The International Federation of Head and Neck Oncologic Societies

Current Concepts in Head and Neck Surgery and Oncology 2018

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Radiotherapy in oropharyngeal cancer

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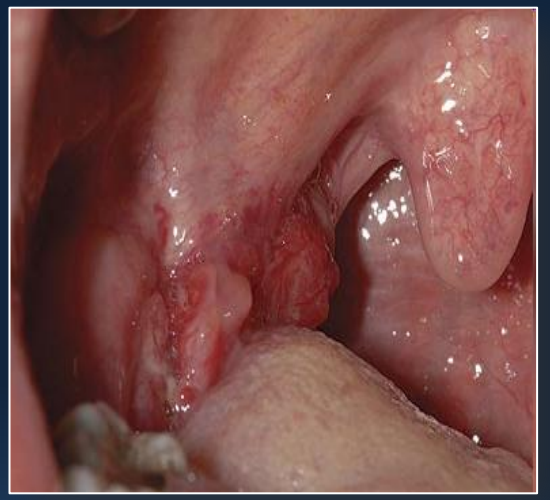
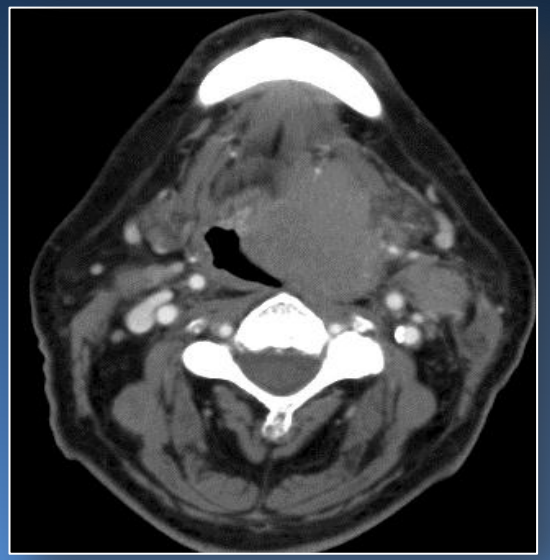
Considerations

Role of RT in non-distant metastatic oropharyngeal cancer depends on

- Early vs Locally advanced disease
- HPV status
- Definitive vs Post-operative RT
- Balance between curative outcomes vs treatment-related morbidity





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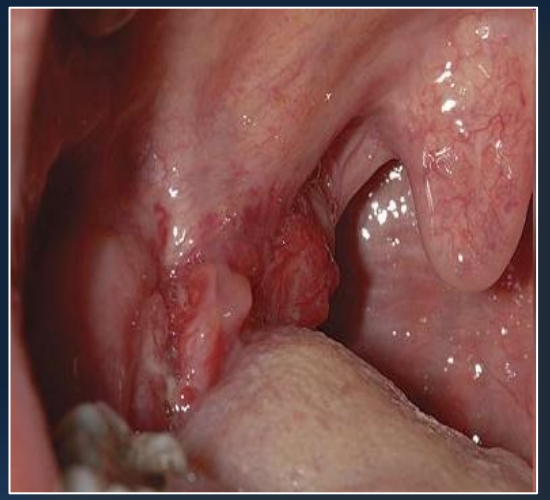
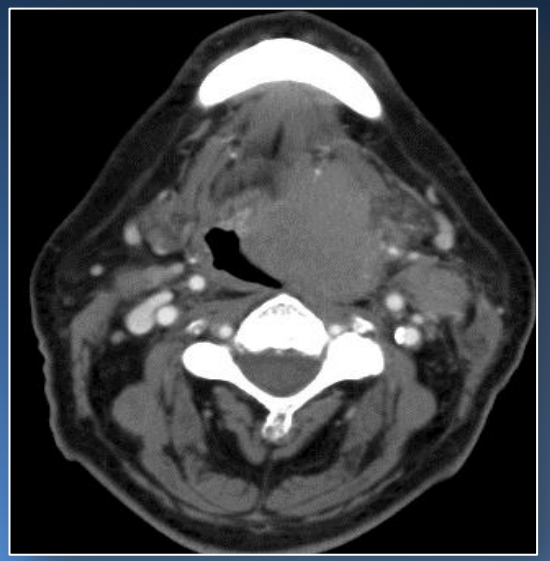




Overview

Surgery vs (Chemo)RT

- Lack of randomised data comparing modalities
- non-randomised institutional reports suggest similar disease control between modalities

Soo KC et al Br J Cancer, 2005

- **Quality of Life**
  - Relationship between QoL & HPV status is unclear
  - Baseline QoL lower in HPV negative patients

Broglie M et al Laryngoscope, 2013

Sharma A et al Otolaryngol Head Neck Surg, 2012

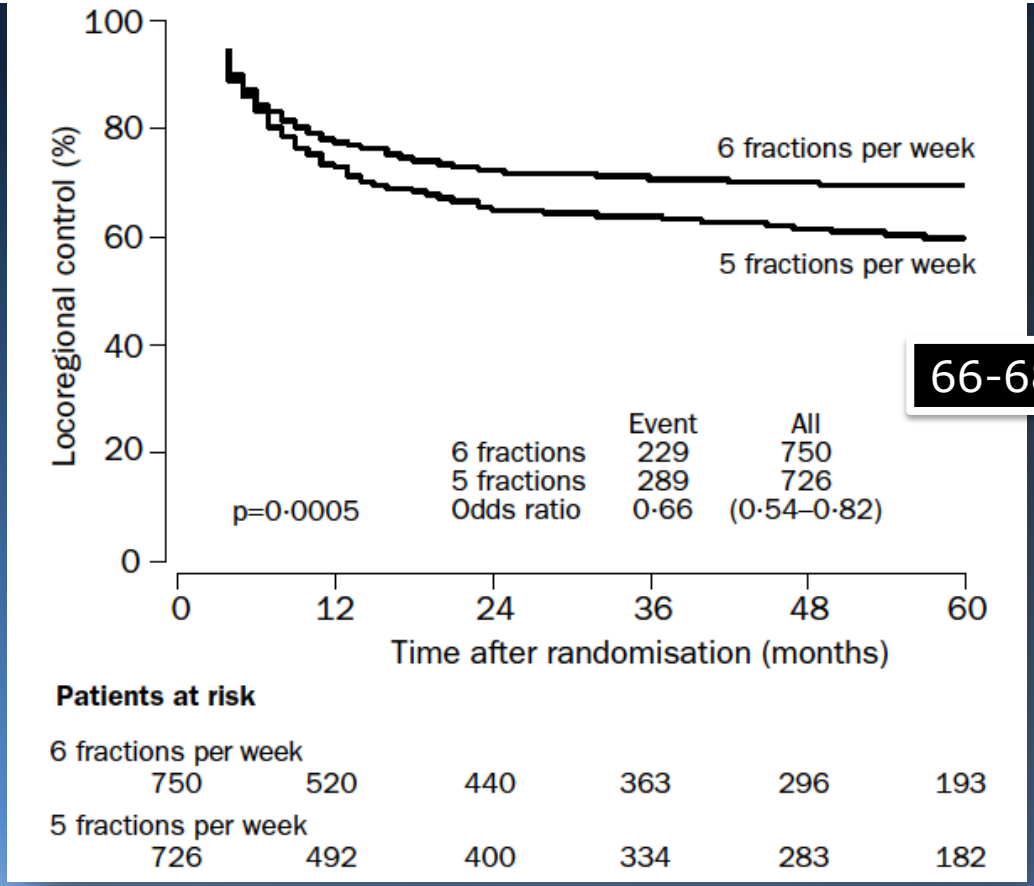
Overview

- Standard of care when using non-surgical approach
- HPV status implication for radiotherapy
- De-escalation strategies
- Intensification strategies
- 8th Edition AJCC/UICC clinical staging
- Treatment guidelines

STANDARD OF CARE

Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial

Jens Overgaard, Hanne Sand Hansen, Lena Specht, Marie Overgaard, Cai Grau, Elo Andersen, Jens Bentzen, Lars Bastholt, Olfred Hansen, Jørgen Johansen, Lisbeth Andersen, Jan F Evensen, on behalf of the Danish Head and Neck Cancer Study Group



