Test of Cure after Treatment

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Disclosures

- No financial relationships or conflict of interest to disclose

Follow-up after treatment of CIN

To confirm that treatment was effective

- Residual disease

To prevent invasive cancer

- Recurrent disease

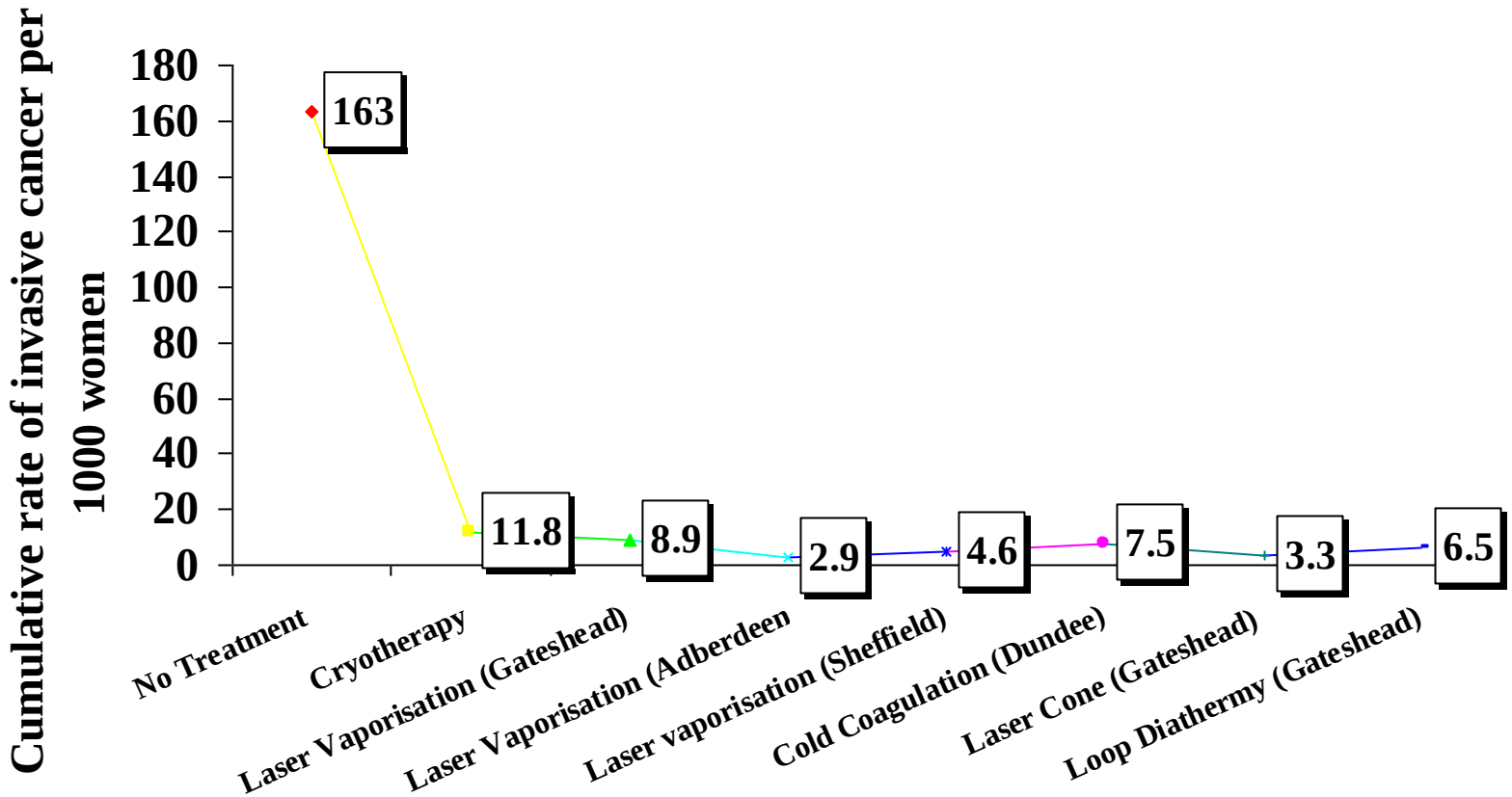
To reassure the woman

To quality assure colposcopy

Treatment Methods

- Hysterectomy
- Excision
  - LLETZ
  - Cone Biopsy
  - Laser Cone
  - NETZ/SWETZ
- Ablation
  - Cold coagulation
  - Laser Ablation
  - Cryotherapy

