

## Research Article

# Prognostic Importance of DUSP22 (Dual Specificity Phosphatase 22) Gene Expression in Low-Grade Lymphomas

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### Abstract

**Objectives:** Dual specificity phosphatase 22 (DUSP22) is a novel phosphatase and has been demonstrated to be a cancer suppressor gene associated with various biological and pathological processes. The aim of this study is to evaluate the prognostic importance of DUSP22 expression in low-grade lymphomas.

**Methods:** Fluorescence in situ hybridization (FISH) was used to detect DUSP22 and 76 cases with indolent lymphoma were evaluated for DUSP22 expression. Thirty-nine had follicular lymphoma (FL), 30 had marginal zone lymphoma (MZL) and 7 had chronic lymphocytic leukemia (CLL).

**Results:** DUSP22 expression was detected in 17 cases (22.3%). The mean overall survival (OS) was found to be longer in cases without DUSP22 compared to cases with DUSP22 expression while event-free survival (EFS) was not different between the cases according to the DUSP22 expression. In univariate analysis, stage (early-stage disease  $p=0.0001$ ), gender (female  $p=0.009$ ) and DUSP22 expression ( $p=0.018$ ) were found to be independent prognostic factors according to Cox regression analysis.

**Conclusion:** There is no sufficient data about the clinical and/or prognostic significance of DUSP22 rearrangement in lymphomas except ALK (-) anaplastic large cell lymphoma. We found that DUSP22 is poor prognostic indicator in cases with low grade lymphomas.

**Keywords:** DUSP22, lymphoma, survival

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Dual specificity phosphatase 22 (DUSP22) is a novel phosphatase and has been demonstrated to be a cancer suppressor gene associated with various biological and pathological processes. Prognostic role of DUSP22 expression in patients with ALK (-) anaplastic large cell lymphoma (ALCL) has been demonstrated but little is known about DUSP22 expression and its prognostic value in other lymphomas.<sup>[1-3]</sup> Here clinical and prognostic

importance of DUSP22 expression has been evaluated in cases with indolent lymphomas and the aim of this study is to detect the prognostic significance of DUSP22 expression in low-grade lymphomas.

### Methods

Eighty-four cases with indolent lymphoma were evaluated for DUSP22 expression. The signal could not be detected in

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**Table 1.** Mean and median overall (OS) and event free survival (EFS) times according to age and stage

	n of Total/Event	Time Mean/Median	p
Age-OS			0.946
18-59	45/13	123.8/164	
60+	31/7	81/-	
Stage-OS			<b>0.005</b>
1+2	29/2	158.2/-	
3+4	47/18	104.8/164	
Age-EFS			0.876
18-59	45/21	87.7/87	
60+	31/12	65/-	
Stage-EFS			<b>0.046</b>
1+2	29/8	94.1/87	
3+4	47/25	79.7/51	

8 cases and 76 cases with indolent lymphoma were evaluated for DUSP22 expression.

Fluorescence in situ hybridization (FISH) was performed 3 mm sections of formalin-fixed, paraffin-embedded tissue. IRF4/DUSP22 (Cytotest, USA) break-apart FISH probe kit was used for rearrangement detection. Slides were analyzed using standard fluorescence microscopy techniques. 100 cell nuclei without overlapping were counted on each slide. The cutoff value for IRF4/DUSP22 was accepted as 15%.

