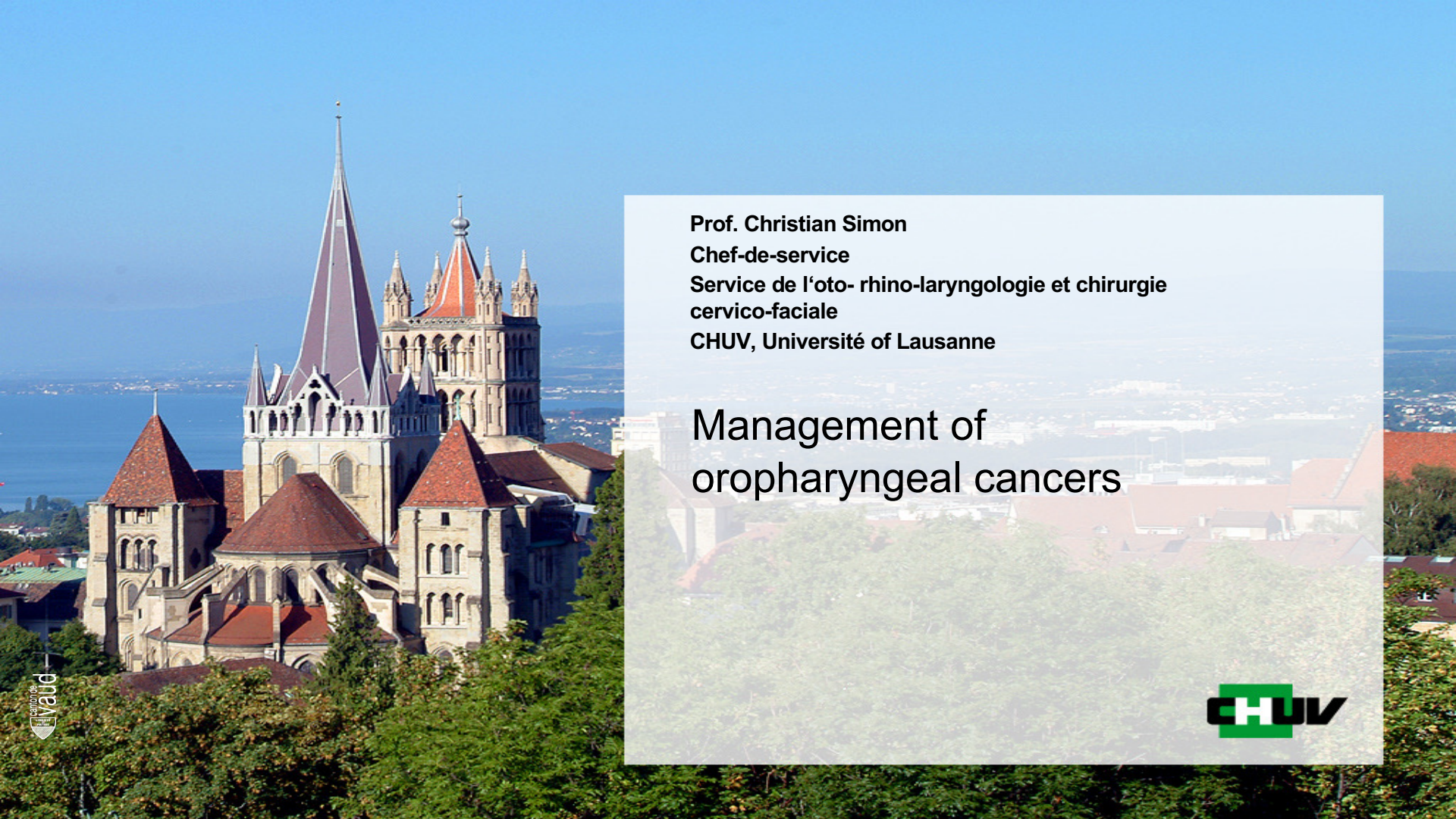

Prof. Christian Simon
Chef-de-service
Service de l'oto- rhino-laryngologie et chirurgie cervico-faciale
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Management of oropharyngeal cancers

Disclosures

- Personal financial interests:

- Consulting and advisory services, speaking or writing engagements, public presentations:
- Pfizer, Merck

- Direct research support:
- Roche

- Non-financial interests:
- PI of EORTC 1420
- Non-remunerated member of the EORTC HNCG

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What will we cover today…

- Etiology, risk factors, and epidemiology
- Early stage disease (7th AJCC)
- Advanced stage disease (7th AJCC)
- De-escalation strategies

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Etiology and risk factors of oropharyngeal carcinomas

- Tobacco: <20 cig./day 1.6 fold increased risk for OPC, >20 cig./day 3.1 fold increased risk for OPC, reduction of risk down to 1.2 10 years after quitting smoking (Ansary et al., 2009)
- Alcohol: 36 fold increased risk for OPC in heavy drinkers and heavy smokers (Ansary et al., 2009)
- Ethnicity: Increased risk in African-Americans in the US (Lambert et al., 2011)

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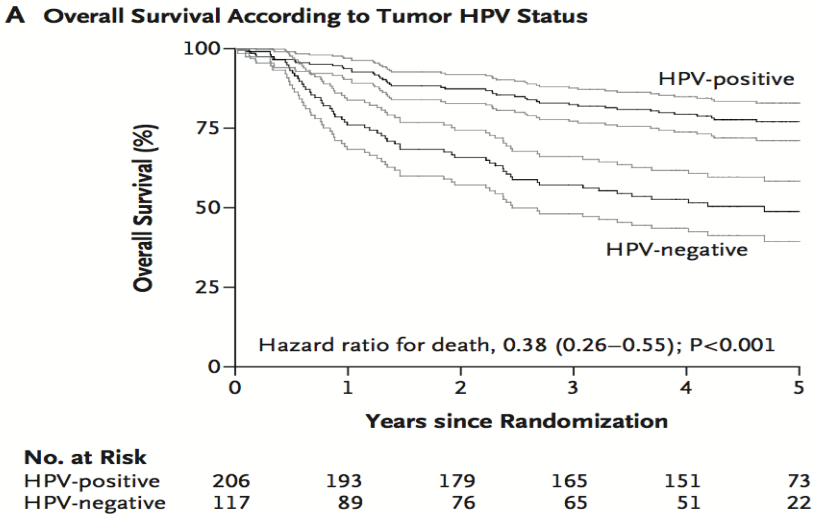
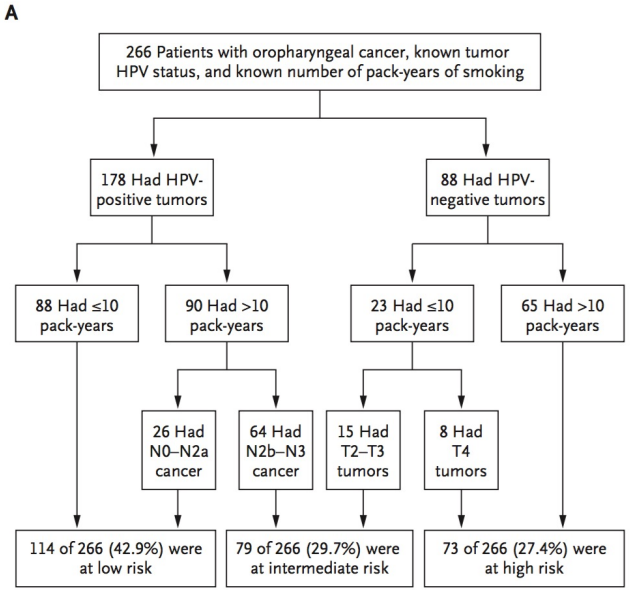
HPV positive oropharyngeal cancers have a better prognosis





Ang et al. New Engl J Med 2010

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Etiology and risk factors of oropharyngeal carcinomas

- HPV:
  - 20-25% HPV-positivity in HNSCC-patients (D´Souza et al, 2007)
  - 40%-80% of OPCs positive for HPV (Miller et al., 2012)
  - Associated mostly with HPV16 (Gillison, 2006)
  - Sexually transmitted disease (Gillison, 2006)

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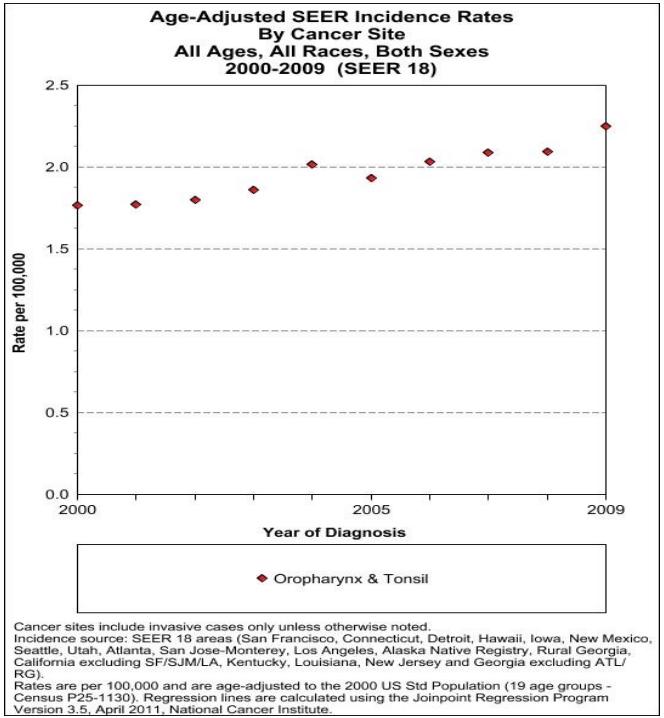
Epidemiology of oroparyngeal cancer