66-68Gy in 33-34 fractions

Overgaard J et al Lancet, 2003

Altered fractionation RT superior to conventionally fractionation RT

- 15 randomised trials comparing conventional RT vs Altered fractionation RT (6515 pts)

- Significant benefit in favour of Altered Fractionation at 5 years
  - Absolute survival benefit of 3.4%
  - Absolute locoregional contol benefit of 6.4%

Bourhis J et al Lancet, 2006

Concurrent chemoRT superior to RT alone

Therapy Modality	Absolute benefit at 5 years*	Risk Reduction*	*P*
All (N=17,493)	4.1 %	10 %	< 0.0001
Adjuvant	2.3 %	2 %	NS
Neoadjuvant	2.2 %	5 %	NS
Concurrent	6.9 %	19 %	< 0.0001

*Relative to Conventional Local-Regional Therapy with RT alone

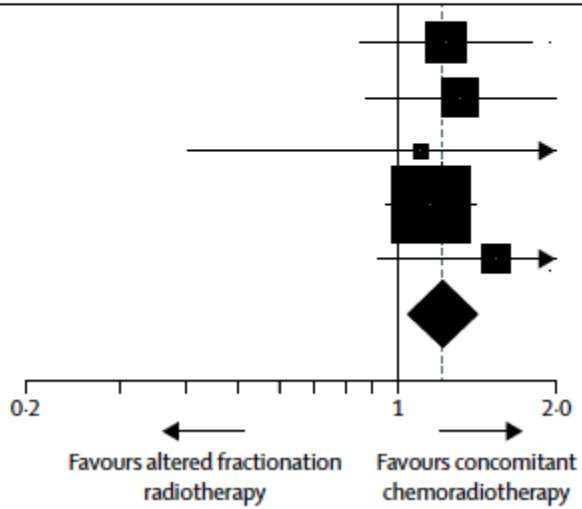
Pignon & Bourhis Lancet, 2000

Chemo-RT superior to altered fractionation RT

	Events (n)/patients (N)		Observed minus expected	Variance	HR (95% CI)
	Altered fractionation radiotherapy	Concomitant chemoradiotherapy			
INRC-HN-9[43]	58/66	55/70	5·9	27·9	1·24 (0·85–1·79)
ORO 9301[55]	50/65	42/64	6·2	22·7	1·32 (0·87–1·98)
EORTC 22962[45]	7/13	9/15	0·4	3·8	1·11 (0·40–3·03)
GORTEC 9902[36]	207/281	196/279	14·7	100·2	1·16 (0·95–1·41)
TMH 1114[37]	34/68	26/65	6·3	14·7	1·54 (0·92–2·56)
Total	**356/493**	**328/493**	**33·6**	**169·4**	**1·22 (1·05–1·42)**

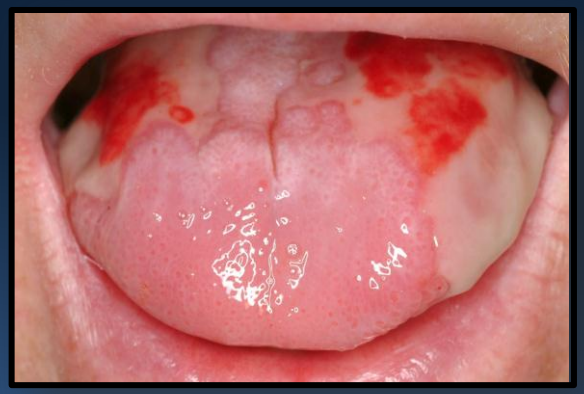
χ^2 test for hetergeneity: p=0·87, I^2=0%