Invasive Cancer after treatment
Cumulative risk per 1000 women



(Soutter, 1997)

HPV testing for recurrence

- Persistence of same HPV type most significant prognostic factor for residual or recurrent CIN
  - Micro-foci of residual disease
  - Risk of developing new disease
  - Persistence of other co-factors

- HR HPV negative very low risk of developing new disease within 3 years

HPV testing for recurrence

HPV test vs cytology: significantly more sensitive, similarly specific

HPV test vs histological examination of resection section margins: significantly more sensitive & specific

But: heterogeneity of studies, treatments, timing of follow-up visits, methods of follow-up

Long term follow-up needed, since high sensitivity of HPV testing might be only valid to short term recurrent disease

IJC
International Journal of Cancer

Long-term risk of recurrent cervical human papillomavirus infection and precancer and cancer following excisional treatment

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Risk of recurrent CIN by HPV genotype

Observational study from Guanacasta cohort

347 treated women with a cervix and >12 months of follow-up (median 6.7 years)

6 CIN2+ all with persistence of same HPV genotype

No recurrent disease in women with new HPV genotype

HPV test of cure

NHS CSP England

- Women treated for all grades CIN
- HPV and cytology at 6 months post-Tx
- Double negative return to routine recall
- Abnormal cytology or cytology neg/HPV positive – refer to colposcopy
- Normal colposcopy – return to routine recall
- National roll out 2012
- Now includes follow up of CGIN

HPV test of cure

Scottish Cervical Screening Programme

- Early implementation sites 2010
- Women treated for any grade CIN
- HPV and cytology at 6 months post-treatment

Sweden

- Cytology at 6 months and HPV at 12 months

HPV test of cure

Republic of Ireland

- HPV and cytology at 6 and 18 months
- 2011

Australia and New Zealand

- National guidelines 2008
- HPV and cytology at 12 and 24 months

NHS CSP HPV Post Tx Study

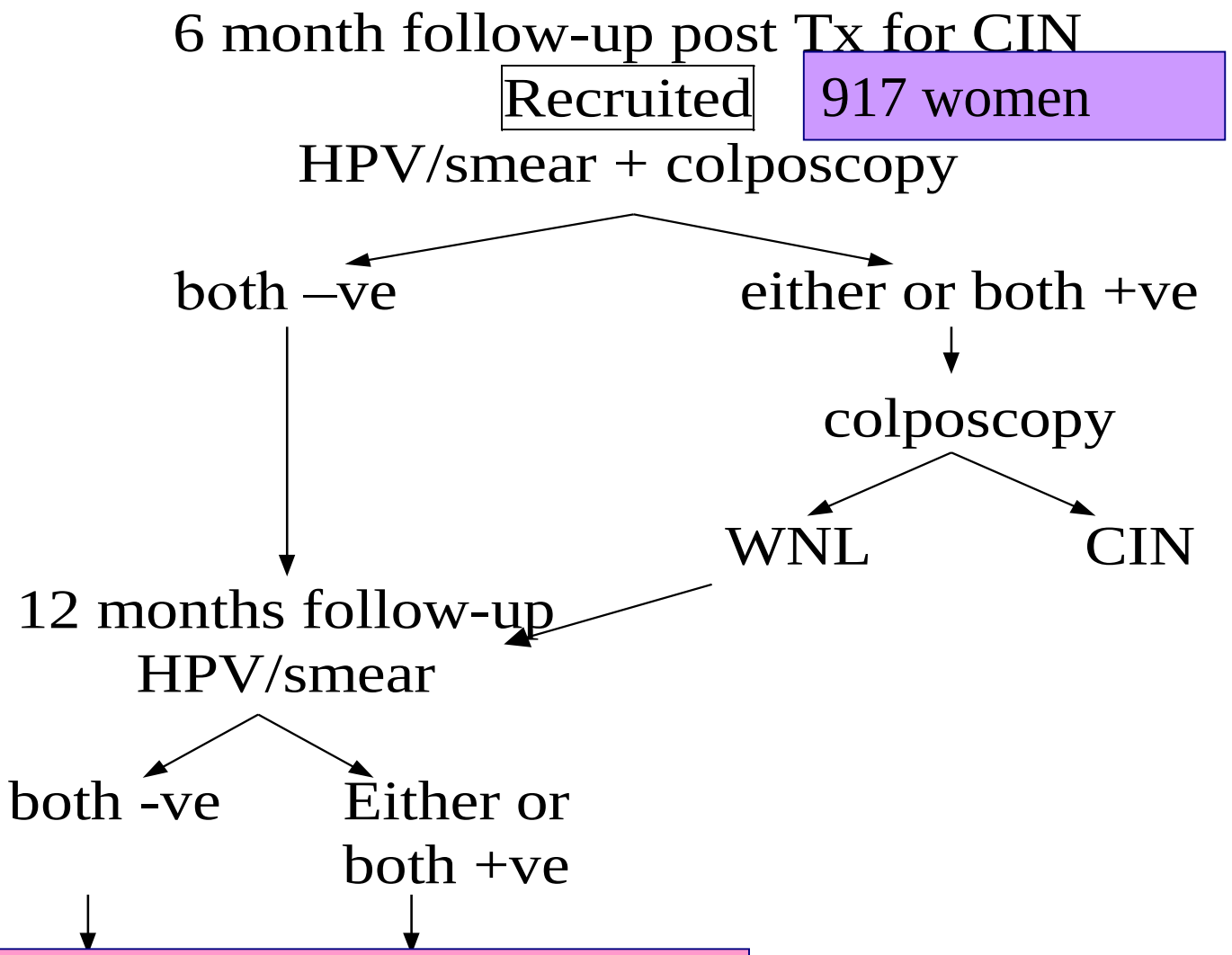
Setting:

NHS CSP national screening programme

- Aberdeen
- Manchester
- London

Women treated 2002-2004

NHS CSP HPV Post Tx Study



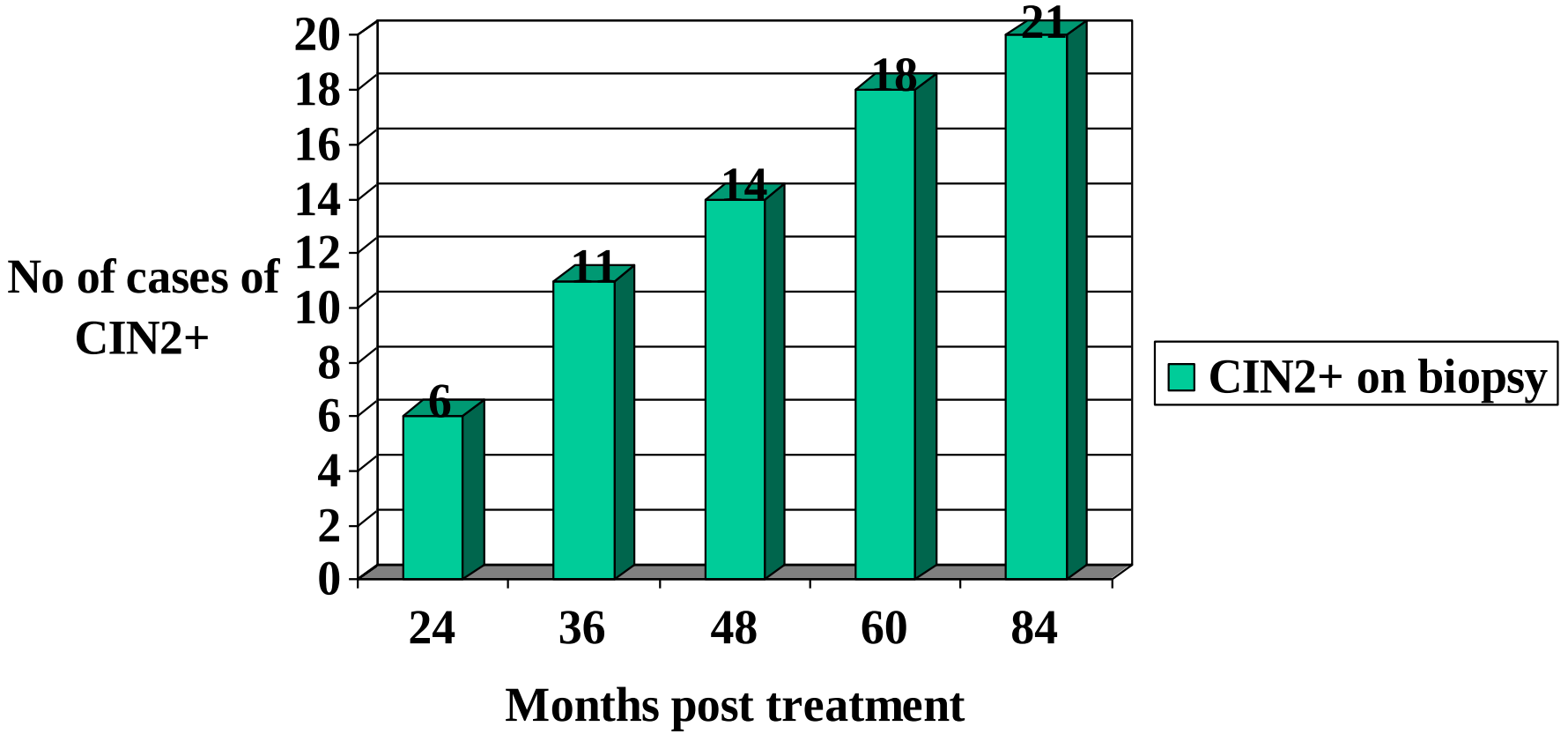
Results: 917 women

Mean age 31.5 years (range 15-72 years)

CIN2/3	700 (76%)
CIN1	217 (24%)

95% treated by LLETZ
77% clear endocervical margins
72 % clear ectocervical margins

Cumulative residual/recurrent CIN2+ post-treatment



Cumulative CIN2+ at follow-up by 6 months cytology and HPV results

	Cumulative CIN2+					
Months post Tx	**36/12**		**60/12**		**84/12**	
	n=617	%	n=445	%	n=159	%
Cytology at 6 months						
Negative	3	0.5	7	1.8	9	6.7
BNA+	3	4.3	3	5.9	4	16.0
HPV DNA at 6 months						
Negative	2	0.4	3	0.8	4	3.3
Positive	4	4.1	7	9.2	9	23.7
Cyt-/HPV-	2	0.4	3	0.9	4	3.5
Cyt+/HPV+	3	7.3	3	9.1	4	23.5

