

# Survivin Expression in Neuroendocrine Tumors (NETs) is Associated with Poor Outcomes

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## Abstract

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- Survivin is a member of inhibitor of apoptosis protein (IAP) family. It is overexpressed in many cancers but is absent in most adult tissues
- We explored the expression of survivin in 132 tissue microarrays (TMAs) of NET patients using immunohistochemistry and correlated with outcomes.
- Patients were also classified according to Ki67 index as low (<3%) or high (≥3%).
- Survivin expression correlated with younger age, larger tumor size at diagnosis, higher grade and tobacco exposure.
- Patients with survivin-positive tumors had significantly worse OS compared to survivin-negative tumors (5.8y vs 18.3y, p<0.001)
- Survivin expression had a positive correlation with Ki-67 in NETs.
- When combined with Ki-67, patients with high Ki-67 and survivin positivity had worse OS, followed by Ki-67 Low/ Survivin positive tumors. Patients with Ki-67 Low and survivin-negative tumors had best outcomes
- We concluded that survivin expression in NETs is associated with aggressive biology and poor outcomes.

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## Introduction

- Survivin (16.5 kDa) is an inhibitor of apoptosis protein (IAP).
- Expressed in most human cancers but is absent in normal adult tissues.
- Considered one of the most specific cancer molecules.
- Recent success of anti-survivin vaccine (SurVaxM) has attracted interest in evaluating survivin as a possible therapeutic target.
- We explored survivin expression in NETs to test its potential as a therapeutic target.

## Objectives

1. Identify survivin expression in NETs through IHC.
2. Correlate survivin expression in NETs with tumor characteristics.
3. Correlate survivin expression in NETs with survival outcomes.

## Methods

We obtained tissue microarrays (TMAs) of 132 surgically resected TMAs between 1990 and 2017. TMAs were stained for survivin using rabbit monoclonal antibody clone EP119. Expression was classified as present or absent. Ki-67 expression was graded as percentage of positive cells and classified as low (<3%) or high ( $\geq 3\%$ ). Retrospective chart review was conducted to obtain tissue characteristics and outcome variables.

Comparisons were made using the Mann-Whitney U and Fisher's exact tests at  $\alpha=0.05$ . The correlation between survivin and Ki67 was evaluated using the Spearman correlation coefficient. Survival outcomes were analyzed using standard Kaplan-Meier methods and the log-rank test.

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## Baseline Patient Characteristics

- Significant associations were seen between survivin expression and age, smoking status, primary site, grade and tumor size.
- 40 out of 68 (59%) survivin-positive tumors were Lung NETs followed by 16 (24%) from gastero-enteropancreatic (GEP) origin.
- Patients with survivin-positive tumors were more likely to be younger with larger, high grade tumors, and have tobacco exposure.
- See Table 1 for details

Table 1 – Patient Characteristics by Survivin Expression

		Survivin Negative	Survivin Positive	Overall	P-value
<b>Overall</b>	N	64 (48.5)	68 (51.5)	132 (100%)	
<b>Age</b>	< 60	18 (28.1%)	36 (52.9%)	54 (40.9%)	0.005
	60+	46 (71.9%)	32 (47.1%)	78 (59.1%)	
<b>Sex</b>	Male	21 (32.8%)	26 (38.2%)	47 (35.6%)	0.59
	Female	43 (67.2%)	42 (61.8%)	85 (64.4%)	
<b>Smoking Status</b>	Never	32 (50.0%)	11 (16.2%)	43 (32.6%)	<.001
	Former	18 (28.1%)	30 (44.1%)	48 (36.4%)	
	Active	14 (21.9%)	27 (39.7%)	41 (31.1%)	
<b>Primary Site</b>	Lung	22 (34.4%)	40 (58.8%)	62 (47.0%)	0.003
	Pancreas	14 (21.9%)	5 (7.4%)	19 (14.4%)	
	Small Intestine	18 (28.1%)	11 (16.2%)	29 (22.0%)	
	Other	7 (10.9%)	12 (17.6%)	19 (14.4%)	
	Unknown	3 (4.7%)		3 (2.3%)	
<b>Grade</b>	I	36 (61.0%)	17 (26.2%)	53 (42.7%)	<.001
	II	12 (20.3%)	10 (15.4%)	22 (17.7%)	
	III	11 (18.6%)	38 (58.5%)	49 (39.5%)	
<b>Tumor Size (cm)</b>	< 15	17 (29.3%)	5 (7.6%)	22 (17.7%)	0.003
	25-40	10 (17.2%)	22 (33.3%)	32 (25.8%)	
	40+	31 (53.4%)	39 (59.1%)	70 (56.5%)	
<b>Ki67 Grade</b>	Low	59 (100.0%)	47 (72.3%)	106 (85.5%)	<.001
	High		18 (27.7%)	18 (14.5%)	

