

# Prognostic importance of p16INK4A and HPV in patients with oropharyngeal cancer treated with concurrent chemoradiation on

## TROG 02.02 phase III trial

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# HPV associated oropharyngeal Ca

- 50 – 90% oropharyngeal cancer (OPC) associated with human papilloma virus (HPV)
- Distinct entity with different risk factors, clinical features and molecular profile
- The E7 viral oncoprotein inactivates Rb which leads to upregulation of p16
- Initial reports of small chemoradiation trials demonstrated superior outcomes in HPV associated OPC

# Study Objective

- To determine the prognostic significance of HPV and p16 in patients with oropharyngeal cancer treated with cisplatin based concurrent chemoradiation on a large international phase III trial

# TROG 02.02 (HeadSTART)

Patients with Stage III (excluding T1-2N1) or IV  
SCCHN  
(stratified by stage, site, hemoglobin)



Randomization



Cisplatin, RT



Tirapazamine,  
cisplatin, RT

# TROG 02.02 (HeadSTART) Results

- No significant difference in overall survival  
*Rischin et al JCO, 2010, in press*
- Radiotherapy deviations had a major adverse impact on treatment outcome  
*Peters et al JCO, 2010, in press*

# Eligibility for Substudy

- Previously untreated Stage III or IV (excluding T1N1 or T2N1) oropharyngeal SCC
- Received  $\geq 60$  Gy
- No major radiation deviations predicted to impact on tumour control

# p16 IHC

Grade 0

68/193 (35%)

Grade 1

11/193 (6%)

Grade 2

23/193 (12%)

Grade 3

91/193 (47%)