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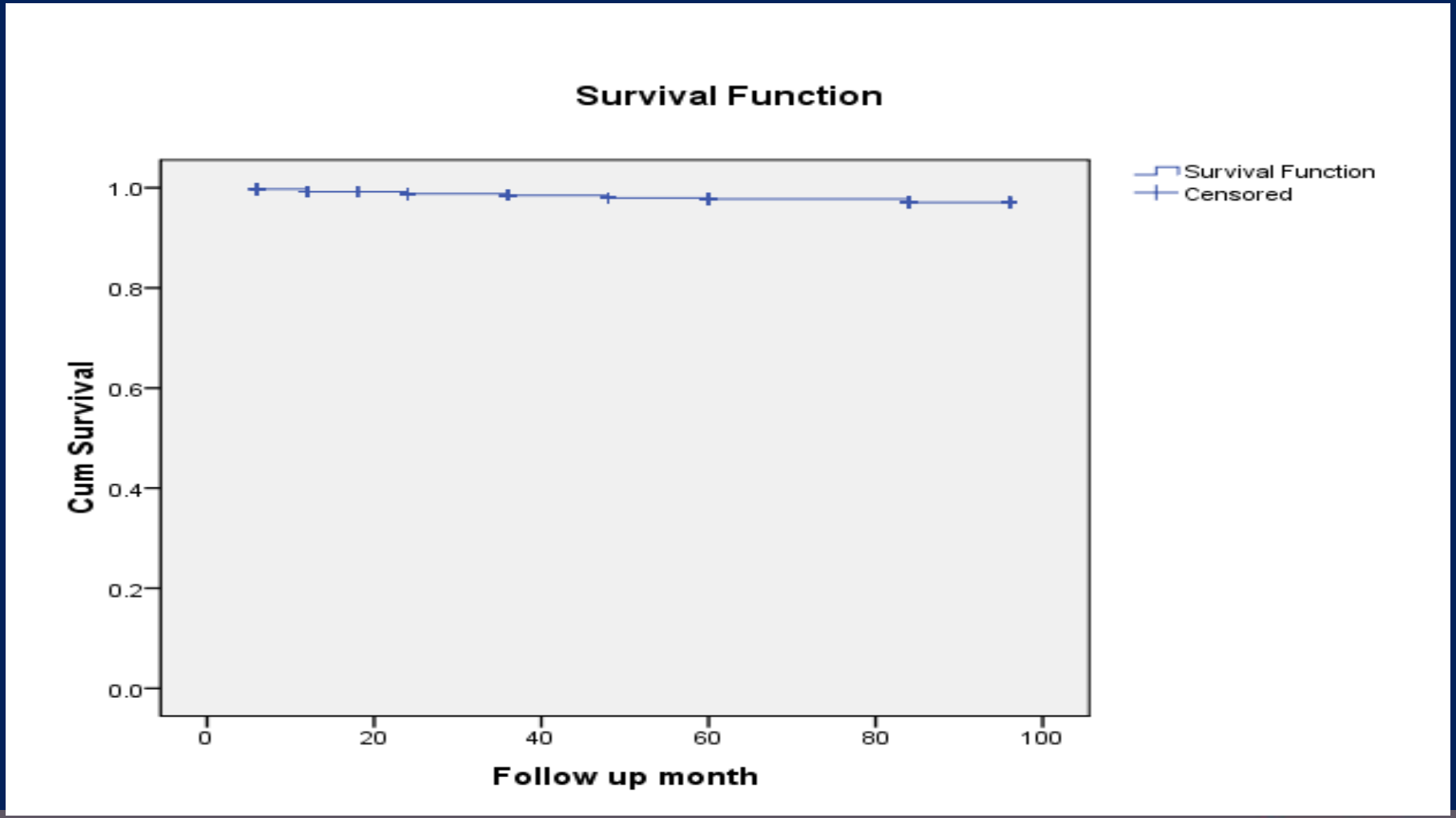
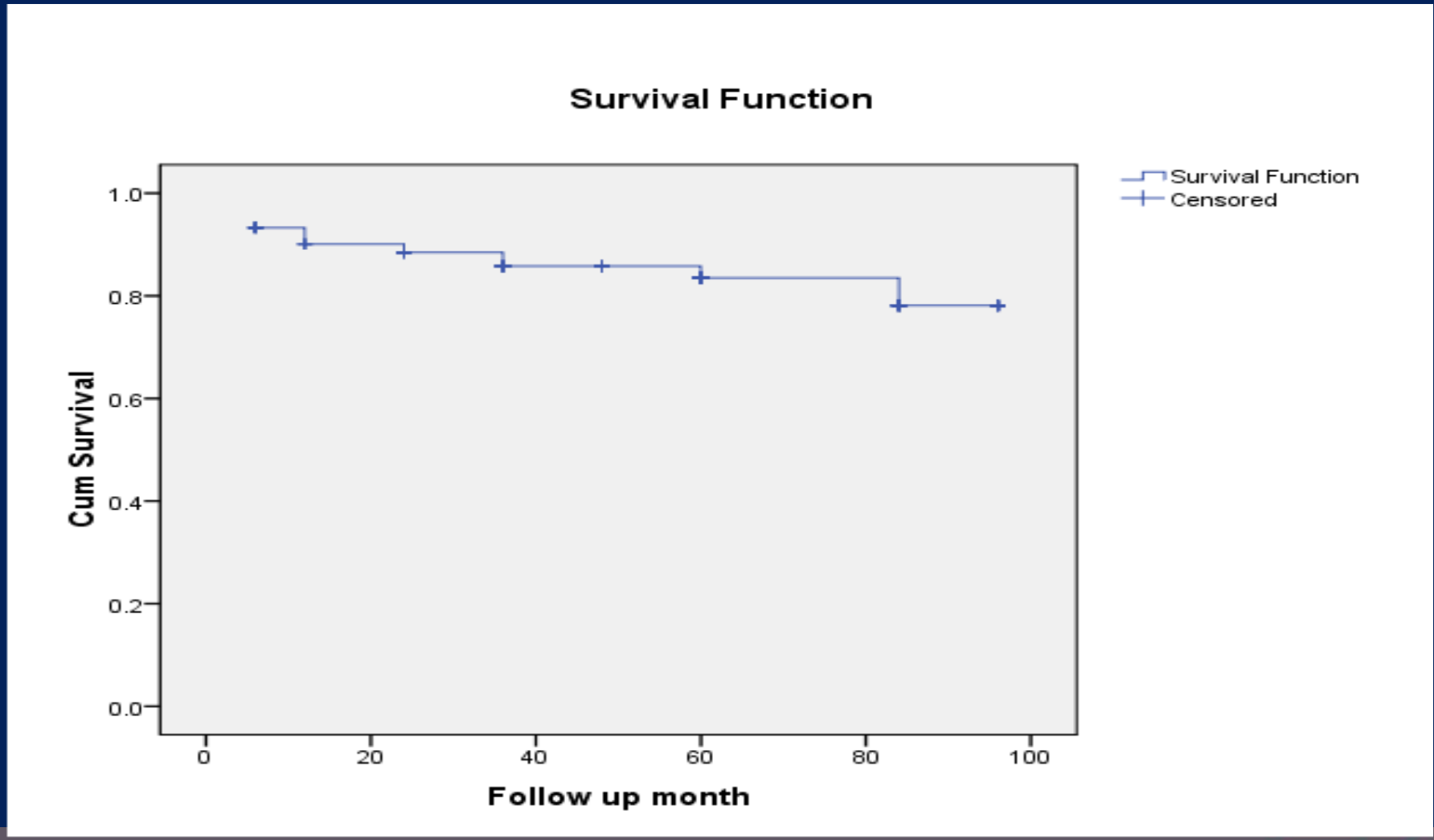
No CIN2+ detected following treatment in women HPV negative at 6 months after treatment (n =783)