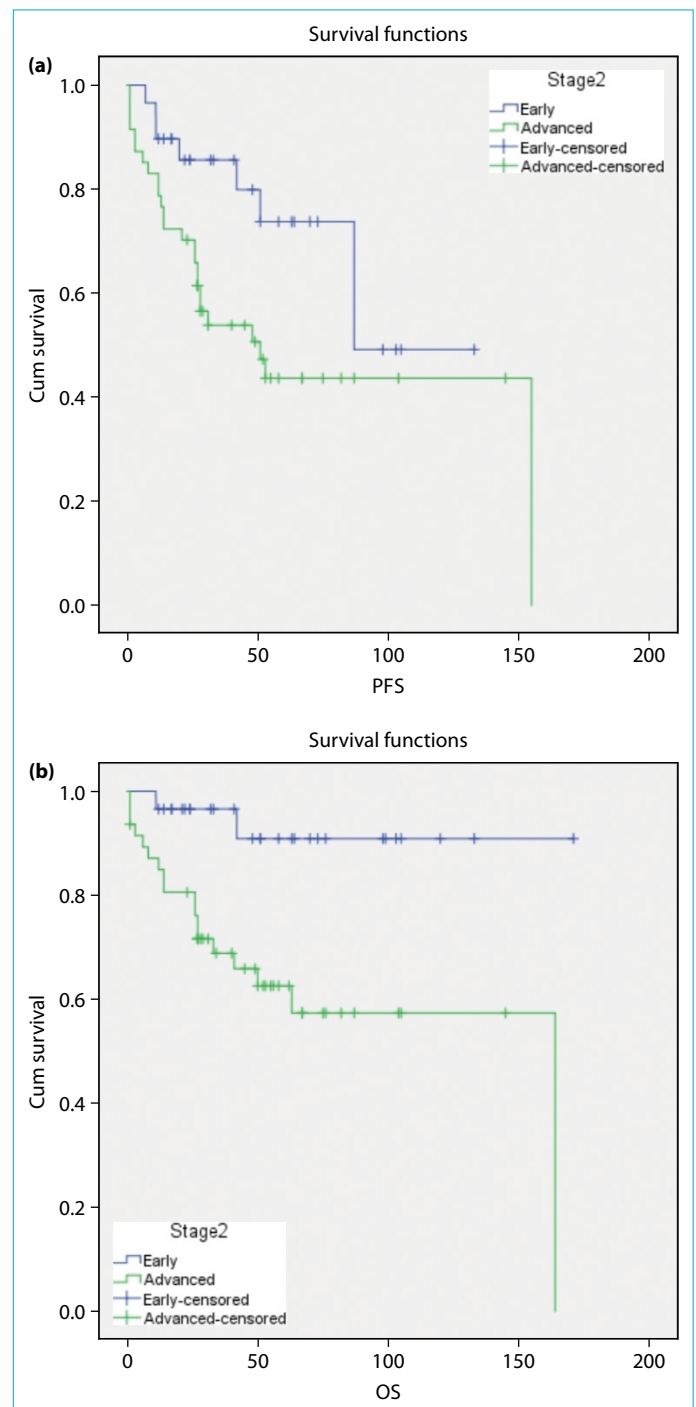
## Results

Female/male ratio was 31/45. Thirty-nine had follicular lymphoma (FL), 30 had marginal zone lymphoma (MZL) and 7 had chronic lymphocytic leukemia (CLL). Among FL, 5 had grade I, 10 cases had grade II, 24 had grade III disease. Among MZL 4 had nodal and 26 had extranodal MZL.

Forty five cases had younger than 60 years, 39 cases had stage 1-2 disease and 37 cases had stage 3-4 disease. OS and EFS were found to be longer in cases with early stage disease but not different in older and younger patients (Table 1).

