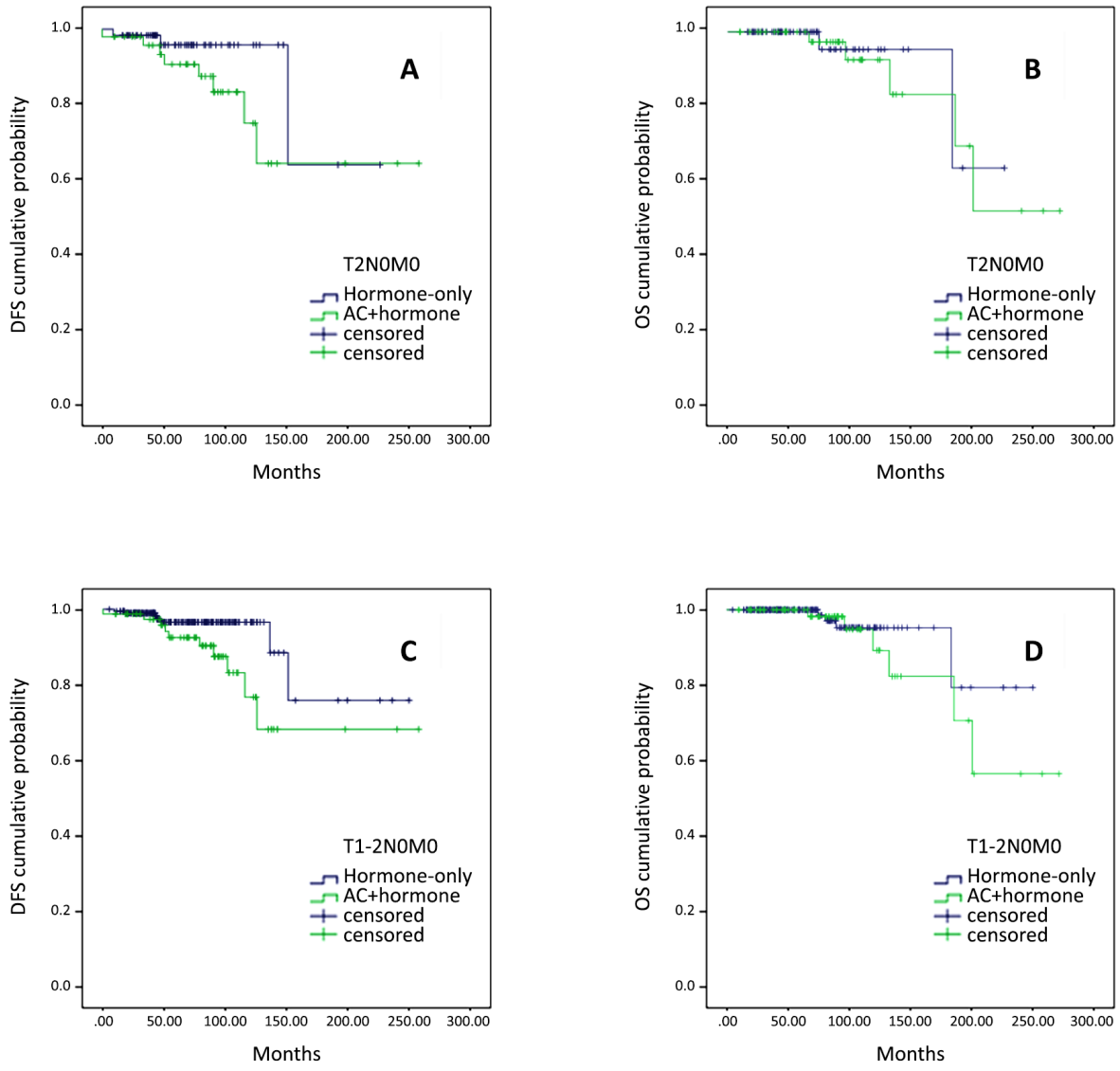

Figure 5. A: DFS plots of adriamycin+cyclophosphamide+hormone and hormone-only groups in grade 2, T2N0M0 subgroup (p=0.16); **B:** OS plots of adriamycin+ cyclophosphamide +hormone and hormone-only groups in grade 2, T2N0M0 subgroup (p=0.78); **C:** DFS plots of adriamycin+ cyclophosphamide +hormone and hormone-only groups in grade 2, T1-T2N0M0 subgroup (p=0.031); **D:** OS plots of adriamycin+ cyclophosphamide +hormone and hormone-only groups in grade 2, T1-T2N0M0 subgroup (p=0.42).