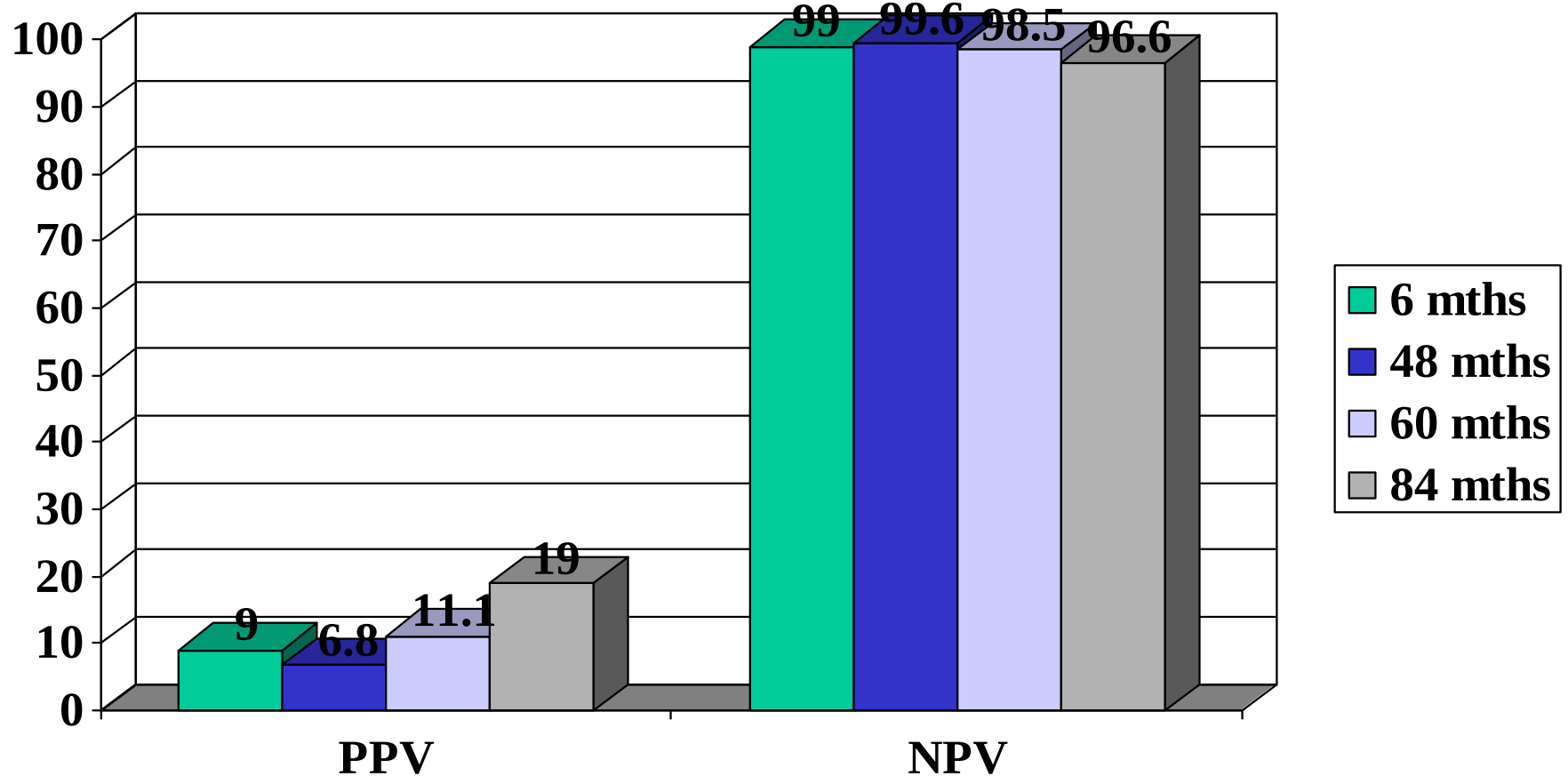
No CIN2+ detected following treatment in women HPV positive at 6 months after treatment (n= 134)



