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İnvaziv Meme Karsinomunda SOX2 Ekspresyonu ve Uzun Dönem Sağkalım: Retrospektif Bir Kohort Çalışması

SOX2 Expression and Long-Term Survival in Invasive Breast Carcinoma: A Retrospective Cohort Study

Tülay Koç[1*], Şahande Elagöz[2]

[1]Sivas Cumhuriyet University, Department of Pathology, Sivas, Turkey, tkoc@cumhuriyet.edu.tr, ORCID: 0000-0001-8612-0238

[2]Memorial Göztepe Hospital, Department of Pathology, İstanbul, Turkey, selagoz65@gmail.com, ORCID: 0000-0001-5897-5642

ÖZET

Amaç: Sex-determining region Y-box 2 (SOX2), tümör progresyonu ve tedavi direnci ile ilişkili, kök hücre özellikleriyle bağlantılı bir transkripsiyon faktörüdür. Bu çalışmada, invaziv meme karsinomlarında SOX2 ekspresyonunun değerlendirilmesi ve klinikopatolojik parametreler ile uzun dönem sağkalım sonuçlarıyla ilişkisinin araştırılması amaçlandı.

Materyal ve Metot: Bu retrospektif kohort çalışmasına, 2009–2013 yılları arasında invaziv meme karsinomu tanısı alan 100 hasta dahil edildi. SOX2 ekspresyonu immünohistokimyasal olarak değerlendirildi ve negatif veya pozitif olarak sınıflandırıldı. SOX2 ekspresyonu ile klinikopatolojik parametreler arasındaki ilişkiler analiz edildi. Genel sağkalım (OS) ve progresyonsuz sağkalım (PFS), Kaplan-Meier analizi ve log-rank testi kullanılarak değerlendirildi. Tek değişkenli ve çok değişkenli sağkalım analizlerinde Cox orantısal risk regresyon modeli kullanıldı.

Bulgular: SOX2 ekspresyonu 27 (%27,0) tümörde pozitifti. Medyan tümör çapı SOX2-pozitif tümörlerde SOX2-negatif tümörlere göre anlamlı olarak daha büyüktü (35 mm'ye karşı 25 mm; p=0,008). SOX2-pozitif hastalarda OS (log-rank p=0,013) ve PFS (log-rank p=0,014) anlamlı olarak daha kötüydü. Tek değişkenli Cox analizinde SOX2 pozitifliği, ölüm riskinde (HR=2,02; %95 GA: 1,15–3,57; p=0,015) ve progresyon riskinde (HR=2,08; %95 GA: 1,14–3,79; p=0,017) artış ile ilişkiliydi. Bununla birlikte, çok değişkenli analiz sonrasında SOX2, OS veya PFS açısından bağımsız prognostik önemini korumadı.

Tartışma ve Sonuç: SOX2 ekspresyonunun daha büyük tümör çapı ve olumsuz uzun dönem sağkalım sonuçlarıyla ilişkili bulunması, daha agresif bir meme kanseri fenotipi ile ilişkisini desteklemektedir. SOX2, olumsuz biyolojik davranış gösteren invaziv meme karsinomlarının belirlenmesine katkı sağlayabilir; ancak prognostik değeri yerleşik klinikopatolojik faktörlerden bağımsız bulunmamıştır.

Anahtar Kelimeler: Meme kanseri, SOX2, Kanser kök hücreleri, İmmünohistokimya, Prognoz

ABSTRACT

Objective: Sex-determining region Y-box 2 (SOX2) is a stemness-associated transcription factor implicated in tumor progression and treatment resistance. This study aimed to evaluate SOX2 expression in invasive breast carcinoma and investigate its association with clinicopathological parameters and long-term survival outcomes.

Material and Methods: This retrospective cohort study included 100 patients with invasive breast carcinoma diagnosed between 2009 and 2013. SOX2 expression was evaluated immunohistochemically and classified as negative or positive. Associations between SOX2 expression and clinicopathological parameters were analyzed. Overall survival (OS) and progression-free survival (PFS) were assessed using Kaplan-Meier analysis and the log-rank test. Cox proportional hazards regression was used for univariable and multivariable survival analyses.