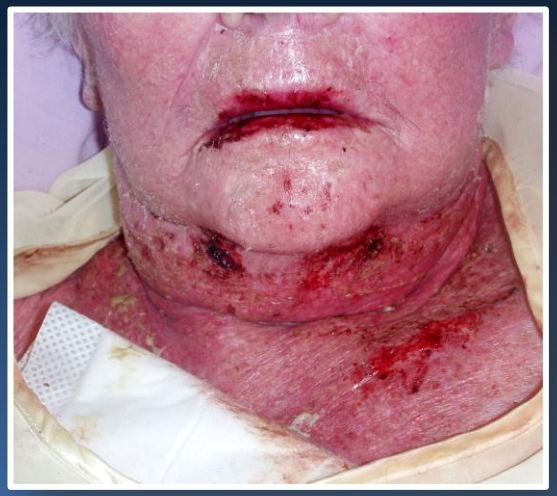
Treatment effect: p=0·0098

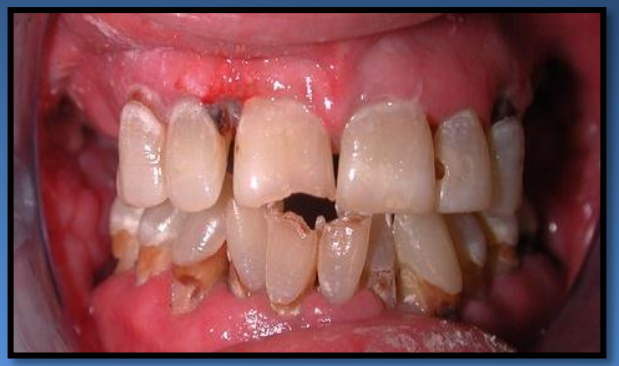


MARCH; updated meta-analysis
Lacas B et al Lancet Oncol, 2017

Treatment intensification vs hightened toxicity

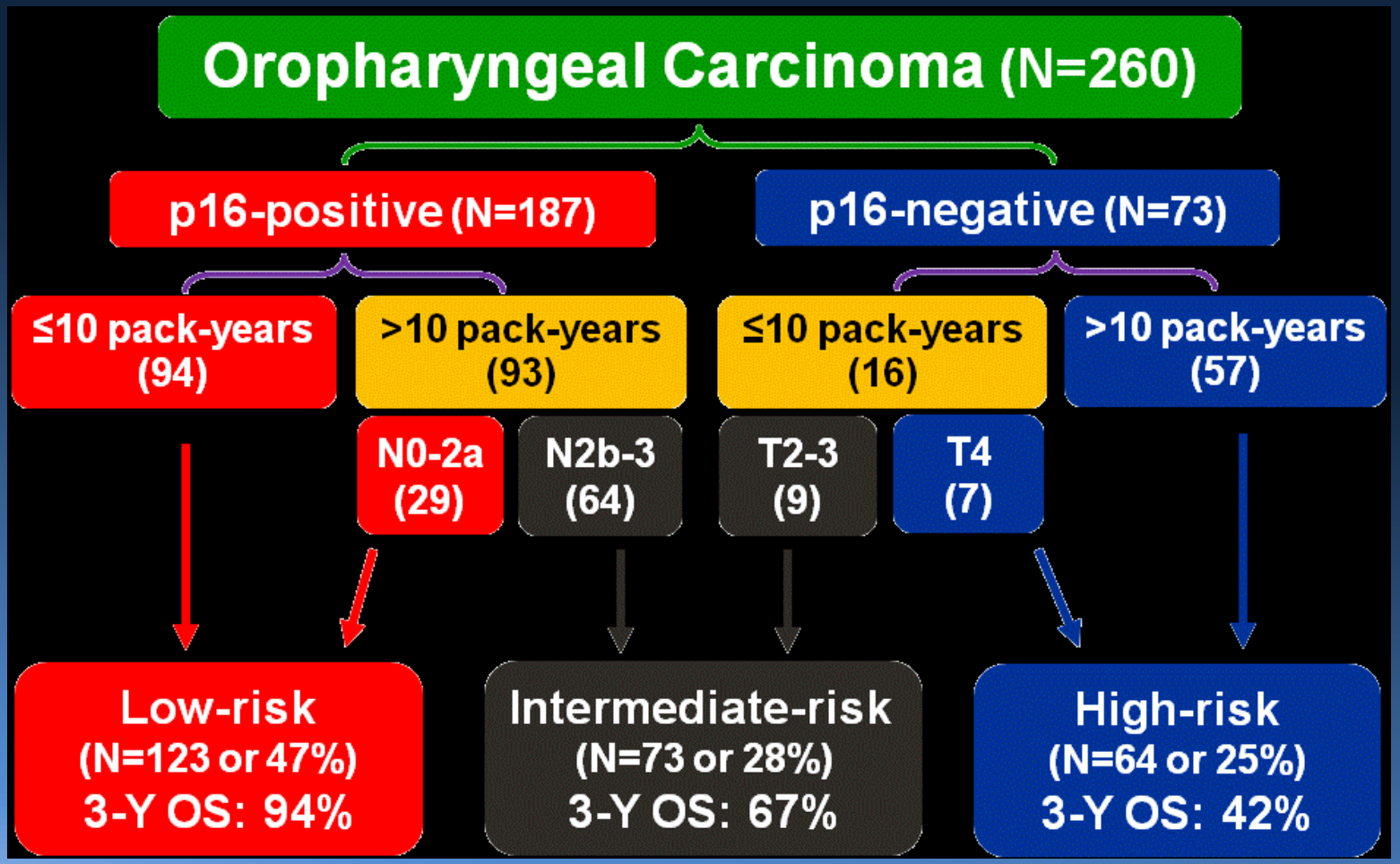






Trotti A et al, Lancet Oncol, 2007
Machtay M et al, JCO, 2008

RTOG 0129



KK Ang et al NEJM, 2010

RTOG 0129

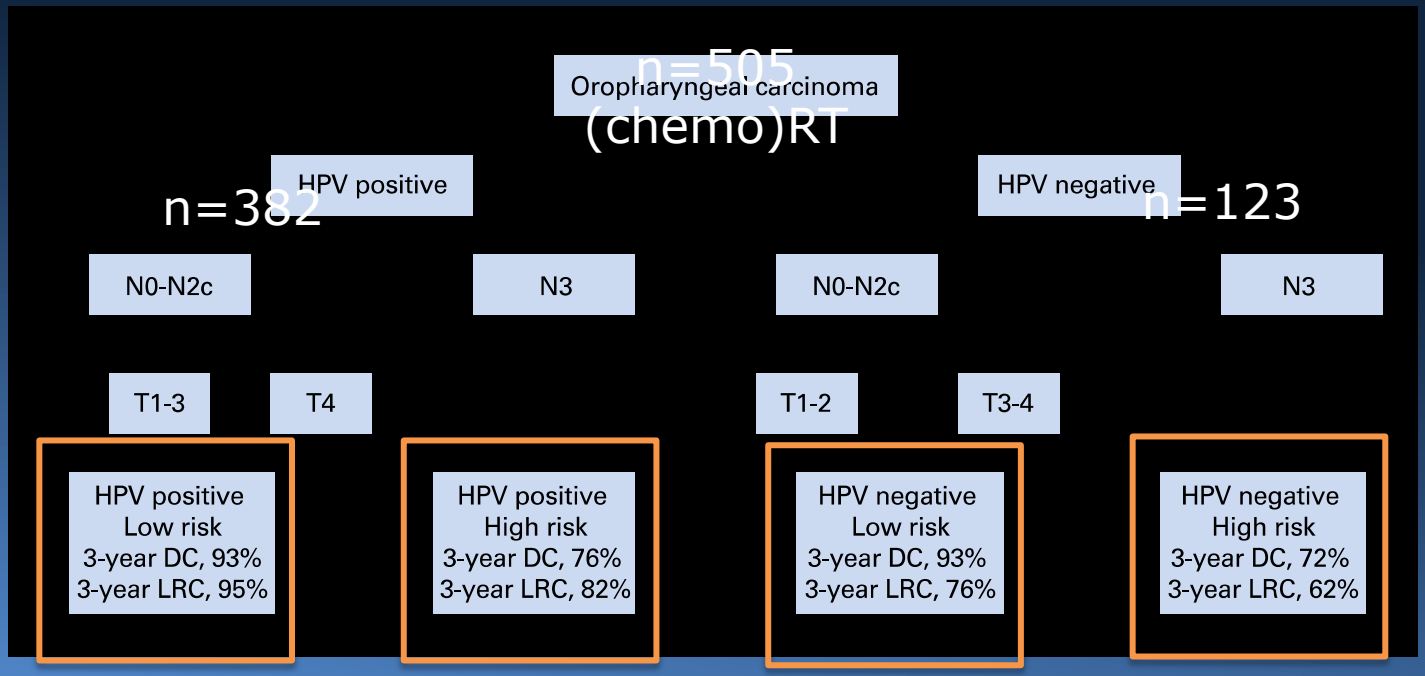
3-Year Outcome by HPV Status

Variable	HPV-Pos (%)	HPV-Neg (%)	p-value
Overall survival	82.4	57.1	<0.001
P-F survival	73.7	43.4	<0.001
Local-regional control	86.4	64.9	<0.001
Distant metastases	8.7	14.6	0.23
2nd primary tumour	5.9	14.6	0.02

KK Ang et al NEJM, 2010

DE-ESCALATION VS INTENSTIFICATION

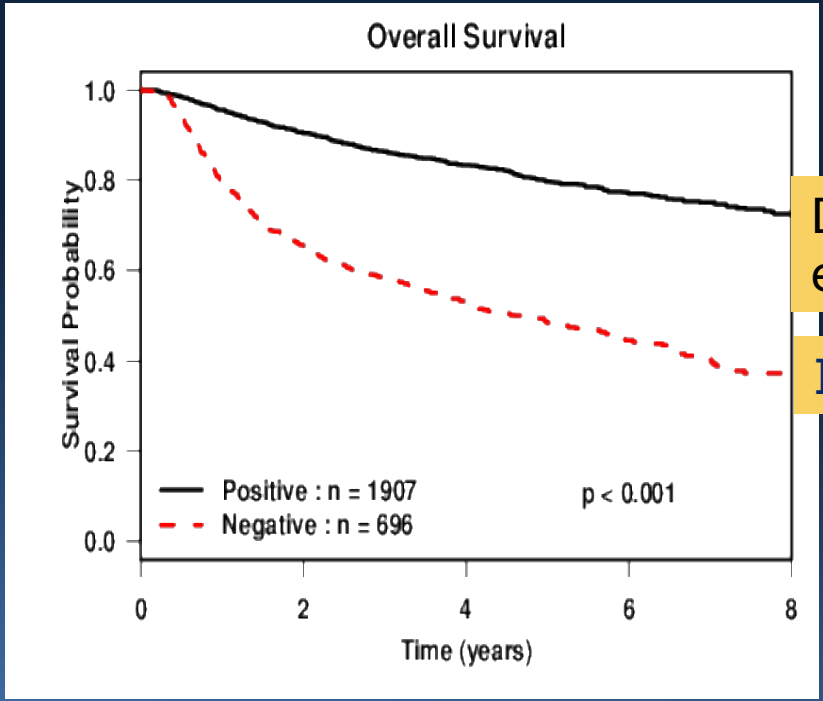
Locoregional & Distant Control following (chemo) RT based on HPV status



