Desescalament en el tractament del càncer d'orofaringe VPH+

En contra ...

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Locally advaced Head & Neck Cancer:
Paradigm of intensification

- Standard fractionated radiotherapy
- Accelerated radiotherapy
- Induction chemotherapy → Standard RT
- Concurrent chemo-radiotherapy
- Concurrent chemo-accelerated radiotherapy
- Concurrent chemo-radiotherapy plus cetuximab
- Induction taxane-based CT → CT_RT

Severe late toxicity

		Patients, n	Number of grade 3–4 events used in max-grade method	Total reported number of grade 3–4 events	Number of toxic events excluded by max-grade method (%)
90-03	Standard radiotherapy alone	266	94	132	38 (29)
90-03	Split-course accelerated radiotherapy alone	274	139	197	58 (29)
95-01	Standard postoperative radiotherapy alone	210	72	106	34 (32)
90-03	Hyperfractionated radiotherapy alone	263	146	230	84 (37)
91-11	Standard radiotherapy alone: larynx	169	74	120	46 (38)
90-03	Concomitant boost radiotherapy alone	266	160	261	101 (39)
95-01	Concurrent chemoradiotherapy (platinum)	206	155	328	173 (53)
97-03	Concurrent chemoradiotherapy (platinum and fluorouracil)	78	53	128	75 (60)
97-03	Concurrent chemoradiotherapy (hydroxyurea and fluorouracil)	76	59	147	88 (60)
97-03	Concurrent chemoradiotherapy (platinum and paclitaxel)	77	66	177	111 (63)
91-11	Concurrent chemoradiotherapy (platinum): larynx	171	136	380	244 (64)
91-11	Induction chemotherapy (platinum and fluorouracil) and standard radiotherapy: larynx	173	133	379	246 (65)
99-14	Concurrent chemoradiotherapy (platinum) with concomitant boost radiotherapy	76	70	233	163 (70)

Table 1: **Acute grade 3–4 events excluded by the max-grade method in 13 treatment groups in head and neck cancer trials ranked by progressive data exclusion**

Trotti A, Lancet Onc 2007

What means de-intensification?

- To select patients with high probability to be cure,
- In which the standard treatment produces significant toxicity

De-intensification is to modify the standard treatment in order to:

reduce the long-term toxicities associated

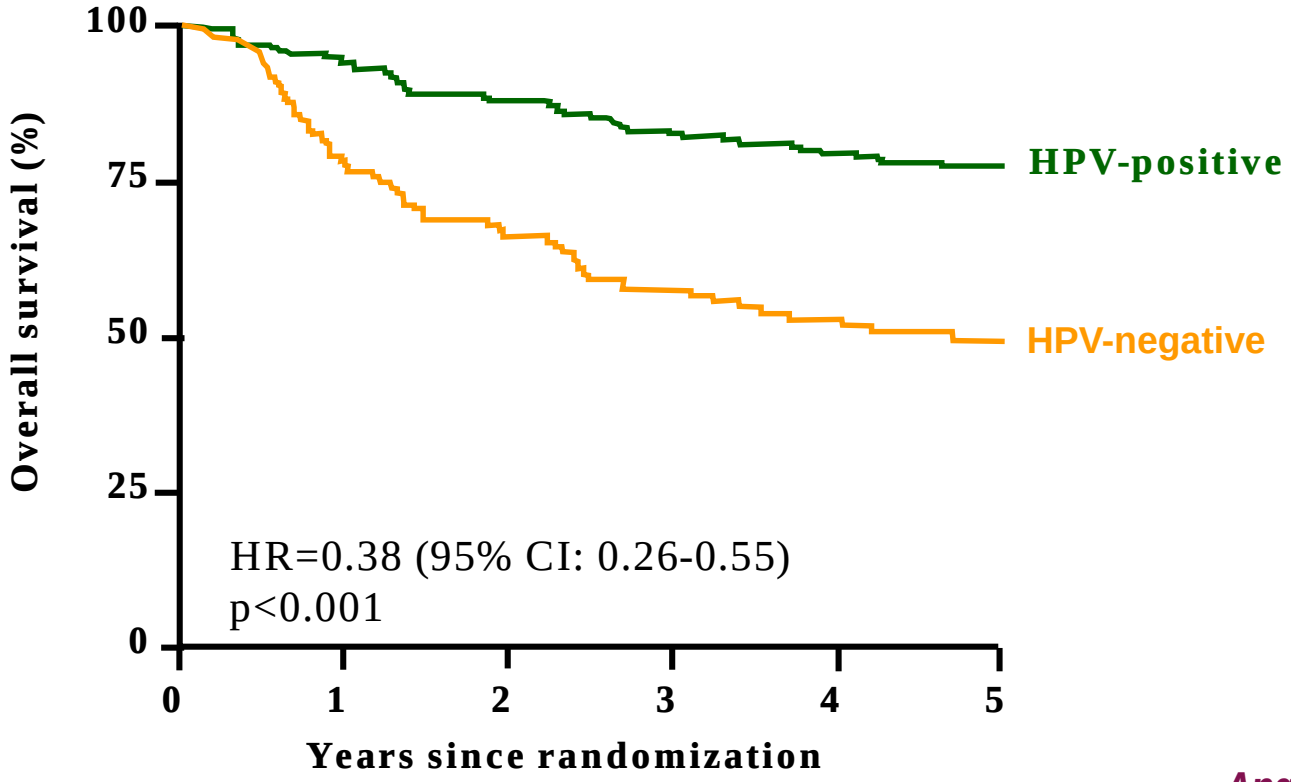
with radiation / chemotherapy

AND

still maintaining the high cure rates

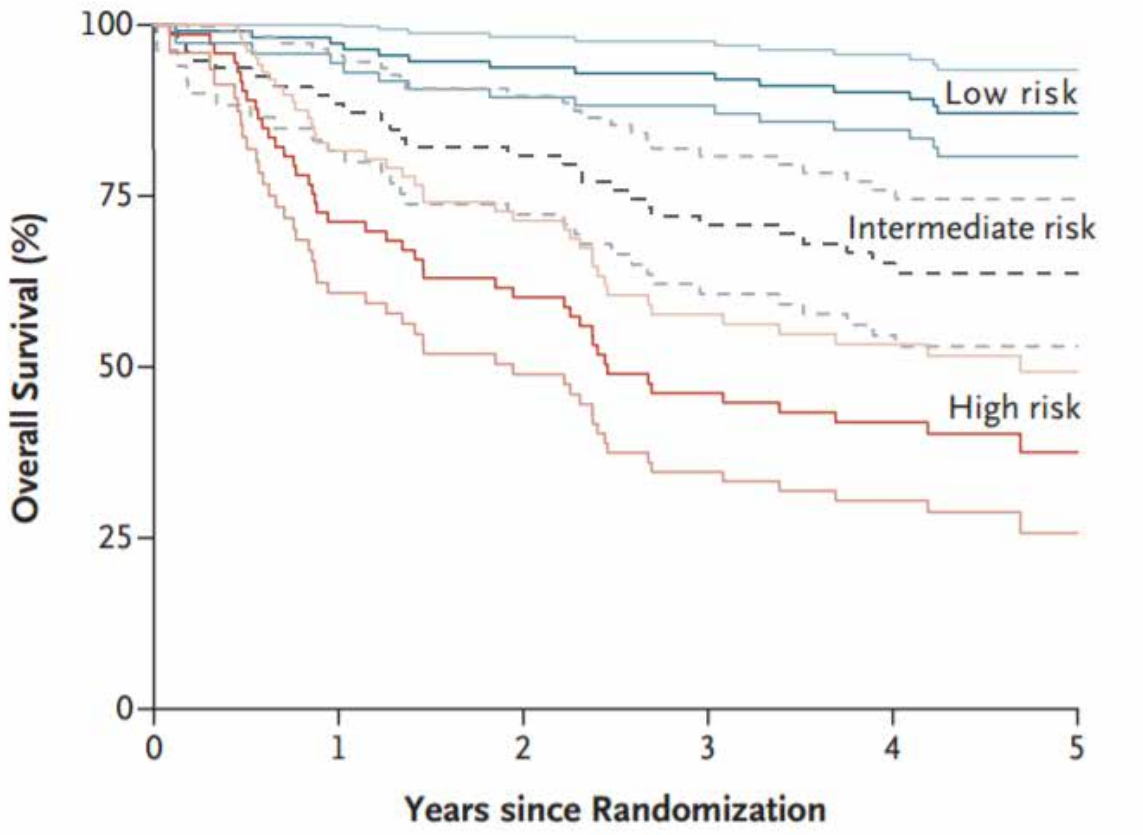
Are HPV + patients a good candidates for de-intensification?