Results: SOX2 expression was positive in 27 (27.0%) tumors. Median tumor diameter was significantly greater in SOX2-positive than in SOX2-negative tumors (35 vs. 25 mm; p=0.008). SOX2-positive patients had significantly poorer OS (log-rank p=0.013) and PFS (log-rank p=0.014). In univariable Cox analysis, SOX2 positivity was associated with increased hazards of death (HR=2.02; 95% CI: 1.15–3.57; p=0.015) and progression (HR=2.08; 95% CI: 1.14–3.79; p=0.017). However, SOX2 did not retain independent prognostic significance for OS or PFS after multivariable adjustment.

Discussion and Conclusion: SOX2 expression was associated with larger tumors and adverse long-term outcomes, supporting its relationship with a more aggressive breast cancer phenotype. SOX2 may identify invasive breast carcinomas with adverse biological behavior, although its prognostic value was not independent of established clinicopathological factors.

Keywords: Breast cancer, SOX2, Cancer stem cells, Immunohistochemistry, Prognosis

Sorumlu Yazar/Corresponding Author: Tülay Koç, Sivas Cumhuriyet University, Department of Pathology, Sivas, Turkey, tkoc@cumhuriyet.edu.tr, 0000-0001-9676-4045

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INTRODUCTION

Breast cancer (BC) remains the most frequently diagnosed malignancy and the leading cause of cancer-related death among women worldwide (1). Although advances in screening, surgery, and systemic therapy have improved outcomes, a substantial proportion of patients still experience recurrence and die of their disease. Conventional prognostic parameters such as tumor size, histological grade, lymph node status, and hormone receptor and *HER2* status form the basis of current risk stratification, yet they do not fully capture the biological heterogeneity of breast carcinoma, and patients with apparently similar clinicopathological features may follow markedly different clinical courses (2). There is therefore continued interest in molecular markers that may refine prognostic assessment and identify patients at higher risk of adverse outcome.

The cancer stem cell (CSC) hypothesis proposes that tumor growth, metastasis, therapeutic resistance, and relapse are driven by a subpopulation of tumor cells with stem-like properties of self-renewal and multilineage differentiation. In breast cancer, such tumor-initiating cells were first prospectively identified by Al-Hajj et al., and considerable evidence has since implicated stemness-associated transcriptional programs in aggressive tumor behavior (3) . *Sex-determining region Y-box 2 (SOX2)*, a member of the SRY-related high-mobility-group (HMG) box family of transcription factors, is one of the core regulators of pluripotency in embryonic stem cells and is one of the four factors sufficient to reprogram adult somatic cells into induced pluripotent stem cells (4,5). Beyond its physiological role in development, *SOX2* is aberrantly expressed or amplified in a wide range of human malignancies, where it has been linked to proliferation, invasion, maintenance of a stem-like phenotype, and resistance to therapy (6).

In breast carcinoma, *SOX2* is not expressed in normal mammary epithelium but is detected in a subset of invasive tumors and in ductal carcinoma in situ, suggesting an early role in mammary carcinogenesis (7,8). Experimental studies have shown that *SOX2* promotes proliferation, anchorage-independent growth, mammosphere formation, and metastatic capacity of breast cancer cells (9–11) , and that it contributes to resistance to tamoxifen through activation of Wnt signalling in stem/progenitor-like cells (12). Immunohistochemical studies in clinical series have reported *SOX2* positivity in approximately 16% to 30% of invasive breast carcinomas and have variably associated it with larger tumor size, lymph node involvement, higher grade, and the basal-like phenotype (7,8,13,14) . A meta-analysis restricted to breast cancer concluded that *SOX2* expression is associated with adverse clinicopathological features,

and pooled analyses across solid tumors indicate that *SOX2* overexpression is associated with shorter overall and disease-free survival (15–17).