LRC; locoregional control
DC; distant control

O'Sullivan B et al JCO, 2013

OS based on HPV status - ICON-S



De-escalate

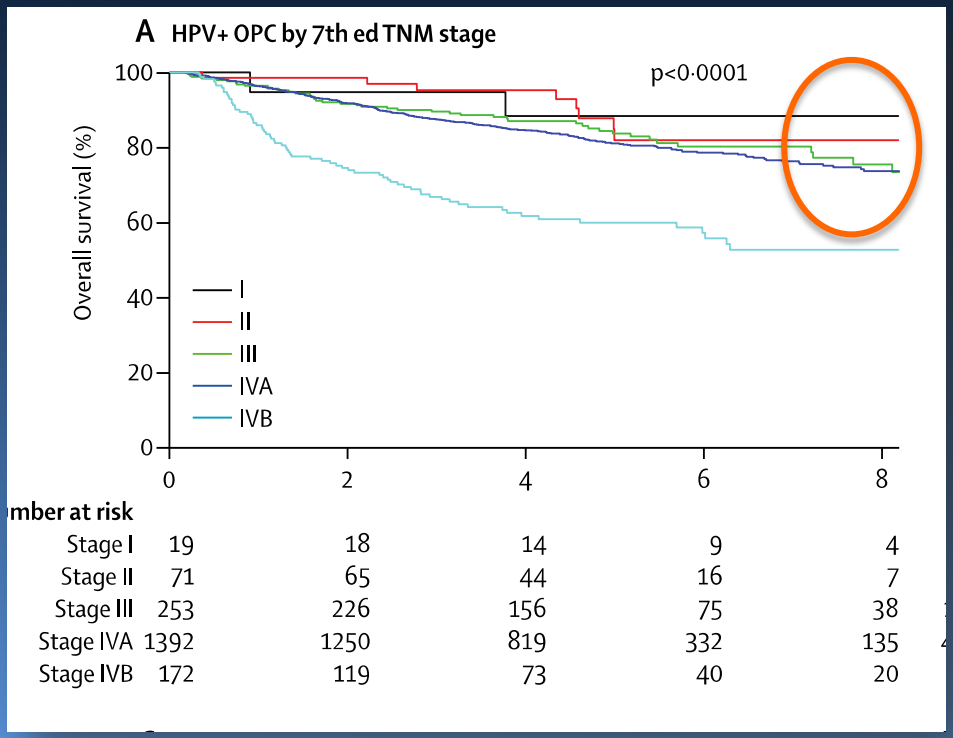
Intensify

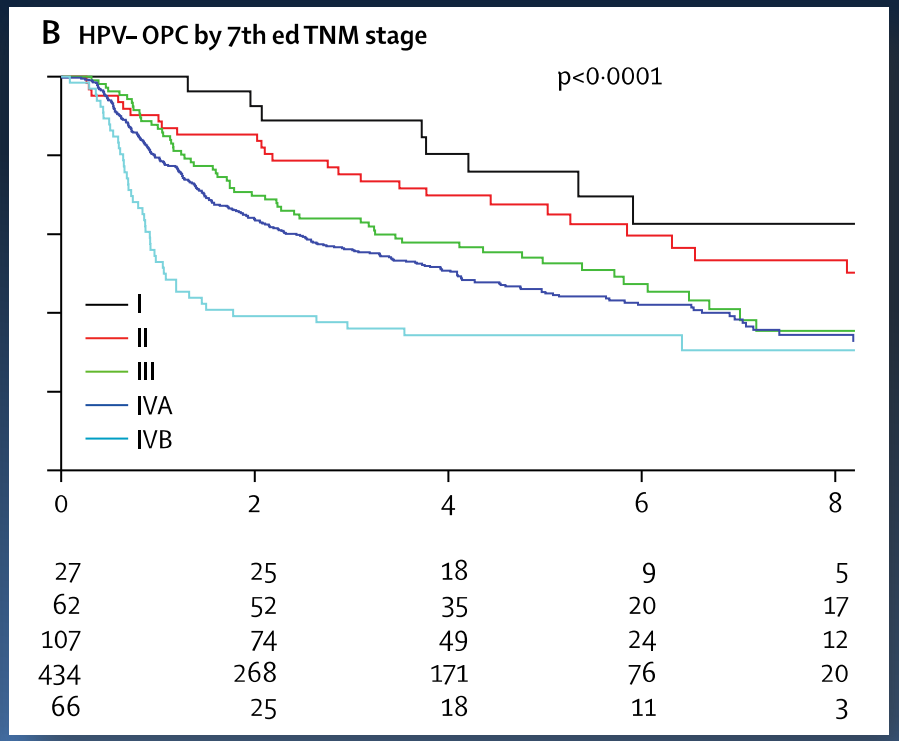
strata	events/total	3 years	5 years	*p*
Total	780 / 2603	79% (77-80)	71% (69-73)	
HPV(-)	385 / 696	58% (55-62)	48% (45-52)	<0.001
HPV(+)	395 / 1907	86% (85-88)	80% (78-82)	

O'Sullivan B et al Lancet Oncol, 2016

Utility of TNM staging (7th edition) ICON-S

Overall Survival by Stage and HPV Status





O'Sullivan B et al Lancet Oncol, 2016

AJCC/UICC 8th Edition Staging

Clinical N category HPV+ OPC

N CATEGORY	N CRITERIA
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6 cm

Lydiatt W et al CA Cancer J Clin, 2017

8th Edition Staging
Clinical N category HPV neg OPC

N CATEGORY	N CRITERIA
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE-negative
N2	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative; or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative; or metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N2a	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative
N2b	Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative; or metastasis in any lymph node(s) and clinically overt ENE-positive
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative
N3b	Metastasis in any node(s) and clinically overt ENE-positive

8th Edition Staging
Clinical TNN category HPV pos OPC

T CATEGORY	N CATEGORY			
	N0	N1	N2	N3
T0	NA	I	II	III
T1	I	I	II	III
T2	I	I	II	III
T3	II	II	II	III
T4	III	III	III	III

[a]Any M1 is stage IV.

Lydiatt W et al CA Cancer J Clin, 2017

DE-ESCALATION STRATEGIES

De-escalation Strategies

- Substitute biologic agent or immunotherapy agent for cytotoxic chemotherapy
- Omit or reduce chemotherapy
- Reduce radiation dose
- Use induction chemotherapy to select responders and then reduce radiation dose
- Surgical excision and stratify further treatment based on pathologic findings

De-escalation Phase III trials OPC HPV positive

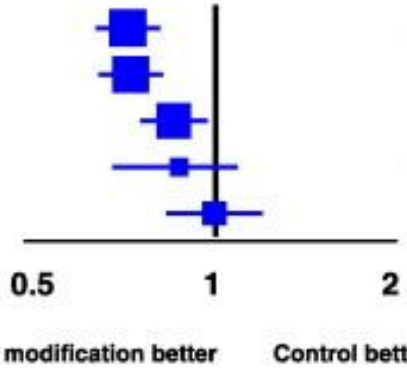
	Eligible	RT	Arm 1	Arm 2	Endpoint
RTOG 1016	All	AF	HD cis x 2	Cetux	OS
De-ESCALaTE	Low risk	CF	HD cis x 3	Cetux	Gr 3 -5 acute and late toxicity
TROG 12.01	Low risk (excludes T4&/or N3)	CF	Weekly cis	Cetux	AUC MDASI-HN Symptom Severity Score
Quarterback	< 20pack yrs TPF responders	CF	70Gy + carbo	56 Gy carbo + cetux	
Adept	Resected N+ ECE	CF	60Gy + cis	60Gy RT	
ECOG 3311	Resected TORS Low risk (exclude T4, N2c-3)	CF	60Gy RT (high risk postop – chemoRT)	50 Gy RT	2 yr PFS
DART-HPV	Resected	CF/AF	60Gy + weekly cis	30 – 36Gy AF + docetaxel	Gr3- 5 toxicities
NRG HN002	Low risk (excludes T4, N2c-3	CF/AF	60 Gy+ weekly cis	60 Gy AF	2yr PFS, dysphagia

INTENSIFICATION STRATEGIES

Hypoxia determinant of outcome

Head and neck cancer - meta analysis - summary

Endpoint	Events / Total		Odds ratio and 95% CI			
	Hypoxic modification	Control		Odds ratio	Risk Reduction	NNT**
Loco-regional control	1203 / 2406	1383 / 2399		0.71 (0.63-0.80)*	8% (5-10%)*	13
Disease specific survival	1175 / 2335	1347 / 2329		0.73 (0.64-0.82)	7% (5-10%)	14
Overall survival	1450 / 2312	1519 / 2305		0.87 (0.77-0.98)	3% (0-6%)	31
Distant metastasis	159 / 1427	179 / 1391		0.87 (0.69-1.09)	2% (-1-4%)	57
Radiotherapy complications	307 / 1864	297 / 1822		1.00 (0.82-1.23)	0% (-3-2%)	>>



Meta Analysis - Hypoxic modification of radiotherapy in HNSCC

* 95% CI.

