Pre-radiotherapy lymphocyte count predicts cisplatin benefit with radiotherapy in oropharynx cancer

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Introduction

- Sub-optimal identification of OPSCC for de-escalated treatment
- Immune markers relatively unexplored
- Absolute lymphocyte count (ALC) might reflect the tumour immunological makeup

Aim

- **Hypothesis:** Patients with high pre-radiotherapy ALC have a good prognosis & may not benefit from the addition of cisplatin to radiotherapy
- **Primary question:** Does pre-radiotherapy ALC predict benefit from cisplatin?
- **Secondary**: Does ALC correlate with tumour infiltrating lymphocyte counts?

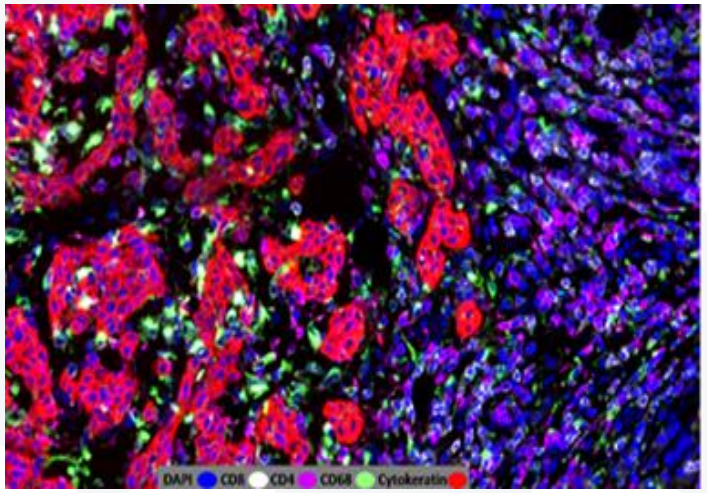
Methods

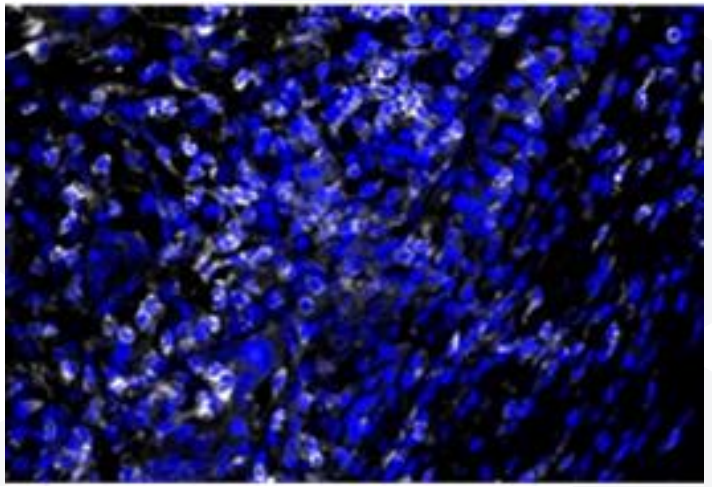
- **Design**: institutionally-approved, retrospective, multi-centre observational study
- **Inclusion criteria**: newly-diagnosed, histologically confirmed OPSCC; treatment with radical radiotherapy (+/- chemotherapy); no prior induction chemotherapy
- ALCs recorded from 4 weeks prior to RT to the end of RT
- **Discovery cohort**: The Christie, 2011 – 2018
- **Validation cohort**: Leeds, 2013- 2020

Methods

- **Statistical analysis:** Primary outcome measure overall survival (OS). Locoregional control (LRC) assessed using competing risk regression. Prognostic factors identified from a Cox proportional hazards analysis. The interaction between pre-radiotherapy ALC & cisplatin use assessed via likelihood ratio-test. Correlations between ALC and TILs reported

- **Translational analysis**: FFPE blocks retrieved (n = 168) & analysed for TILs using multiplex immunohistochemistry for pan-cytokeratin, CD68, CD4 & CD8