RTOG 0129; 330 stage III-IV oropharynx patients:
standard vs accelerated RT plus cisplatin



Ang et al. NEJM 2010

Survival outcomes by HPV status
RTOG 0129 study



Low risk: 93% 3y
HPV + / ≤10 pack-y
HPV + / ≥10 pack-y /N0-N2a

Intermediate risk: 71% 3y
HPV + / ≥10 pack-y /N2b-N3
HPV - / ≤10 pack-y /T2-T3

High risk: 46% 3y
HPV - / ≤10 pack-y /T4
HPV - / >10 pack-y

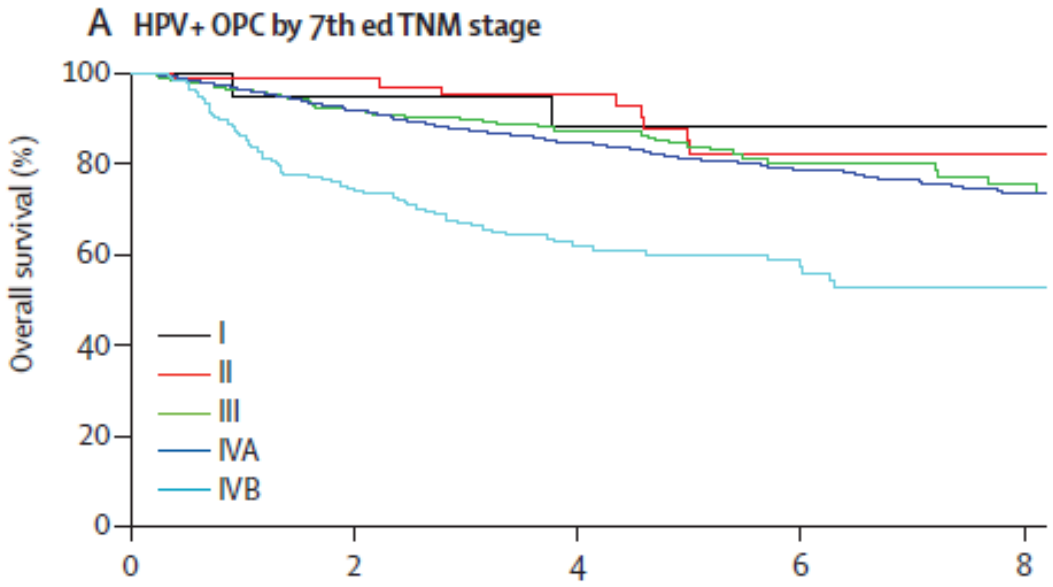
Ang et al. NEJM 2010

Survival according HPV in clinical trials

Regimen	Group	Time	HPV +	HPV -	P
Induction + CT-RT	ECOG	2-y	95%	62%	0.005
QT-RT	TROG 2.2	2-y	94%	77%	0.007
Tax-Induc. + CT-RT	TAX324	5-y	82%	35%	<0.001
RT-cetuximab	Bonner	3-y	88%	42%	HR;0.18
Radiotherapy	DHANCA 5	3-y	62%	26%	0.003
Relapse	RTOG 0129-0522	2-y	55%	28%	<0.001

Fakhry JNCI 2008, Rischin JCO 2009, Posner An Onc 2011, Rosental JCO 2016, Lassen JCO 2009, Fakhry JCO 2014

HPV + survival according 7th ed TNM



	HPV+	
	Hazard ratio (95% CI)	p*
7th edition TNM stage	..	..
I	Reference	..
II	1·19 (0·25–5·62)	0·83
III	2·52 (0·61–10·41)	0·2
IVA	3·41 (0·84–13·85)	0·086
IVB	7·91 (1·92–32·59)	0·004

O'Sullivan, B. Lancet Onc 2016

Staging for HPV-related oropharyngeal cancer (ICON-S)

- Non-metastatic oropharyngeal cancer patients from 7 cancer centres
- One is the training cohort and six formed the validation cohorts
- Compare overall survival at 5 years
- Recursive partitioning analysis and adjusted hazard ratio (AHR) modelling methods to derive new classifications
- 1907 patients with HPV+ oropharyngeal cancer; 661 (35%) in the training centre and 1246 (65%) at the validation centres.
- They proposed a International Collaboration on Oropharyngeal cancer Network for Staging

O'Sullivan, B. Lancet Onc 2016

ICON-S (Internat. Collaboration Oroph. Network-Staging)

	7th edition TNM N category	ICON-S N category	ICON-S T category			
			T1	T2	T3	T4*
Gross lymph node						
None	N0	N0	1·00, n=19	1·20 (0·25–5·65), n=71	3·41 (0·77–15·16), n=54	4·33 (0·93–20·21), n=29
Unilateral neck, <6 cm	N1, N2a, N2b	N1	1·57 (0·38–6·54), n=394	2·84 (0·69–11·60), n=478	3·56 (0·85–14·83), n=201	7·30 (1·74–30·65), n=92
Bilateral or contralateral neck, <6 cm	N2c	N2	2·13 (0·44–10·31), n=61	3·51 (0·81–15·12), n=129	4·99 (1·18–20·99), n=119	9·07 (2·19–37·66), n=127
>6 cm	N3	N3	8·85 (1·97–39·85), n=30	4·88 (1·03–23·19), n=38	13·04 (3·00–56·74), n=38	11·47 (2·60–50·59), n=27

Data are hazard ratio (95% CI), number of patients. Hazard ratios are adjusted for age, smoking pack-years, and use of cytotoxic chemotherapy (yes vs no). ICON-S=International Collaboration on Oropharyngeal cancer Network for Staging. *ICON-S T definitions are unchanged from the 7th edition TNM classification, except there is no subdivision within T4 because survival was identical between T4a and T4b.