** Numbers of patients Needed to Treat to achieve benefit in one patients.

Nimorazole Study (DAHANCA 5)

DAHANCA 5-85
SUPRAGLOTTIC and PHARYNX CARCINOMA

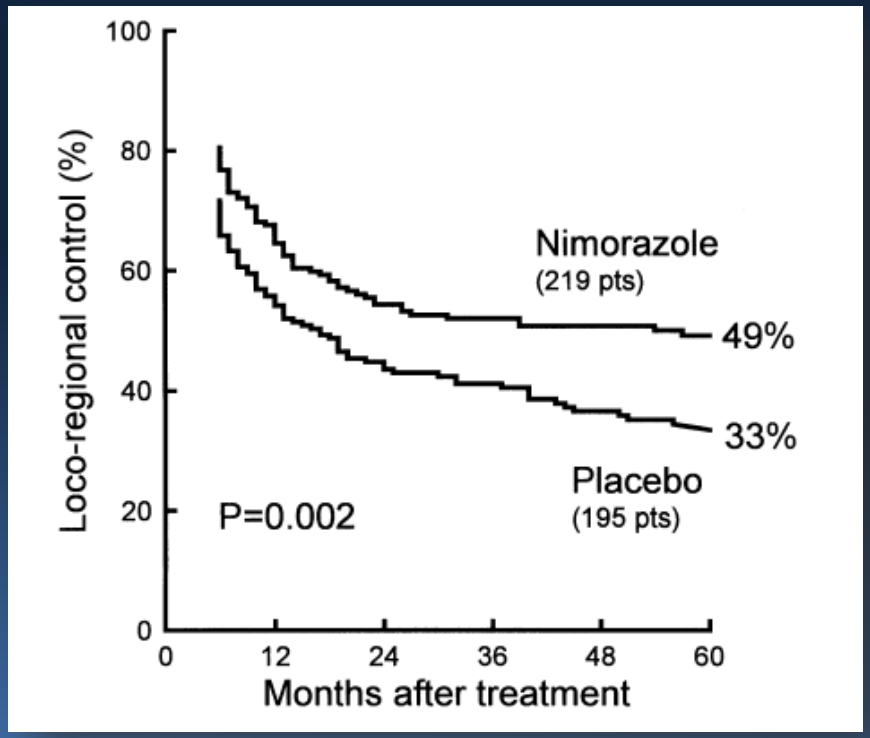
STRATIFY:

T-size
Region
Sex
Hemoglobin*
Institution

RANDOMIZE

RT + Nimorazole (219 pts)
(NIM: 1.2 g/m2 x 30)
(RT: 62-68 Gy/ 31-34 fx, 5 Fx/wk)

RT + Placebo (195 pts)
(RT: 62-68 Gy/ 31-34 fx, 5 Fx/wk)



Overgaard J et al Radiother Oncol, 1998

Immunotherapy Trials

KEYNOTE-012

Recurrent and/or metastatic HNSCC

Single agent Pembrolizumab (anti-PD1 checkpoint inhibitor)

Total cohort = 192

- Cohort B -132 pts 200mg Q3W

61% had received ≥2 therapies

Overall Response Rate = 17.7%

- HPV pos = 21.9%
- HPV neg = 15.9%

Median FU duration in responders 12.5 months

Grade 3-4 treatment-related AEs = 12%

Mehra R et al JCO, 2016

Immunotherapy Trials

KEYNOTE-055

R/M HNSCC progressed following platinum/cetuximab

Single agent Pembrolizumab (200mg Q3W)

Total cohort = 172 patients

- First 50 patients

84% had ≥2 prior lines of therapy

Overall Response Rate 18.0%

Grade 3-4 treatment-related AEs = 12%

Identification of reliable biomarker predictor of response ongoing

Bauml J et al JCO, 2016

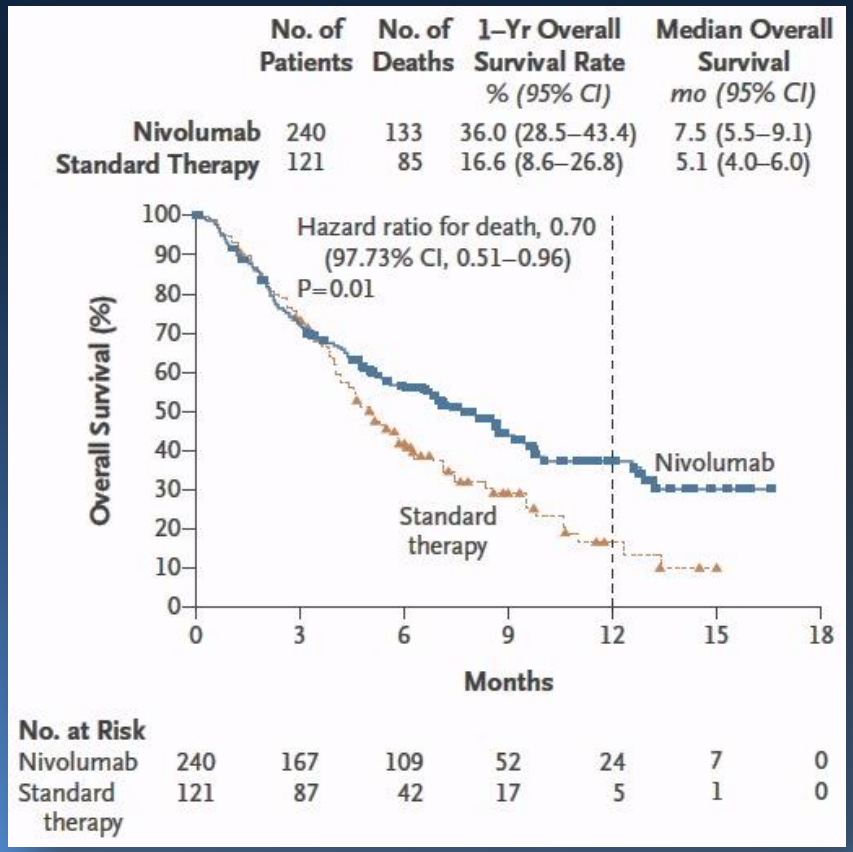
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck

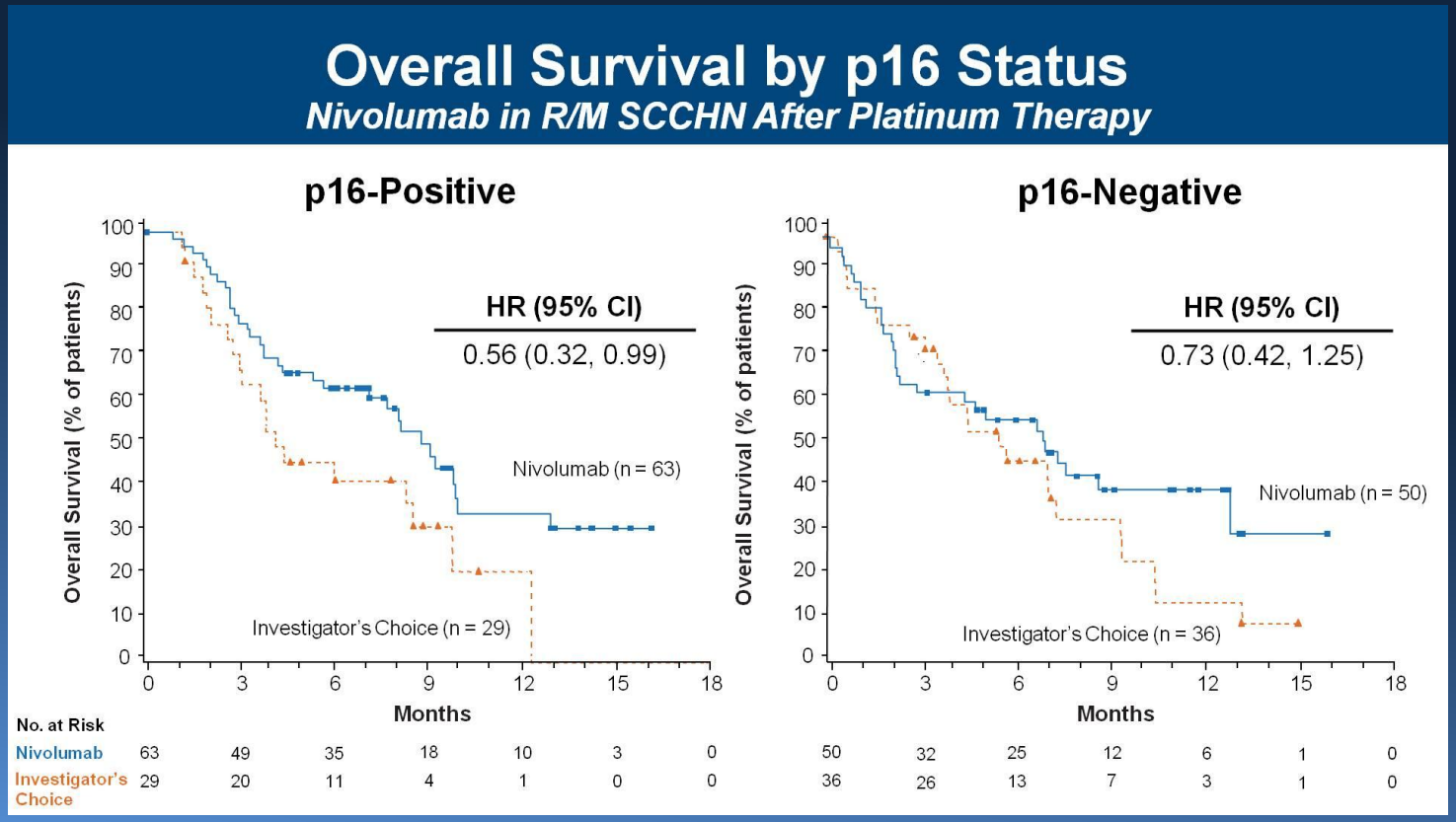
R.L. Ferris, G. Blumenschein, Jr., J. Fayette, J. Guigay, A.D. Colevas, L. Licitra, K. Harrington, S. Kasper, E.E. Vokes, C. Even, F. Worden, N.F. Saba, L.C. Iglesias Docampo, R. Haddad, T. Rordorf, N. Kiyota, M. Tahara, M. Monga, M. Lynch, W.J. Geese, J. Kopit, J.W. Shaw, and M.L. Gillison