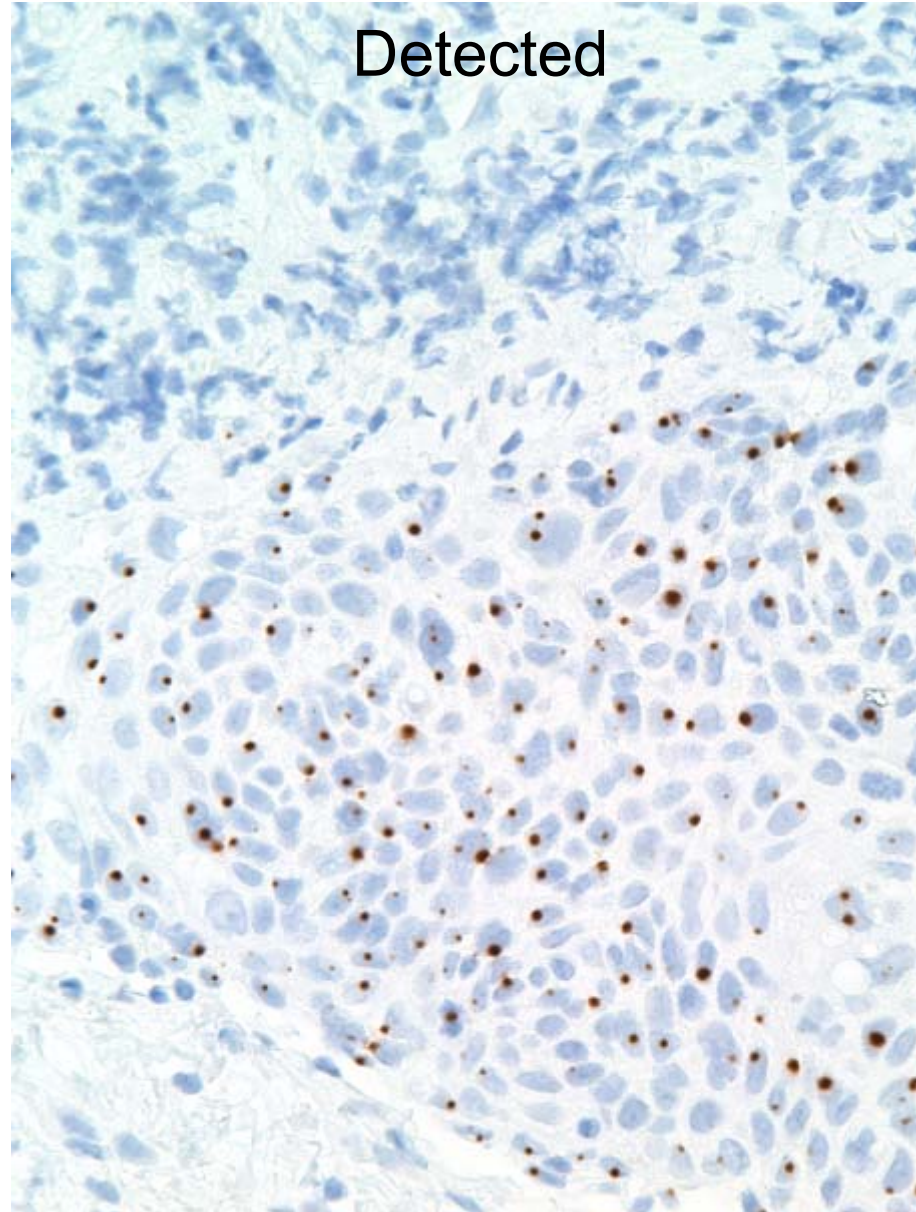
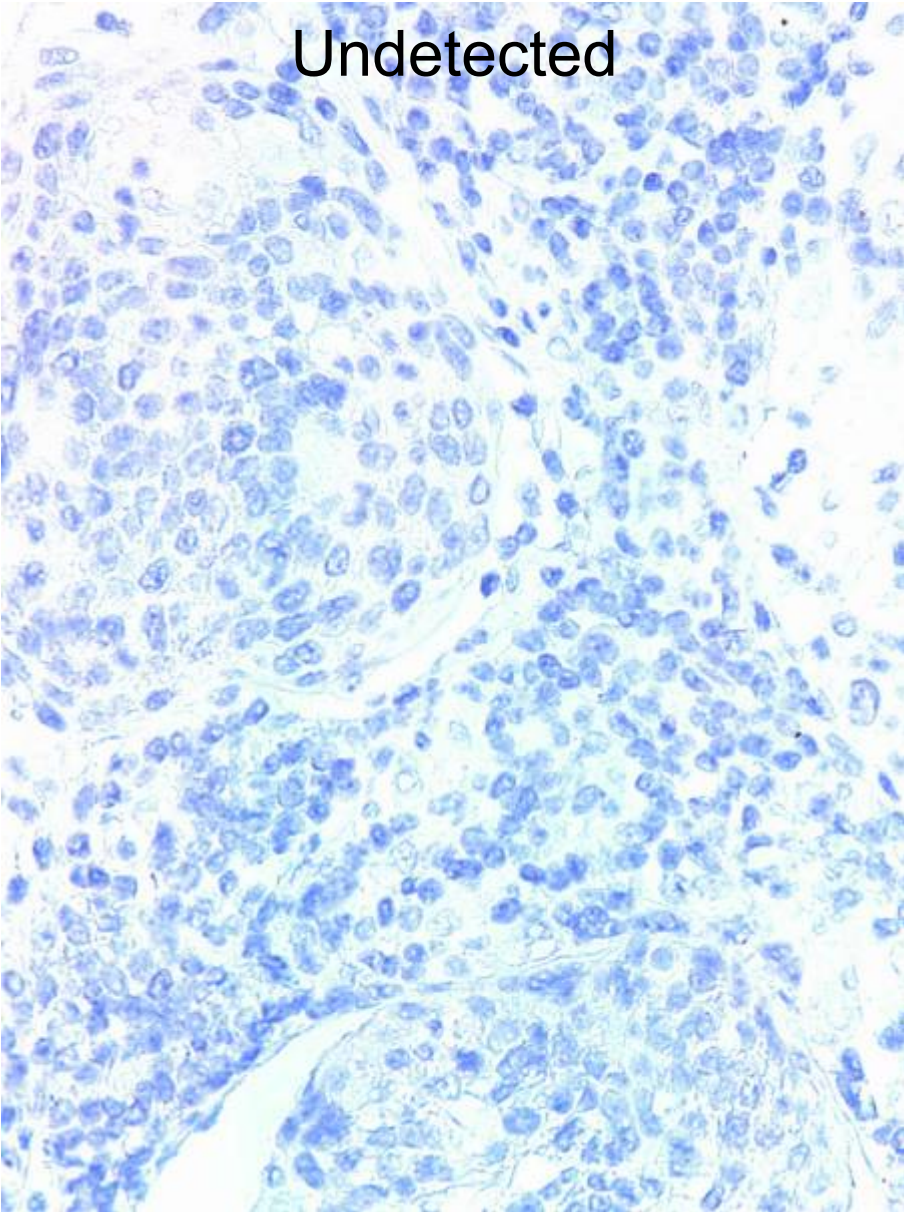
x20 mag

