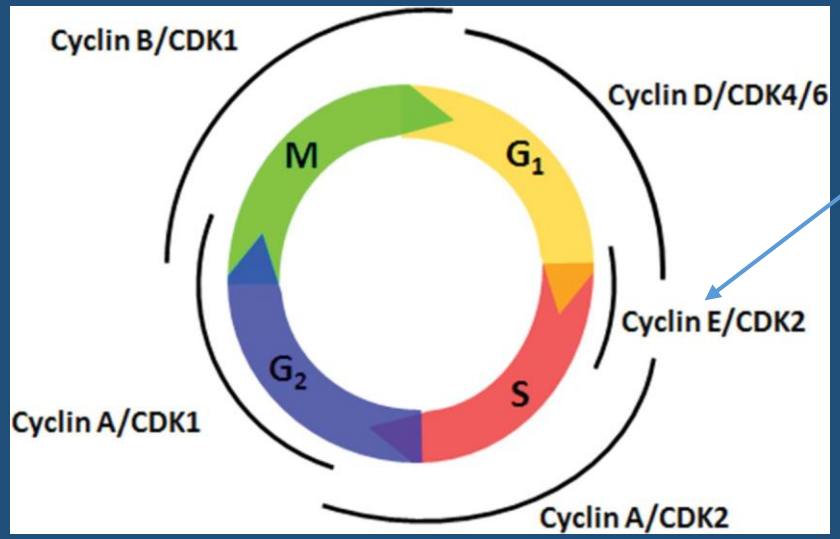
Cytoplasmic cyclin E is an independent marker of aggressive tumour biology and breast cancer-specific mortality in older women

Simon Johnston

5th Symposium on primary breast cancer in older women

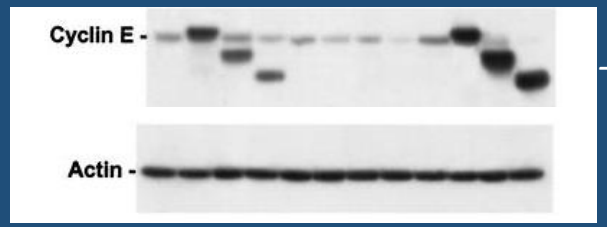
Cyclin E - background



Cyclin E promotes the transition from G1 to S phase by activating cyclin-dependent kinase 2 (CDK2)

- data on prognostic value of cyclin E expression equivocal

In breast cancer cells, tumour-specific proteolysis yields hyperactive LMW cyclin E



- LMW isoforms highly prognostic

LMW cyclin E lacks nuclear localisation sequence

↓

Accumulates in cytoplasm

Cytoplasmic cyclin E highly prognostic in multicohort study (N=2,494)

- this included a Nottingham cohort of older women (N=517 age >70 at diagnosis)

Nottingham cohort of older women

Dedicated clinic
1973 – 2010

1,758 women > 70 yrs at diagnosis

Unique biology: less aggressive
More likely to die of competing causes

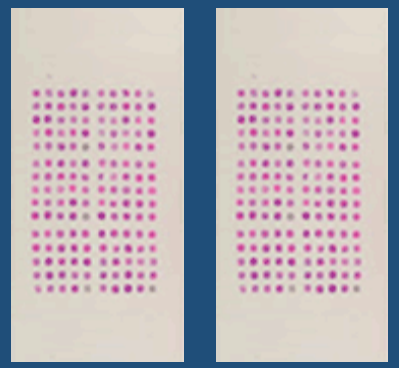
Primary surgery, N=813

Cytoplasmic cyclin E (MDA)

Primary outcome measure: BCSS

Median follow-up
6.3 years

TMA construction from FFPE tissue, N=517



Panel of biomarkers (Nottingham)

ER, PR, HER2, HER3, HER4, EGFR, BRCA1, BRCA2, P53, Ki67, BCL2, CK5/6, CK7/8, CK14, CK17, CK18, CK19, MDM2, MDM4, VEGF, CD44 and LKB1