Nevertheless, the independent prognostic value of *SOX2* in breast cancer has not been firmly established. Most studies have been limited by modest sample sizes, heterogeneous scoring criteria, short follow-up, and a paucity of multivariable survival analyses, and their findings have not been entirely consistent(6,15). Long-term survival data are particularly scarce. The aim of the present study was to evaluate the immunohistochemical expression of *SOX2* in a series of invasive breast carcinomas with extended clinical follow-up, to examine its association with established clinicopathological parameters, and to determine whether *SOX2* expression provides prognostic information for overall and progression-free survival, both alone and after adjustment for conventional prognostic factors.

MATERIALS AND METHODS

Study Design and Patient Selection

This retrospective cohort study included 100 patients diagnosed with invasive breast carcinoma at the Department of Pathology, Faculty of Medicine, Cumhuriyet University, Sivas, Türkiye, between 2009-2013. Patients with available formalin-fixed, paraffin-embedded tumor tissue, complete histopathological data, and adequate clinical follow-up were included in the study.

Demographic, clinicopathological, and follow-up data were obtained retrospectively from pathology records and hospital information systems. The variables evaluated included age at diagnosis, tumor size, histological type, histological grade, tumor stage, lymph node status, lymphovascular invasion (LVI), multifocality, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), Ki-67 proliferation index, recurrence, distant metastasis, progression-free survival (PFS), and overall survival (OS).

Ethical approval for this study was obtained from the Cumhuriyet University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Decision No. 09/23, dated September 29, 2014).

Histopathological Evaluation

All cases were reviewed histopathologically using hematoxylin and eosin-stained sections. Histological type, histological grade, tumor size, lymph node involvement, LVI, and other

pathological parameters were recorded. Histological grading was performed according to the Nottingham modification of the Scarff-Bloom-Richardson grading system. Tumor staging was determined according to the TNM classification applicable during the study period.

ER, *PR*, *HER2*, and *Ki-67* results were obtained from the original pathology reports and/or reassessed from available immunohistochemical slides when appropriate.

SOX2 Immunohistochemistry and Evaluation

For immunohistochemical analysis, representative formalin-fixed, paraffin-embedded tumor blocks were selected, and 3-µm-thick sections were prepared. *SOX2* immunohistochemistry was performed using a rabbit monoclonal anti-*SOX2* antibody (clone SP76; Cell Marque, USA) on a Ventana Benchmark XT automated immunohistochemistry staining system. Squamous cell carcinoma of the lung was used as a positive control.

Only nuclear staining in tumor cells was considered specific for *SOX2* expression. *SOX2* immunostaining was independently evaluated by two pathologists who were blinded to the patients' clinical outcomes. The evaluation was performed across the entire tumor section rather than being restricted to hotspot areas.

Both the proportion of positively stained tumor cells and staining intensity were evaluated separately using the Allred scoring system. The proportion score was assigned as follows: 0, no staining; 1, ≤1%; 2, 1–10%; 3, 11–33%; 4, 34–66%; and 5, 67–100% positive tumor cells. Staining intensity was scored as 0, no staining; 1, weak; 2, moderate; and 3, strong. The proportion and intensity scores were summed to obtain a total score ranging from 0 to 8. A total score of 0–1 was considered negative, whereas a total score ≥2 was considered positive for *SOX2* expression. For descriptive purposes, total scores of 2–3, 4–6, and 7–8 were categorized as weak, moderate, and strong expression, respectively.

Follow-up and Survival Outcomes

Overall survival was defined as the interval, in months, from [diagnosis/surgery; specify according to original dataset] to death from any cause or the last documented follow-up for patients who were alive. Patients who were alive at the last follow-up were censored.

Progression-free survival was defined as the interval from [diagnosis/surgery] to documented disease progression/recurrence or the last follow-up without progression. In the dataset, PFS status was coded as 1 for censored observations and 2 for progression events.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 23, IBM Corp., Armonk, NY, USA. Continuous variables were evaluated for distributional characteristics and were presented as appropriate using mean ± standard deviation and/or median values. Comparisons of continuous variables between SOX2-negative and SOX2-positive tumors were performed using the Mann-Whitney U test when appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Survival probabilities were estimated using the Kaplan-Meier method, and survival distributions between SOX2-negative and SOX2-positive groups were compared using the log-rank test. Cox proportional hazards regression analysis was performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for OS and PFS. SOX2 expression was initially evaluated using univariable Cox regression. Multivariable Cox regression models incorporating established clinicopathological prognostic factors were subsequently constructed to determine whether SOX2 provided independent prognostic information.