# HPV 16/18 ISH

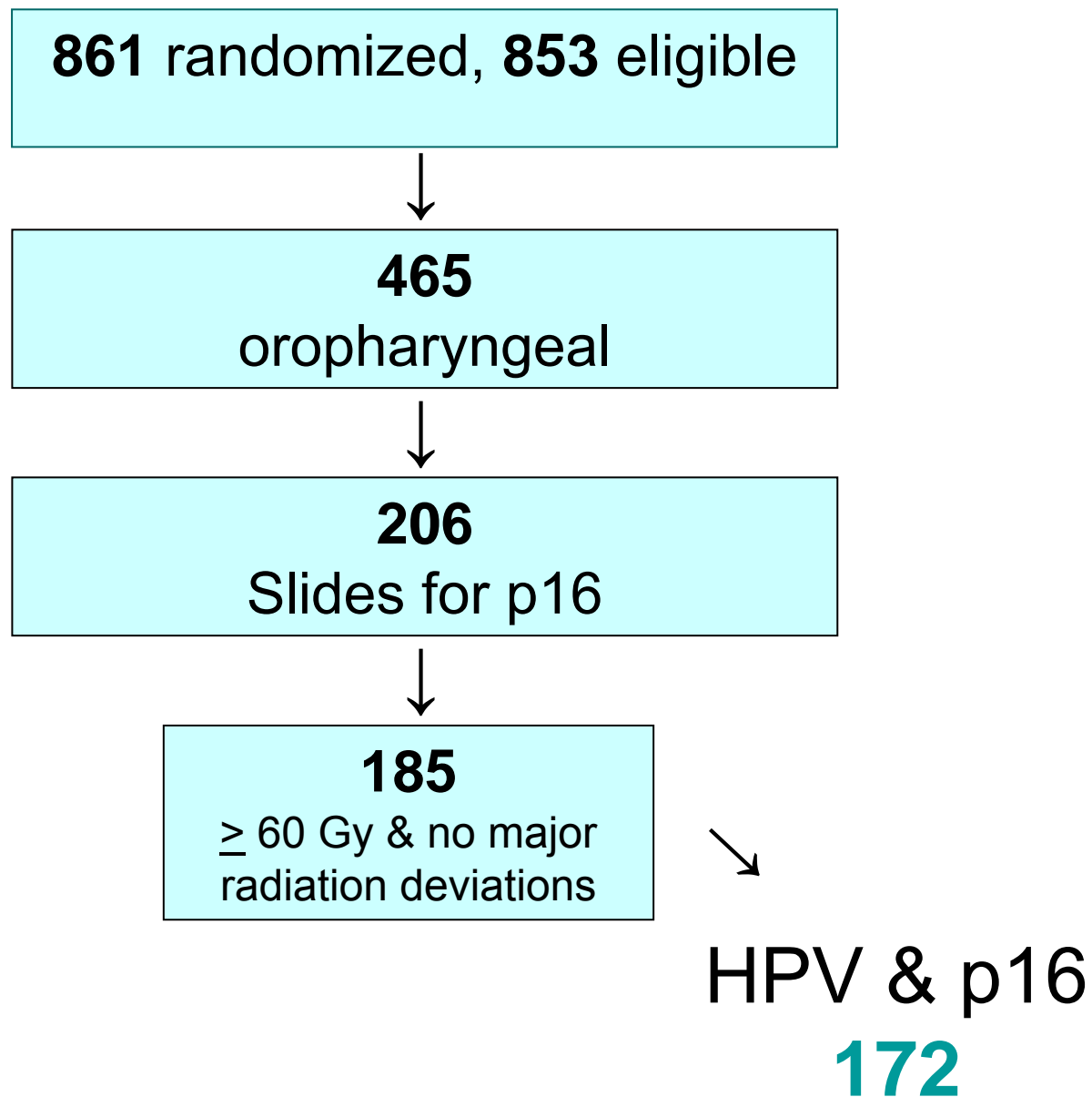
Undetected

Detected

x40 mag



# Patients



# p16 and HPV results

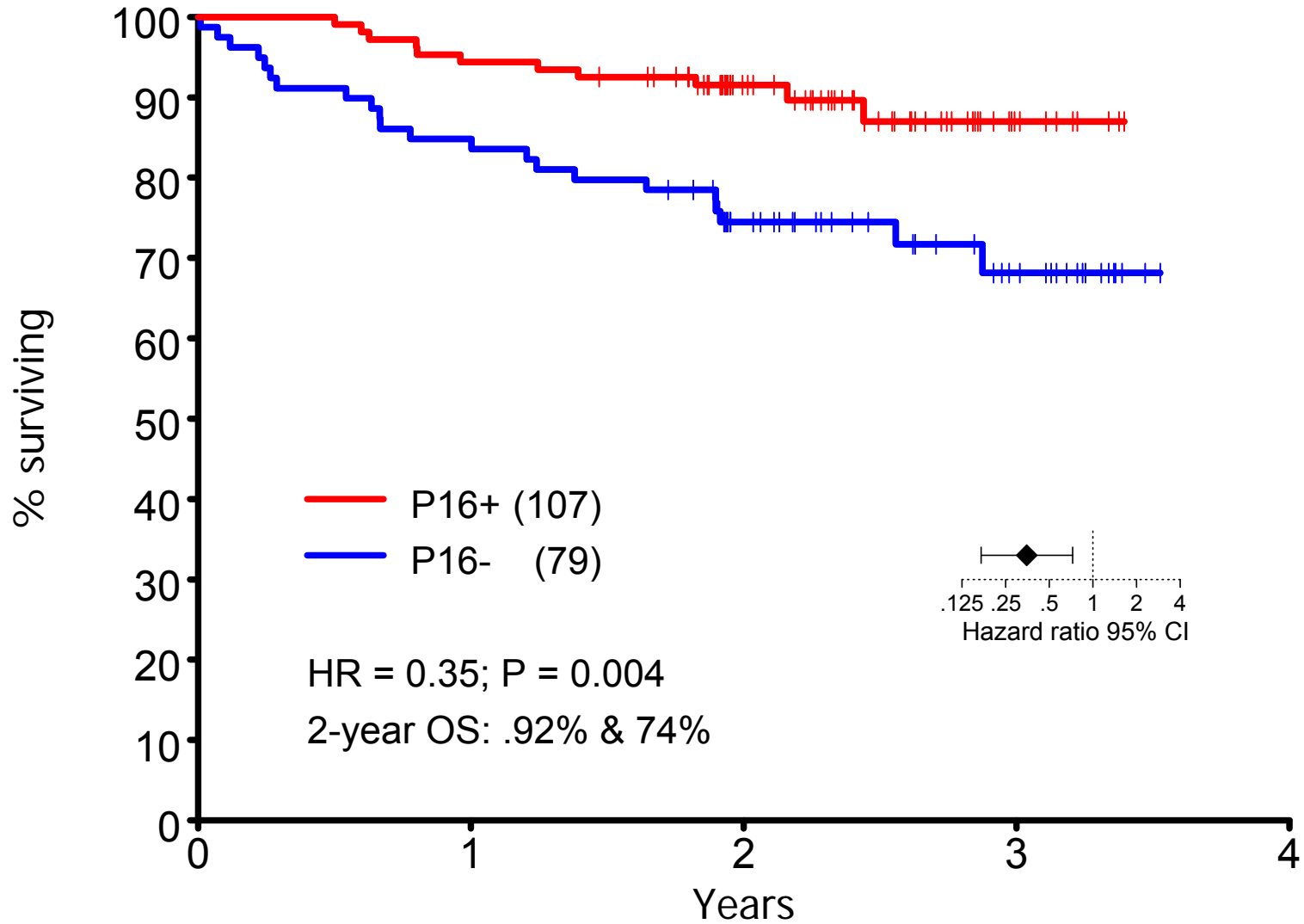
- 172 patients tested for HPV and p16
- 102/172 (59%) p16 positive
- 88/100 evaluable p16 positive patients were HPV positive by ISH and/or PCR
- ANZ patients 53/96 (55%) p16 +
- North American pts 44/58 (76%) p16+