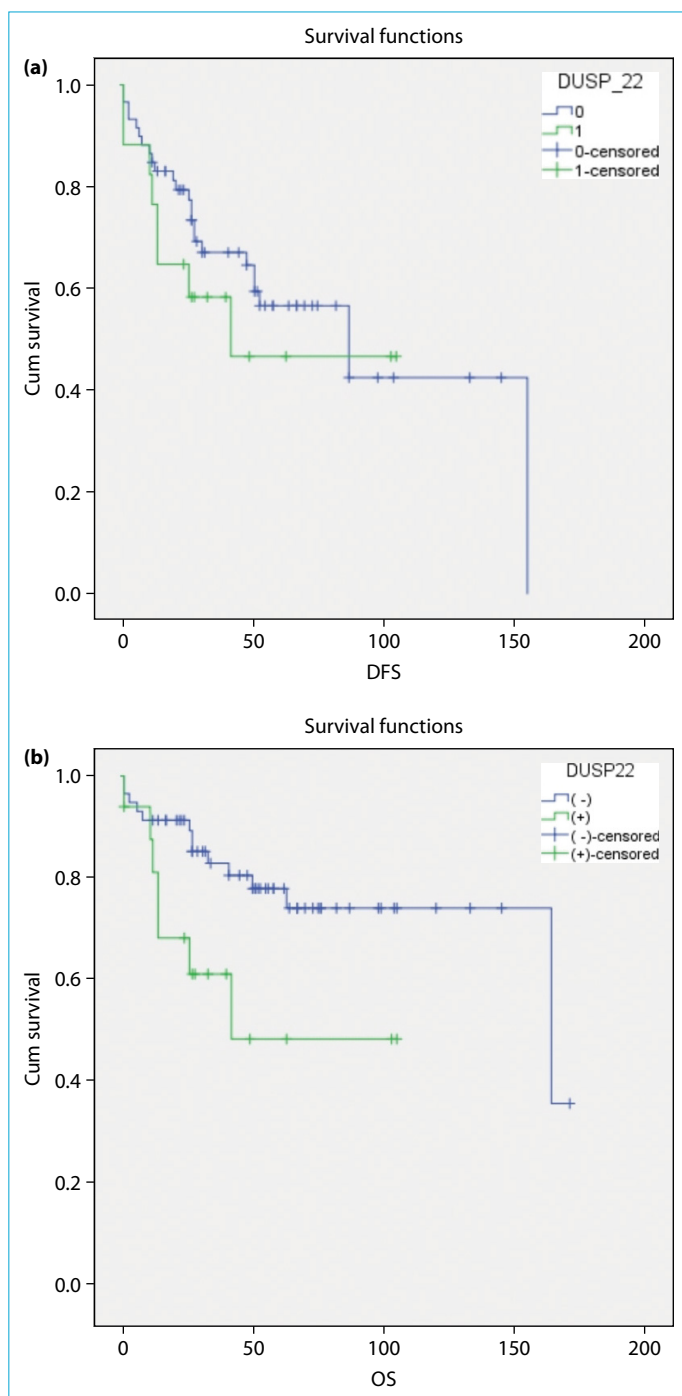
All of the patients were treated by rituximab containing chemotherapy regimens. Complete response was achieved in 42 cases and partial response in 11 cases; 8 cases did not respond to treatment. During this analysis 43 cases were living without disease, 12 cases were living with the disease and 21 cases died.

DUSP22 expression was detected in 17 cases (22.3%): 4 of 31 women and 13 of 45 men. DUSP22 expression was detected 10 of 39 cases with FL, 6 of 30 cases with MZL and 1 of 7 cases with CLL. The mean OS was found to be longer in cases without DUSP22 compared to cases with DUSP22 expression (126 vs 58 months  $p=0.036$ ). However, no significant differences were found between the cases with and



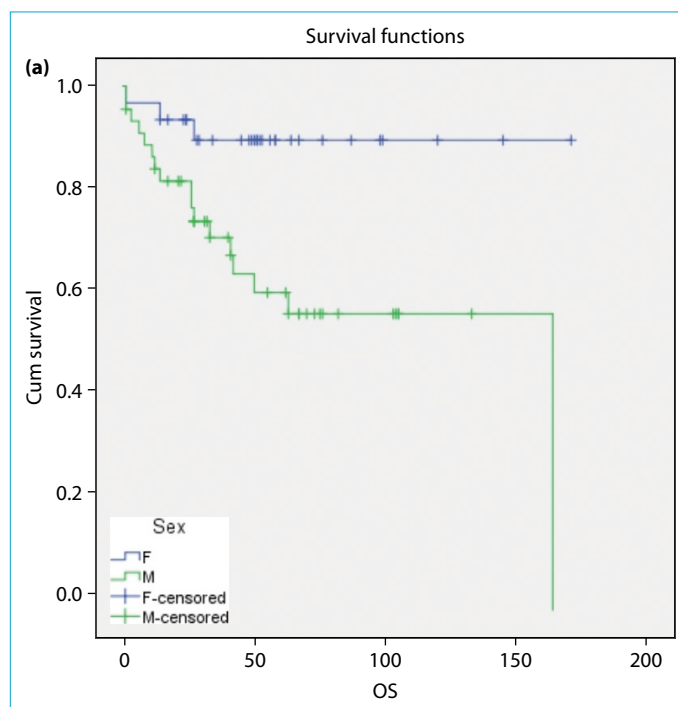
**Figure 1.** (a) Progression free survival curves according to disease stage. (b) Overall survival curves according to disease stage.