- Incidence of oropharyngeal cancer (OPC) in the US is 2.2/100.000 in 2009 (SEER 2013)
- Early stage OPC between 16.5% and 26% of all OPCs (Carvalho 2005)



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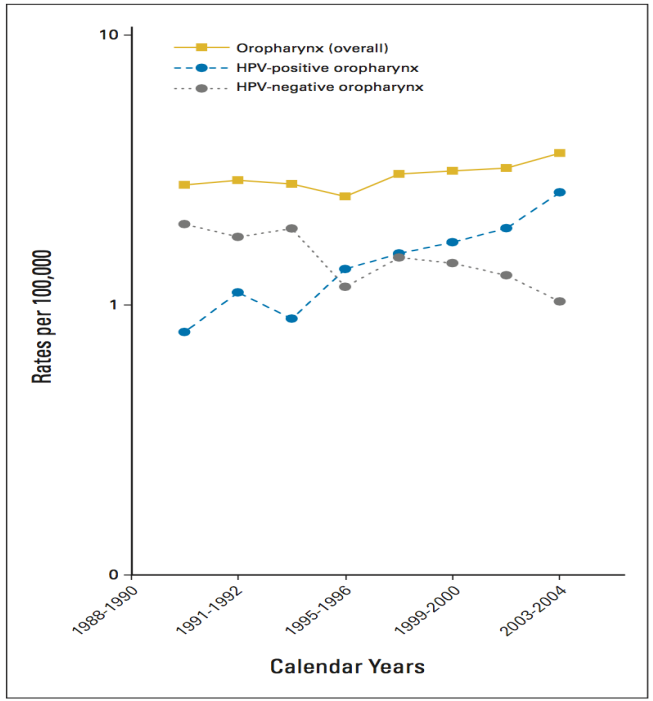
Epidemiology: HPV and oropharyngeal cancer (US)



Chaturvedi et al. JCO 2011

- Population level incidence/100.000 of HPV positive OPC increased from 0,8 (1988) to 2,6 (2004) corresponding to an increase of 225%
- Incidence of HPV negative OPC declined by 50%

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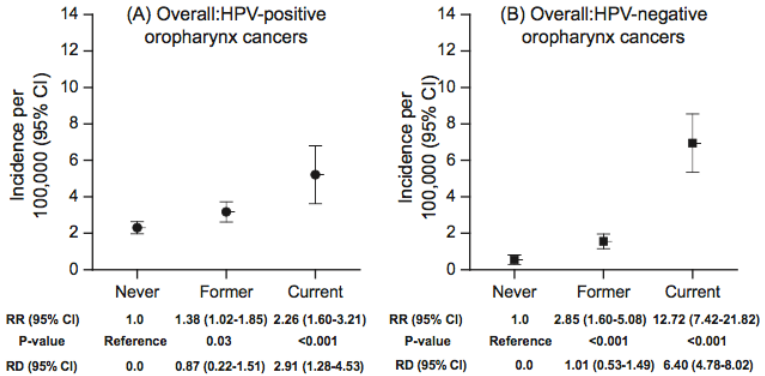
Smoking and HPV positive oropharyngeal cancer



Relative risk (RR) to develop an HPV-positive tumor higher in former and current smokers

Charturvedi et al. Oral Oncology 2016

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8th AJCC classification

TABLE 1. Clinical and Pathologic T Category for Human Papillomavirus-Associated (p16-Positive) Oropharyngeal Cancer, 8th Edition Staging Manual[a]

T CATEGORY	T CRITERIA
T0	No primary identified
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond[b]

[a]Table 1 is used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, with permission[2]). [b]Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

TABLE 2. Clinical and Pathologic T Category for Non-Human Papillomavirus-Associated (p16-Negative) Oropharyngeal Cancer, 8th Edition Staging Manual[a]

T CATEGORY	T CRITERIA
Tx	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible[b]
T4b	Very advanced local disease; tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

[a]Table 2 is used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, with permission[2]). [b]Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

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8th AJCC classification

TABLE 3. Clinical N Category Human Papillomavirus-Associated (p16-Positive) Oropharyngeal Cancer, 8th Edition Staging Manual[a]

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

[a]Table 3 is used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, with permission[2]).

TABLE 4. Clinical N Category for Non-Human Papillomavirus-Associated (p16-Negative) Oropharyngeal Cancer, 8th Edition Staging Manual[a]

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

Abbreviations: ENE, extranodal extension. [a]Table 4 is used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, with permission[2]).

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8th AJCC clinical staging for HPV-positive OPC

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

***Figure 4*: Proposed ICON-S stage tabulation grid for 8th edition TNM**
Note that distant metastatic disease (M1) is considered stage IV.

O'Sullivan Lancet Oncology 2016

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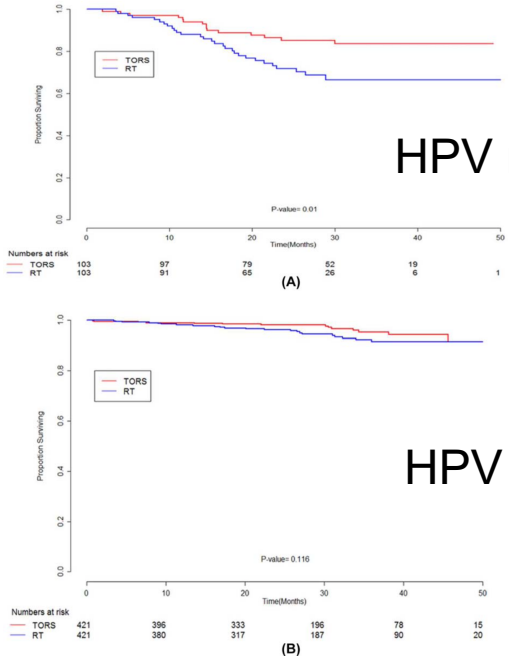
Advantage of surgery over RT for HPV negative disease



HPV negative

HPV positive

FIGURE 3 Overall survival curves in A, human papillomavirus (HPV)-negative and B, in patients with HPV-positive oropharyngeal cancer by treatment type. RT, radiotherapy; TORS, transoral robotic surgery [Color figure can be viewed at wileyonlinelibrary.com]

Mamoud et al. Head Neck 2018

- RWE studies will become increasingly used to compare clinical outcomes in real-world observational trials of clinical interventions (which might not necessarily require regulatory approval) to determine optimal treatment strategies…

Klonoff et al. Journal of Diabetes Science and Technology 2020

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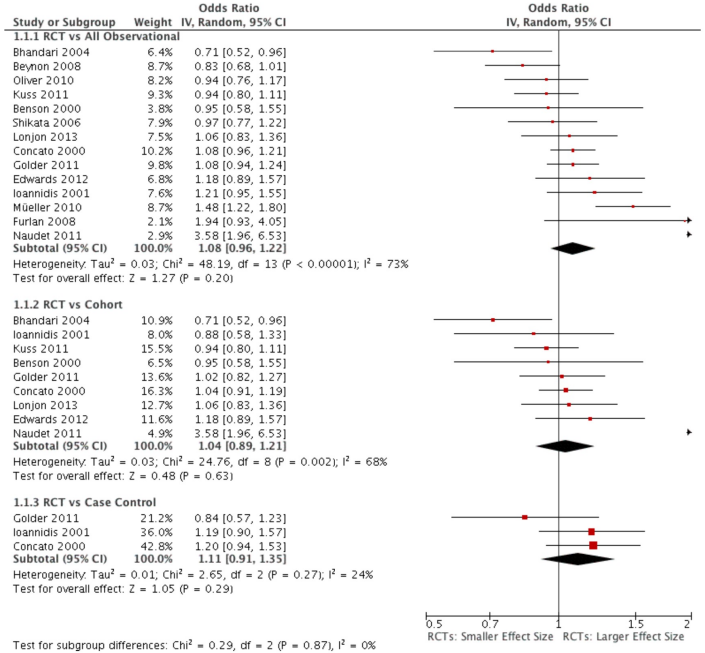
No difference of effect size measured by RCTs vs. RWE

Figure 4. Forest plot of comparison: 1 RCT vs Observational, outcome: 1.2 Pooled Ratio of Odds Ratios--Study Design.