Overall Survival



Ferris RL (Gillison M) et al NEJM, 2016

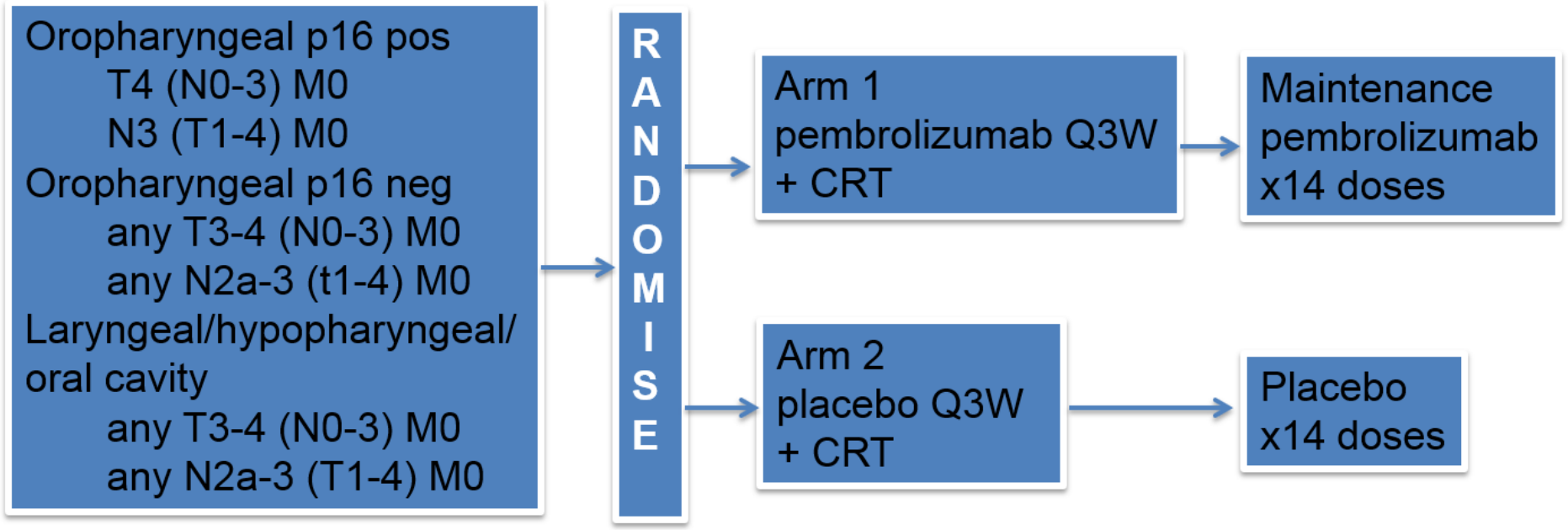
Checkpoint inhibitors - impact of HPV status



- Overall survival benefit was seen with Nivolumab regardless of HPV st

Presented By Robert Ferris at 2016 ASCO Annual Meeting

KEYNOTE 412


Oropharyngeal p16 pos
T4 (N0-3) M0
N3 (T1-4) M0
Oropharyngeal p16 neg
any T3-4 (N0-3) M0
any N2a-3 (t1-4) M0
Laryngeal/hypopharyngeal/ oral cavity
any T3-4 (N0-3) M0
any N2a-3 (T1-4) M0
RANDOMISE
Arm 1
pembrolizumab Q3W + CRT
Maintenance pembrolizumab x14 doses
Arm 2
placebo Q3W + CRT
Placebo x14 doses

Unilateral vs bilateral elective neck irradiation

- **Unilateral neck irradiation**
  - Tonsil/ soft palate T1-2 N0-2a
    (lateralized >1cm lateral to the midline)

- **Bilateral neck irradiation**
  - Tonsil/soft palate T3-4
  - Base of tongue (any T-stage)

- **Retropharyngeal nodes**
  - Tonsil/soft palate T3-4
  - T1 tonsil/soft palate and $\geq$N2b (7th Edition)
  - T3-4 BOT
  - N3

Dose/fractionation for definitive radiotherapy

		3D-CRT			IMRT		
Schedule	**Site**	**Dose (Gy)**	**Fractions**	**Weeks**	**Dose (Gy)**	**Fractions**	**Weeks**
Conventional*	Gross disease	70	35	7	70	35	7
	Intermediate	60	30	6	63	35	7
	Elective	50	25	5	56	35	7
Accelerated (DAHANCA)**	Gross disease	68	34	6	68	34	6
	Intermediate	60	30	6	61.2	34	6
	Elective	50	25	5	54.4	34	6
Hypofractionated (T1 larynx*)**	Field-based	63	28	5.5			

***Conventional fractionation & concurrent systemic therapy**

- T3-4N0-3, anyT with N2b-c or N3 (7th Edition)

****** **DAHANCA Fractionation**

- T1-2N0-N1 (occasionally N2a)
- contra-indication to conventional fractionation & systemic therapy for advanced disease

Princess Alexandra Hospital, Radiation Oncology, 2017

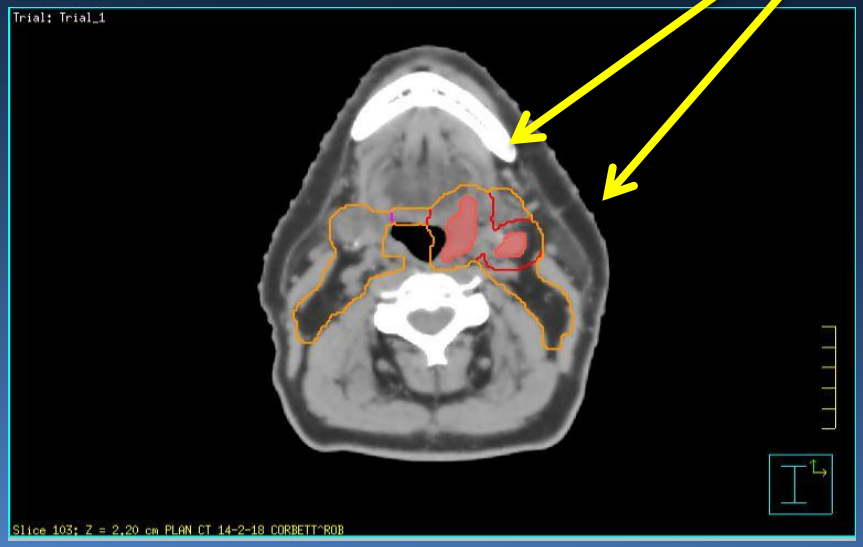
Doses of adjuvant radiotherapy

		3D-CRT			IMRT		
Schedule	**Site**	**Dose (Gy)**	**Fractions**	**Weeks**	**Dose (Gy)**	**Fractions**	**Weeks**
Conventional	Microscopic positive margin	66	33	6.4	63	30	6
	Tumour bed	60	30	6	60	30	6
	Operative bed	54	27	5.3	54-57	30	6
	Elective	50	25	5	54	30	6