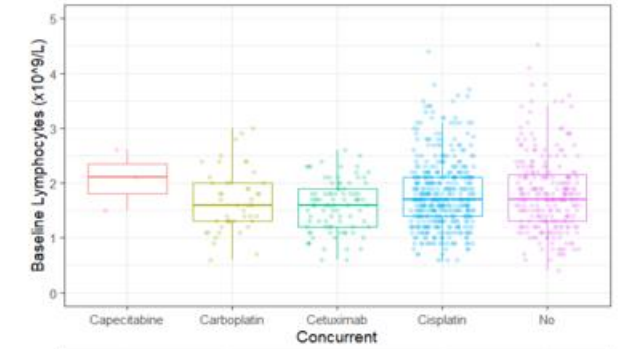
Discovery & Validation Cohort (i)

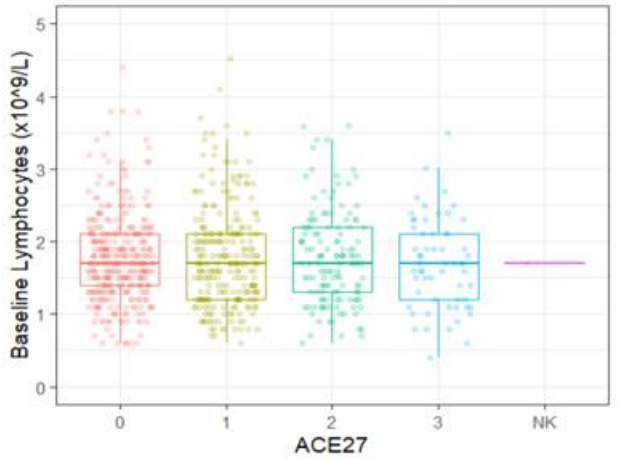
	Variable	Discovery cohort (n = 791)	Validation cohort (n = 609)
Median (range) age (yrs)	years, range	59 (28 - 87)	58 (30 - 86)
PS (ECOG) – N (%)	0	463 (59)	
	1	240 (30)	
	2	68 (9)	
	3	17 (2)	
	Unknown	3 (<1)	609
ACE-27 score – N (%)	0	346 (44)	
	1	253 (32)	
	2	132 (17)	
	3	59 (7)	
	Unknown	1 (<1)	609
Smoking history – N (%)	Never-smoker / <10 pyh	208 (26)	309 (39)
	Ex-smoker (≥10 pyh)	327 (41)	160 (20)
	Current smoker	216 (27)	134 (17)
	Unknown	7 (1)	6 (1)

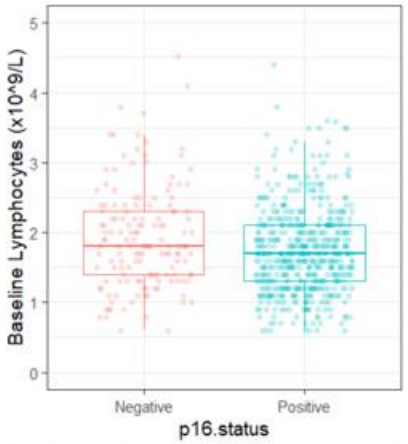
Discovery & Validation Cohort(ii)

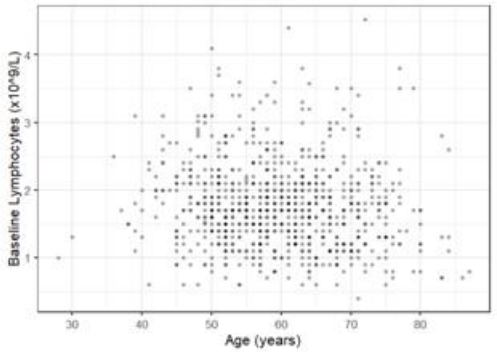
	Variable	Discovery cohort (n = 791)	Validation cohort (n = 609)
Tumour p16 status N (%)	Positive Negative Unknown	532 (67) 149 (19) 110 (14)	407 (67) 99 (16) 103 (17)
TNMv8 stage group N (%)	1 2 3 4a/b Unknown	288 (36) 161 (20) 124 (16) 86 (11) 132 (17)	232 (38) 86 (14) 106 (17) 80 (13) 105 (17)
Concurrent systemic therapy use N (%)	Cisplatin Carboplatin Cetuximab None	411 (52) 46 (6) 88 (11) 246 (31)	411 (67) 31 (5) 14 (2) 153 (25)
ALC (x10^9/L): median (range)		1.7 (0.4 - 4.5)	1.6 (0.2 - 14)