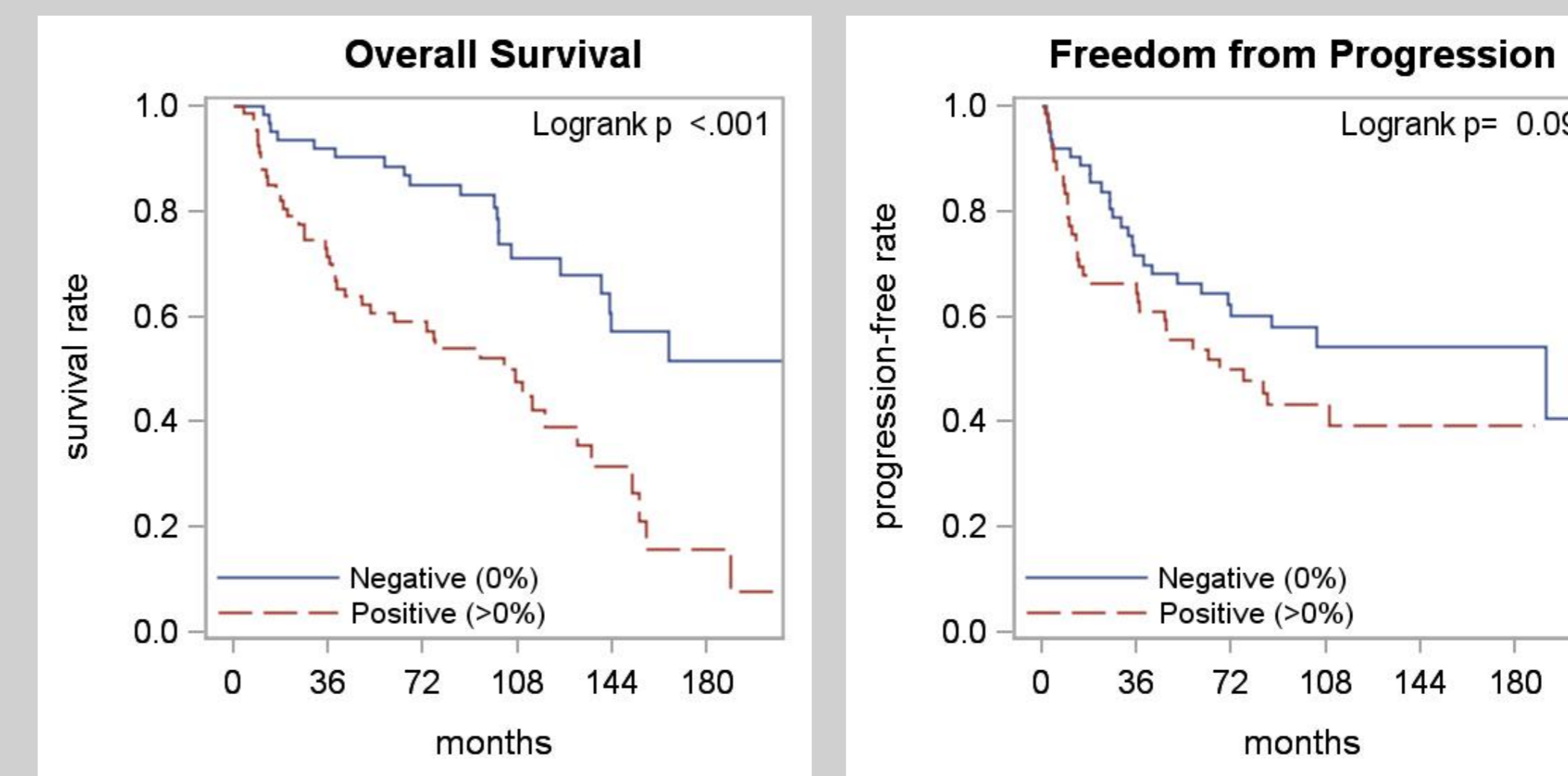
## Survival Outcomes

- Survivin positivity was associated with poor median overall survival (5.8y vs 18.3y, p<0.001) HR 2.89 (95% CI: 1.68-4.95)
- Association with freedom from progression in survivin-positive patients (5.6 vs 16 years, p=0.09) was not statistically significant – This can be due to variability in first-line therapy.