All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics and SOX2 Expression

A total of 100 patients with invasive breast carcinoma were included in the study. SOX2 immunoreactivity was absent in 73 (73.0%) tumors and present in 27 (27.0%). Among SOX2-positive tumors, two showed weak, 21 moderate, and four strong expression (Figure 1 and 2).

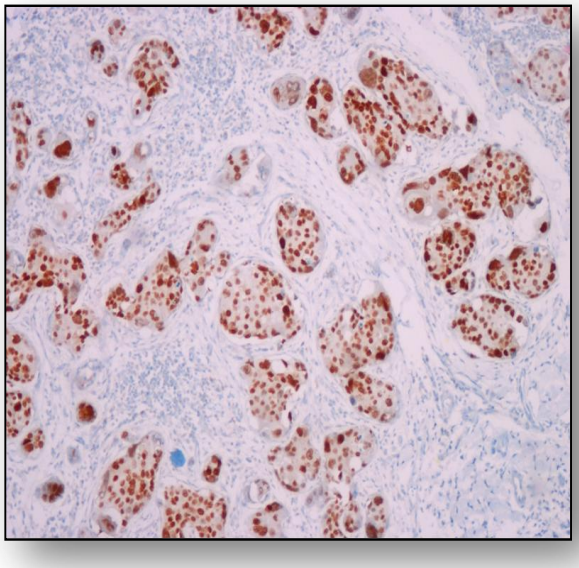

Figure 1. SOX2 positive, strong expression (X200)

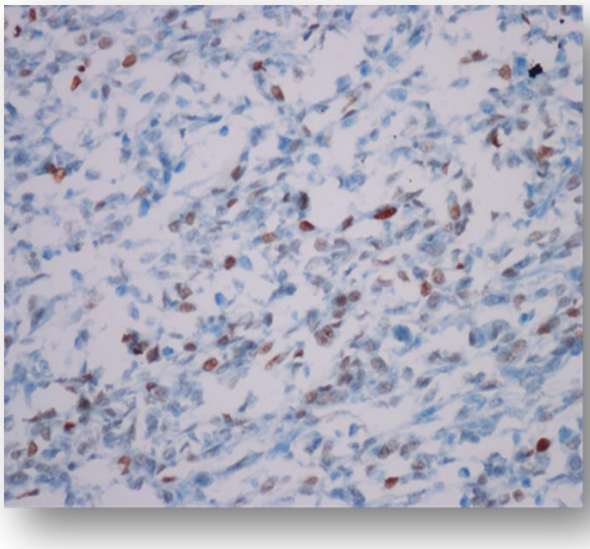

Figure 2. SOX2 positive, weak expression (X200)

SOX2-positive tumors were significantly larger than SOX2-negative tumors. The median tumor diameter was 35 mm in the SOX2-positive group compared with 25 mm in the SOX2-negative group (p=0.008). Mean tumor diameters were 44.1 mm and 32.0 mm, respectively.

No statistically significant associations were identified between SOX2 expression and histological grade (p=0.464), lymph node metastasis (p=0.815), LVI (p=0.653), ER status (p=0.820), PR status (p=0.119), HER2 status (p=0.493), or Ki-67 category (p=0.244). The association between SOX2 expression and tumor stage approached, but did not reach,

conventional statistical significance (p=0.052). A similar trend was observed for recurrence (p=0.083) (Table 1).