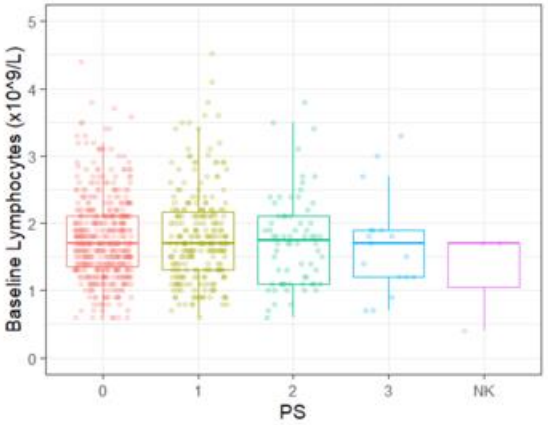
Distribution of pre-RT ALCs does not differ according to clinical factors

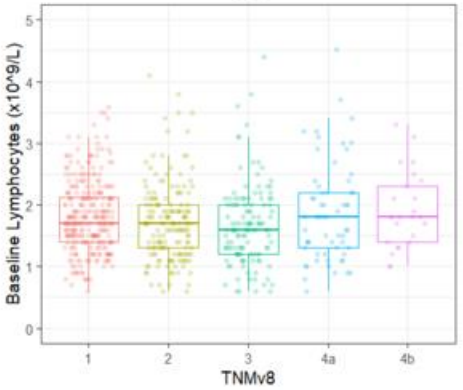