Addition of chemotherapy in the presence of positive margins and/or ECE HPV+ or HPV_

Princess Alexandra Hospital, Radiation Oncology, Guidelines 2018

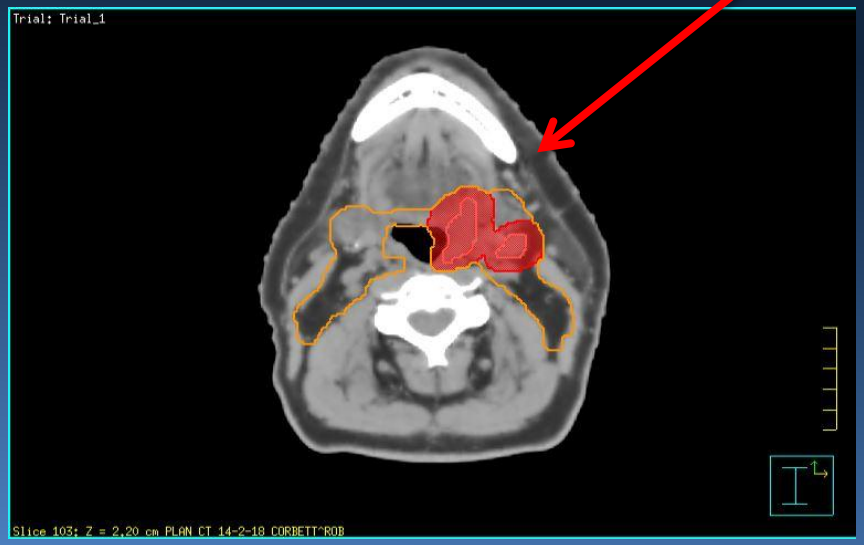
T2N1M0 Base of Tongue SCC p16+



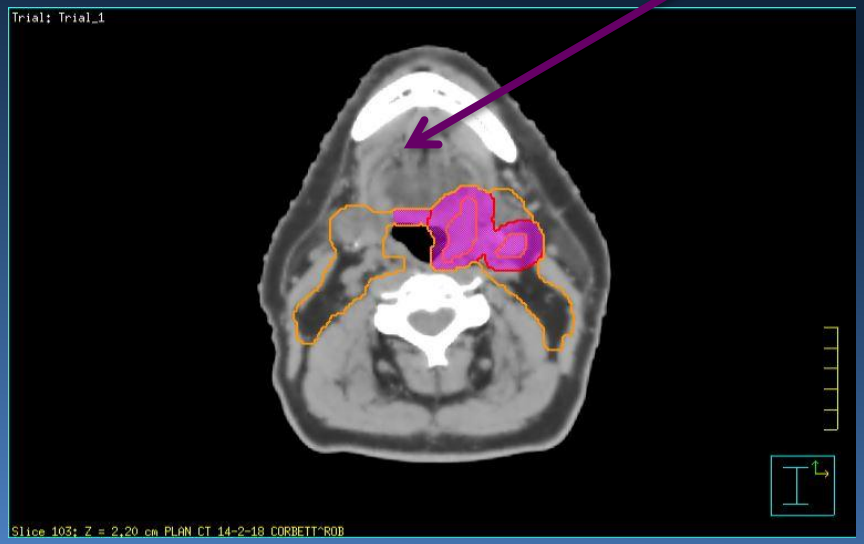
Gross Tumour Volume

T2N1M0 Base of Tongue SCC p16+

CTV 70Gy = GTV + 0.5cm



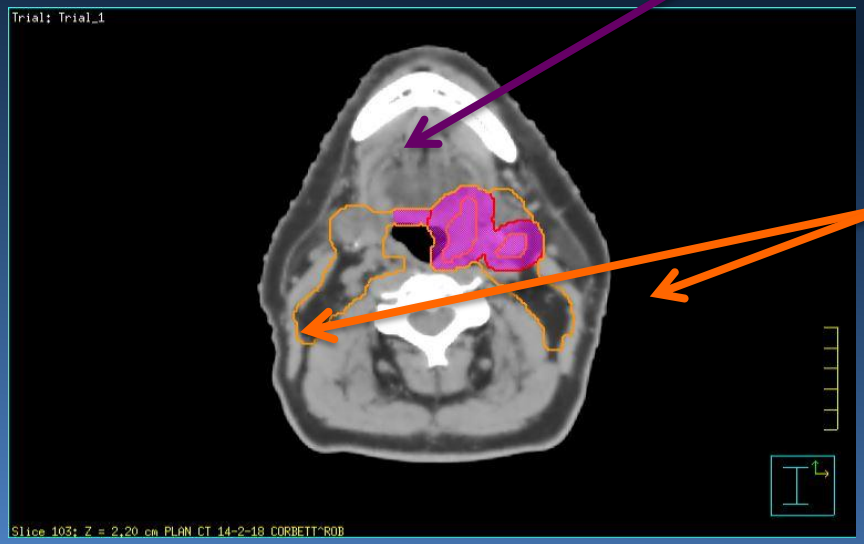
T2N1M0 Base of Tongue SCC p16+



CTV 63Gy (intermediate)

- CTV70Gy
- remaining BOT

T2N1M0 Base of Tongue SCC p16+



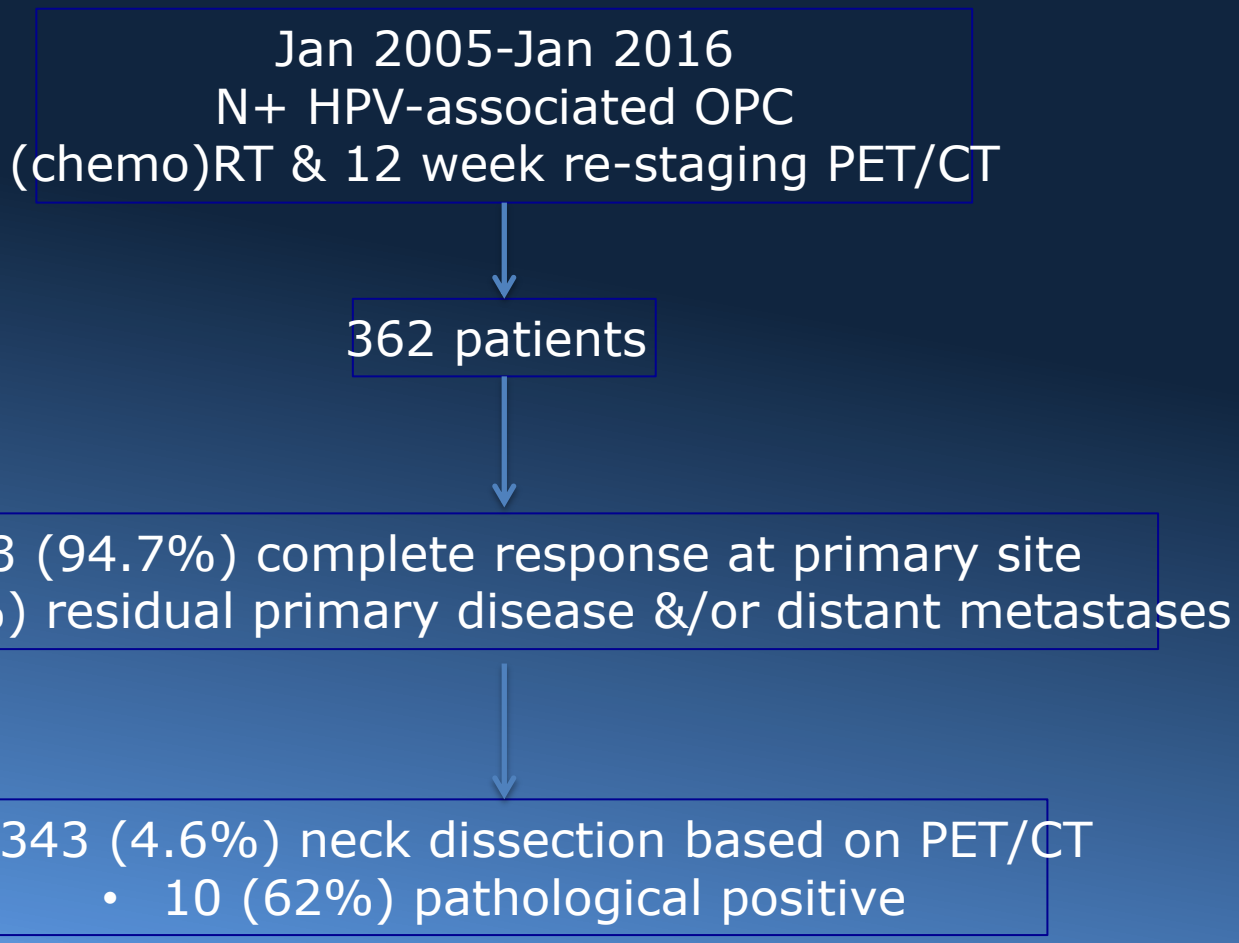
CTV 63Gy (intermediate)