Table 2 – Survival Outcomes by Survivin Expression

		5-yr Rate (95% CI)	10-yr Rate (95% CI)	Median Time, mo (95% CI)	Median F/U, mo (Range)
<b>Overall Survival</b>	<b>Total</b>	0.74 (0.65, 0.81)	0.54 (0.44, 0.64)	135.9 (106.8, 156.9)	118.1 (0.9, 230.6)
	<b>Neg (0%)</b>	0.89 (0.77, 0.94)	0.71 (0.56, 0.82)	220.1 (139.8, NR)	121.3 (3.4, 230.6)
	<b>Pos(&gt;0%)</b>	0.61 (0.48, 0.71)	0.39 (0.26, 0.52)	102.9 (48.7, 130.8)	115.7 (0.9, 209.5)
<b>Freedom from progression</b>	<b>Total</b>	0.60 (0.51, 0.68)	0.47 (0.37, 0.56)	104.4 (60.5, NR)	
	<b>Neg(0%)</b>	0.66 (0.53, 0.77)	0.54 (0.39, 0.67)	191.5 (70.6, NR)	
	<b>Pos(&gt;0%)</b>	0.54 (0.40, 0.65)	0.39 (0.26, 0.53)	67.7 (36.3, NR)	

Figure 1 – Survival Outcomes by Survivin Expression



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## Correlation with Ki-67 Index

- We found a moderate positive correlation between survivin and Ki-67
- Survivin<sup>+</sup> tumors tended to have high Ki-67 ( $r_s = 0.54$ ,  $p < 0.001$ ).
- There was no correlation between survivin and TPH expression in NETs ( $r_s = -0.17$ ,  $p = 0.06$ )

## Survival Outcomes Based on Survivin and Ki-67

- Patients were divided into 3 groups based on presence or absence of survivin and Ki-67 index
- Ki-67 Low/survivin<sup>-</sup> tumors had the best outcomes with median overall survival of 18.3 years, followed by Ki67 Low/survivin<sup>+</sup> with 9.1 years, followed by Ki67 High/survivin<sup>+</sup> tumors with 6.3 years ( $p < 0.001$ ).

Table 3 – Survival Outcomes Based on Survivin/ Ki67 Index

		5-yr Rate (95% CI)	10-yr Rate (95% CI)	Median Time (95% CI)
Overall Survival	Total	0.74 (0.66, 0.81)	0.55 (0.45, 0.64)	139.8 (106.8, 156.9)
	Ki67 High / Survivin +	0.56 (0.31, 0.75)	0.31 (0.09, 0.56)	76.2 (24.6, 188.9)
	Ki67 Low / Survivin +	0.63 (0.48, 0.75)	0.42 (0.26, 0.57)	109.7 (52.0, 135.9)
	Ki67 Low / Survivin -	0.89 (0.78, 0.95)	0.71 (0.55, 0.82)	220.1 (142.7, NR)
Freedom from Progression	Total	0.61 (0.51, 0.69)	0.48 (0.37, 0.57)	
	Ki67 High / Survivin +	0.50 (0.23, 0.71)	0.41 (0.17, 0.65)	
	Ki67 Low / Survivin +	0.55 (0.39, 0.68)	0.38 (0.22, 0.54)	
	Ki67 Low / Survivin -	0.65 (0.51, 0.76)	0.55 (0.40, 0.68)	