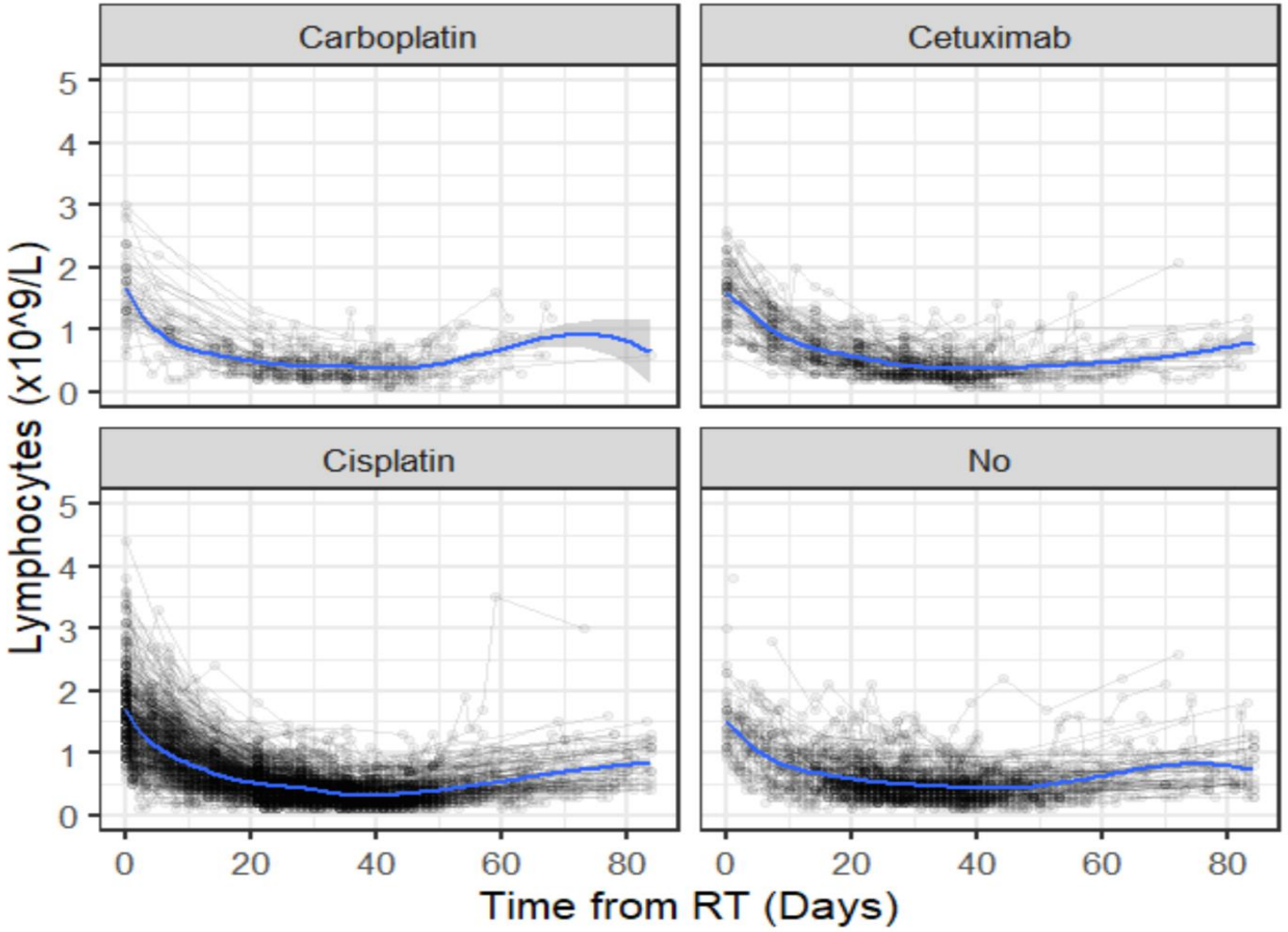












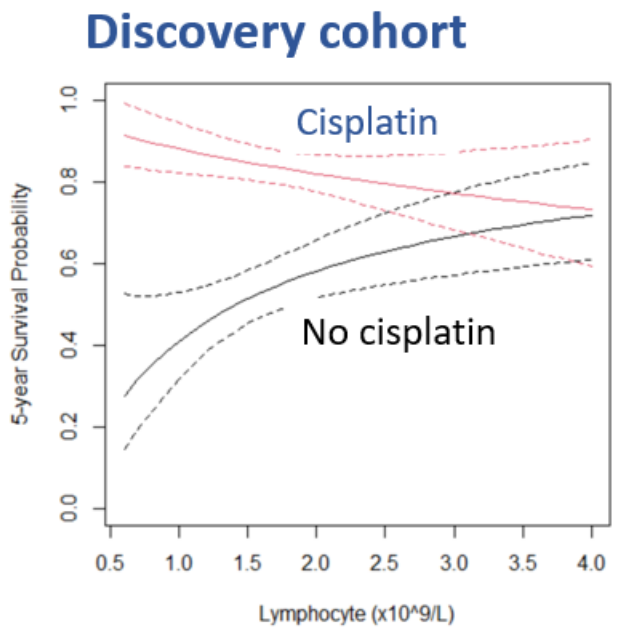
ALCs fall during RT irrespective of concurrent systemic therapy type