Predictive values of cytology and HPV tests taken at 6 months for CIN2+ by 3, 5 and 7 years post-Tx

	NPV			PPV		
Years post Tx	3 n=617	5 n=445	7 n=159	3 n=617	5 n=445	7 n=159
HPV	99.6	99.2	96.8	3.9	8.4	19.1
Cyt	99.4	98.2	93.7	4.1	5.5	13.7
HPV-/cyt-	99.6	99.1	96.6			
HPV+/cyt+				6.8	8.3	19.0

HR HV status at 6 months and detection of recurrent disease at 4 and 5 years of follow-up



Relative Risk of CIN2+ after 60 months follow up (reference cyt-ve/HPV-ve)

ToC result	Relative Risk	95% CI
Cytology at 6 months		
Negative	1.3	(0.88-1.99)
BNA +	3.94	(1.70-9.13)
HPV DNA at 6 months		
Negative	0.78	(0.26-2.28)
Positive	3.93	(2.50-6.19)
Cyt-/HPV-	1.00	
Cyt+/HPV+	5.8	2.5-13.8

Relative Risk of CIN2+ at 36, 60 and 84 months follow up (reference cyt-ve/HPV-ve)

	Relative Risk	95% CI
36 months		
Cyt+/HPV+	7.8	3.6-16.9
60 months		
Cyt+/HPV+	5.8	2.5-13.8
84 months		
Cyt+/HPV+	3.8	1.7-8.7

Long-term follow-up after treatment of CIN

Increased risk of recurrent CIN and cancer >10 years post treatment

Swedish case-control study (Strander 2007)

Loss of protection from HPV- test seen >6 years and 8 months after treatment

- Persistence
- Re-infection
- New infection

Cost of Follow-up (NHS Scotland)

Current follow-up: *First smear at colposcopy clinic and for 5 years before return to routine recall* = £1,202,350

Test of cure: *Discharged to follow-up in primary care. Double negative at 6 months return to routine recall* = £449,050

Costs to women attending for follow-up

- Primary care = £9.20
- Hospital = £27.40

Other issues

Self-sampling for HPV post-treatment. Higher rates of HrHPV positivity from self-collected vaginal and urine samples cf LBC (Stanczuk 2015)

HPV platform performance (Tidy 2015)

