

STAT3 is associated with recurrence-free survival in papillary thyroid carcinoma

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Introduction

STAT3 (signal transducer and activator of transcription 3) is a signaling molecule that functions downstream of various cytokine and growth factor receptor signaling pathways to regulate cell growth, survival, and differentiation^{1,2}. Constitutive activation of this pathway is relevant to cancer development and unfavorable prognosis in many types of malignancy. Previous studies on the role of STAT3 in thyroid cancer have yielded conflicting results; it was identified as a negative regulator of tumor growth³, and on the other hand, as a positive regulator⁴. In this study, the relationship between STAT3 activity and prognosis in papillary thyroid carcinoma (PTC) using immunohistochemistry with an anti-STAT3 antibody was retrospectively examined.

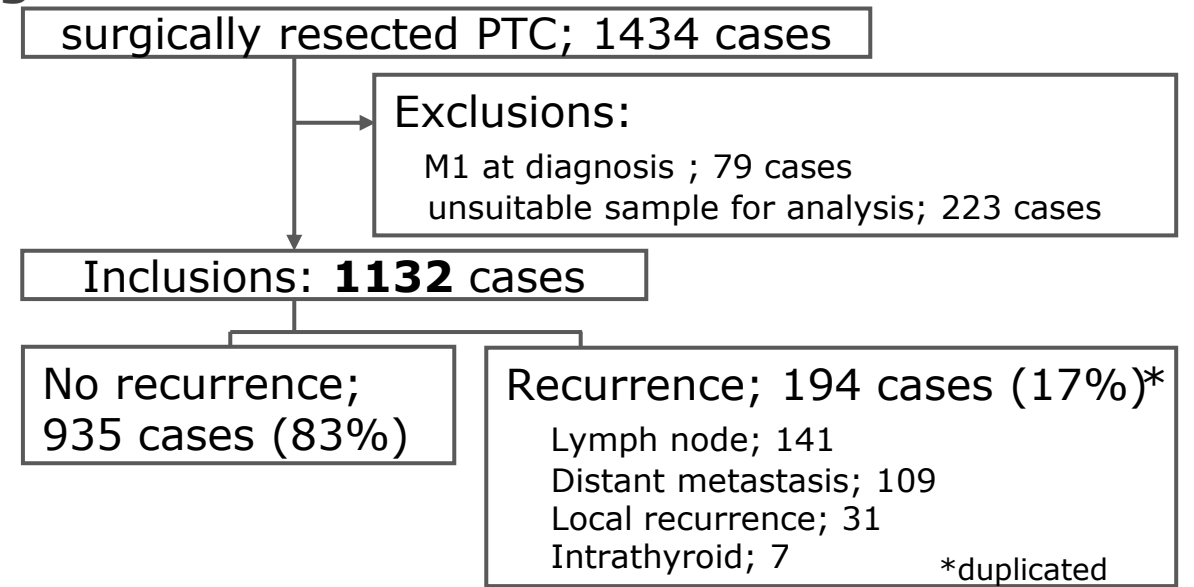
Materials and methods

Pathologically evaluated 1132 PTC cases with M0 diagnosed between 1993 and 2012 were included.
 <<IHC>> · Tissue Microarray of 1mm in diameter
 · STAT3 (124H6) 1:300 (Cell Signaling Tech.)

The scoring focused on nuclear STAT3 (n-STAT3), which represents the activated form of STAT3. The expression of n-STAT3 of primary thyroid carcinoma was determined using the H-score.

The relationship between n-STAT3 staining intensity and recurrence-free survival (RFS) was examined.

Figure 1. Recruitment of cases.



Results

Figure 2. Representative images of n-STAT 3 staining intensity by H score.