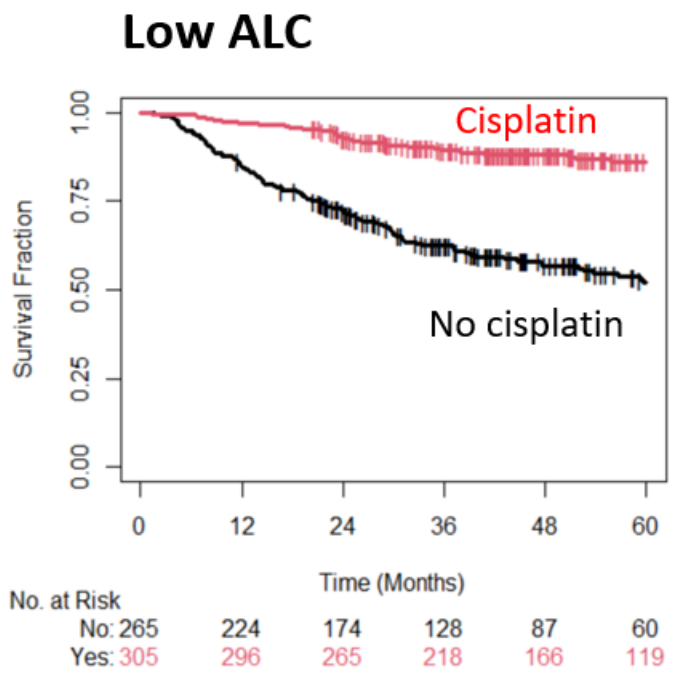
Pre-RT ALC is prognostic AND predictive - interaction with cisplatin use

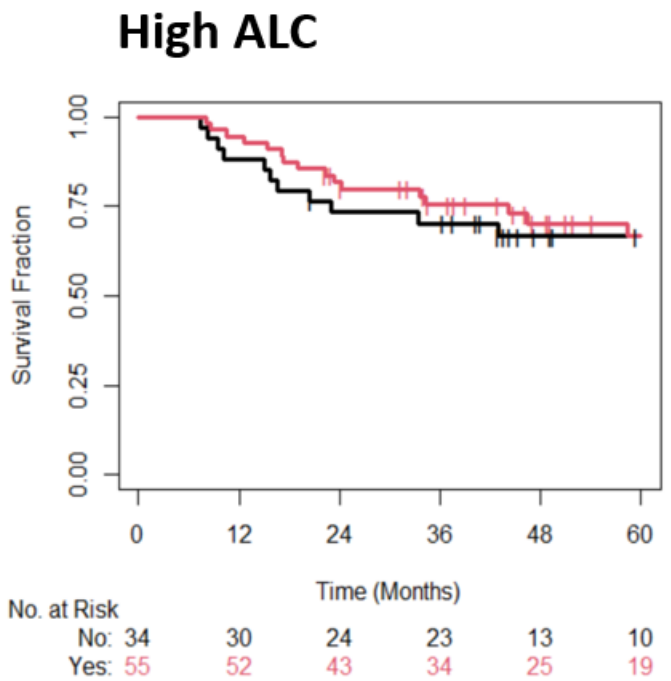
Pre-RT ALC prognostic on multivariable analysis (HR 0.64, 95% CI 0.42-0.98, p = 0.04)

	Discovery cohort Multivariable analysis		Validation cohort: Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Concurrent cisplatin use: Yes vs. no	0.39 (0.21 - 0.75)	0.004	0.39 (0.21 - 0.74)	0.004
log (pre-RT ALC)	0.48 (0.29 - 0.79)	0.004	0.44 (0.24- 0.78)	0.006
Cisplatin Yes: ALC	2.53 (1.03 - 6.19)	0.043	2.53 (0.98 - 6.52)	0.055

