



BACKGROUND

Alterations in the **tumor suppressor genes** (TSG) *RB1*, *PTEN* and *TP53* are associated with decreased survival and aggressive variants of prostate cancer (AVPC).

We previously developed and validated a signature of **low expression of TSG** (TSG_{low}) associated with poor outcomes in mHSPC patients treated with androgen deprivation therapy (ADT) +/- docetaxel

OBJECTIVE

The aim of the present study was to assessed **TSG signature in mHSPC patients treated with androgen receptor pathway inhibitors (ARPI)** and explore clinical characteristics at progression

PATIENTS AND METHODS

- Multicenter retrospective study of mHSPC patients treated with ADT + ARPI

- TSG (*RB1*, *TP53*, *PTEN*) expression was assessed by nCounter

- TSG_{low} was considered when ≥ 2 out of 3 TSG presented low expression of a previously established cut-off, TSG_{wt} in the remaining cases

- TSG expression was correlated with castration resistance-free survival (CRPC-FS) by Kaplan Meier and Cox analysis.

- The presence of AVPC criteria at CRPC progression was analyzed according TSG status in mHSPC samples.

REFERENCES

1. Aparicio *Clinical Cancer Research* 2011
2. Jimenez *Eur Urol Oncol* 2024

Tumor suppressor gene signature based on *RB1*, *PTEN* and *TP53* predicts early progression in metastatic hormone-sensitive prostate cancer (mHSPC) patients

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RESULTS

BASELINE CHARACTERISTICS

137 patients were included with a median follow-up of 30.7m (2.7-91m). Baseline characteristics are summarized in **Table 1**

	All patients	TSG_{low}	TSG_{wt}	P-value
Patients, N (%)	137	23 (16.8)	114 (83.2)	
Age (years)				
Median (range)	71.8 (50.1 - 82.8)	71.1 (55 - 82.6)	72.4 (50.1 - 93)	0.888
PSA at diagnosis (ng/ml)				
Median (range)	30 (1.8 - 4600)	16 (3.1 - 4600)	33 (1.8 - 3226)	0.542
ECOG performance status score, N (%)				
0	42 (30.7)	6 (26.1)	36 (31.6)	0.004
1 or 2	82 (59.9)	17 (73.9)	65 (57)	
NA	13 (9.5)	-	13 (11.4)	
Stage at diagnosis, N (%)				
<IV	28 (20.4)	3 (13)	25 (21.9)	0.406
IV	106 (77.4)	20 (87)	86 (75.4)	
NA	3 (2.2)	-	3 (2.6)	
Gleason sum at diagnosis, N (%)				
≤ 7	31 (22.6)	1 (4.3)	30 (26.3)	0.028
≥ 8	103 (75.2)	21 (91.3)	82 (71.9)	
NA	3 (2.2)	1 (4.3)	2 (1.8)	
Presence of visceral metastases, N (%)				
Yes	22 (16.1)	8 (34.8)	14 (12.1)	0.013
No	115 (83.9)	15 (65.2)	100 (87.7)	
Disease volume, N (%)				
High	73 (53.3)	16 (69.6)	57 (50)	0.11
Low	64 (46.7)	7 (30.4)	57 (50)	
Risk, N (%)				
High	61 (44.5)	15 (65.2)	46 (40.4)	0.038
Low	76 (55.5)	8 (34.8)	68 (59.6)	