Anglemyer et al. Cochrane Library 2014

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Treatment options for early-stage OPCs (7th AJCC edition)

- Single-modality treatment
  - IMRT
  - Organ preservation surgery
    - TORS
    - TLM
    - Conventional transoral surgery

Anatomic Stage/Prognostic Groups: Oropharynx,

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

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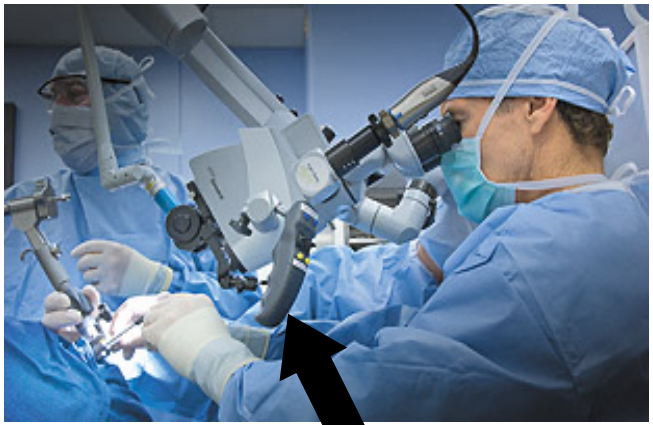
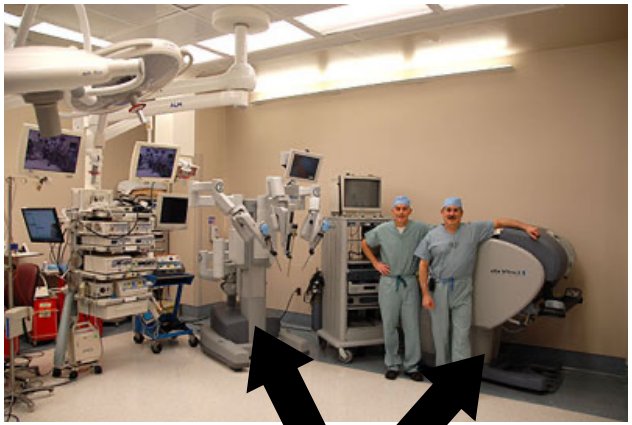
There are two modern types of trans-oral surgery for early stage OPCs

TLM



microscope

TORS



Robot with endoscope

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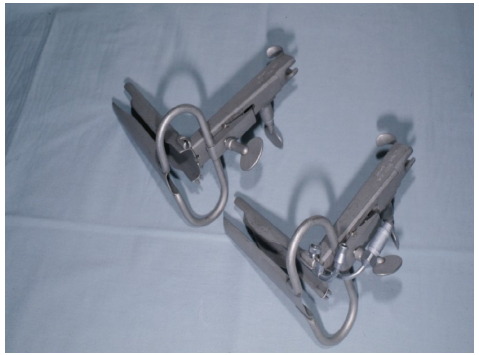
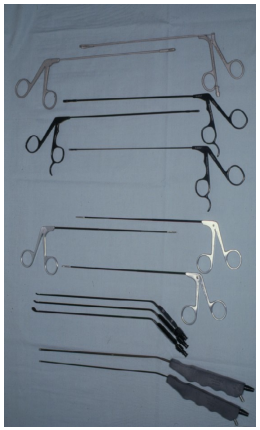
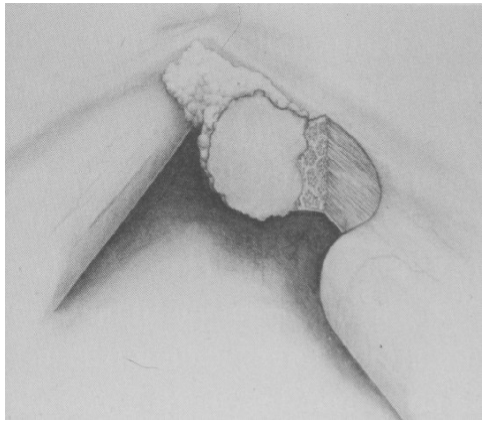
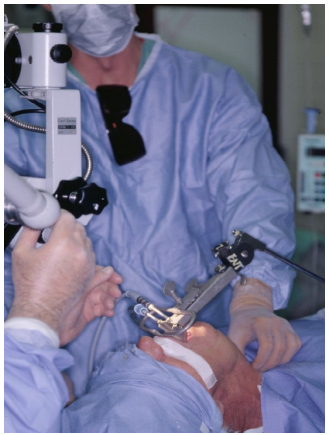
TLM: Techniques and instruments









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Set-up

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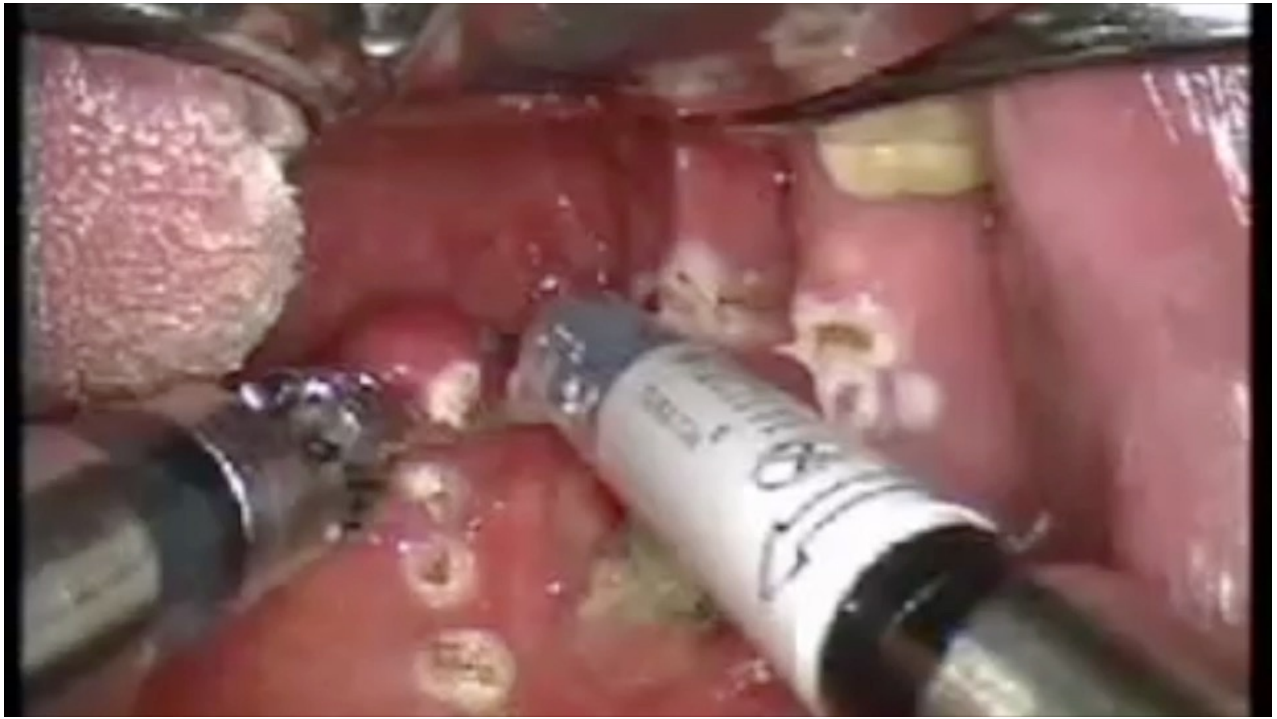
TORS 2010



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TORS 2019

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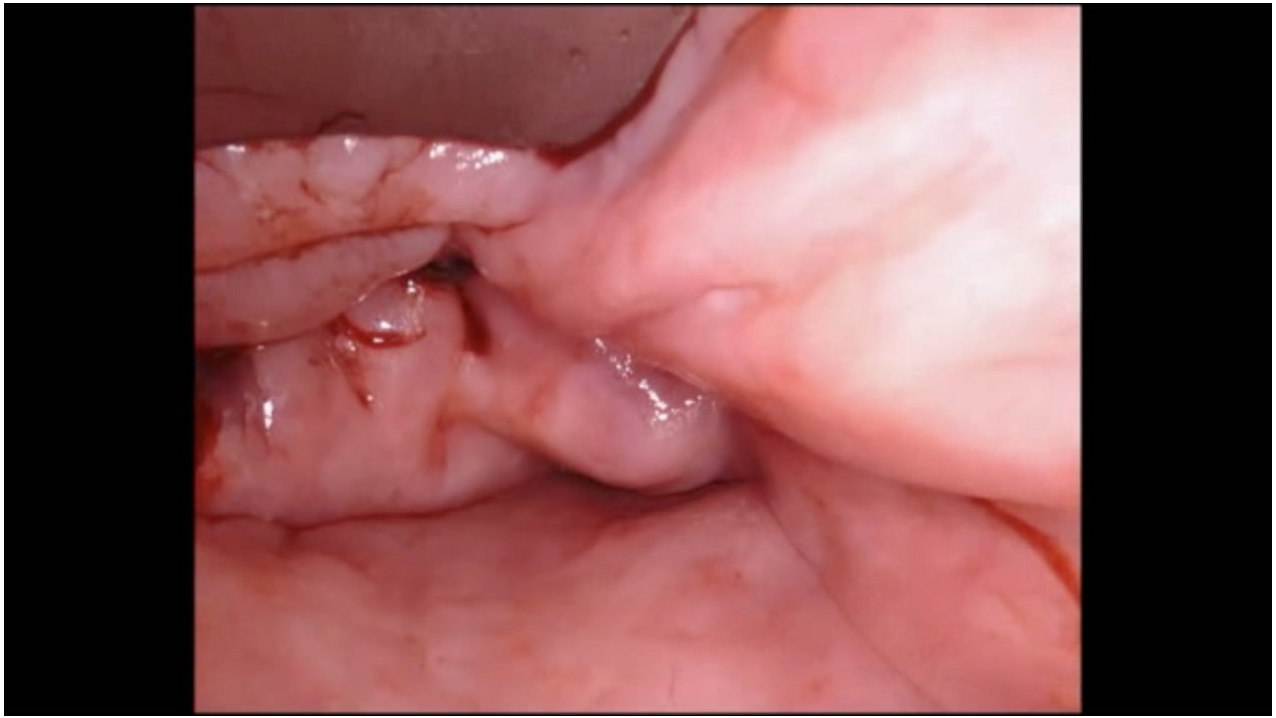
Trans-oral part of the resection