Patients with low pre-RT ALC benefit from addition of cisplatin to radiotherapy







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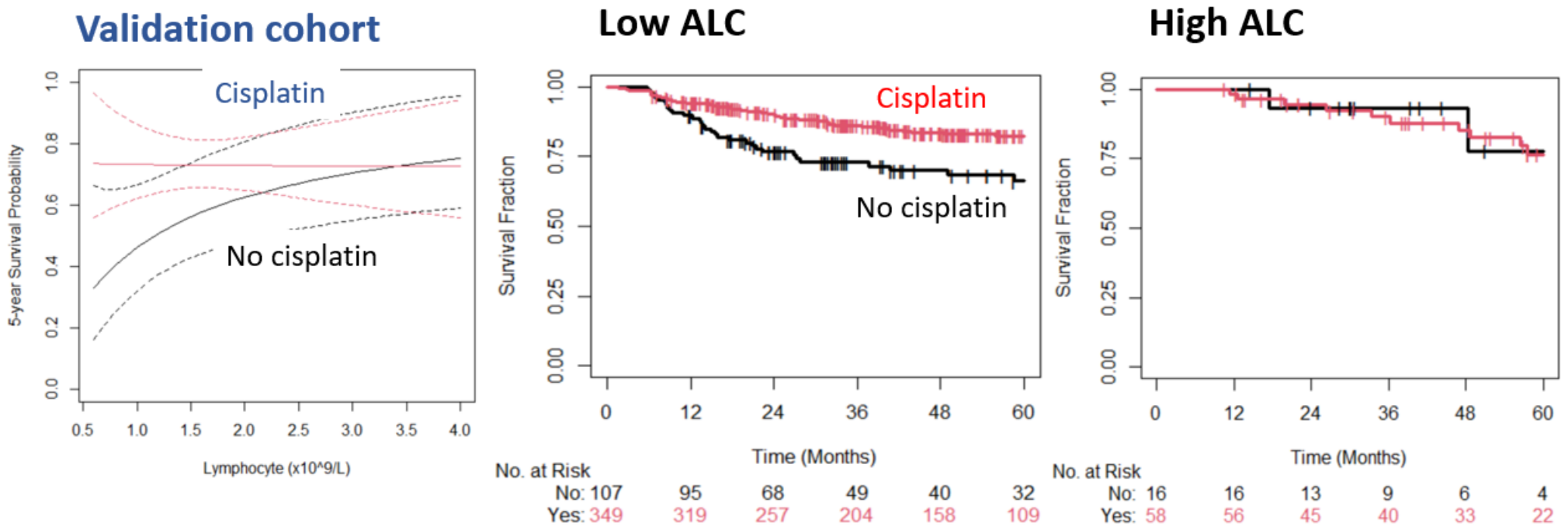
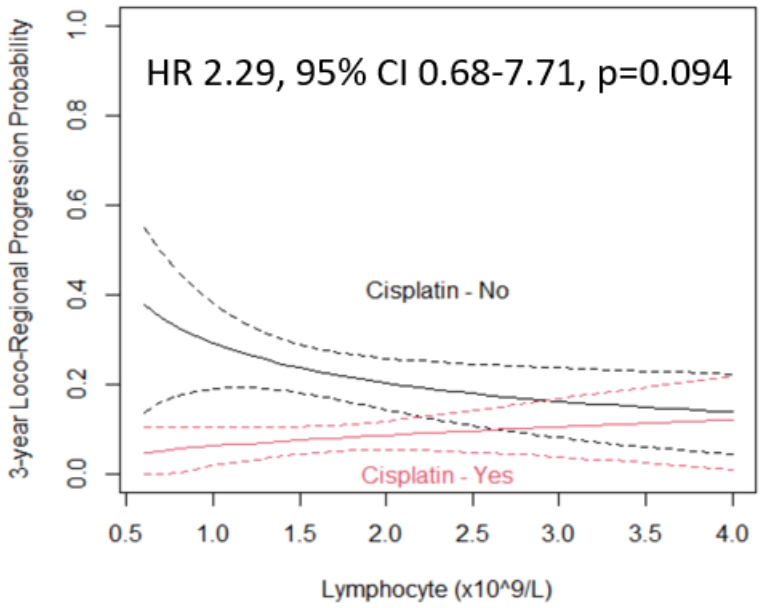
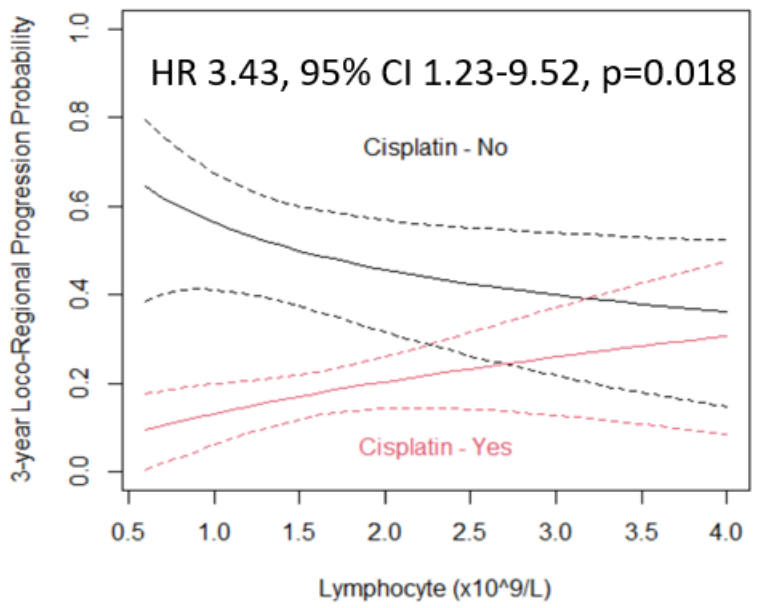