Table 1: Baseline characteristics

16.8% of patients were classified as TSG_{low}

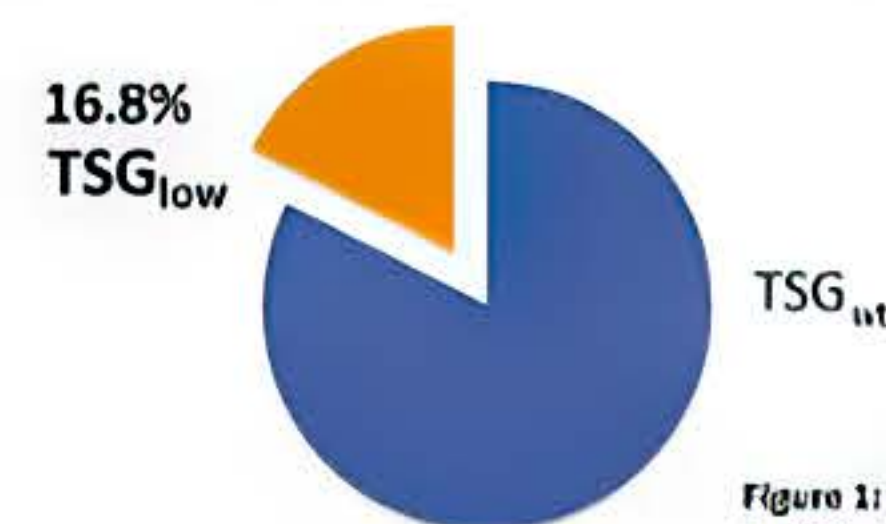


Figure 1: Piechart of patients according to TSG signature