Table 1. Association between SOX2 expression and clinicopathological characteristics in patients with invasive breast carcinoma

Clinicopathological characteristic	SOX2-negative (n=73)	SOX2-positive (n=27)	p-value
Age, years, mean ± SD	55.0 ± 12.8	54.3 ± 14.8	0.477
Tumor size, mm, median	25	35	0.008
Tumor size, mm, mean ± SD	32.0 ± 20.5	44.1 ± 27.1	—
Tumor stage, n (%)			0.052
Stage I	18 (24.7)	1 (3.7)	
Stage II	31 (42.5)	12 (44.4)	
Stage III	17 (23.3)	12 (44.4)	
Stage IV	7 (9.6)	2 (7.4)	
Histological grade, n (%)			0.464
Grade 1	12 (16.4)	2 (7.4)	
Grade 2	42 (57.5)	16 (59.3)	
Grade 3	19 (26.0)	9 (33.3)	
Lymph node metastasis, n (%)†			0.815
Negative	31 (44.9)	10 (40.0)	
Positive	38 (55.1)	15 (60.0)	
Not assessed‡	4	2	
Lymphovascular invasion,n(%)			0.653
Negative	40 (54.8)	13 (48.1)	
Positive	33 (45.2)	14 (51.9)	
ER status, n (%)			0.820
Negative	30 (41.1)	10 (37.0)	
Positive	43 (58.9)	17 (63.0)	
PR status, n (%)			0.119
Negative	30 (41.1)	16 (59.3)	
Positive	43 (58.9)	11 (40.7)	
HER2 status, n (%)			0.493
Negative	45 (61.6)	14 (51.9)	
Positive	28 (38.4)	13 (48.1)	
Ki-67 category, n (%)			0.244
Low	25 (34.2)	11 (40.7)	
Intermediate	23 (31.5)	4 (14.8)	
High	25 (34.2)	12 (44.4)	
Recurrence, n (%)			0.083
No	70 (95.9)	23 (85.2)	
Yes	3 (4.1)	4 (14.8)	

SOX2, sex-determining region Y-box 2; SD, standard deviation; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

† Percentages for lymph node metastasis were calculated using only patients with evaluable lymph node specimens (SOX2-negative, n=69; SOX2-positive, n=25; total n=94).
‡ Lymph node status was not assessed in six patients because lymph node specimens were unavailable for histopathological evaluation.

SOX2 Expression and Overall Survival

During long-term follow-up, 53 deaths occurred among the 100 patients. Thirty-four of 73 patients (46.6%) with SOX2-negative tumors and 19 of 27 patients (70.4%) with SOX2-positive tumors died during follow-up .

Kaplan-Meier analysis demonstrated significantly poorer OS among patients with SOX2-positive tumors (log-rank p=0.013). Median OS was 60 months in the SOX2-positive group compared with 200 months in the SOX2-negative group. The estimated 5-year OS rates were 48.1% and 71.2%, respectively, whereas the estimated 10-year OS rates were 33.3% and 63.0%, respectively (Table 2).

In univariable Cox proportional hazards analysis, SOX2 positivity was associated with an approximately twofold increase in the hazard of death compared with SOX2 negativity (HR=2.02, 95% CI: 1.15–3.57; p=0.015).

After adjustment for established clinicopathological parameters in the multivariable Cox model, the magnitude of the association was attenuated. SOX2 positivity remained associated with an increased hazard of death, but the association did not reach conventional statistical significance (HR=1.74, 95% CI: 0.97–3.12; p=0.063). Thus, SOX2 expression was associated with adverse OS in univariable analysis but was not demonstrated to be an independent prognostic factor for OS after adjustment for clinicopathological variables.

Table 2. Long-term survival outcomes according to SOX2 expression

Outcome	SOX2-negative (n=73)	SOX2-positive (n=27)	p-value*
Deaths, n (%)	34 (46.6)	19 (70.4)	—
Median OS, months	200	60	0.013
5-year OS, %	71.2	48.1	
10-year OS, %	63.0	33.3	
Progression events, n (%)	27 (37.0)	18 (66.7)	—
Median PFS, months	Not reached	47	**0.014**
5-year PFS, %	69.9	40.7	
10-year PFS, %	65.7	33.3	

OS, overall survival; PFS, progression-free survival.
*p-values were calculated using the log-rank test.