# Patient Characteristics

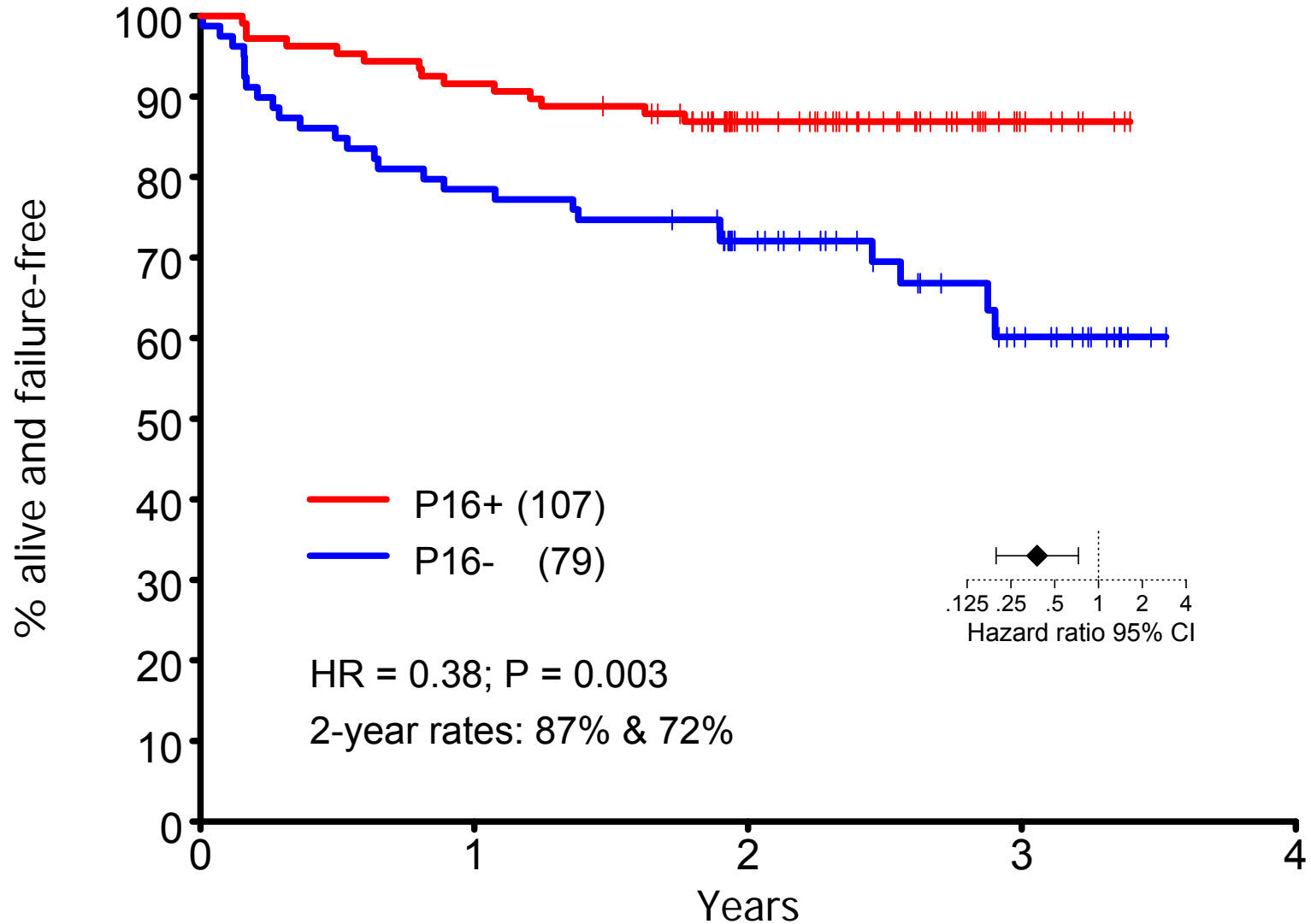
	p16 neg	p16 pos
Male	81%	87%
Median age (years)	58	54
T Stage 3-4	85%	63%*
N stage 2-3	65%	86%*
ECOG PS 0	57%	78%*
Current smoker	45%	15%*