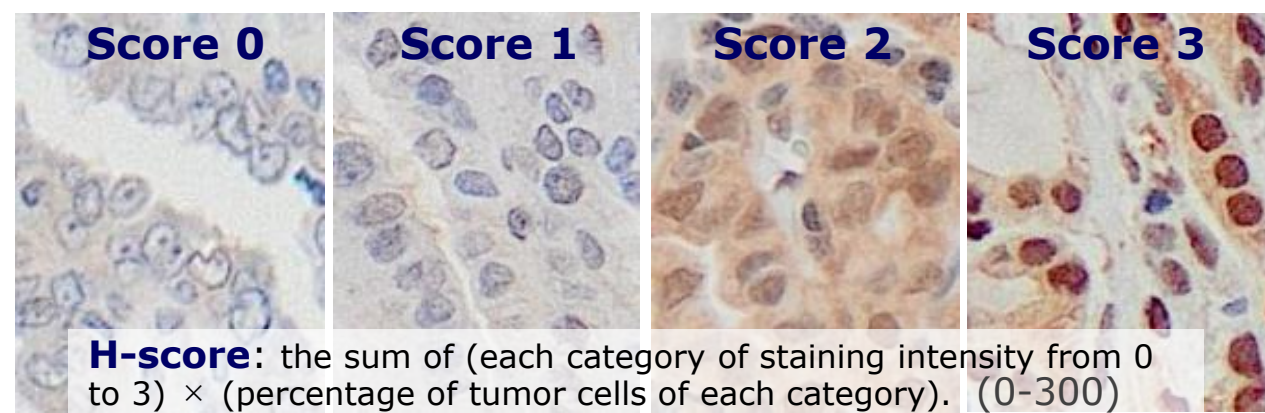


Figure 4. H-score distribution of STAT3 by recurrence.