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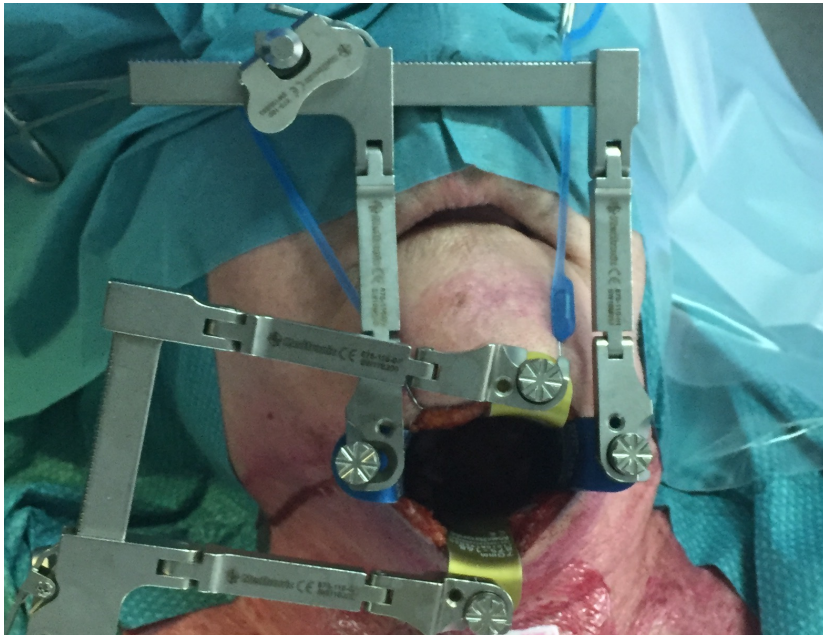
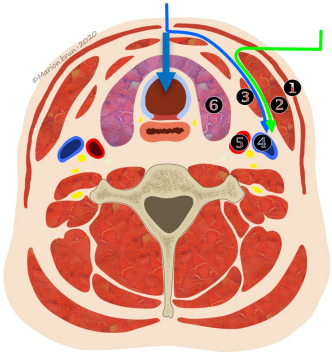
Treatment: RESA





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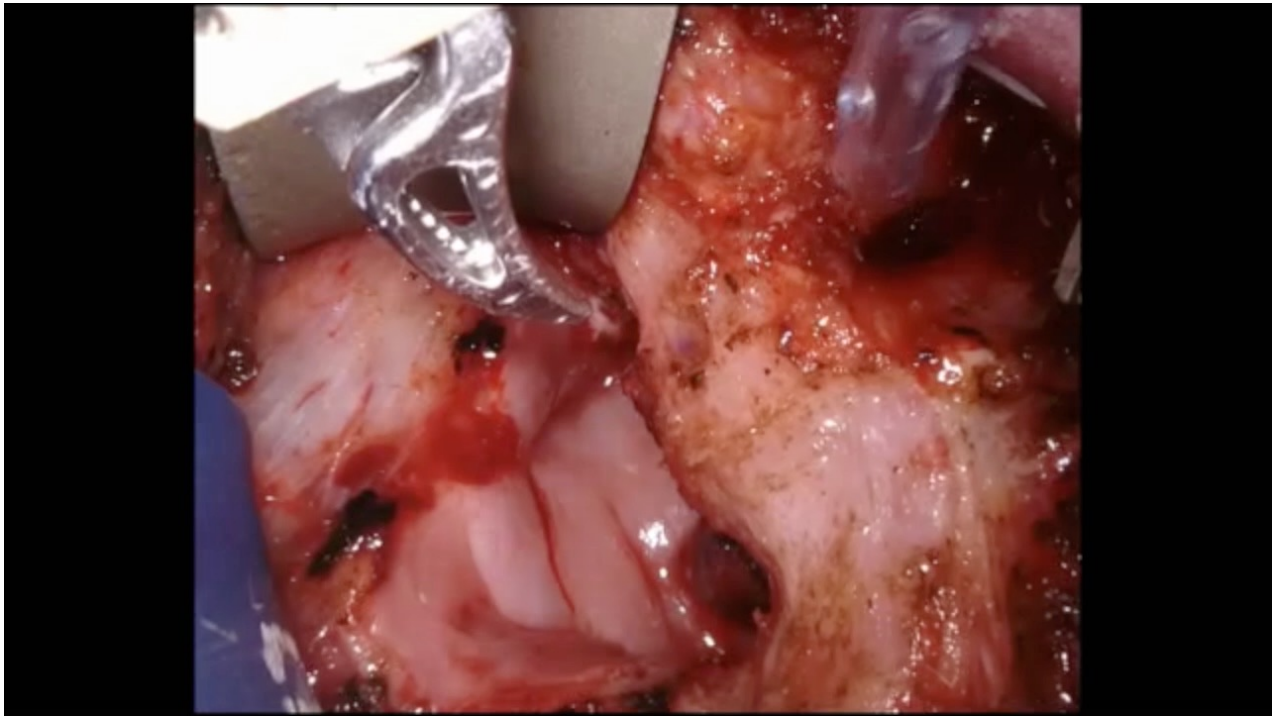
Trans-hyoid part of the resection



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Positive margin rate of various TOS techniques based on a meta-analysis of the literature

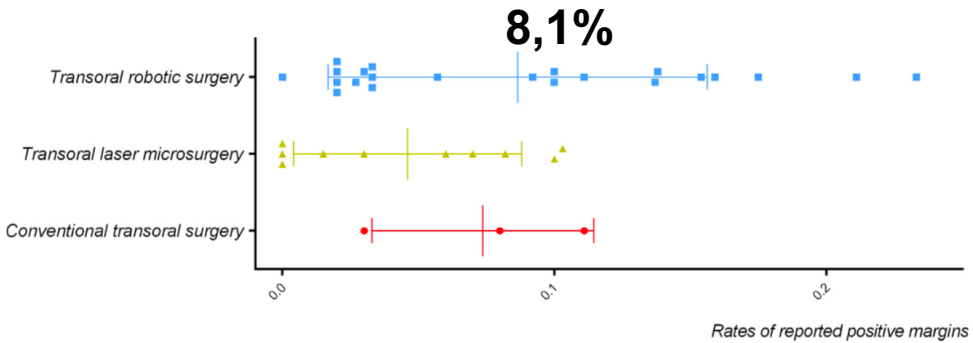

Fig. 4. The rates of reported positive margins according to the surgical approach, in series of transoral surgery for oropharyngeal carcinoma.

Gorphe et al. Oral Oncology 2019

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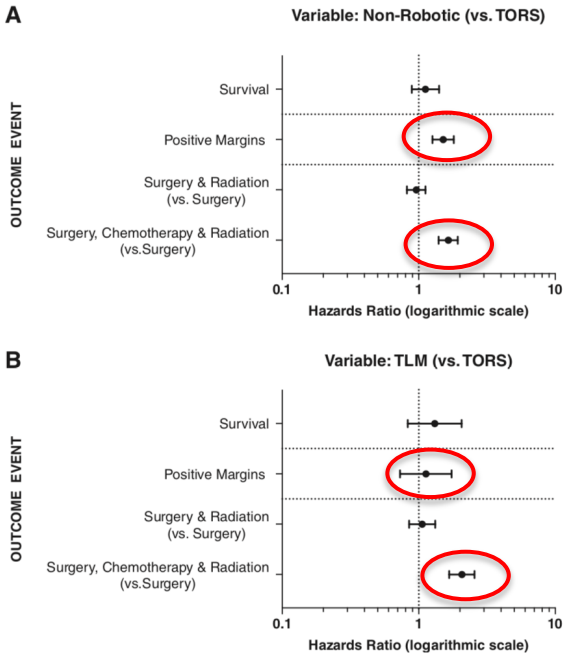
TORS vs. TLM vs. non-robotic surgery



Greater hazard ratio for positive margins in case of non-robotic

Greater hazard ratio for adjuvant CRT in case of non-robotic

No difference between TLM and TORS with respect to positive margin rate

Greater hazard ratio for adjuvant CRT in case of TLM

Li et al. Laryngoscope 2018

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OS of early T-stage OPCs is superior for TORS vs. non-robotic surgery

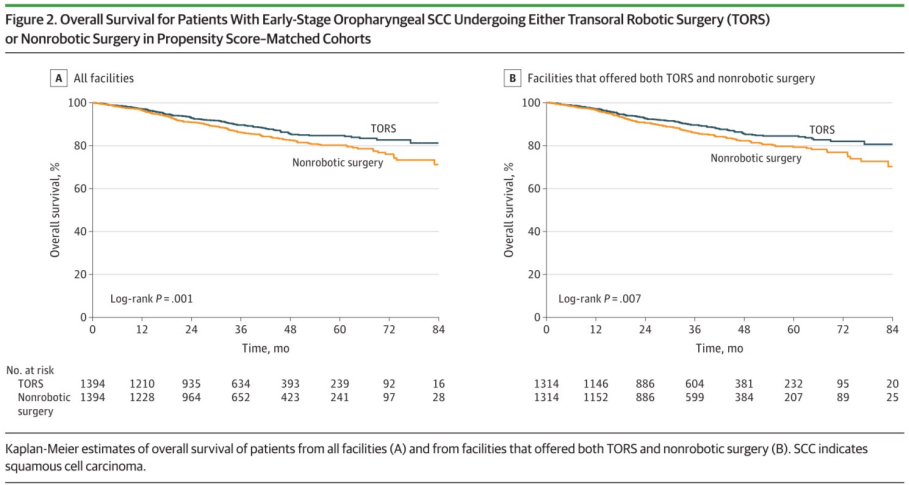

Figure 2. Overall Survival for Patients With Early-Stage Oropharyngeal SCC Undergoing Either Transoral Robotic Surgery (TORS) or Nonrobotic Surgery in Propensity Score–Matched Cohorts

Kaplan-Meier estimates of overall survival of patients from all facilities (A) and from facilities that offered both TORS and nonrobotic surgery (B). SCC indicates squamous cell carcinoma.