CLINICAL OUTCOMES

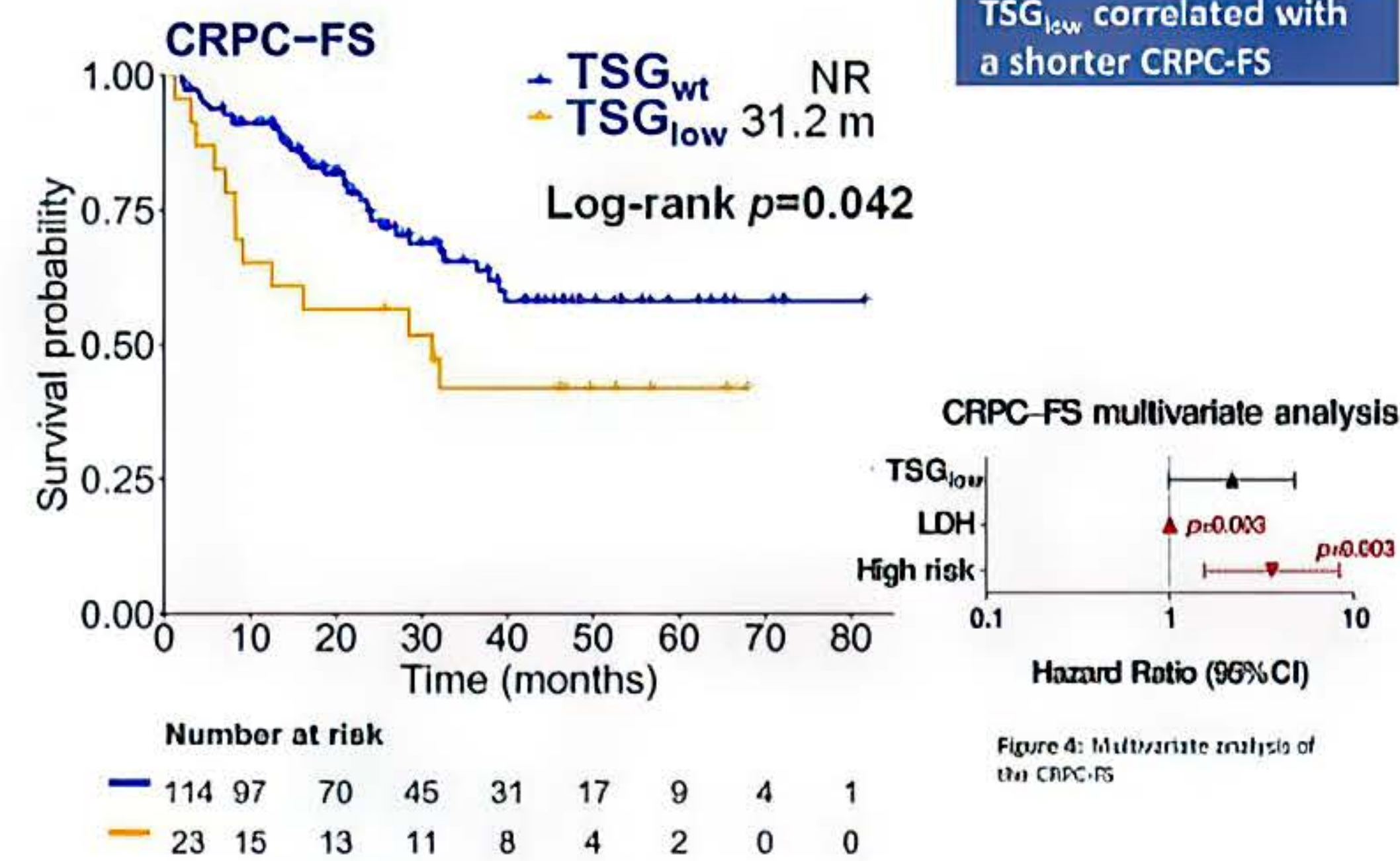


Figure 2A: Kaplan-Meier curves showing the CRPC-FS according to the TSG signature