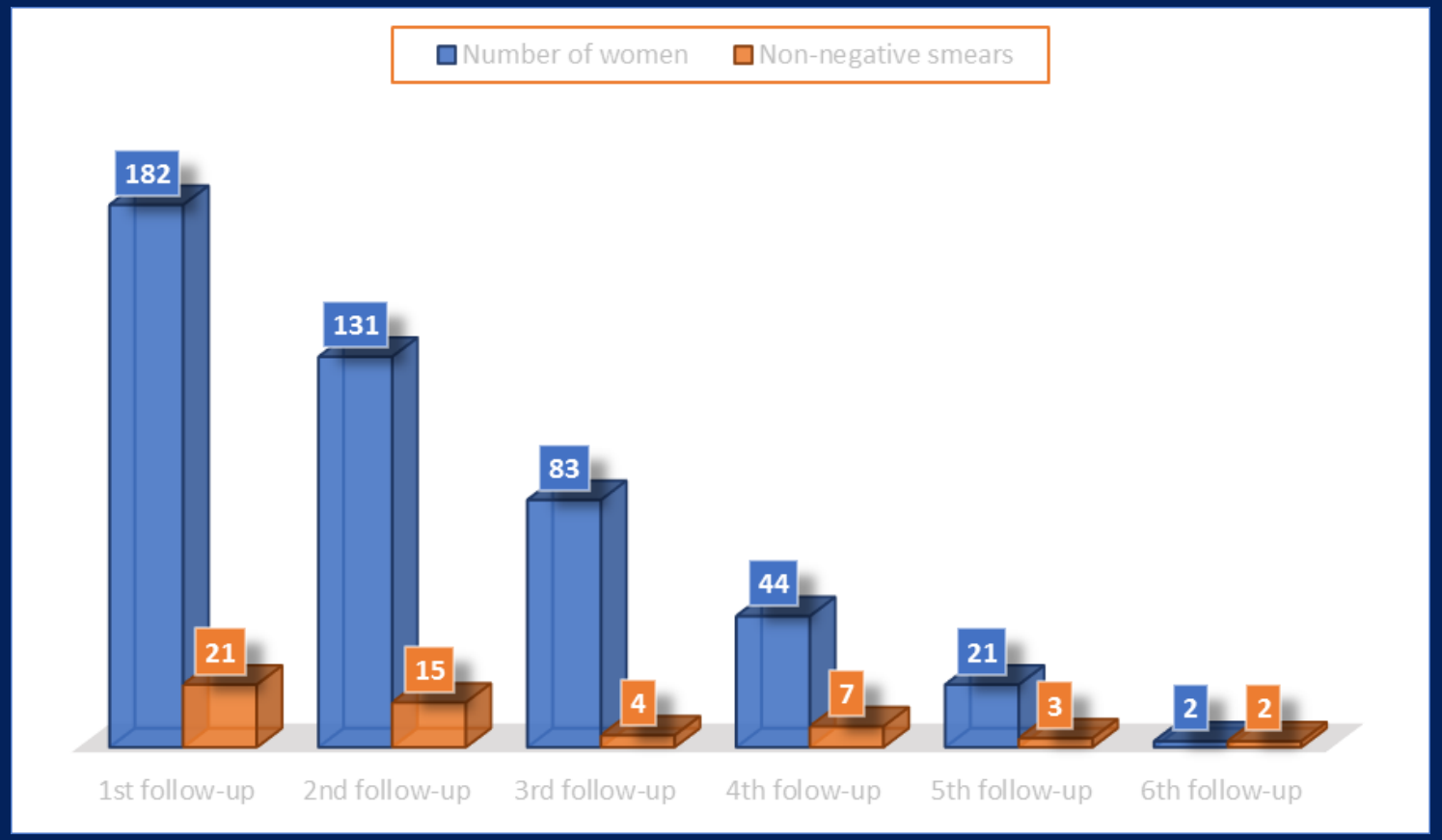
Follow-up after local treatment of microinvasive cervical cancer (FIGO 1A1) (Cairns 2010)

MAGS (Microinvasive, Glandular and SMILE study) Test of cure and early dischange in follow up if Microinvasive cancer, CGIN and SMILE)

Aberdeen UK Test of Cure follow-up

Kalampokas
BSCCP 2017

hrHPV+/cyto neg at Test of Cure after follow-up colposcopy +/- biopsy neg



Kalampokas
BSCCP 2017

Conclusions

HPV testing has an important role for low risk women: in reducing intensive follow-up

- Rapid return to recall
- Reduce intensive follow-up
- Reassurance

Conclusions

HPV persistence at 6 months follow-up significantly associated residual risk of recurrence up to 7 years of follow-up

High negative predictive value of ‘double negative’ still seen at 5 years

By 7-9 years, decline in NPV seen

Return to routine recall with cytology after double negative at 6 months

HPV+/cyto neg with normal colposcopy

HPV re-test at 3-5 years (and beyond)

Thanks

NHS CSP who funded HPV Test of Cure study