Table 5: **Re-termed ICON-S T and N categories and corresponding hazard ratios for risk of death within each T category**

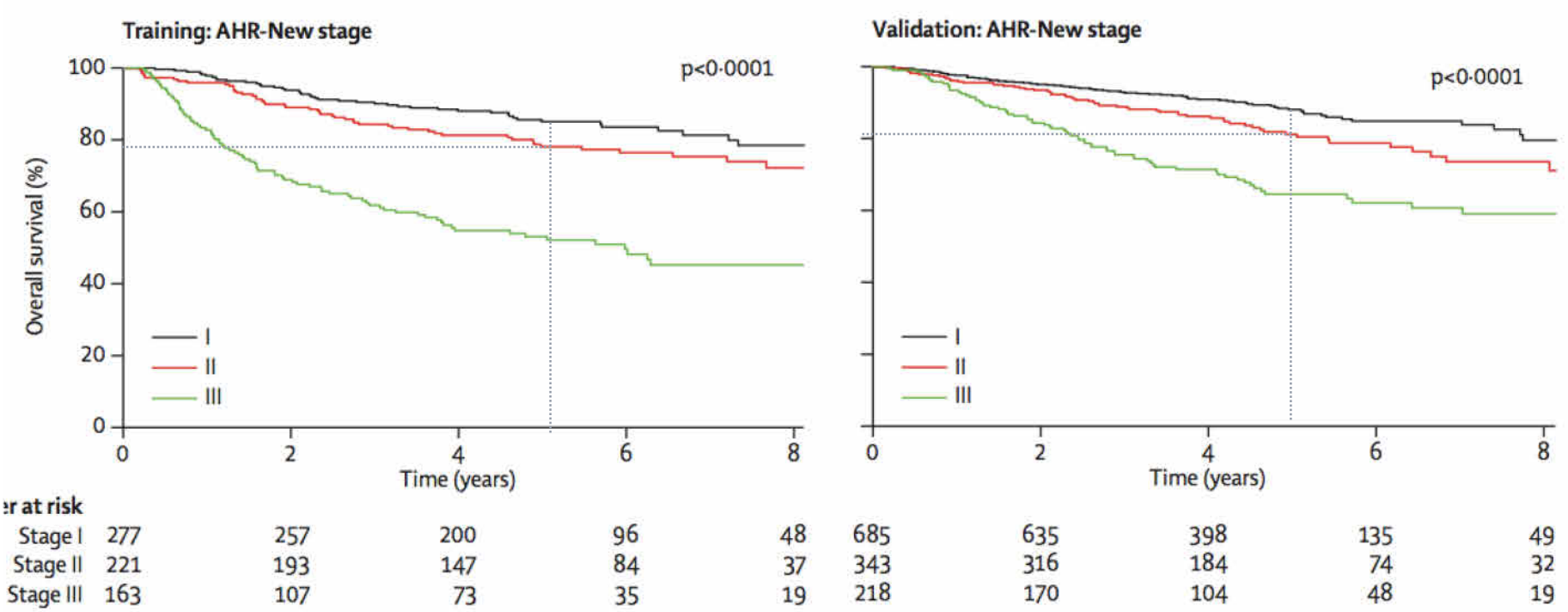
AHR-New stage classification	T1	T2	T3	T4
N0	I	I	II	III
N1	I	I	II	III
N2a	I	I	II	III
N2b	I	I	II	III
N2c	II	II	II	III
N3	III	III	III	III

N stage updated

ICON-S stage classification	T1	T2	T3	T4
N0	I	I	II	III
N1	I	I	II	III
N2	II	II	II	III
N3	III	III	III	III

O'Sullivan, B. Lancet Onc 2016

Staging for HPV-related oropharyngeal cancer (ICON-S)



er at risk										
Stage I	277	257	200	96	48	685	635	398	135	49
Stage II	221	193	147	84	37	343	316	184	74	32
Stage III	163	107	73	35	19	218	170	104	48	19

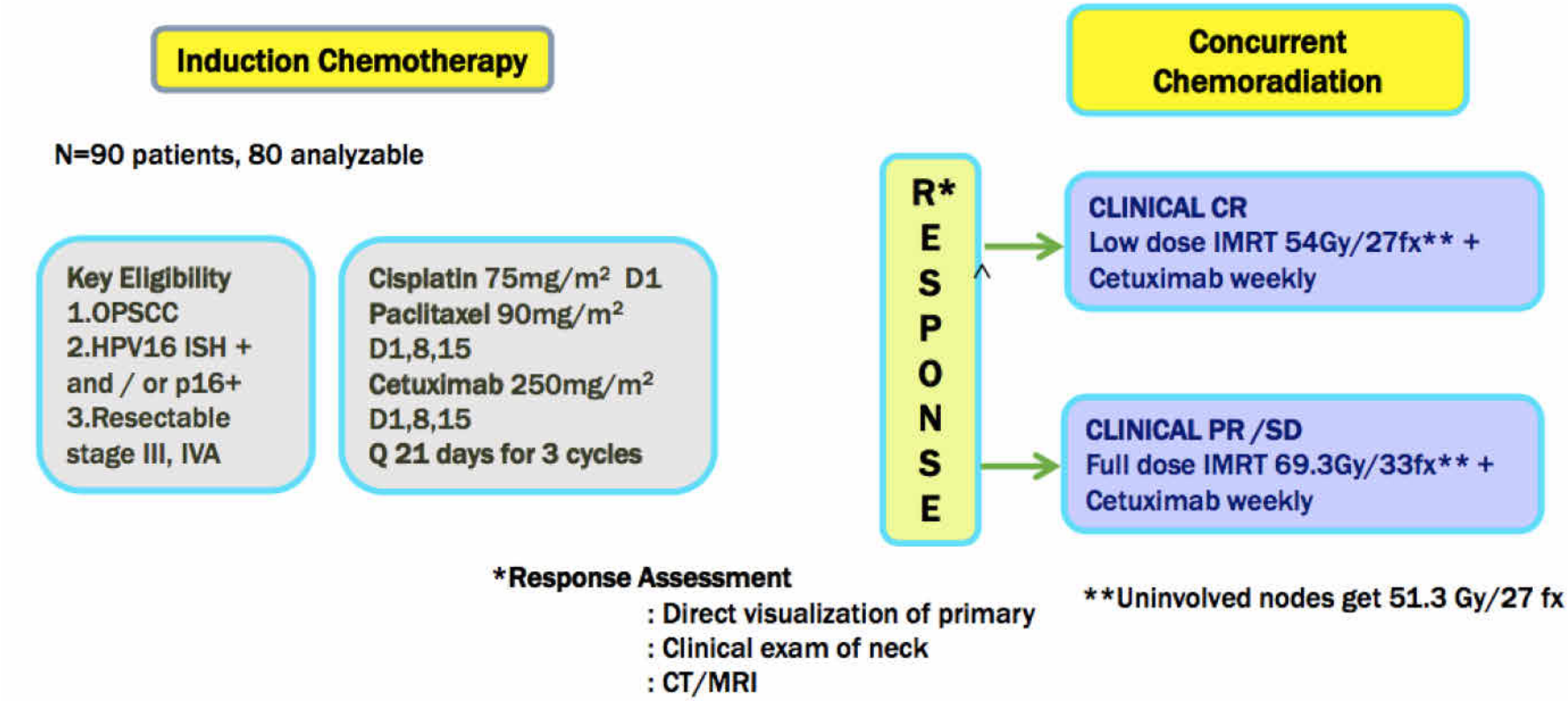
O'Sullivan, B. Lancet Onc 2016

Strategies for de-intensification

- Select chemo responders, reduce RT dose
- Select chemo responders, reduce RT volume
- Reduce dose of RT and cisplatin
- Replace cisplatin with cetuximab
- Reduce RT (60 Gy) and cis vs. RT alone (*HN002*)
- TORS resection, reduce adjuvant RT dose

Select chemo responders, reduce RT dose

E1308: Phase II Trial of Induction CT & Cetuximab with Low or Standard Dose in HPV + Resectable Carcinoma



Cmelak, et al. JCO 2014, 32:5s (Abst 6006) Marur, et al. JCO 2016, Dec 28: JCO2016683300

