Intraprostatic sympathetic nerve count predicts prostate cancer recurrence

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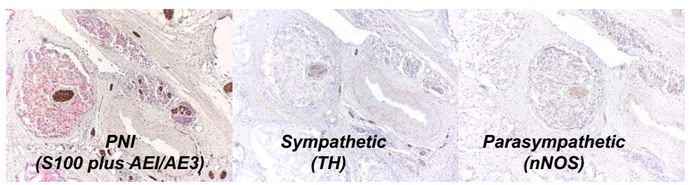
Introduction & Objectives

Perineural invasion (PNI) is commonly seen in prostate cancer but is not an independent predictor of biochemical recurrence (BCR)[1]. Recent evidence suggests the autonomic nervous system influences prostate cancer development and progression[2].

In this study we sought to investigate which autonomic nerve subtypes are involved in PNI in prostate cancer and how these relate to other clinical and pathological variables including BCR.

Methods

- 98 men with clinically localised prostate cancer and known PNI on radical prostatectomy histopathology, balanced for recurrence, were included.
- Relevant clinical data was retrieved from a prospectively collected database.
- Serial sections of bio-banked formalin-fixed paraffin-embedded radical prostatectomy tissue were stained with S100 (pan-nerve marker) plus AE1/AE3, Tyrosine Hydroxylase (TH, sympathetic) and neuronal Nitric Oxide Synthase (nNOS, parasympathetic). (below)
- 3 hotspot regions of intraprostatic PNI were selected for analysis in each participant. Both PNI and non-PNI affected nerve bundles in each hotspot were identified and, based on staining, each bundle was classified as pure sympathetic, pure parasympathetic, mixed bundle or double negative (non-adrenergic, non-nitrergic).



Results

Baseline Characteristics	
Age Mean (range)	63 (48-77)
Pre-operative PSA Median (IQR)	8.9 (6-14)
RP Gleason Score Median (IQR)	7 (7-8)
PSA recurrence	42%
Follow up Median (IQR)	85 months (72-101)

Average nerve count per hotspot per participant		
	PNI	**Non-PNI**
Total nerves	4.23	2.17
Mixed	3.03	1.78
Parasympathetic	0.98	0.32
Sympathetic	0.19	0.03
Non-adrenergic, non-nitrergic	0.03	0.03

Most nerves identified were of a mixed bundle type (Figure 2).

Figure 2: Nerve type as a percentage of total nerves studied

Mann-Whitney U testing revealed a significant relationship between pathological T stage and several study variables (Figure 3). No significant association was seen between Gleason Score and any PNI subtype.

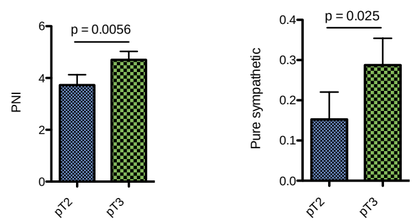


Figure 3: Relationship between study variables and pT stage; Total PNI nerves (left), Total pure sympathetic nerves (right)

Results Cont.

The number of PNI nerves identified correlated with pT stage but did not predict BCR. Multivariable cox regression demonstrated two independent predictors of BCR: pure sympathetic non-PNI nerves (HR 6.97, p=0.03) and non-adrenergic, non-nitrergic PNI nerves (HR 10.56, p<0.005). There was no significant association between other nerve subtypes and BCR.

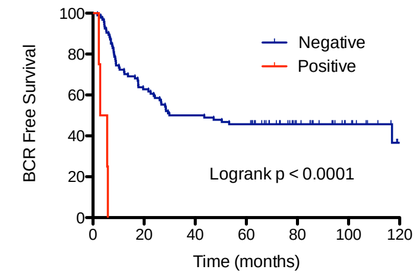


Figure 4. BCR-free survival stratified by pure sympathetic non-PNI nerve count

Conclusions

Our work has revealed two independent neural predictors of biochemical recurrence after radical prostatectomy, providing further evidence for a regulatory role of the autonomic nervous system in prostate cancer.
A greater understanding of the mechanisms underpinning this relationship may also translate into future therapeutic opportunities.

References

1. Reeves et al. CUAJ 2015; 9(5-6):E252-5;
2. Magnon et al. Science 2013; 341: 1236361