- CTV70Gy
- remaining BOT

CTV56Gy (elective)

- Ipsilateral (RP, Ib-V)
- Contralateral (II-IV)

Node positive HPV-associated OPC outcomes with (chemo)RT

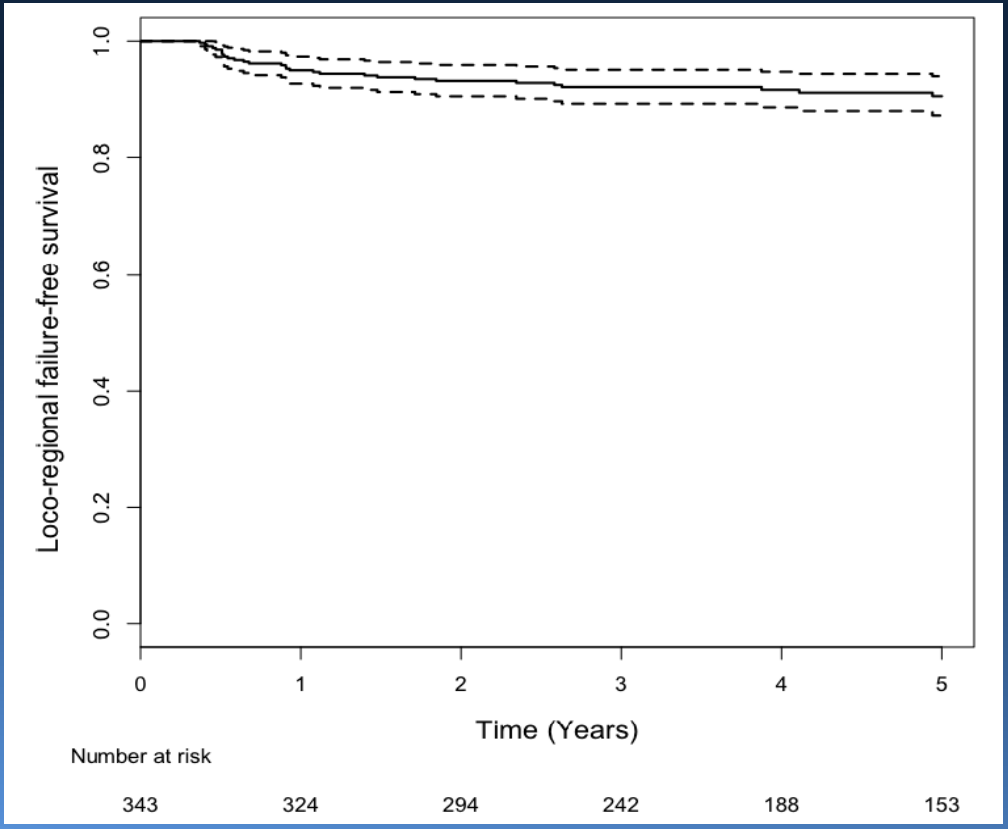


Porceddu SV et al ASCO, 2018

Node positive HPV-associated OPC outcomes with (chemo)RT

Kaplan-Meier Loco-Regional Failure Free Survival

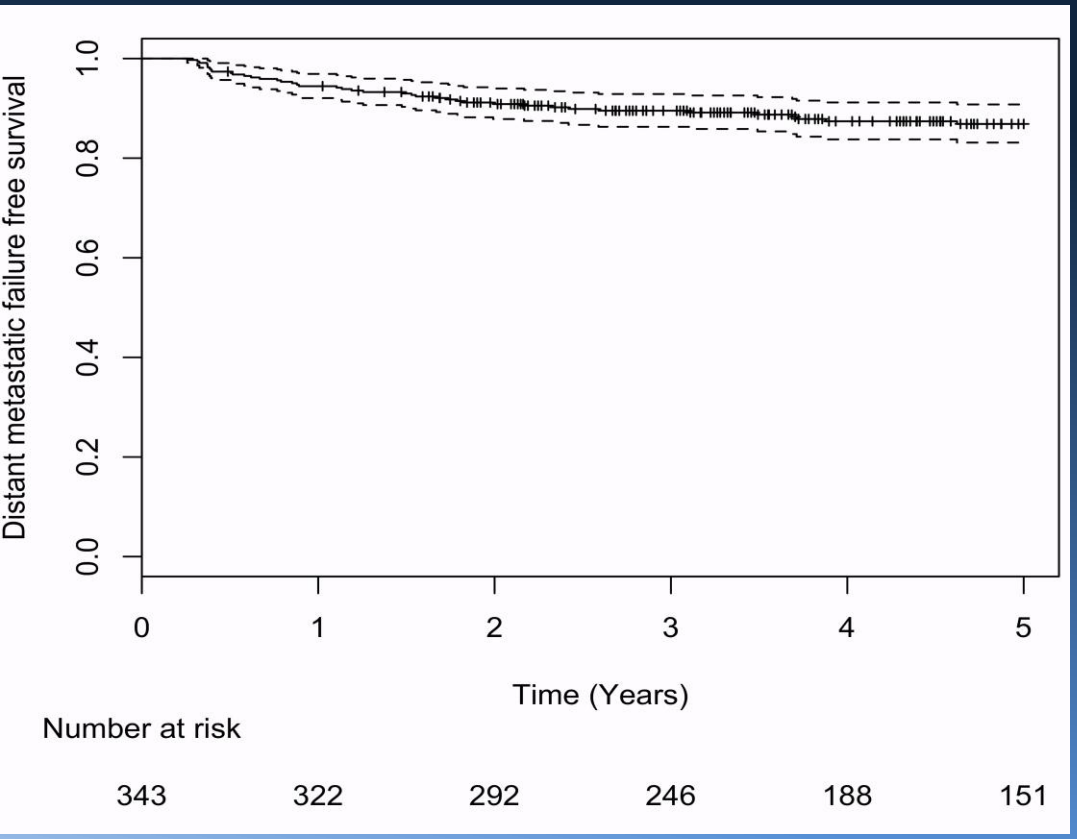
5-year LR FFS
90.6% (95% CI: 87.3-94.0)



Porceddu SV et al ASCO, 2018

Node positive HPV-associated OPC outcomes with (chemo)RT

Kaplan-Meier Distant Metastatic failure free survival



5-year DM FFS
86.9% (95% CI: 83.1-90.8)

Porceddu SV et al ASCO, 2018

Concluding remarks

- Debate for (chemo)RT vs surgery (PORT) unresolved
- Emergence of HPV-associated OPC has seen a move toward de-escalation trials
- Treatment intensification for non-HPV-associated OPC and non OPC warrants further investigation
- Role of definitive immunotherapy with (chemo)RT remains undefined