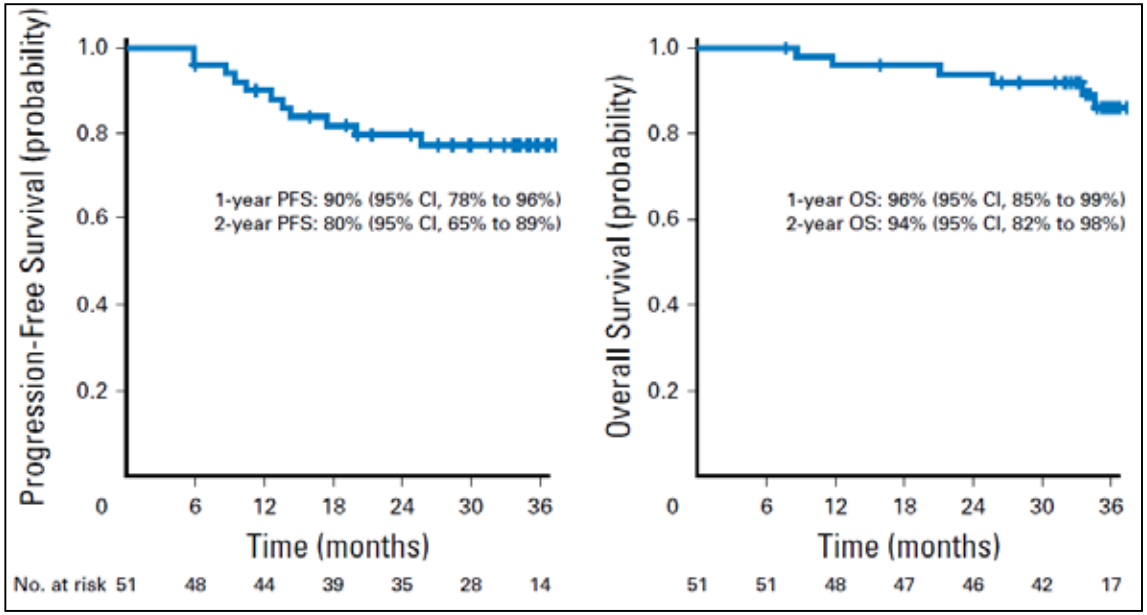


Fig 2. PFS (A) and OS (B) in cohort with clinical complete response to induction chemotherapy treated with low-dose radiation of 54 Gy (n = 51). OS, overall survival; PFS, progression-free survival.

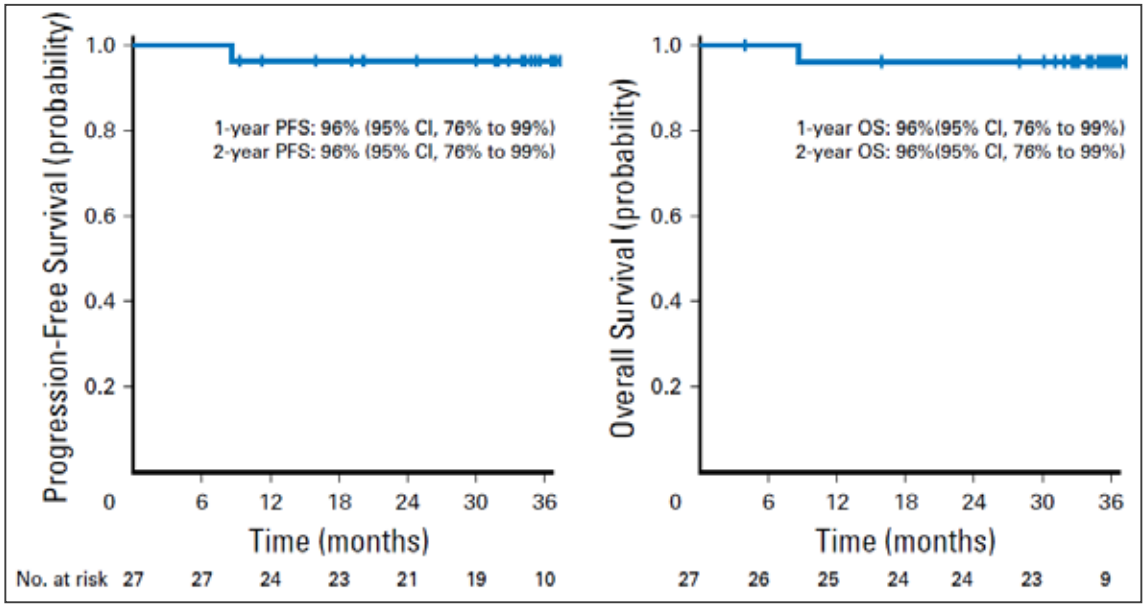


Fig 3. PFS (A) and OS (B) in favorable cohort (non-T4, non-N2c, ≤ 10 pack-year smokers) with clinical complete response to induction chemotherapy treated with low-dose radiation of 54 Gy (n = 27). OS, overall survival; PFS, progression-free survival.

Select chemo responders, reduce RT dose

E1308: Phase II Trial _ Comments

27 patients with <T4, <N2c, <10 pack-year IC + 54 Gy ® 2-y PFS 96%

35 patients with T4, or N2c, or > 10 pack-year IC + 54 Gy ® 2-y PFS 71%

21 patients post IC **NO cCR** IC + 54 Gy ® 8 patients reduced dose
® surgery ± biopsy + reduced dose

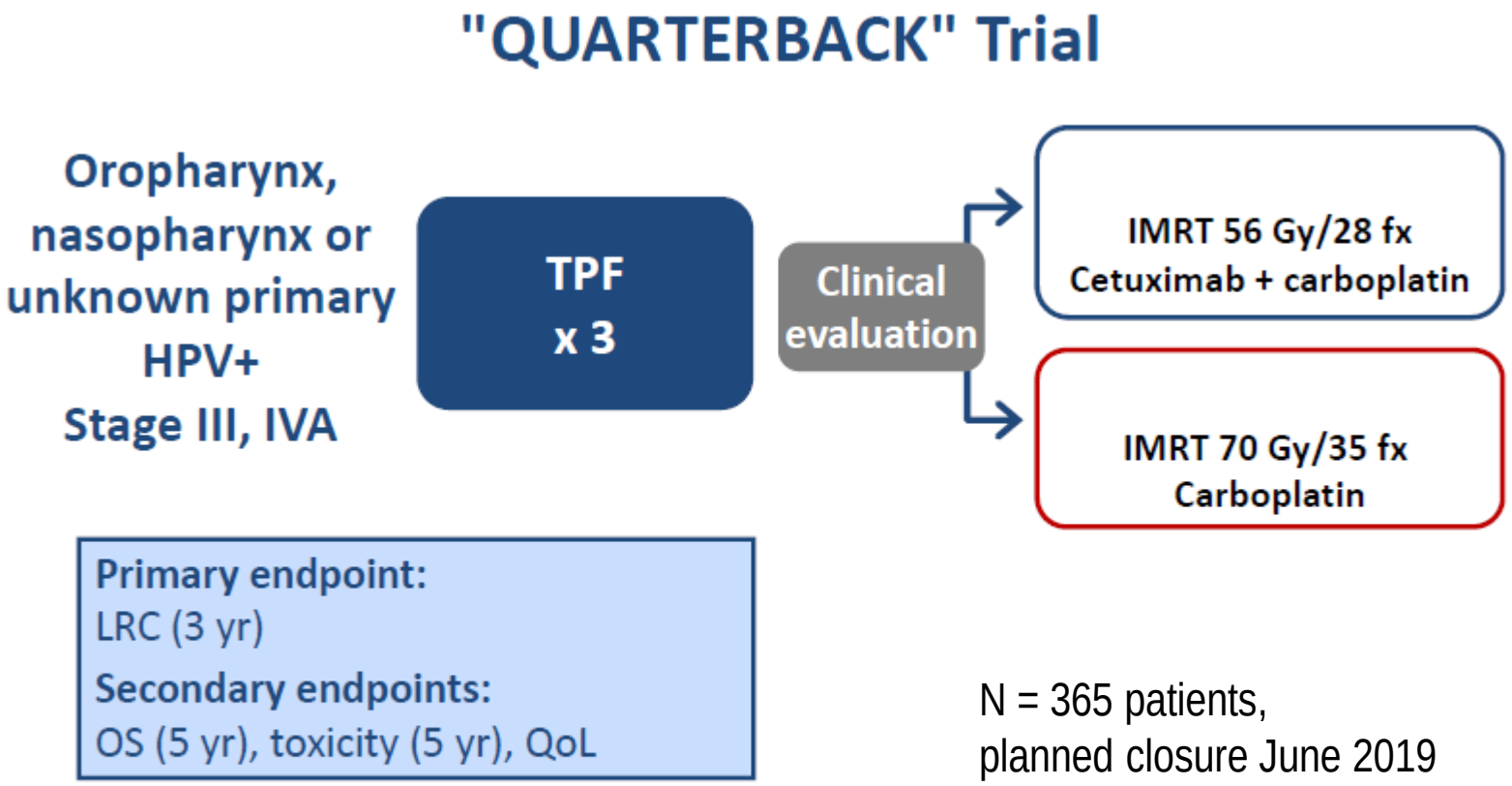
Nodal cCR was seen in only 46 patients (58%)