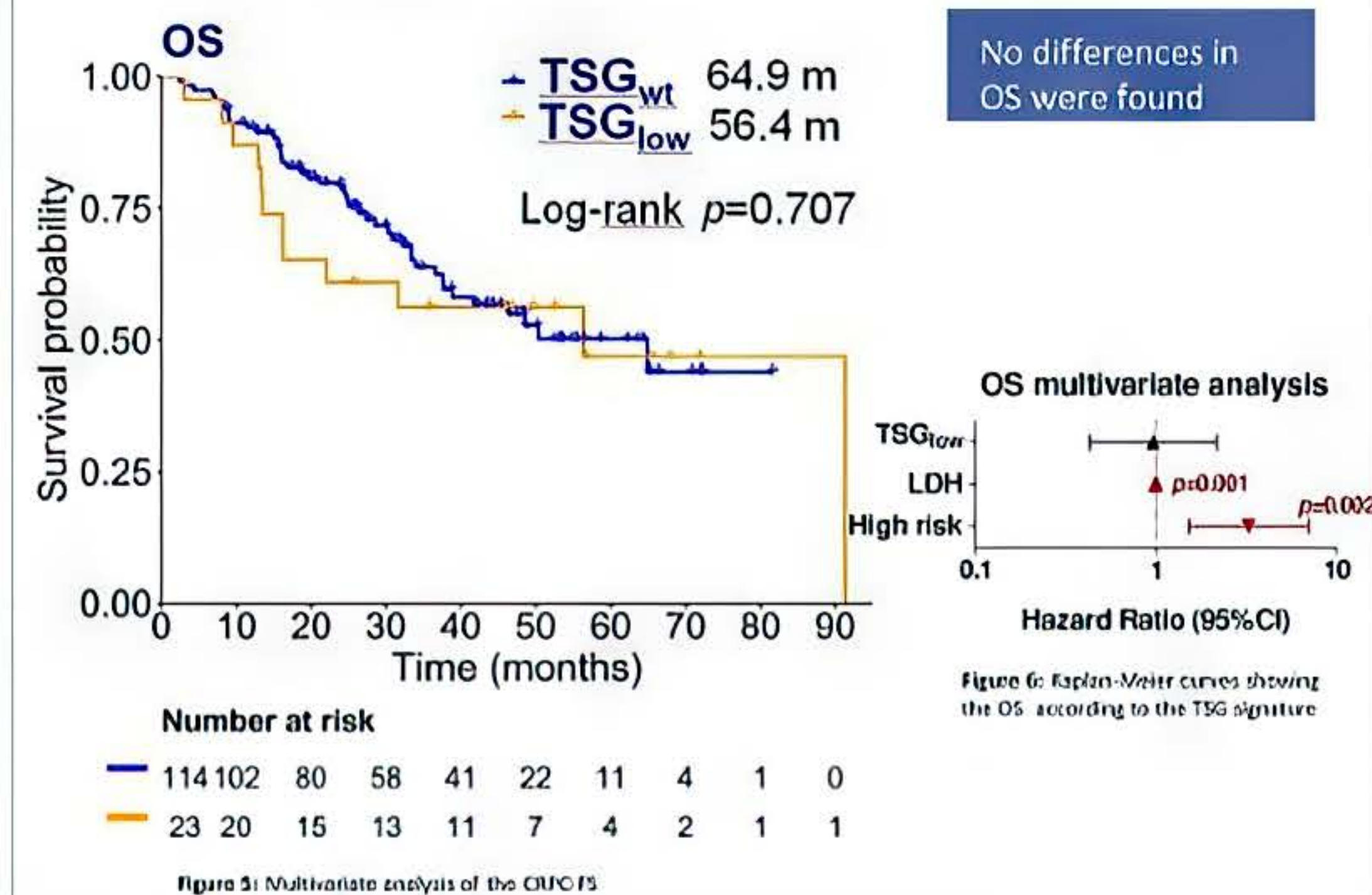


Figure 3: Multivariate analysis of the CRPC-FS

CONCLUSIONS

TSG_{low} expression is associated with early CRPC progression in mHSPC patients treated with ARPI and could help to predict the **development of AVPC**. This supports the development of new therapeutic strategies in this patients.

TSG & AGGRESSIVE PROSTATE CANCER

Among the 48 patients that developed CRPC, 42 had available clinical data. Patients with TSG_{low} tumors presented **higher frequency of AVPC**

	All patients	TSG_{low}	TSG_{wt}	p-value
Patients, N (%)	42	9 (21.9)	32 (78.1)	
AVPC criteria, N (%)	13 (30.9)	6 (66.7)	6 (18.7)	0.01
Visceral metastasis only, N (%)	3 (7.1)	2 (22.2)	1 (3.1)	0.11
Lytic bone metastasis, N (%)	5 (11.9)	2 (22.2)	3 (9.4)	0.28
Bulky nodes or prostate mass, N (%)	7 (16.7)	4 (44.4)	3 (9.4)	0.024
Low PSA, N (%)	4 (9.5)	2 (22.2)	2 (6.2)	0.13
Neuroendocrine markers + high LDH/CEA, N (%)	5 (11.9)	1 (11.1)	4 (12.5)	0.43
Primary castration resistance, N (%)	3 (7.1)	1 (11.1)	2 (6.2)	0.53
Small cell morphology, N (%)	4 (9.5)	1 (11.1)	3 (9.4)	0.7