without DUSP22 expression according to mean of event-free survival (EFS) (58 vs 82 months  $p=0.717$ ). Figures 1a and 1b show PFS and OS curves according to disease stage. The OS was found to be longer in DUSP22 (-) females than males (157 vs 104 months  $p=0.018$ ) but was not different in females and males with DUSP22 (+) expression (35 vs 56 months  $p=0.827$ ). Figures 2a and 2b show PFS and OS curves according to DUSP22 expression. Figure 3 shows OS



**Figure 2.** (a) Disease free survival curves according to DUSP22 expression. (b) Overall survival curves according to DUSP22 expression.

curves according to sex. PFS and OS were not different according to the subtype of lymphoma. In univariate analysis, overall survival (OS) was found to be longer in cases with early-stage disease ( $p=0.0001$ ) and in females ( $p=0.009$ ). Sex (OR: 3.5, 95% CI: 1.0-12.1,  $p=0.046$ ), stage (OR: 9.97, 95% CI: 1.7-36.7,  $p=0.008$ ) and DUSP22 expression (OR: 3.39, 95% CI: 1.2-9.3,  $p=0.018$ ) were found to be independent prognostic factors according to Cox regression analysis (Table 2).



**Figure 3.** Overall survival curves according to gender.

## Discussion

JNK pathway- associated phosphatase (JKAP), also known as DUSP22 belonging to the low molecular weight atypical DUSP family. DUSP22 is a novel dual specificity phosphatase is extensively expressed in various types of mammalian cells such as T cells, B cells, and NK cells and may be involved in several important biological processes. DUSP22 may activate the Jnk signalling pathway and this activation has been implicated in a number of important physiological processes, from embryonic morphogenesis to cell survival and apoptosis. tumor development, cardiac hypertrophy, ischemia/reperfusion injury, diabetes, hyperglycemia-induced apoptosis and several neurodegenerative disorders.<sup>[4-8]</sup> When DUSP22 is expressed in Jurkat T cells, it suppresses T cell antigen receptor-induced activation of Erk2, but DUSP22 expression in B-cells needs to be further investigated. On the other hand mitogen-activated protein kinases (MAPKs) are also involved in a variety of intracellular events including gene expression, cell proliferation, and programmed cell death.

DUSP22 is selectively associated with apoptosis signal-regulating kinase 1 (ASK1), MAPK kinase 7 (MKK7), and JNK1/2. DUSP22 has also reported to regulate MAPK signal transduction. The effect of DUSP22 on MAPKs, however, is controversial since there have been several conflicting reports regarding its substrate specificity. One report showed that DUSP22 dephosphorylates ERK2 in vitro while other studies showed that DUSP22 enhances JNK activation but not

**Table 2.** Results of Cox regression analysis

	B	SE	Wald	df	p	OR	95.0% CI for OR	
							Lower	Upper
Sex	1.255	0.630	3.972	1	<b>0.046</b>	3.508	1.021	12.052
Age	-0.234	0.486	0.231	1	0.631	0.792	0.305	2.053
DUSP_22	1.221	0.514	5.645	1	<b>0.018</b>	3.390	1.238	9.278
Stage 2	2.076	0.780	7.088	1	<b>0.008</b>	7.975	1.729	36.774

df: Degrees of freedom; B: Beta coefficient; SE: Standart error; DUSP\_22: Dual Specificity Phosphatase 22; CI: Confidence interval; OR: Odd ratios.

p38 and ERK2.<sup>[4, 9, 10]</sup> Little is known about the functional roles of DUSP22 and the underlying mechanisms. Therefore, further studies are required to clarify the physiological role of DUSP22.

DUSP22 selectively upregulates JNK phosphorylation levels DUSP22 appears to play a role in the regulation of MAPK signaling.<sup>[11]</sup> DUSP22 also has been demonstrated to be a cancer suppressor gene associated with numerous biological and pathological processes.<sup>[10, 12]</sup>