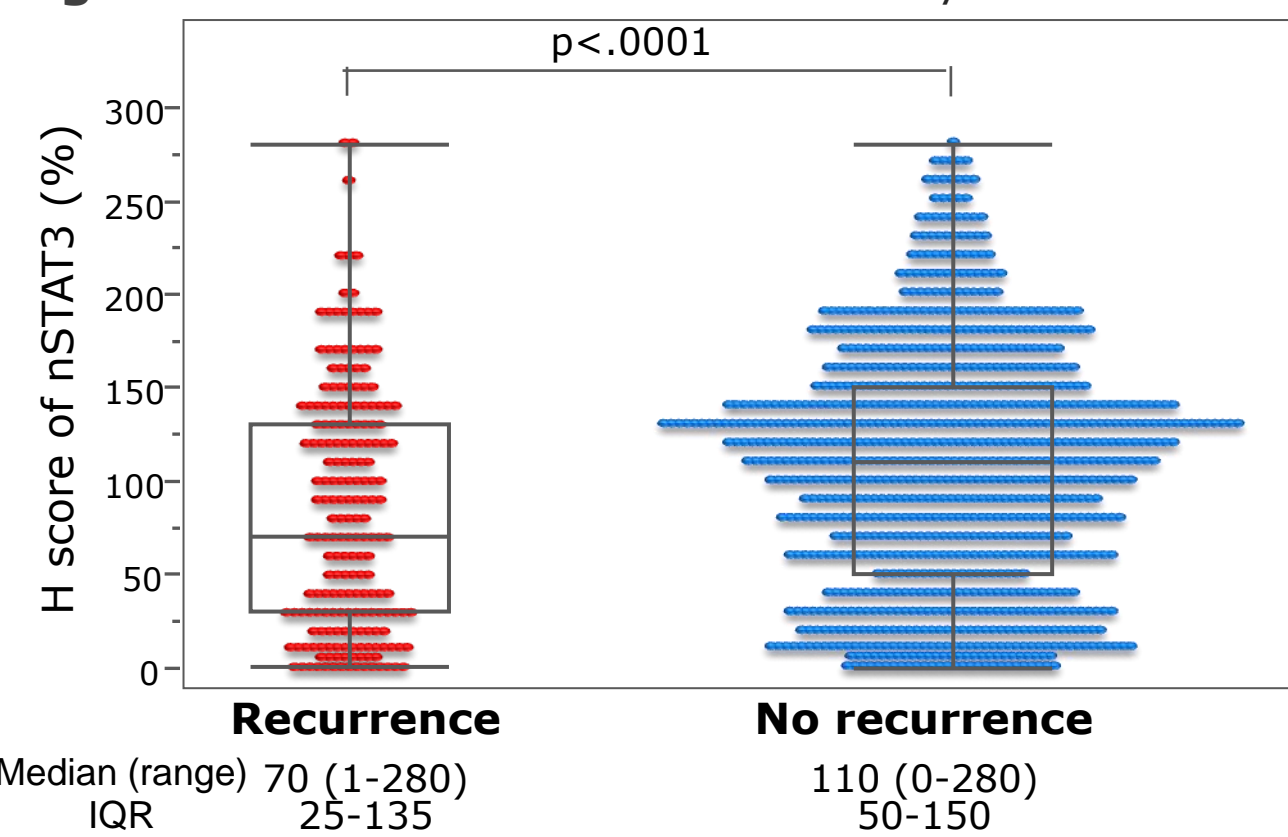


Figure 3. Receiver Operating Characteristic (ROC) Curve Analysis.

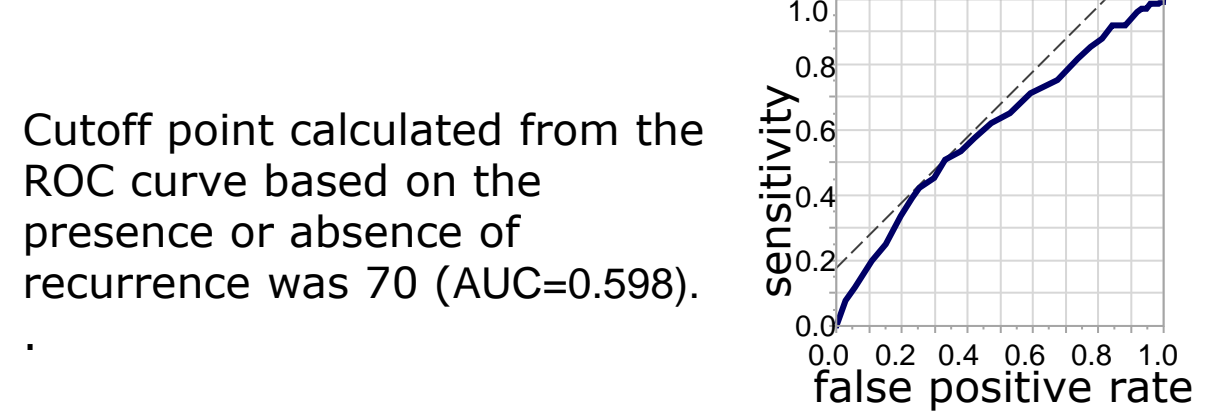


Table 1. Correlation between the clinicopathological features and the expressions of n-STAT3.

	All N=1132	n-STAT3 expression		p-value
		High N=813	Low N=398	
Age, ≥55 y.o	555 (49%)	386 (51%)	169 (46%)	0.1307
Sex, Male	248 (22%)	165 (22%)	83 (22%)	0.7407
Tumor size, ≥40mm	148 (13%)	86 (11%)	62 (17%)	0.0097
Ex, present	584 (52%)	384 (50%)	200 (54%)	0.2216
LNM, N1b	344 (30%)	213 (27%)	131 (35%)	0.0093
Max size of LNM, ≥3cm	112 (10%)	67 (28%)	45 (34%)	0.2730
Number of LNM, ≥5	284 (25%)	209 (27%)	130 (35%)	0.0070