Of the 56 patients asigned to 54 Gy, five patients received full dose

Of the 51 patients treated with to 54 Gy:

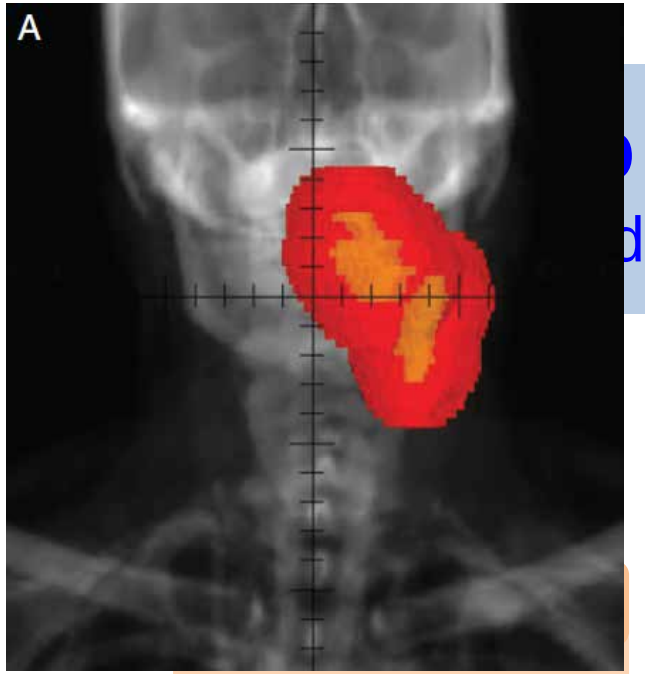
- 4 primary failures
- 2 Nodal failures
- 1 distant metastasis

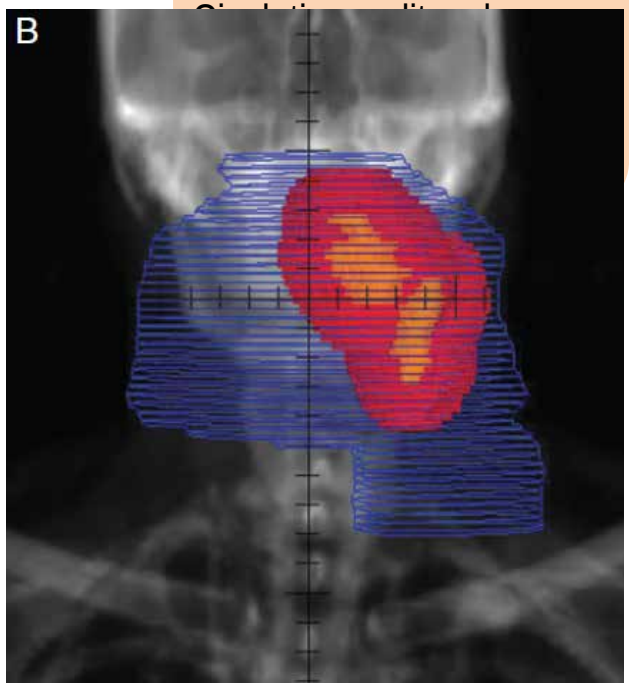
Select chemo responders, reduce RT dose



N = 365 patients,
planned closure June 2019

www.clinicaltrials.gov/ct2/show/NCT01706939





responders, reduce RT volume

d volume de-escalation (RAVD)

≥50% reduction

< 50% reduction

Concurrent chemo-radiotherapy
paclitaxel, fluorouracil, hydroxyurea, 1.5 Gy x2/d RT dose of 75 Gy To thee gross tumour plus margin
paclitaxel, fluorouracil, hydroxyurea, 1.5 Gy x2/d RT 75 Gy (gross tumour) first uninvolved node to a dose of 45 Gy

Villaflor et al. Ann Oncol 2016

Select chemo responders, reduce RT volume

Response-adapted volume de-escalation (RAVD)

- IC response was evaluable in 89 patients.
- 37 patients (41.6%) had GR and 52 (58.4%) had NR
- Trend for improved PFS in GR; 86% vs NR; 69% (P = 0.086)
- The 2-year overall survival were: GR; 83% vs NR; 85%
- G-tube placement during treatment

  (50.0% GR versus 73.5% NR, P = 0.040)
- G-tube dependent at 6-month

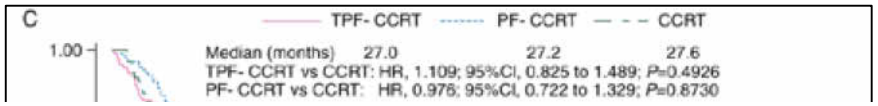
  (5.7% GR versus 32.6% NR, P = 0.005)

Villaflor et al. Ann Oncol 2016

Select chemo responders, reduce RT: Comments

- Data immature; only 2 years follow-up
- Why using IC, when it has failed in 3 clinical trials