Figure 2 – Correlation of survivin with Ki-67 and TPH

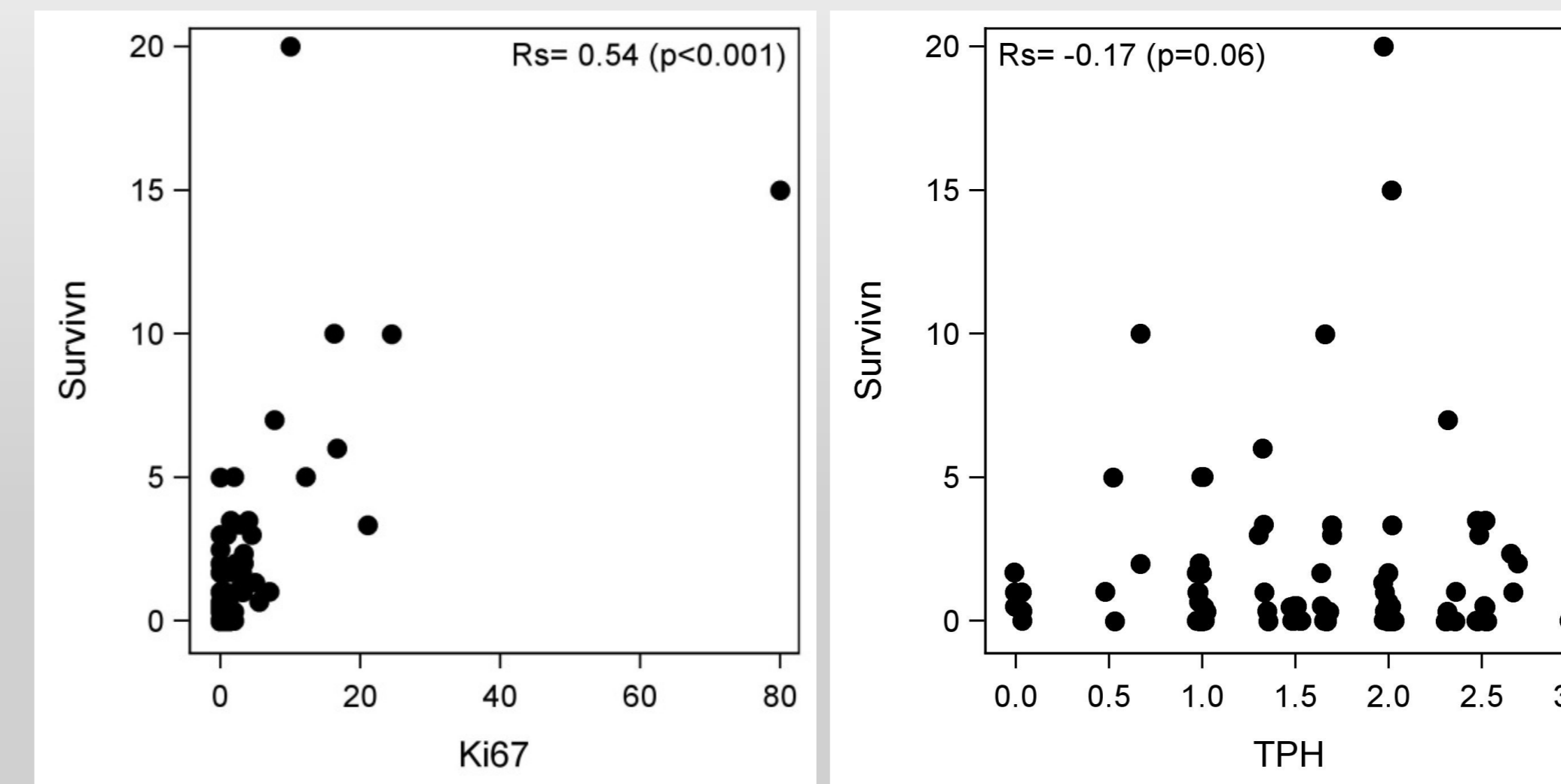
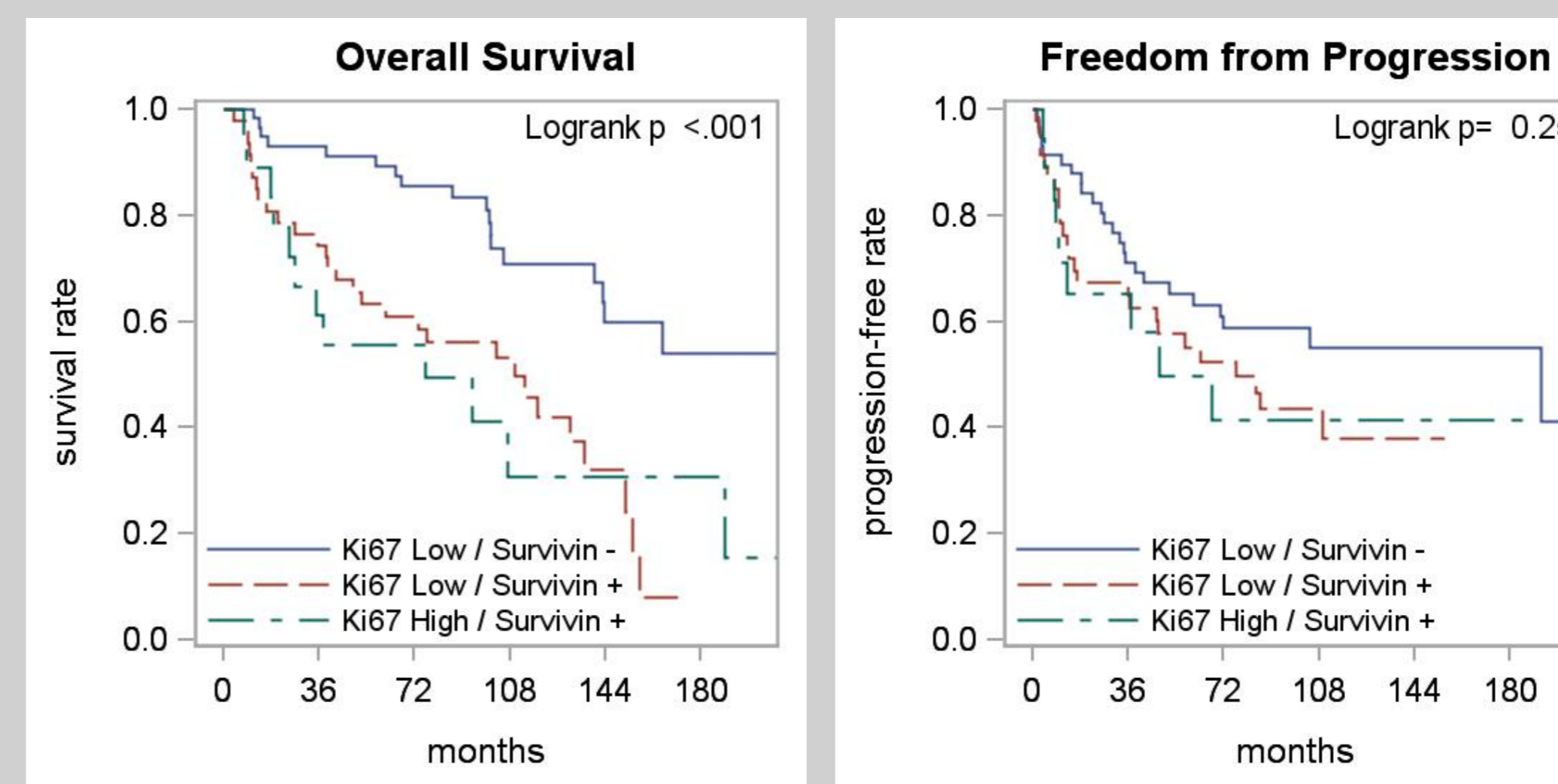


Figure 3 – Survival Outcomes Based on Survivin/ Ki67 Index



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## Results Summary

Patients with survivin-positive tumors were more likely to be younger with larger, high grade tumors, and have tobacco exposure. )

Survivin positivity was associated with poor median overall survival (5.8y vs 18.3y,  $p < 0.001$ )

Patients with Ki67 High/survivin<sup>+</sup> tumors had worse OS = 6.3 years ( $p < 0.001$ ).

There was a moderate positive correlation between survivin and Ki67 expression; survivin<sup>+</sup> tumors tended to have high Ki67 ( $r_s = 0.54$ ,  $p < 0.001$ ).

## Conclusion

Survivin expression in NETs is associated with aggressive biology and poor outcomes. There is a significant need to develop additional therapies for this population and survivin can be a potential target in these patients.

## Acknowledgements

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