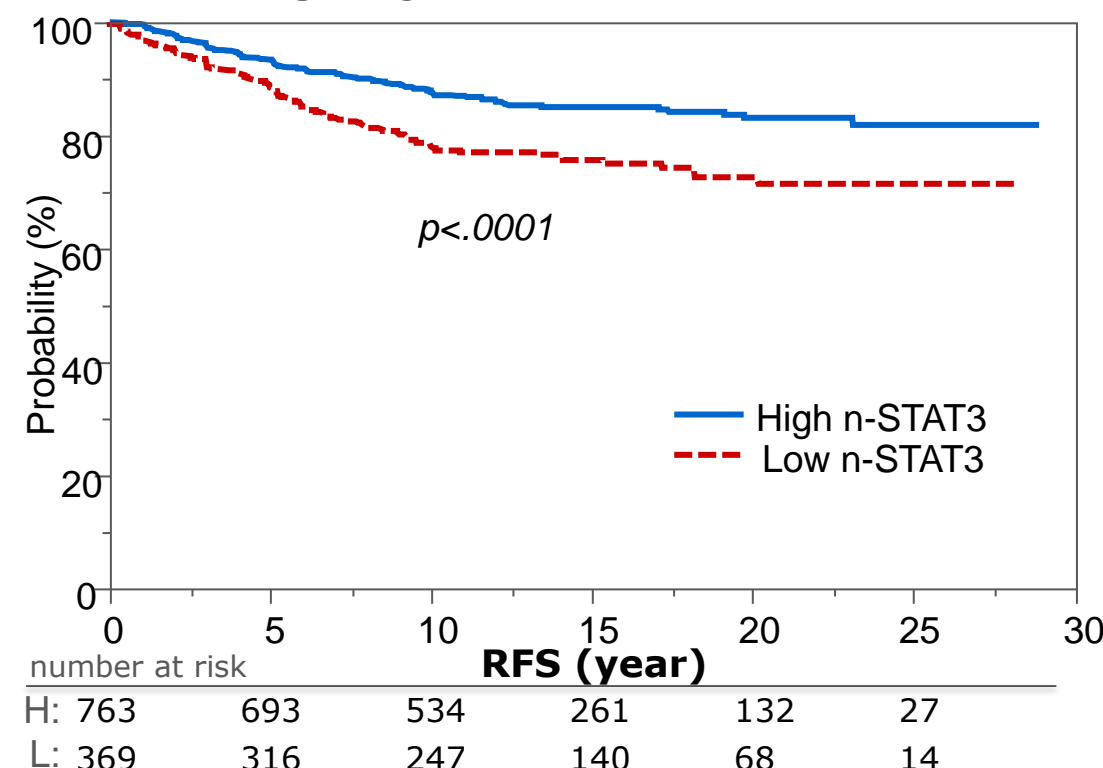
Ex: Extrathyroidal extension
LNM: lymph node metastasis

Table 2. Univariate and multivariate logistic regression analyses for RFS in the patients.

factors	univariate			multivariate		
	HR	95%CI	p-value	HR	95%CI	p-value
age, ≥55	3.11	2.29-4.28	<0.0001	3.98	2.62-6.15	<0.0001
Sex, male	1.70	1.24-2.30	0.0007	1.07	0.72-1.58	0.7303
Tumor size, ≥4cm	3.35	2.44-4.55	<0.0001	2.13	1.39-3.20	0.0004
Ex, present	3.93	2.82-5.60	<0.0001	2.60	1.49-4.86	0.0014
N1b, present	3.00	2.27-3.99	<0.0001	1.53	0.83-3.12	0.2030
Max size of LNM, >30mm	2.38	1.63-3.46	<0.0001	1.76	1.19-2.62	0.0048
Number of LNM, ≥5	2.33	1.76-3.09	<0.0001	1.20	0.76-1.95	0.4400
n-STAT3*, ≥70	0.56	0.42-0.74	<0.0001	0.66	0.45-0.97	0.0320

*: H score of STAT3

Figure 5. RFS according to the expression of n-STAT3.



Conclusion

Nuclear STAT3 staining intensity in PTC was associated with better prognosis, as measured by RFS in our study. Further studies are needed to investigate how STAT3 contributes to the favorable prognosis of thyroid cancer.

¹Nat Rev Cancer. 2019 Feb;19(2):82-96.
²Cancers (Basel). 2014 Mar 6;6(1):526-44.

³Proc. Natl. Acad. Sci. USA 2012, 109, E2361-E2370
⁴Int J Clin Exp Pathol. 2011 Apr;4(4):356-62.