Table 2: AVPC characteristics at CRPC progression according to TSG signature

AVPC ACCORDING TO TSG EXPRESSION

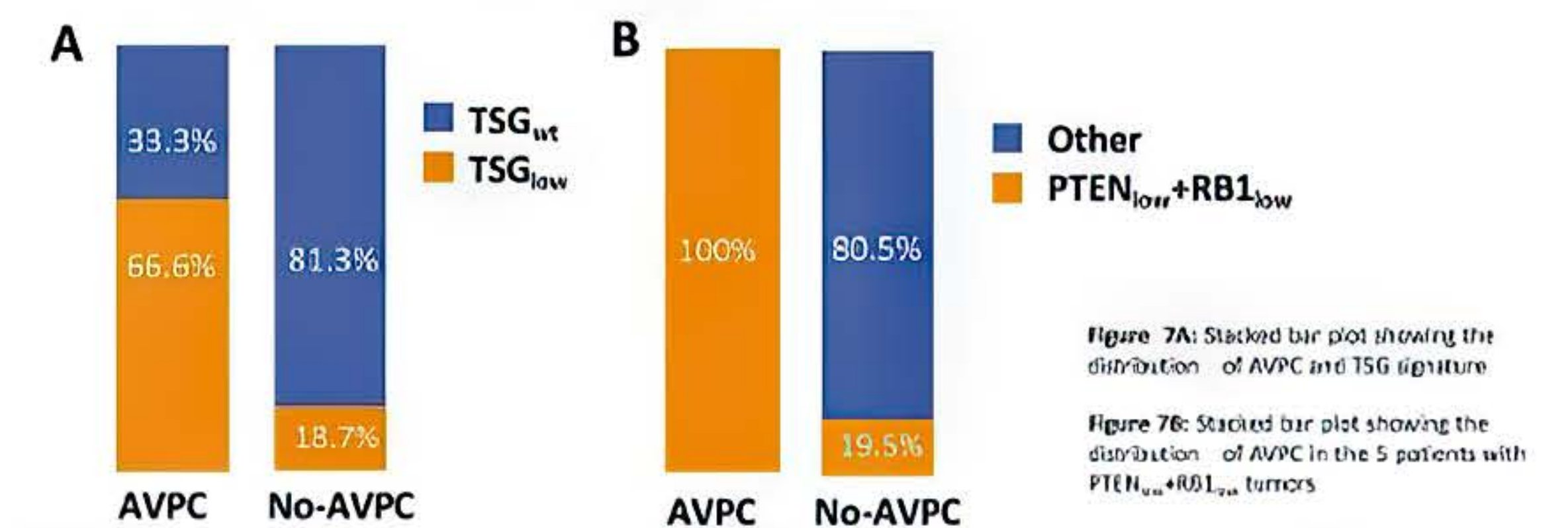


Figure 7A: Stacked bar plot showing the distribution of AVPC and TSG signature

Figure 7B: Stacked bar plot showing the distribution of AVPC in the 5 patients with $PTEN_{low}+RB1_{low}$ tumors

A CRPC metastatic biopsy was performed in 5 patients, all showed **neuroendocrine dedifferentiation**

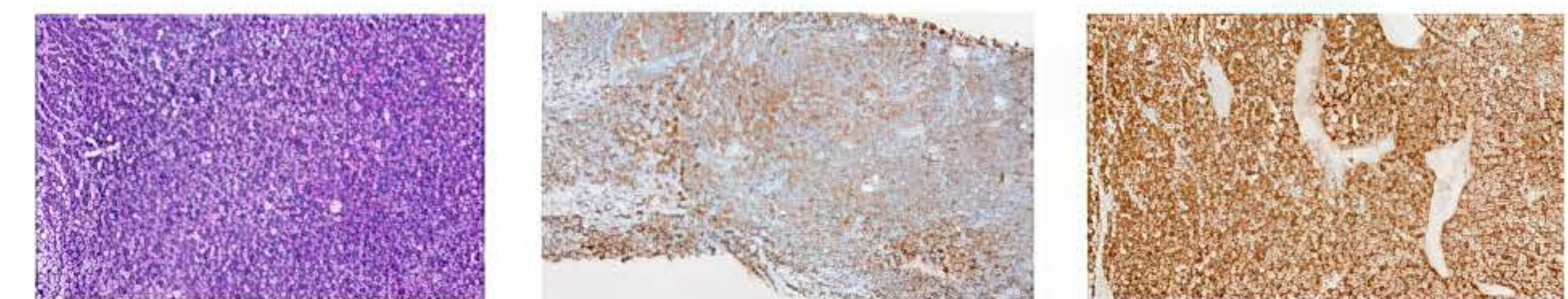


Figure 8: Metastatic biopsies showing small cell carcinoma features, with positive immunostaining for synaptophysin (middle) and chromogranin (right)