Nguyen et al. JAMA Onc. 2020

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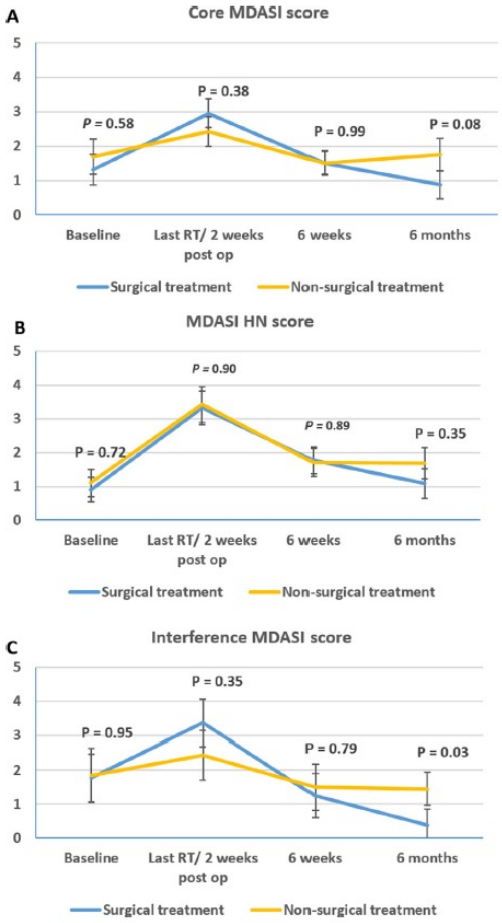
Comparing functional outcome between surgery and RT



- <u>MD Anderson Symptom Inventory</u>
- Core items: Pain, fatigue etc.
- Head and Neck items: Mucus, taste etc.
- Interference items: Relationship, work etc.

Amit et al. Oral Oncol 2019

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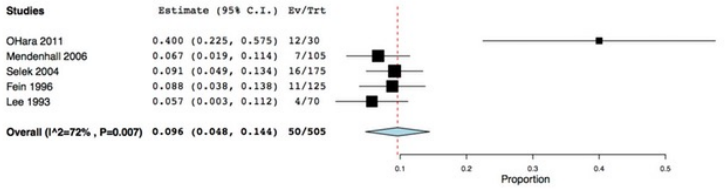
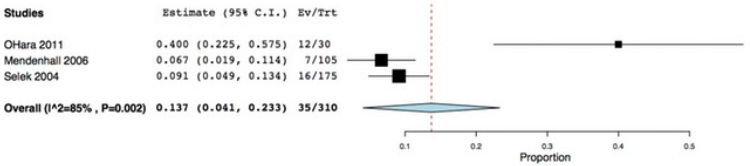
The 5years-DSS of RT (A) versus TOS (B) for early stage OPC is equivalent

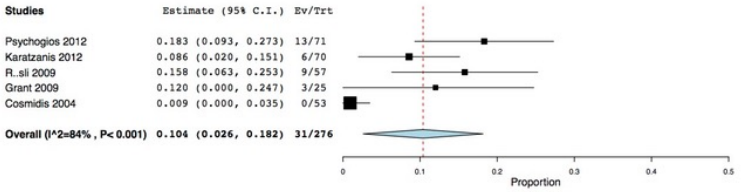
A



B



C



Morisod et al., Head and Neck 2014

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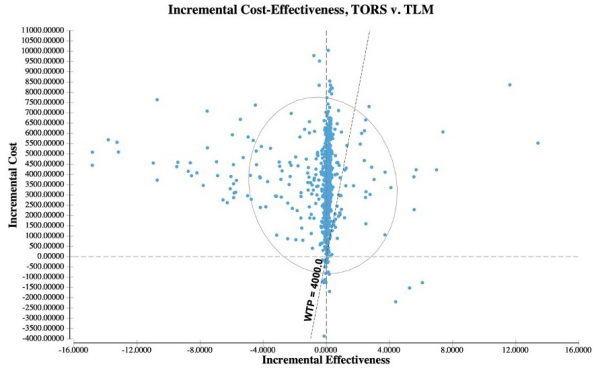
TORS is less cost-effective than TLM

	TORS	TLM
Months	342.72	342.62
QALMs	216.31	216.40
Cost (CFH)	56879.13	53518.28

Figure 5 -PSA, base case analysis



Parimbelli et al. BMC Health Serv Res 2022

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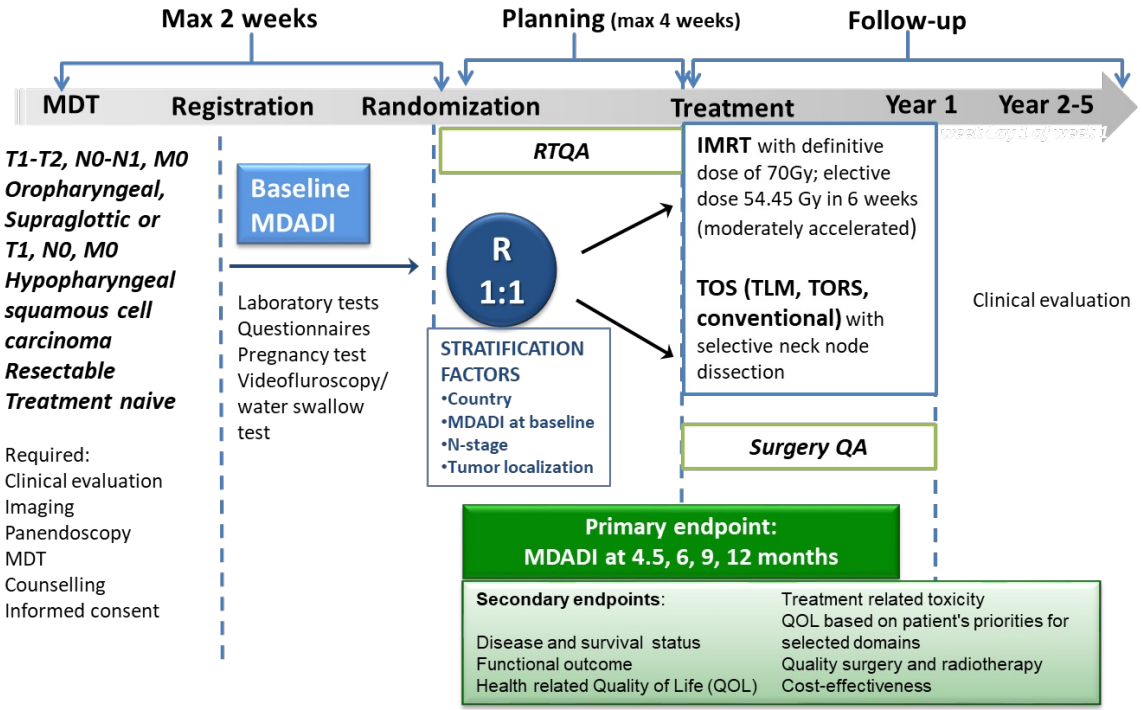
EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

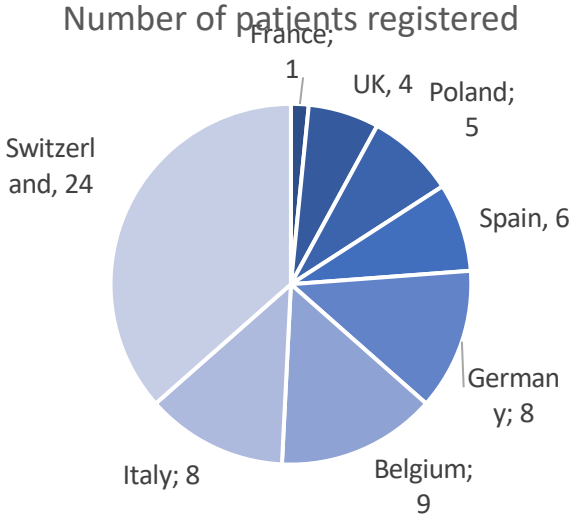
EORTC 1420-HNCG-ROG

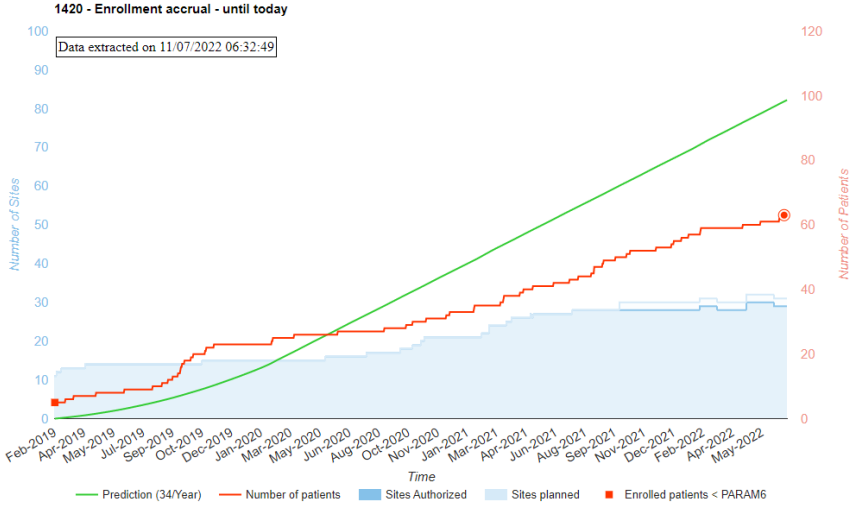
Phase III study assessing the “best of” radiotherapy compared to the “best of” surgery (trans-oral surgery (TOS)) in patients with T1-T2, N0-N1 oropharyngeal, supraglottic carcinoma and with T1, N0 hypopharyngeal carcinoma