SOX2 Expression and Progression-Free Survival

A total of 45 progression events occurred during follow-up. Progression was documented in 27 of 73 patients (37.0%) with SOX2-negative tumors and in 18 of 27 patients (66.7%) with SOX2-positive tumors.

Kaplan-Meier analysis demonstrated significantly poorer PFS in the SOX2-positive group (log-rank p=0.014). The estimated 5-year PFS rate was 40.7% among patients with SOX2-positive tumors compared with 69.9% among those with *SOX2*-negative tumors. At 10 years, the corresponding PFS estimates were 33.3% and 65.7%, respectively. Median PFS was 47 months in the *SOX2*-positive group, whereas median PFS was not reached in the *SOX2*-negative group during the observation period (Table 2).

In univariable Cox proportional hazards analysis, *SOX2* positivity was associated with an approximately twofold increased hazard of disease progression compared with *SOX2* negativity (HR=2.08, 95% CI: 1.14–3.79; p=0.017). After multivariable adjustment, *SOX2* expression did not retain independent prognostic significance for PFS (HR=1.36, 95% CI: 0.72–2.55; p=0.340) (Table 3).

Table 3. Cox proportional hazards regression analyses of SOX2 expression for overall and progression-free survival

Survival outcome	Analysis	HR	95% CI	p-value
Overall survival (OS)	Univariable	2.02	1.15–3.57	0.015
	Multivariable	1.74	0.97–3.12	0.063
Progression-free survival (PFS)	Univariable	2.08	1.14–3.79	0.017
	Multivariable	1.36	0.72–2.55	0.340

SOX2, sex-determining region Y-box 2; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

DISCUSSION

Genetic and epigenetic interplay is central to developmental regulation, and its disruption drives carcinogenesis. *SOX2*, a key pluripotency gene, regulates BC biology and processes such as EMT, invasion, and drug resistance (18) . In this retrospective cohort of 100 patients with invasive breast carcinoma followed for a long period, nuclear *SOX2* expression was detected in 27% of tumors and was significantly associated with larger tumor size. Patients with *SOX2*-positive tumors had substantially poorer overall and progression-free survival than those with *SOX2*-negative tumors, with approximately twofold higher hazards of death and progression in univariable analysis. However, these associations were attenuated and lost

conventional statistical significance after adjustment for established clinicopathological prognostic factors, indicating that *SOX2* expression in this series marked a biologically more aggressive tumor phenotype rather than acting as an independent prognostic determinant.

The frequency of *SOX2* positivity observed here (27%) is closely comparable to the 28% reported by Lengerke et al. in 95 early-stage postmenopausal breast carcinomas and lies within the range of 16% to 30% described in other immunohistochemical series (7,8,13,14). Differences among studies are likely attributable to variation in antibodies, scoring thresholds, and case composition, particularly the proportion of basal-like or triple-negative tumors, in which *SOX2* expression was originally described as enriched (7) . The absence of a significant association with *ER, PR, HER2, or Ki-67* status in our cohort suggests that *SOX2* expression is not confined to a single molecular subtype; this is consistent with the findings of Lengerke et al., who similarly observed no relationship between *SOX2* and hormone receptor status or intrinsic subtype , although other authors have reported enrichment in less differentiated and basal-like tumors (7,8,13).

The association between *SOX2* expression and tumor size is one of the most consistently reported findings in the literature. Lengerke et al. found *SOX2* positivity to be significantly related to larger tumor size and to lymph node involvement, and a breast cancer–specific meta-analysis likewise linked *SOX2* to unfavorable clinicopathological features (8,15). Our results reinforce this relationship: median tumor diameter was 35 mm in *SOX2*-positive versus 25 mm in *SOX2*-negative tumors. This observation is biologically plausible, since *SOX2* has been shown to promote proliferation and anchorage-independent growth of breast cancer cells, in part through transcriptional activation of cyclin D1 and modulation of β-catenin signalling (9,10). In contrast to some series, we did not detect a significant association with lymph node metastasis or histological grade, and the associations with tumor stage and recurrence approached but did not reach significance. These borderline findings are compatible with a genuine but modest effect that our sample size was underpowered to confirm.