Pre-RT ALC: cisplatin OS finding likely driven by loco-regional cancer control

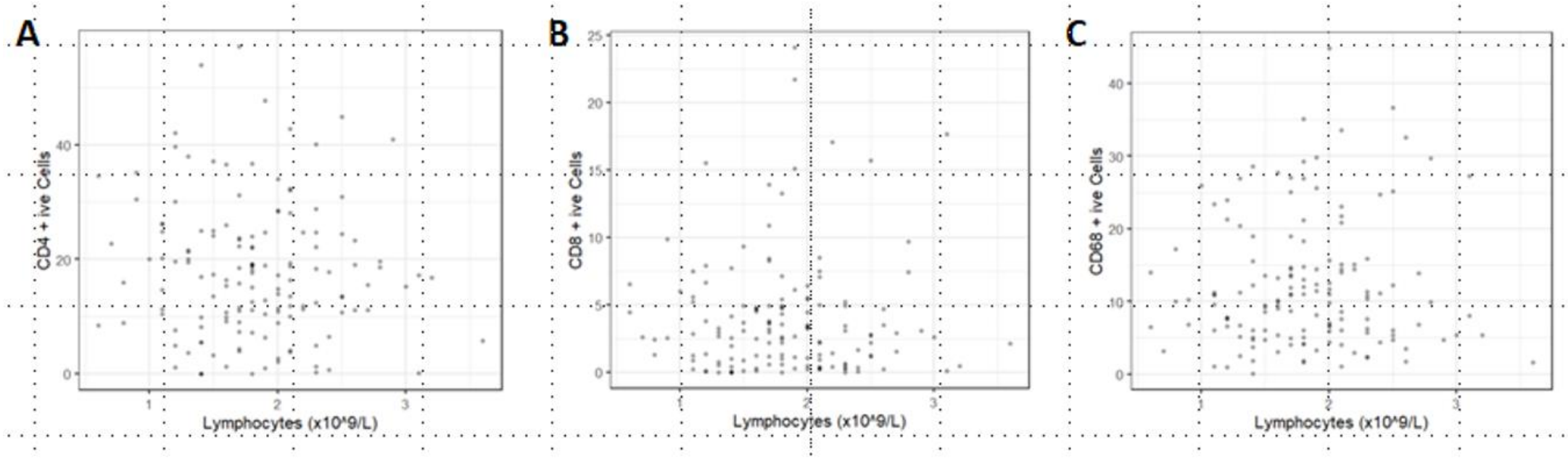
Discovery cohort:



Validation cohort:



Pre-RT ALC does not correlate with tumour-infiltrating CD4, CD8 or CD68 positive cells



Conclusion

- OPSCC patients with low pre-RT ALC & poor prognosis benefit from cisplatin
- As no relationship with number of TILs, increased pre-RT ALCs might associate with enhanced dynamic trafficking of T cells from blood into tumour
- Our finding, validated in a large independent cohort, suggests patients with good-prognosis OPSCC & high pre-RT ALC may not require concurrent cisplatin
- Such patients would then benefit from a reduction in long-term side-effects and improved health-related quality of life
- These findings should be evaluated prospectively in a clinical trial

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Questions?