ter than administering hormonotherapy alone in hormone receptor-positive, lymph node-negative, and HER2-negative breast cancer patients with either T1 or T2 disease stage. Indeed, an admittedly non-statistically significant trend was observed favoring hormone therapy alone in terms of both disease recurrence and OS. Second, we found that LVI, tumor grade, menopausal status, and T stage (at least stages T1 and 2) have no impact on DFS or OS in this particular subgroup of patients. Clearly, whether there is any benefit of chemotherapy in T3N0M0, node-negative, hormone-positive and HER2-negative patients must be clarified prospectively in larger sample populations.

References

1. Siegel R, DeSantis C, Virgo K et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012;62:220-241.
2. Ravdin PM, Cronin KA, Howlader N et al. The decrease in breast-cancer incidence in 2003 in the United States. N Engl J Med 2007;356:1670-1674.
3. Berry DA, Cronin KA, Plevritis SK et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353:1784-1792.
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Peto R, Davies C, Godwin J et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 2012;379:432-444.
5. Burstein HJ, Temin S, Anderson H et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. J Clin Oncol 2014;32:2255-69.
6. Fisher B, Dignam J, Wolmark N et al. Tamoxifen and chemotherapy for lymph-node negative estrogen receptor-positive breast cancer. J Natl Cancer Inst 1997;89:1673-1682.
7. Berry DA, Cirrincione C, Henderson IC et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA 2006;295:1658-1667.
8. Paik S, Shak S, Tang G et al. A multigene assay to predict recurrence of tamoxifen-treated, node negative breast cancer. N Engl J Med 2004;351:2817-2826.
9. Sparano JA. TAILORx: Trial Assigning Individualized Options for Treatment (Rx). Clin Breast Cancer 2006;7:347-350.
10. Cardoso F, Van't Veer L, Rutgers E et al. Clinical application of the 70-gene profile: the MINDACT trial. J Clin Oncol 2008; 26:729-735.
11. Edge SB, Byrd DR, Compton CC et al. American Joint Committee on Cancer Staging Manual. New York: Springer, 2010.
12. Harris L, Fritsche H, Mennel R et al. American Society of Clinical Oncology. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol 2007;25:5287-5312.
13. Wolff AC, Hammond ME, Schwartz JN et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007;25:118-145.
14. Henderson IC, Patek AJ. The relationship between prognostic and predictive factors in the management of breast cancer. Breast Cancer Res Treat 1998;52:261-288.
15. Loprinzi CL, Ravdin PM. Decision-making for patients with resectable breast cancer: individualized decisions for and by patients and their physicians. J Natl Compr Canc Netw 2003;1:189-196.
16. Pritchard KI, Shepherd LE, O'Malley FP et al. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. N Engl J Med 2006;354:2103-2111.
17. Pinder SE, Ellis IO, Galea M et al. Pathological prognostic factors in breast cancer. III. Vascular invasion: relationship invasion recurrence and survival in a large study with long-term follow-up. Histopathology 1994;24:41-47.
18. Ejlertsen B, Jensen MB, Rank F et al. Population-based study of peritumoral lymphovascular invasion and outcome among patients with operable breast cancer. J Natl Cancer Inst 2009;101:729-735.
19. Viale G, Giobbie-Hurder A, Gusterson BA et al. Adverse prognostic value of peritumoral vascular invasion: is it abrogated by adequate endocrine adjuvant therapy? Results from two International Breast Cancer Study Group randomized trials of chemoendocrine adjuvant therapy for early breast cancer. Ann Oncol 2010;21:245-254.
20. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer 1989;63:181-187.
21. Rakha EA, El-Sayed ME, Lee AH. Prognostic significance of Nottingham histologic grade in invasive breast carcinoma. J Clin Oncol 2008;26:3153-3158.