The most notable finding of this study is the marked difference in long-term outcome between *SOX2*-positive and *SOX2*-negative tumors. Median overall survival was 60 months in the *SOX2*-positive group compared with 200 months in the *SOX2*-negative group, and 10-year overall and progression-free survival rates were roughly half of those observed in *SOX2*-negative patients. These results are in keeping with the broader oncological literature, in which *SOX2* overexpression has been associated with shorter overall survival (pooled HR approximately 1.5 to 1.7) and disease-free survival in meta-analyses across solid tumors

(16,17), and with the reported association between *SOX2* and adverse outcome in breast cancer specifically (11,14,15). The poorer progression-free survival of *SOX2*-positive tumors may reflect the role of *SOX2* in maintaining a treatment-resistant stem-like cell population; experimentally, *SOX2* confers resistance to tamoxifen via Wnt pathway activation, and *SOX2* levels are higher in tumors from patients who fail endocrine therapy (12) .

Importantly, after multivariable adjustment the hazard ratios for *SOX2* decreased (from 2.02 to 1.74 for overall survival and from 2.08 to 1.36 for progression-free survival) and their confidence intervals included unity. The greater attenuation for progression-free survival, together with the persisting strong effect of tumor stage in the adjusted model, suggests that a substantial part of the prognostic information carried by *SOX2* is mediated through its association with tumor size and stage. Thus, in our cohort *SOX2* behaved as a marker of a more advanced and aggressive tumor phenotype rather than as an independent predictor. Similar patterns, in which stem cell markers lose independent significance once conventional parameters are considered, have been described for other CSC-associated proteins in breast cancer, and this pattern underscores the importance of reporting multivariable analyses, which are lacking in many published *SOX2* series (6,15). It should be noted, however, that with 53 deaths and 45 progression events the multivariable models had limited power, and the residual hazard ratio for overall survival (HR 1.74; p=0.063) leaves open the possibility of an independent effect that a larger study might confirm.

Our study has several strengths. The cohort was drawn from a single institution with uniform histopathological review, and SOX2 expression was independently assessed by two pathologists blinded to clinical outcomes using a standardized Allred-based nuclear scoring system across the entire tumor section. Several limitations must also be acknowledged. The retrospective design and the modest sample size, particularly the small number of *SOX2*-positive cases (n=27), limited statistical power, especially for subgroup analyses by molecular subtype and for the multivariable models. Only four tumors showed strong *SOX2* expression, precluding meaningful analysis of expression intensity. Treatment data were not incorporated into the survival models, and treatment heterogeneity over the study period may have influenced outcomes. Immunohistochemical assessment on single sections may not fully reflect intratumoral heterogeneity of *SOX2* expression, and *SOX2* gene amplification status was not evaluated. Finally, the cut-off used to define positivity, although consistent with previous work, has not been prospectively validated.

CONCLUSION

SOX2 was expressed in approximately one quarter of invasive breast carcinomas in this series and was associated with larger tumor size and with significantly poorer long-term overall and progression-free survival. Although *SOX2* did not retain independent prognostic significance after adjustment for conventional clinicopathological factors, its association with an aggressive tumor phenotype and adverse outcome supports its biological relevance in breast cancer. Larger prospective studies with standardized scoring, incorporation of treatment data, and molecular subtype–specific analyses are warranted to clarify whether *SOX2* can contribute to prognostic stratification or represent a therapeutic target, particularly in the context of endocrine resistance.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Ethics Approval and Consent

Ethical approval for this study was obtained from the Cumhuriyet University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Decision No. 09/23, dated September 29, 2014).

Conflict of Interest

No conflict of interest was declared by the authors.

Author Contributions

Concept: T.K., Ş.E.; Design: T.K., Ş.E.; Supervision: Ş.E.; Data Collection and/or Processing: T.K.; Analysis and/or Interpretation: T.K., Ş.E.; Literature Review: T.K.; Manuscript Preparation: T.K.; Critical Review: T.K., Ş.E.

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