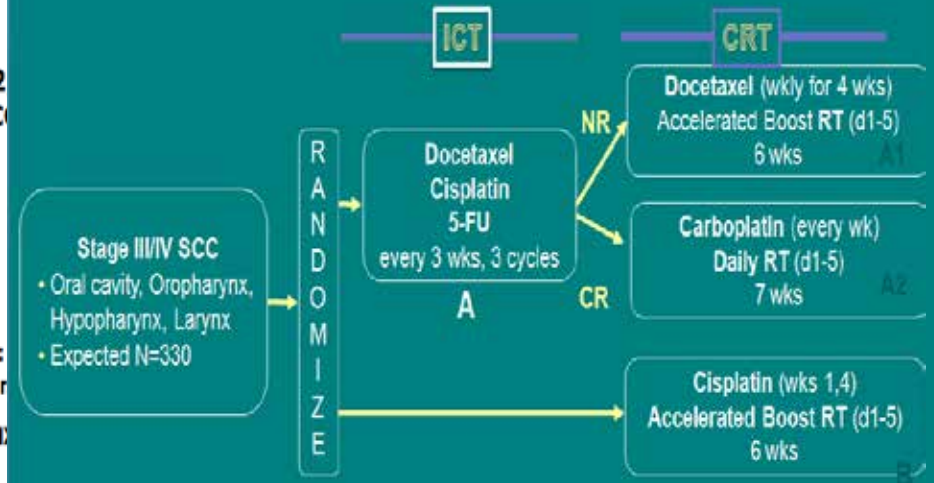
Study design



DeCIDE Schema

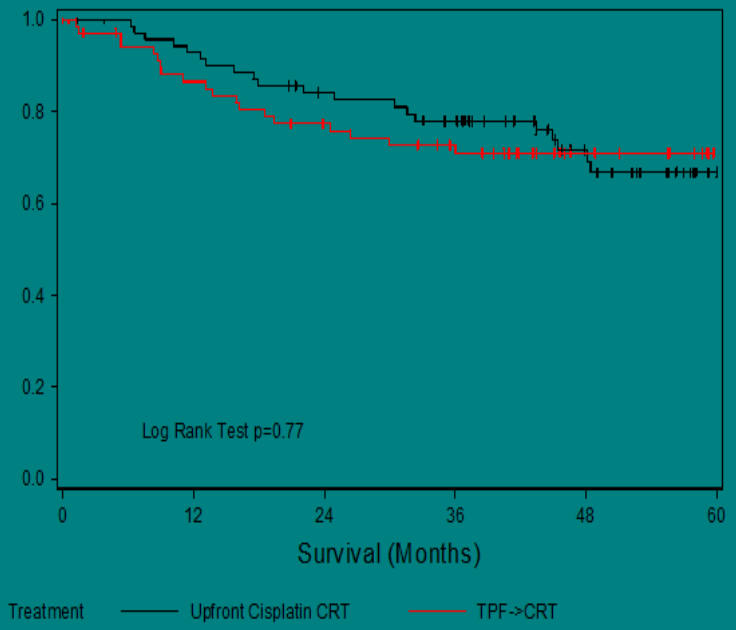
Overall Survival by Treatment Arm

PARADIGM Study Design



Haddad Lancet Onc 2013

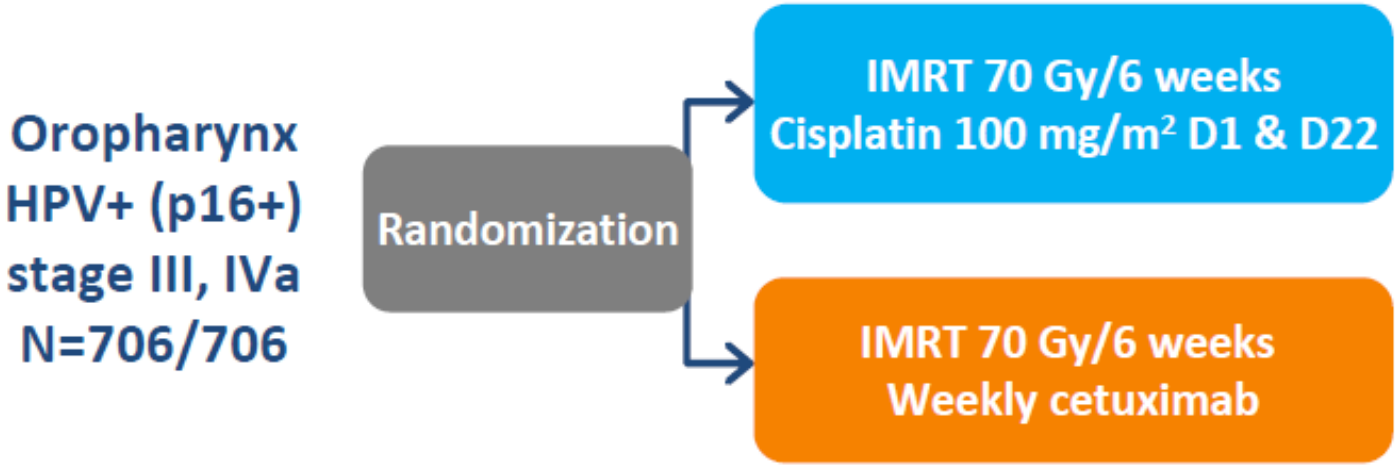
PARADIGM: Overall Survival



Replace cisplatin with cetuximab (survival)

- RTOG 1016 phase III trial

This trial is now closed to accrual. N = 987 patients



Replace cisplatin with cetuximab

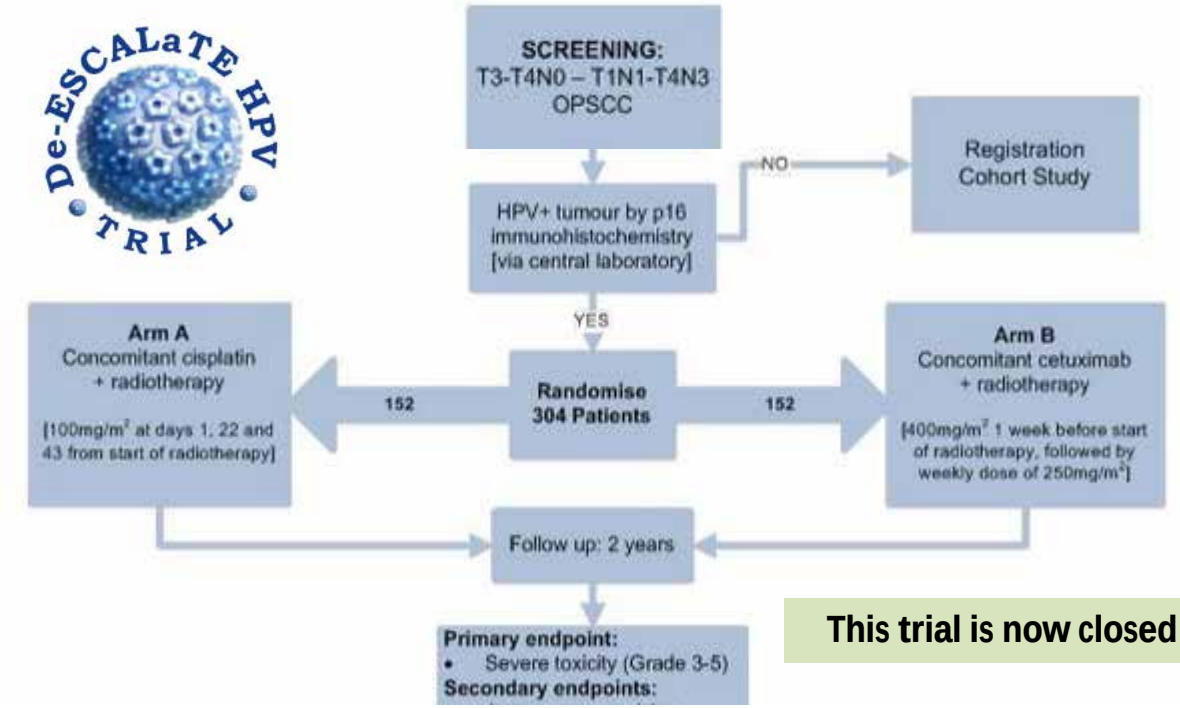
- **TROG 12.01 phase III trial[2]**

Expected date of accrual completion: June 2017

idem RTOG but with conventional RT and weekly cisplatin (40 mg/m2)

- **Des-ESCALATE trial**

Pragmatic, randomised, international, multi-centre, open label, Phase III clinical trial determining the optimum treatment for patients with HPV+ OPSCC.



This trial is now closed to recruitment.

Replace cisplatin with cetuximab

Tremplin study; IC ® CisRT vs CetRT

Lefebvre et al. JCO. 2013

Table 3. Acute Toxicity

Variable	Cisplatin No.	Cisplatin %	Cetuximab No.	Cetuximab %
No. of patients	58*		56	
Mucositis grade				
3	25	43	24	43
4	2	3	1	2
In-field skin toxicity grade				
3	14	24	29	52
4	1	2	3	5
Other toxicity, any grade, justifying protocol modification				
Renal	9	15.5	0	
Hematologic	8	14	0	
Poor performance	7	12	1	1.7
Infusion-related reaction	0		3	5
Protocol modification due to acute toxicity	33	57	19	34

*Two patients did not start treatment.