Results

Table – analysis of tumour biology and breast cancer-specific survival

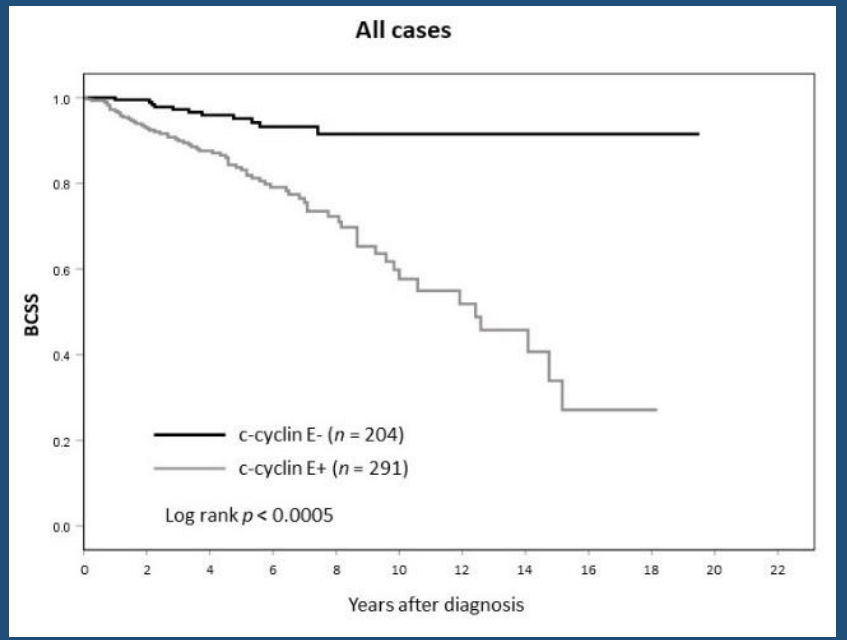
biological feature / biomarker		univariate analysis			multivariate analysis		
		HR	95% CI	*p*	HR	95% CI	*p*
c-cyclin E	negative	*reference*			*reference*		
	positive	4.84	2.56 – 9.15	<0.0005	4.96	2.05 – 11.96	<0.0005
grade	1-2	*reference*			*reference*		
	3	2.39	1.36 – 4.20	0.002	1.31	0.62 – 2.75	0.480
ER	negative	*reference*			*reference*		
	positive	0.377	0.21 – 0.68	0.001	0.83	0.39 – 1.73	0.611
PR	negative	*reference*			*n/a*		
	positive	0.69	0.44 – 1.07	0.097			
HER2	negative	*reference*			*reference*		
	positive	2.41	1.27 – 4.57	0.007	1.90	0.68 – 5.30	0.222
Ki67	negative	*reference*			*reference*		
	positive	1.79	1.15 – 2.80	0.010	1.74	0.88 – 3.41	0.110

The University of Nottingham

LN status not routinely assessed over the period of sample collection

Multivariate analysis with markers of disease biology in clinical use

Cytoplasmic cyclin E exclusively predicts BCSS (HR = 5.0, 95% CI 2.1-12.0; $p<0.0005$)



Translational relevance

Patients >70 yrs with low cytoplasmic cyclin E expression are unlikely to die of breast cancer

Implies that these patients may not require an aggressive treatment strategy

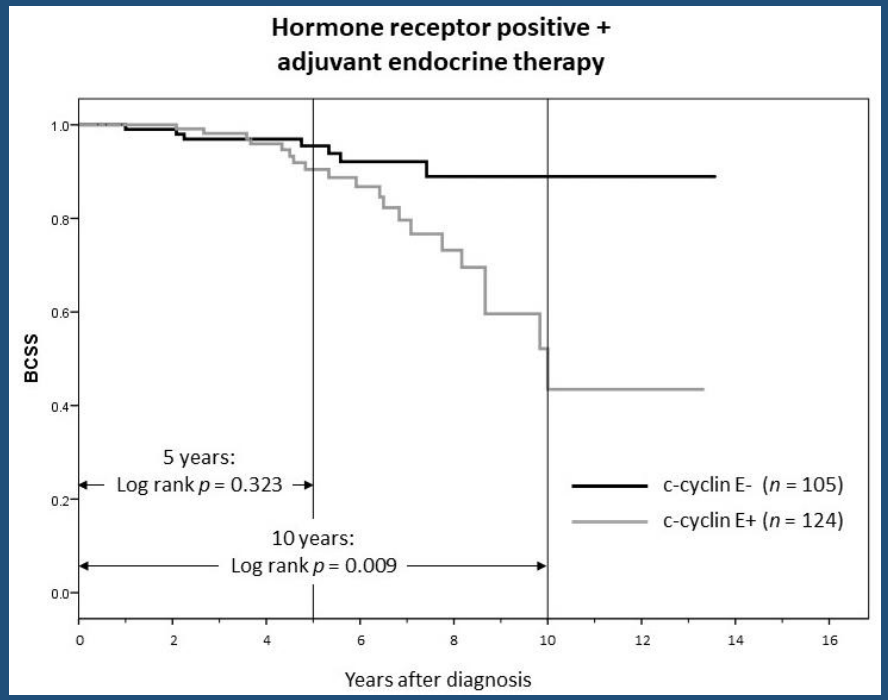
- initial therapy modality
- adjuvant therapy intensity / duration

Patients with ER+ tumours and low cytoplasmic cyclin E may be adequately treated by endocrine therapy

- patients with complex co-morbidities / psychosocial factors
- screen using c-cyclin E and geriatric assessment tool

Adjuvant endocrine therapy negates the poor prognostic effect of c-cyclin E positivity, but only for as long as it is given (up to 5 years)

- rationale for extended duration endocrine therapy in c-cyclin E +ve cases (e.g. 10 *versus* 5 years)



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