Multi-center, randomized phase 3 trial



Accrual (cut off 12/07/2022)





TOTAL: 65 patients, 63 patients randomized

TOP recruiters:

CHUV

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Département d'oncologie
Centre de thérapies expérimentales

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What answers could “Best-of” give us

If Best-of shows an advantage for TOS over IMRT:

TOS-based treatment should be chosen whenever foreseeing a “reasonable” probability of single-modality treatment

If Best-of shows equivalence between TOS over IMRT: Treatment decision based on patient preferences and individual toxicity profiles

If Best-of shows an advantage for IMRT over TOS:

IMRT-based treatment would be preferred, except in case of the cisplatin-unfit patient

Treatment options for advanced-stage OPCs (7th AJCC edition)

- Multi-modality treatment
  - Non-surgical
    - Combined CRT
      - HPV+: De-escalation
      - HPV-: Escalation
  - Surgical
    - Surgery, followed by risk-stratified adjuvant RT or CRT
      - HPV+: De-escalation
      - HPV-: Escalation

Anatomic Stage/Prognostic Groups: Oropharynx,

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

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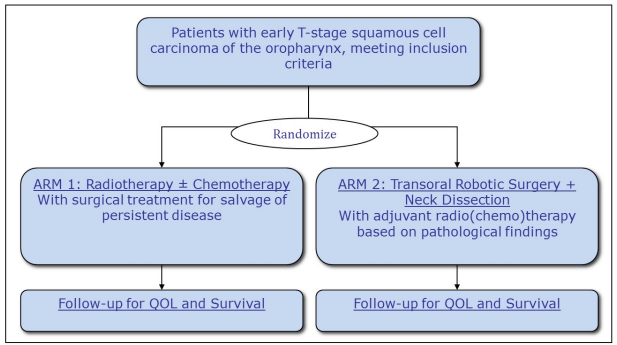
ORATOR-trial

ORATOR Schema



Western

Nichols et al. Lancet Oncol 2019

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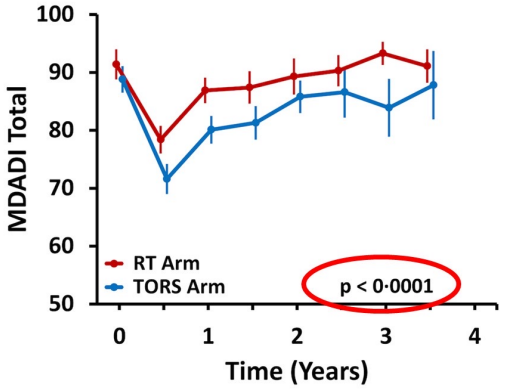
ORATOR-trial: RT-based treatment statistically better than surgery-based treatment: A consequence of surgical quality?



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Baseline Characteristics

Characteristic	All Patients (n=68)	RT Arm (n=34)	TORS + ND Arm (n=34)	p-value
Dropout after randomization	2 (2.9)	2 (5.9)	0 (0)	0.49
Primary Treatment		RT: 9 (28.1) CRT: 23 (71.9)	Surgery: 10 (29.4) S + RT: 16 (47.0) S + CRT: 8 (23.5)	

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Presented By Anthony Nichols at 2019 ASCO Annual Meeting
Nichols et al. Lancet Oncology 2019

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ORATOR-trial: RT-based treatment statistically better than surgery-based treatment: A consequence of surgical quality?

Supplemental Table 1. Participating institutions.

Institution	Principal Investigator	N
London Regional Cancer Program, London, Canada	Dr. Anthony Nichols Dr. David Palma	41
British Columbia Cancer Agency, Vancouver, Canada	Dr. Eitan Prisman	13
McGill University, Montreal, Canada	Dr. Michael Hier	6
University Health Network, Toronto, Canada	Dr. John de Almeida	5
Royal Adelaide Hospital, Adelaide, Australia	Dr. Suren Krishnan	2
The Ottawa Hospital, Ottawa, Canada	Dr. Stephanie Johnson-Obaseki	1

A tracheostomy is strongly recommended, but not mandatory in all cases to provide airway protection due to swelling and bleeding.

staging was pT1 in 15 patients, pT2 in 15 patients, pT3 in four patients, pN0 in ten patients, pN1 in seven patients, and pN2 in 17 patients.

No restrictions as to the bilateral involvement of the base-of-tongue and soft palate

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On longitudinal analysis swallowing differences persist

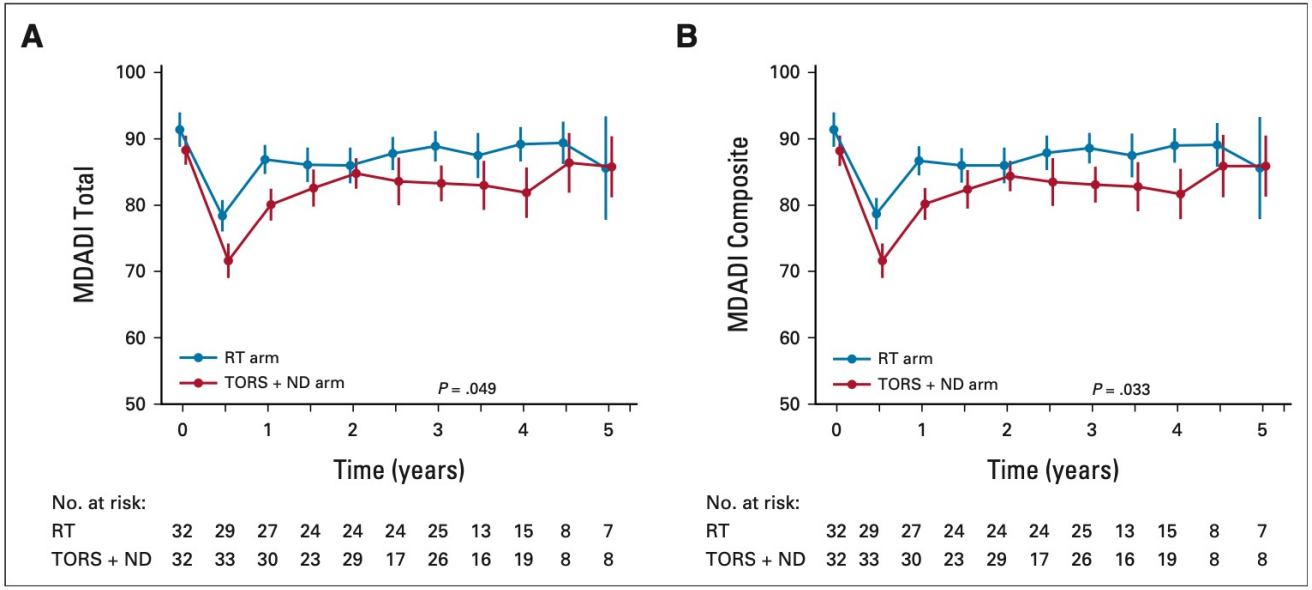

FIG 2. Changes in MDADI (A) total and (B) composite quality-of-life scores over time by treatment arm. Error bars represent standard errors. MDADI, MD Anderson Dysphagia Inventory; RT, radiotherapy; TORS + ND, transoral robotic surgery plus neck dissection.

Nichols et al. JCO 2022

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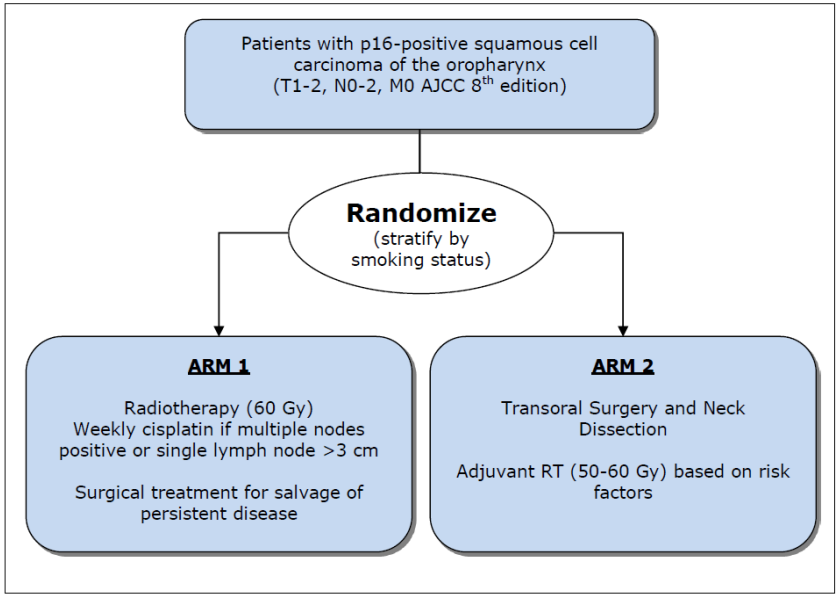
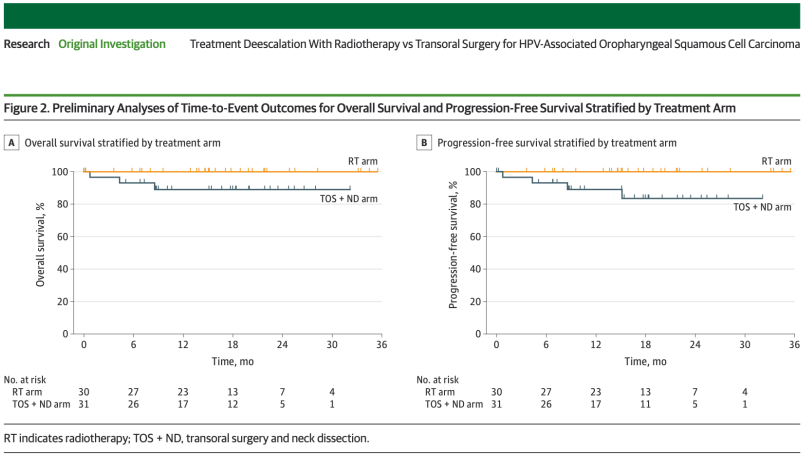
ORATOR 2