TTCC 2007-01; IC ® CisRT vs CetRT

Hitt et al. ASCO. 2016

Safety: Specific Advents

	TPF, n (%	Cis+RT, n (%)	Cet+RT, r (%)
	Grades III–IV	Grade III–IV	Grade III–IV
Mucositis	36.2	31.7	44.6
Dysphagia	3.7	6.3	4.5
Vomiting	5.0	2.9	0.5
Anaemia	14.8	13.7	0.0
Neutropenia	3.7	4.9	1.0
Febrile neutropenia	14.6	3.9	1.0
Thrombopenia	1.2	1.5	0.0
Renal failure	2.1	1.5	1.0
Neurotoxicity	0.0	0.0	0.0
Ototoxicity	0.0	0.0	0.0
Dermitis	9.3	2.0	21.8
Skin toxicity	2.9	0.0	6.9
Any SAE	45	28.8	22.8

Reduce RT (60Gy) and cisplatin (30 mg)

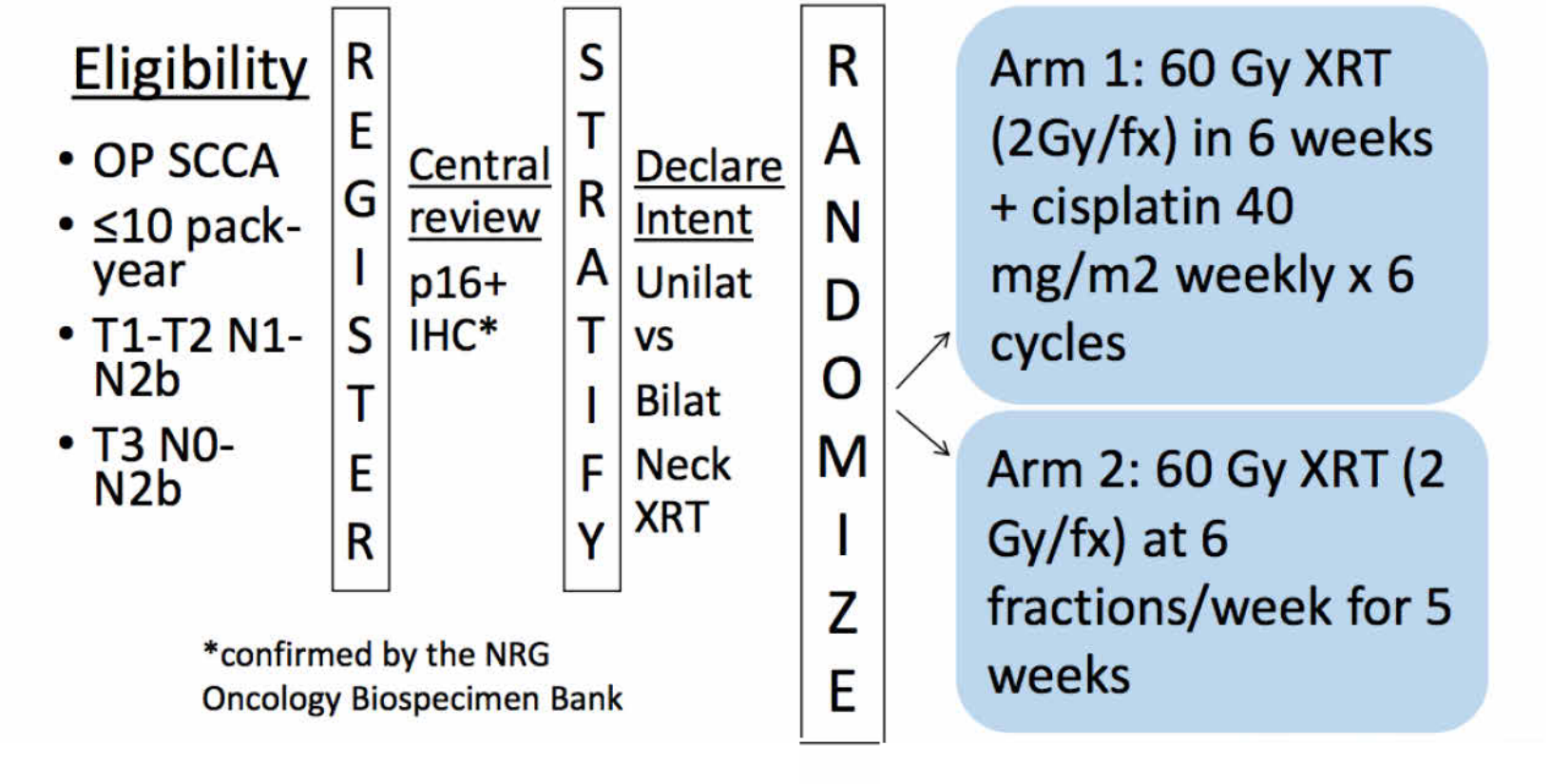
Phase 2 Trial of De-intensified CT_RT for Favorable-Risk HPV-Associated Oropharyngeal Carcinoma

- T0 to T3, N0 to N2c, M0; HPV +; minimal smoking history
- 60 Gy IMRT with weekly cisplatinum 30 mg/m^2
- Pathological evaluation mandatory (primary & nodes)
- N = 43 patients
- The pCR rate was 86% (37 of 43)
- Grade 3 toxicity: mucositis 45%, general 48%, vomiting 34%, dysphagia 55%, xerostomia 75%
- No significant differences in modified barium swallow studies before and after CT_RT

Chera et al. Int J Radiat Oncol Biol Phys. 2015;93:976-85

Reduce RT (60 Gy) and cis vs. RT alone

NRG HN002: A Randomized Phase II Trial for P16 +, Non-Smoking, LR Advanced Oropharyngeal Cancer



Clinical selection of patients for de-intensification schemas

Studies point to a common, **clinically identifiable profile** that **consistently achieves excellent outcomes** within current standards of care