\* P < 0.05

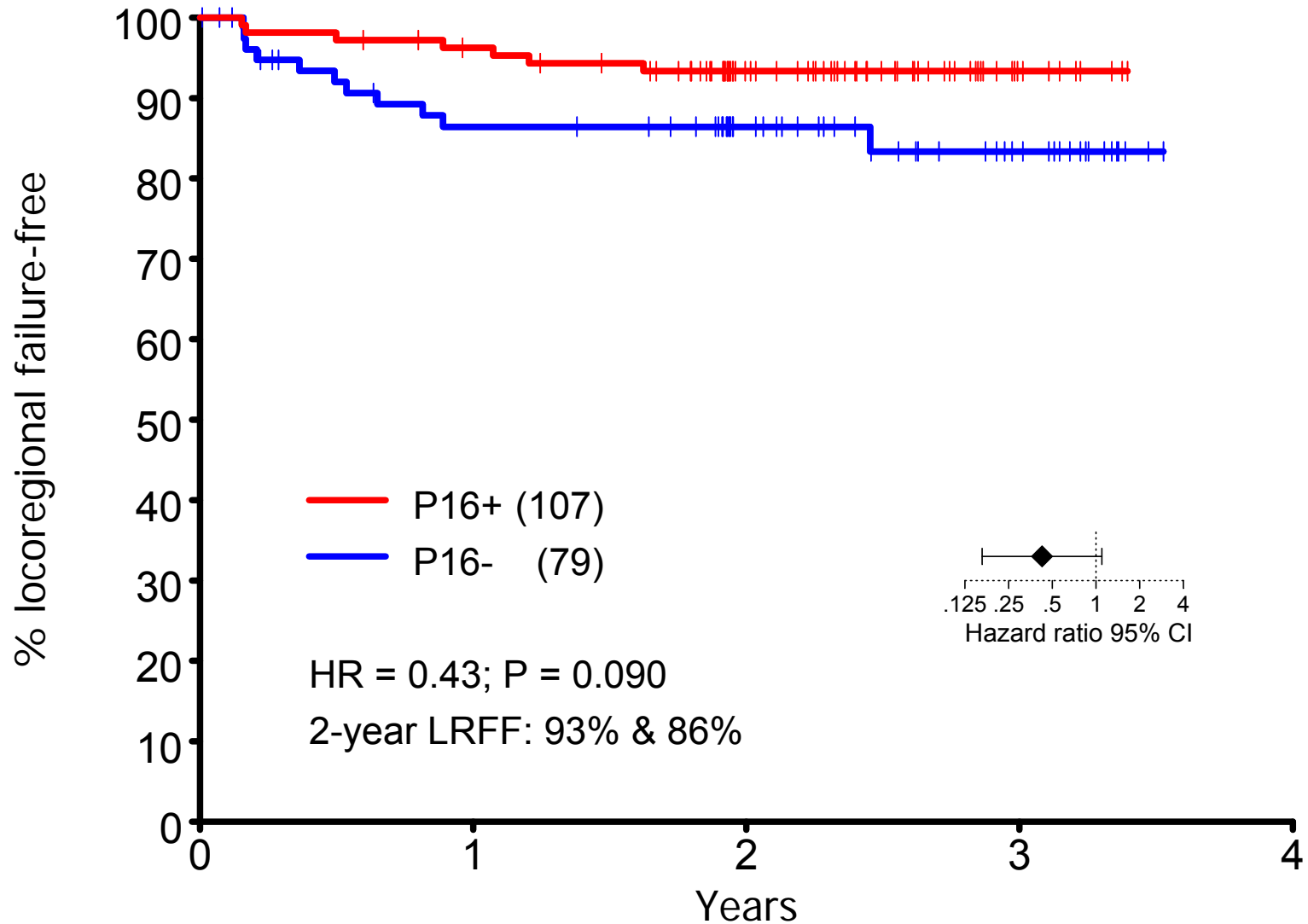
# Overall Survival – p16



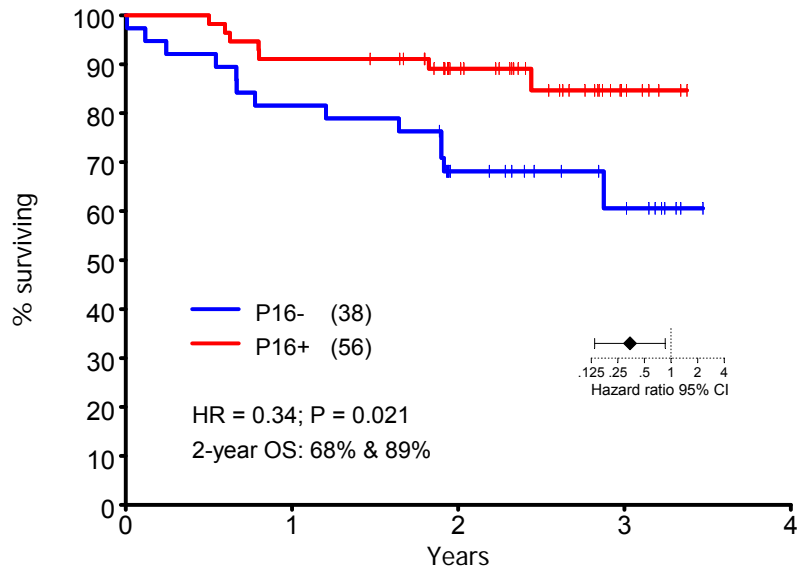
# Failure-Free Survival - p16



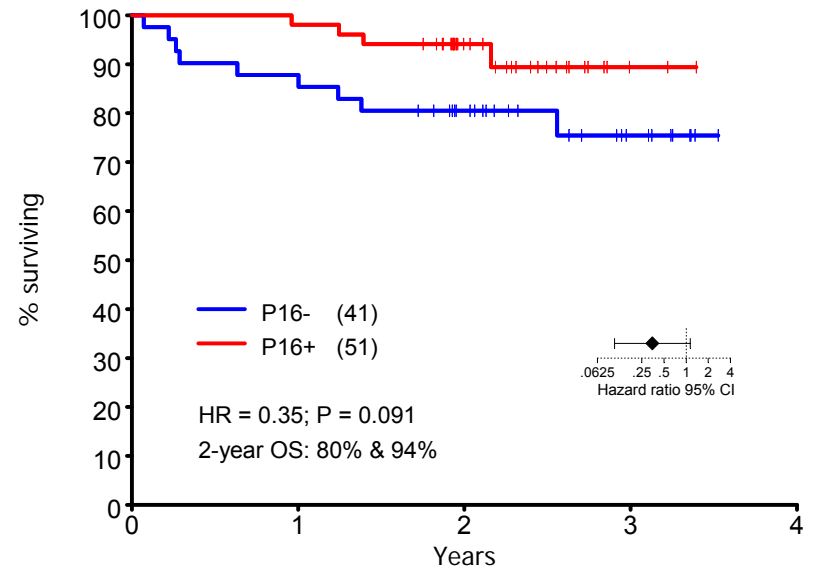
# Time to Locoregional Failure - p16



# Overall Survival – p16 by arm

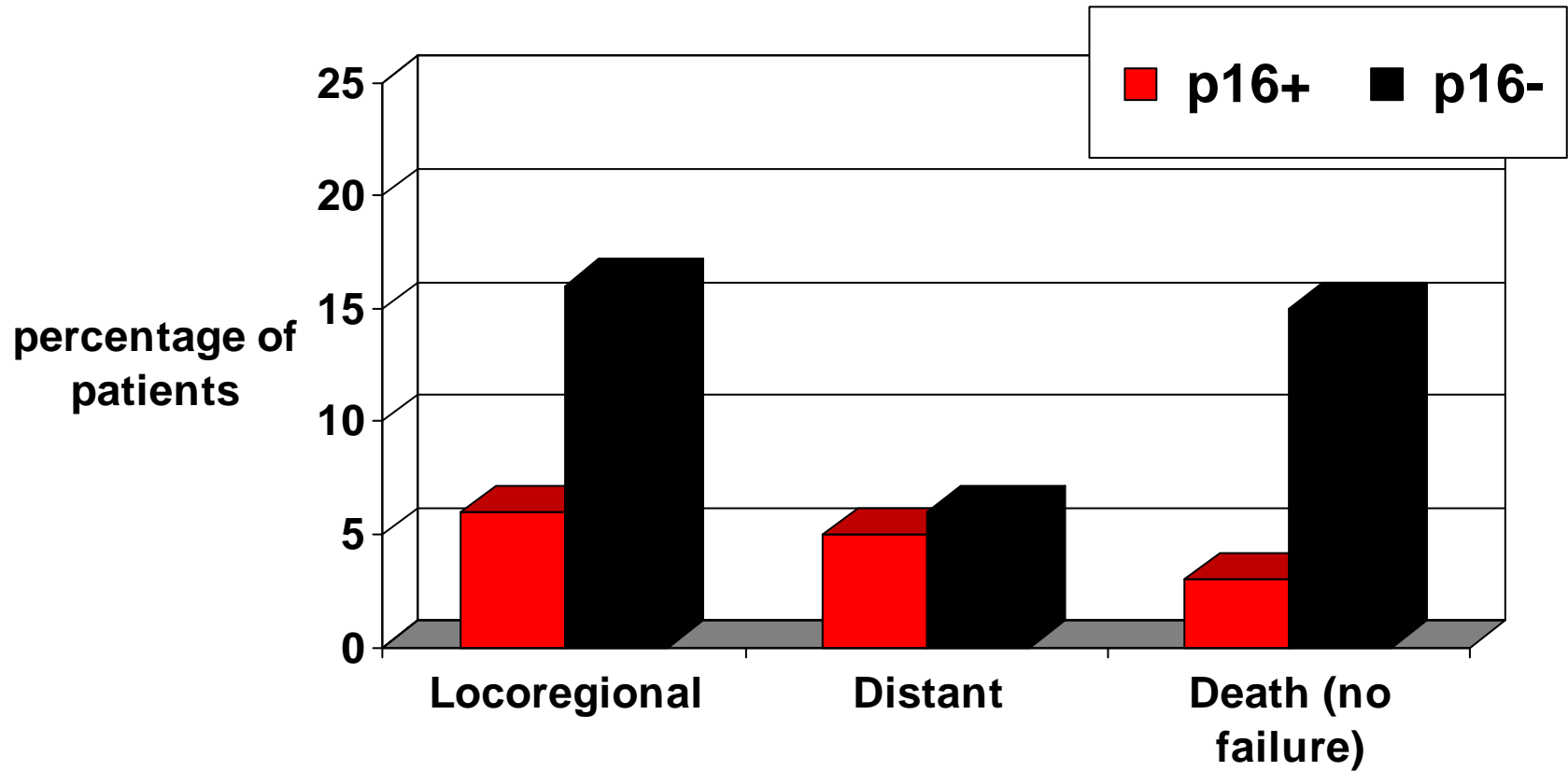


CIS

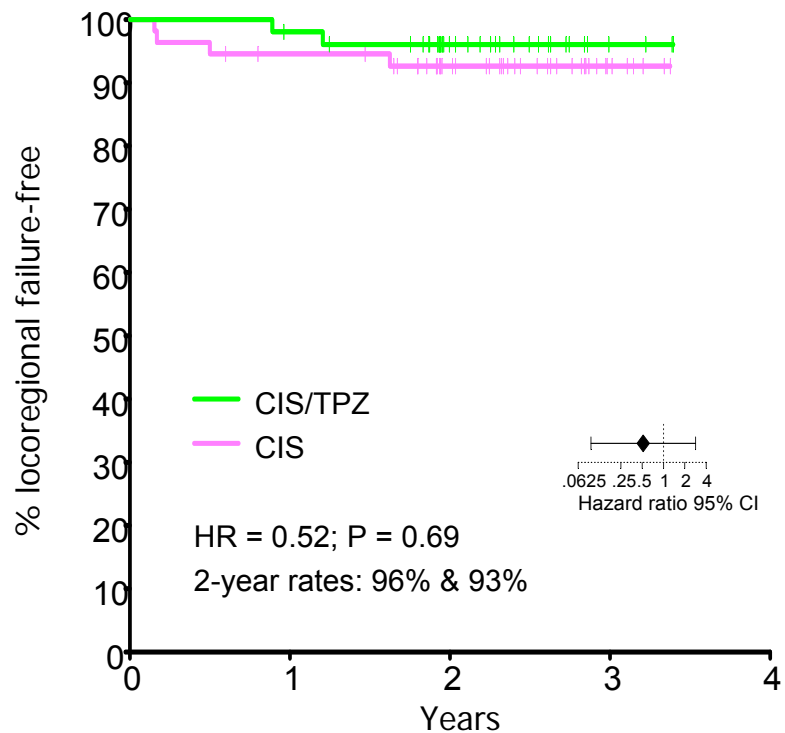


CIS/TPZ

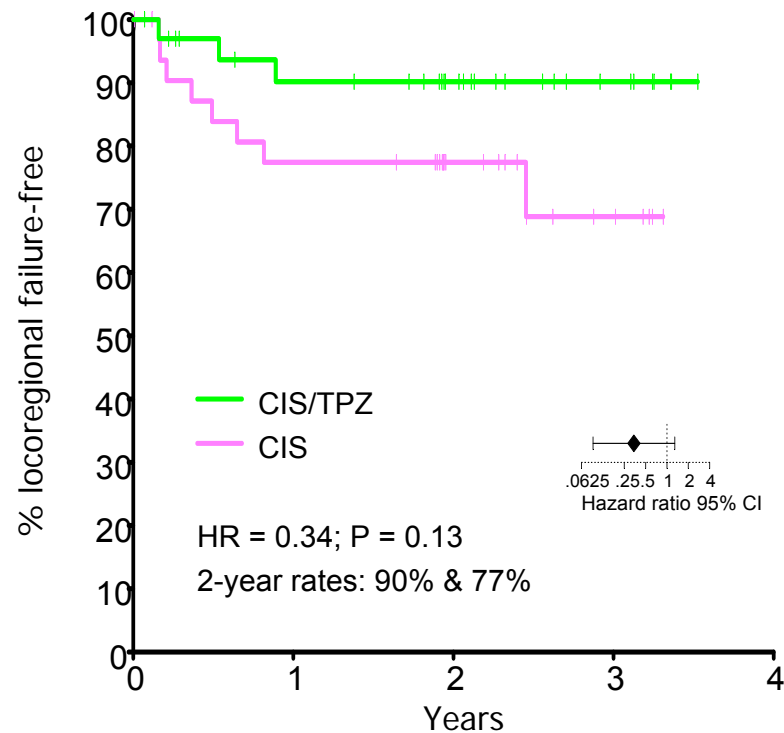
# Site of First Failure



# Time to Locoregional Failure by Treatment Arm



**p16 +**



**p16-**

# Multivariable analysis of overall survival

			Overall survival	
factor	level		HR	2P
p16	+:-		0.45	0.04
T category	1,2 : 3,4		0.41	0.10
N category	neg : pos		0.66	0.38
ECOG	0:1,2		0.69	0.32
Hb	High:low		0.49	0.06

	n	Treat ment	2 yr OS HPV+	2 yr OS HPV-	LRC HPV +	LRC HPV-
ECOG 2399	62	IC+ CRT	95%	62%	-	-
Dahanca 5	74	RT+/- nimorazole	85%	46%	72%	38%
TAX 324	119	IC+ CRT	90%	45%	-	-
RTOG 0129	323	CRT	88%	66%	86%	75%
TROG 02.02	185	CRT	92%	74%	93%	86%

# Conclusions (1)

- HPV positive oropharyngeal cancer treated with cisplatin based concurrent chemoradiation confirmed to be associated with better prognosis
- Currently inadequate data to justify changing management based upon HPV status

## Conclusions (2)

- Information about HPV status essential for interpretation of trials of (chemo)radiation in head and neck cancer
- Future head and neck cancer trials require stratification by HPV status
- Separate trials in HPV positive oropharyngeal cancer warranted to determine optimal therapy in this population