Palma et al. Jama Onco 2022

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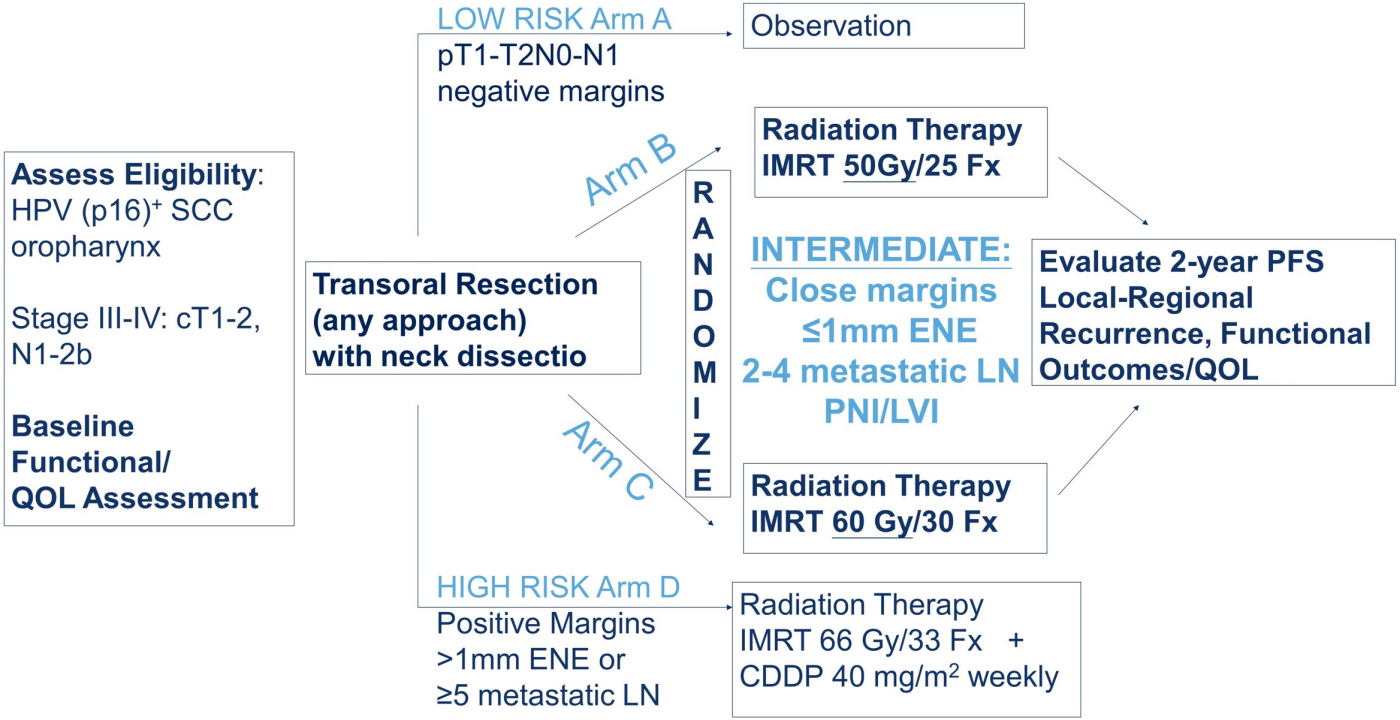
ECOG-ACRIN E3311 schema



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Patients and Methods

From December 2013 - July 2017, 68 of 87 credentialed surgeons (Ferris, *Oral Oncology* 2020) performed transoral resection (TOS) for 519 p16+ OPC patients (cT1-2 stage III/IV AJCC7 without matted neck nodes)

Post-operative management was determined by pathologically assessed risk

Among 360 eligible and treated patients,

- Arm A enrolled (N=38) 11%
- Arms B (50Gy, N=100) or C (60Gy, N=109) randomized 58%
- Arm D (N=113) enrolled 31%

Arm D assignment was based on >1mm ENE (77%), > 4 nodes (27%), and/or positive margins (11%). Positive margin rate 3.3% overall.

Gr. 3/4 oral bleeding = 5.9%; Gr. 5 = 0.2% (1/495 patients).

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Results

Arm	N	3-year PFS	90% CI	Deaths (without recurrence)	Recurrences	LRF	DM
A	38	96.9%	(91.9%, 100%)	0	1	0	1
B	100	94.9%	(91.3%, 98.6%)	1	4	2	2
C	109	93.5%	(89.4%, 97.9%)	1	5	1	4
D	113	90.7%	(86.2%, 95.4%)	3	7	4	3

- **There were 2 treatment-related deaths (one surgical and one Arm D)**
- **TOS + low-dose radiation is worthy of further study, since the primary endpoint of the upper bound of the 90% CI (in the intermediate risk group) exceeding 85% was met**

Sites of Recurrence:

Arm A: 1 distant (pulmonary and pleural masses and nodules)
Arm B: 1 primary & nodal, 1 nodal, 2 distant (LUL lesion; lung)
Arm C: 1 primary, 4 distant (mediastinum; lung; lung; right upper lobe)
Arm D: 2 primary, 2 nodal, 3 distant (T11 lytic lesion; liver; brain)

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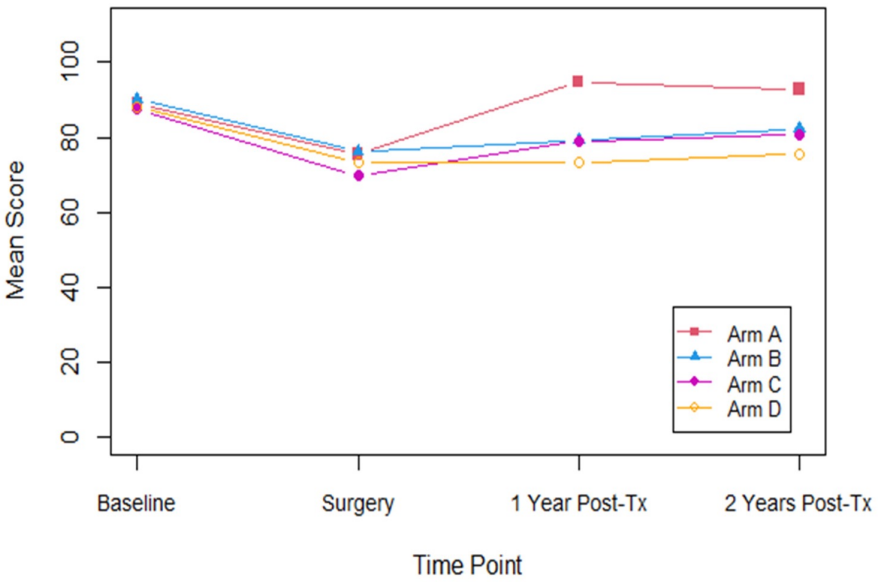
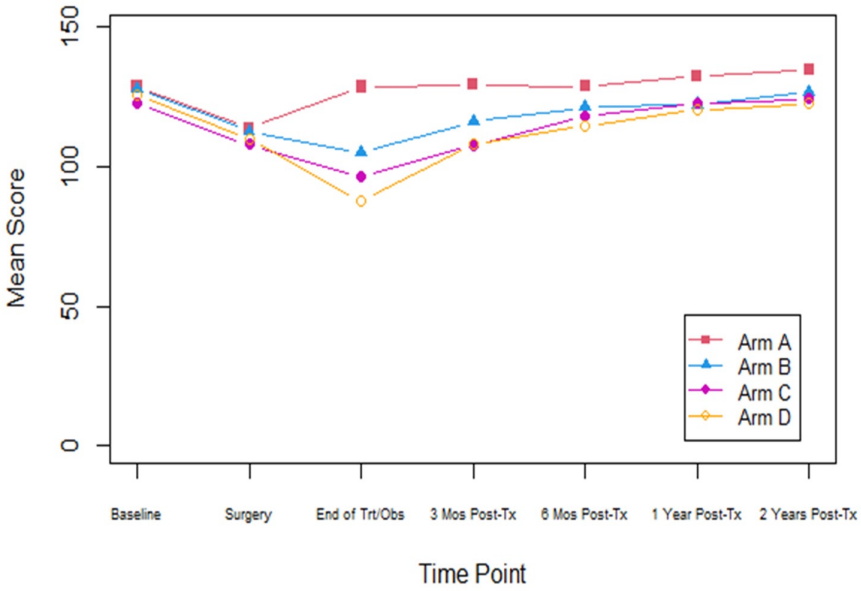
MDADI Composite Scores



FACT H&N Total Scores



QOL endpoint: Change in FACT-H&N total score from baseline to 6 months post-RT. Comparison defined a-priori as "improved" (change ≥ 7 points) or "stable" (-6 <- change <- 6) vs. "worsened" (change ≤ -7 points).