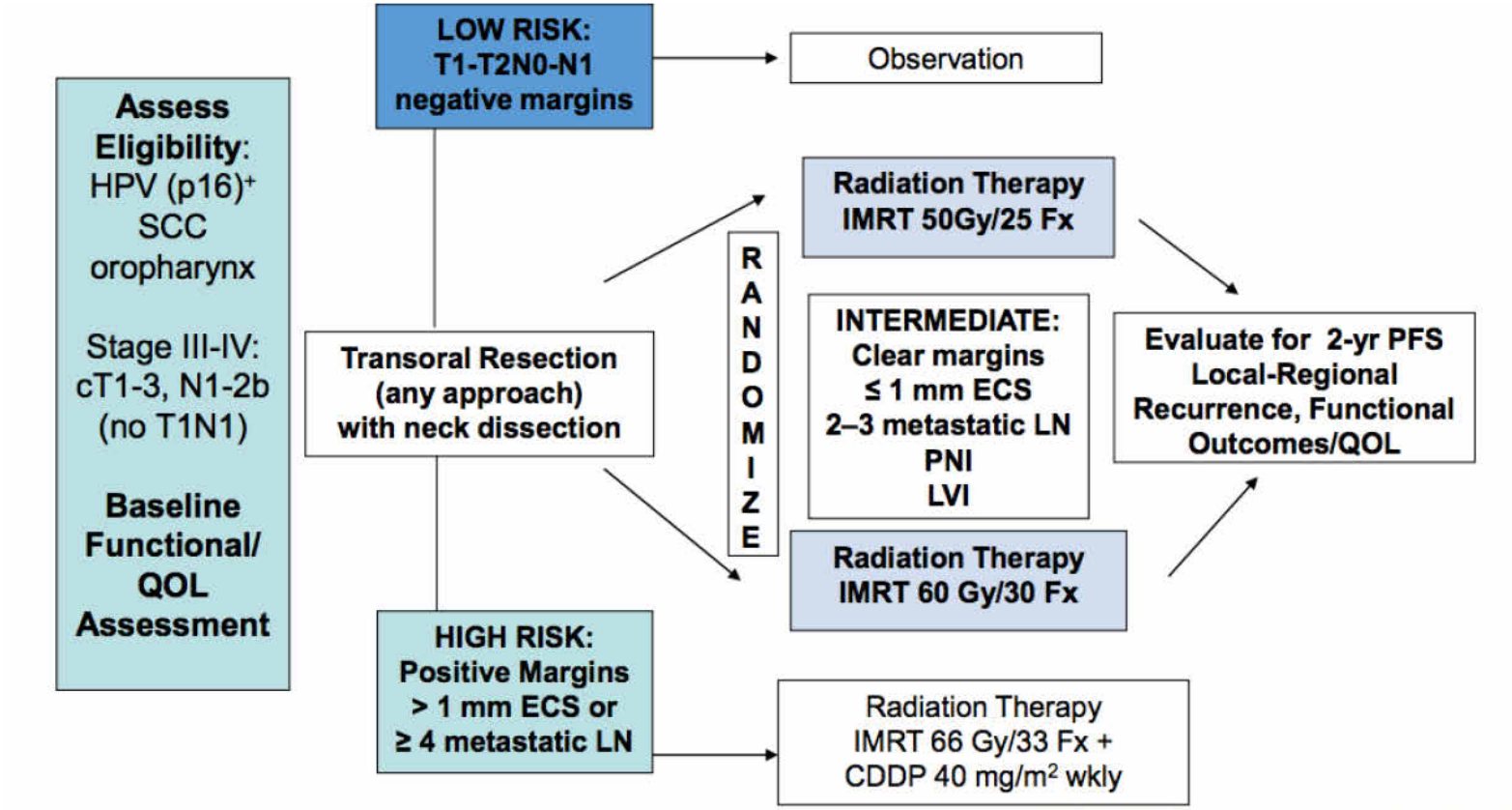
- Oropharyngeal cancer
- P16+
- Minimal smoking history
- Non bulky primary (not T4)
- Non extensive pattern of disease spread (not N2c-N3)

TORS

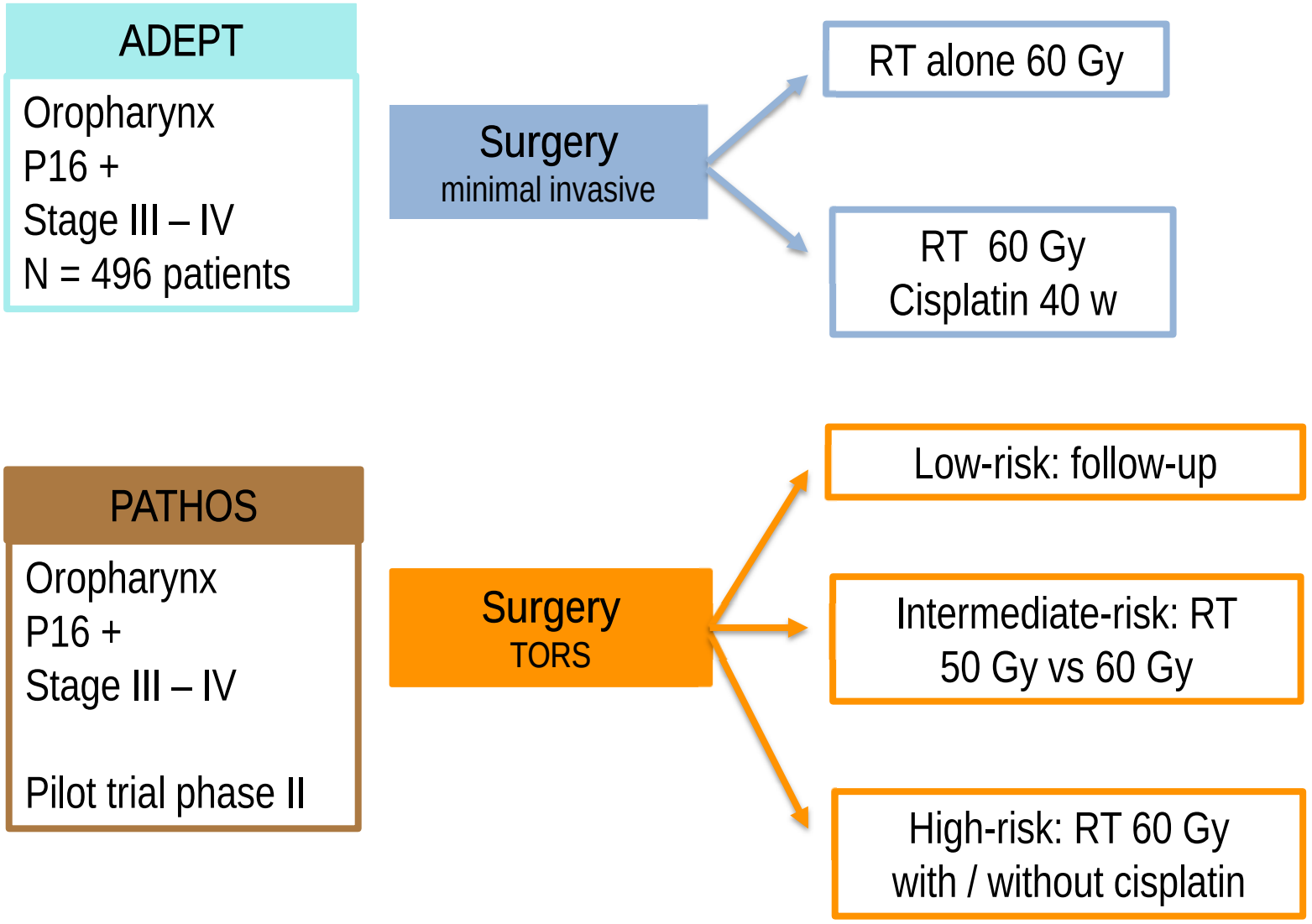
- 2005, the first experiences in robotic head and neck surgery
- In 2009, the FDA approved the use of the da Vinci Robotic Surgical System for TORS, including selected T1 to T2 tumors
- Several institutions have reported oncologic results after TORS
- Reports are limited by small numbers, limited follow-up, or heterogeneity

TORS resection, reduce adjuvant RT dose

ECOG 3311 P16+ Trial – Low Risk OPSCC: Adjuvant Therapy Based on Pathologic Staging of Surgically Excised HPV+ OP SCCA



TORS resection, reduce adjuvant RT dose



TORS versus IMRT

ORATOR

Oropharynx
P16 +
Stage I – III
N = 68 patients

phase II trial

Randomization

- RT ± CT
- TORS

Primary endpoint is QOL
(MD Anderson Dysphagia test)

Best Of

Oropharynx
P16 +
Stage T1-2 N0
N = 170 patients

phase III trial

Randomization

- IMRT Simultaneous integrated boost
- TORS, trans-oral laser microsurgery

Primary endpoint is QOL
(MD Anderson Dysphagia test)

Study Start Date:
EORTC-1420-HNCG-ROG

March 2017
ClinicalTrials.gov id: NCT02984410

CONCLUSIONS

- Treatment **de-escalation is experimental** and should be conducted in controlled clinicaltrials
- De-escalation is hypothesized to improve long-term side effects.
- Appropriate potential candidates for de-escalation can be identified by widely translatable clinical selection factors
- There are different strategies for de-intensification
- Recent radiation de-escalation trials, have provided **preliminary** evidence of efficacy
  - There is a need of **longer follow-up**
  - The information is **reduced and immature**
- Dose de-escalation is also being explored in the postoperative (TORS/TLM) setting.

Moltes gràcies