The importance and prognostic role of DUSP22 has been studied most commonly in cases with peripheral T cell lymphomas (PTCL). The silencing of DUSP22 in PTCL with 6p25.3 rearrangements pointed out this gene as a candidate tumor suppressor whose inactivation may contribute to the pathogenesis of PTCL subtypes, notably ALCL (essentially cutaneous) and T-MF.<sup>[1, 2, 13-17]</sup> Recent studies have shown that 30% of ALK (-) ALCL have chromosomal rearrangements for DUSP22 and 8% have chromosomal rearrangements for TP63. These rearrangements are mutually exclusive of each other and are absent in ALK-positive ALCLs.<sup>[2]</sup> Furthermore, DUSP22 rearranged cases have favorable outcomes similar to ALK-positive ALCL. The most commonly detected DUSP22 rearrangements are seen 28% of cases of primary cutaneous ALCL and 30% of systemic ALK (-) ALCL which may secondarily involve the skin. Molecular studies have identified DUSP22 rearranged ALK (-) ALCL as having a prognosis similar to ALK (+) ALCL. Regarding treatment, ALK (+) ALCL is generally responsive to doxorubicin-containing regimens.<sup>[2]</sup>

DUSP22 rearrangement has been evaluated for the prognostic importance in biopsy specimens of 138 patients with nodal PTCLs in Danish cohort. Twenty seven of these 138 cases had ALK (-) disease and 5 (19%) had DUSP22 rearrangements. In this study it has been reported that patients with DUSP22-rearranged ALK (-) ALCL had a similar OS to that of ALK (+) cases. Interestingly all of these 5 ALK (+) patients achieved complete remission.<sup>[3]</sup> In another study it has been shown better outcome in ALK (-) cases showing DUSP22 expression have unique subset: morphologically monomorphic and lacking cytotoxic granules.<sup>[18]</sup>

DUSP22 rearrangement has been studied in limited number of the cases with solid tumor. In a study covering 92 cases with colorectal cancer it has been studied prognostic significance of DUSP22 expression by QuantiGenePlex assay. DUSP22 mRNA has been found to be reduced in primary colorectal cancer tissues, compared to the adjacent normal tissues. Low expression of DUSP22 in cancer has been found to be correlated with significantly with large tumor size but not other tumor characteristics including histopathological type, tumor invasion, lymph node metastases, TNM stage, and Duke's stage and also overall survival. However interestingly, low expression level of DUSP22 in stage IV patients has been found to be correlated with poor survival outcome.<sup>[19]</sup>

We found poor outcome in cases with low grade lymphomas showing DUSP22 expression. Although DUSP22 expression was found to be related with shorter OS but EFS was not found to be different according to the DUSP22 expression. This may be due to the retrospective nature of the study and absence of periodic imaging. Our study group was low grade lymphoma and there may be progression without clinical symptom; so we could not detect the real progression time. However we found that DUSP22 is an independent poor risk factor together with male sex and advanced stage disease in univariate analysis. This is an interesting finding and must be validated with further studies.

In conclusion little is known about the functional role and expression of DUSP22 in malignant tumors, except favorable prognostic role in ALK (-) ALCL. The silencing of DUSP22 in PTCLs especially in ALK (-) anaplastic large cell lymphoma suggests that this gene is a candidate tumor suppressor gene and its inactivation may contribute to the pathogenesis of PTCL subtypes. There is no sufficient data about the clinical and/or prognostic significance of DUSP22 rearrangement in other lymphomas. We found a poor prognosis in cases with DUSP22 expression in low grade B cell lymphomas. How can we define this controversy? It is known that DUSP22 regulates MAPK signal transduction but the effect of DUSP22 on MAPKs is controversial. Since there have been several conflicting reports regarding its substrate specificity: there is controversial reports about

this matter: while one report showing the DUSP22 dephosphorylation on ERK2 in vitro, while other showing the DUSP22 enhancing effect on JNK activation but not p38 and ERK2. Therefore, further studies are required to clarify the physiological role of DUSP22. We found poor overall survival in cases with DUSP22 expression and we need further studies about the prognostic significance of DUSP22 expression in indolent lymphomas.

### Disclosures

**Ethics Committee Approval:** The Cukurova University Clinical Research Ethics Committee granted approval for this study (Date: 10.6.2016, Number: 54).

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**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – S.P., E.K.B., M.E., G.S., M.B.; Design – S.P., E.K.B., M.E., G.S., M.B.; Supervision – S.P., E.K.B., M.E.; Data collection &/or processing – G.S., M.B.; Analysis and/or interpretation – S.P., M.E., G.S., M.B.; Literature search – S.P., E.K.B., M.E., G.S., M.B.; Writing – M.E., G.S., M.B.; Critical review – S.P., E.K.B., M.E., G.S., M.B.

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