Arms B/C vs. D: 56% in Arms B/C vs. 38% in Arm D (p-value = 0.011)
Arm B vs. C: 63% in Arm B vs. 49% in Arm C (p-value=0.056)

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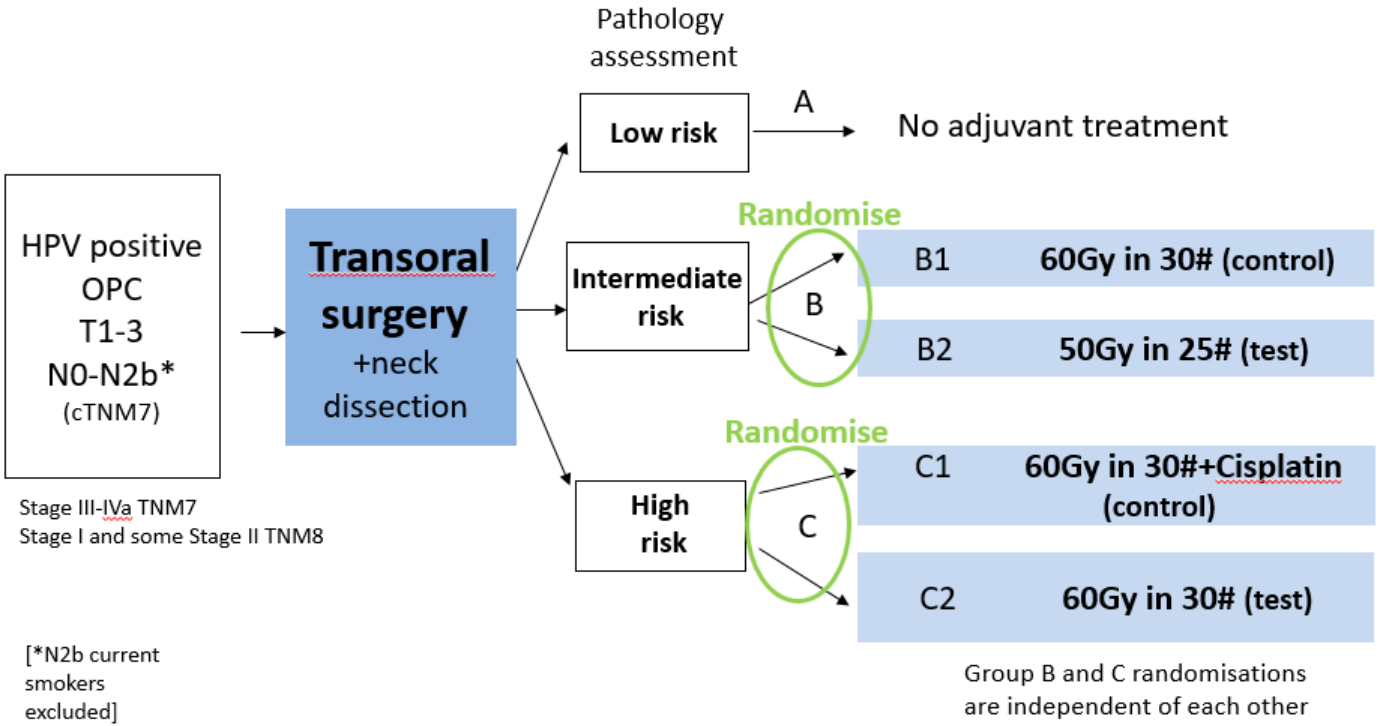
PATHOS

Post-operative adjuvant treatment for HPV-positive tumours



❄ Endpoints: phase II- swallowing function (MDADI) at 12months, phase III- Overall Survival

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No benefit by introducing TORS

Multimodality setting

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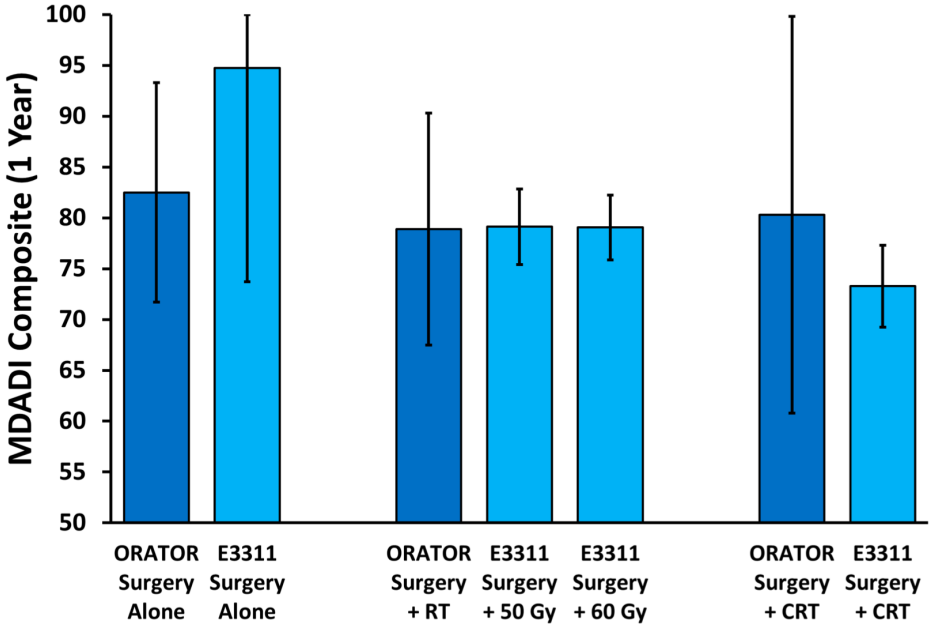
However, data should be interpreted with caution…



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Different QA programs in TORS/TOS trials

Table 1
Current clinical surgical trials with surgical quality assurance platforms.

Trial	Trial design and objective	Quality assurance program
ECOG 3311 (NCT 0189849) Phase II	- Three arms after transoral surgery ○ Low risk (T1,2; N0-1, negative margins) ○ Intermediate risk (close margins, ≥grade II ECS, 2–4 met. nodes): randomisation into 50Gy vs. 60Gy ○ High risk (ECS > grade II, ≥5 met. nodes): CRT - Primary end-point: 2 years PFS - Secondary end-points: Swallowing recovery, quality of life, toxicity	- Twenty transoral resections in the oropharynx - Five of which transoral cancer cases - Submission of 10 most recent for review with histology and operative reports - Credentialing by a credentialing committee - Accreditation granted per technique - Affiliation with cooperative group
ORATOR (NCT 01590355) Phase II	- Two arms ○ TORS ± RT/CRT ○ RT/CRT - Primary end-point: 1 year MDADI - Secondary end-points: quality of life, oncological outcome, toxicity	- Completion of overall 10 TORS cases - One case to be proctored by the PI - In case of positive margins, the surgeon may attempt to clear the margin
PATHOS (NCT 02215265) Phase II	- Three arms ○ Low risk (no adverse pathological risk features) ○ Intermediate risk (T1-3, N2a-b, PI, VI, close margins (1–5 mm)): randomisation into 50Gy vs. 60Gy ○ High risk (positive margins, ECS) - Primary end-point: 1 year MDADI - Secondary end-points: Quality of life, toxicity, oncological outcome	- Documentation of five transoral cases of OPSCCs - Rewards for successful resections (R0-resections)
EORTC 1420 'Best of' (NCT 02984410) Phase III	- Two arms ○ Transoral surgery ○ IMRT - Primary end-point: Evolution of MDADI over 1 year - Secondary end-points: quality of life, oncological outcome, cost-effectiveness	- Documentation of 25 TOS cases (20 oropharyngeal cases) - Review of five cases done within the last year with histology and operative reports - Credentialing by a credentialing committee - Definition of margins (≥3 mm negative) and number of nodes to be resected (≥18), positive and close margins have to be re-resected - Complications, postoperative bleeding, NG-tube and tracheostomy rates as outcome measures
CompARE (UKCRN ID 18621) Phase III	- Four arms ○ CRT ○ Cisplatin plus dose escalated RT ○ Surgery plus CRT ○ CRT plus PD-L1 immunotherapy - Primary end-point: Survival - Secondary end-point: quality of life, oncological outcome, cost-effectiveness	- Review of five cases done within the last year with histology and operative reports - Credentialing by a credentialing committee - Definition of margins (≥3 mm negative), positive and close margins have to be re-resected - Complications, postoperative bleeding, NG-tube and tracheostomy rates as outcome measures

TORS, transoral robotic surgery; MDADI, MD Anderson Dysphagia Inventory; OPSCC, oropharyngeal squamous cell carcinoma; TOS, trans oral surgery; ECOG, Eastern Cooperative Oncology Group; RT, radiotherapy; EORTC, European Organisation for Research and Treatment of Cancer; ECS, extra-capsular spread; CRT, chemo-radiation therapy; PFS, progression-free survival.

Simon et al.
Eu J Cancer 2018

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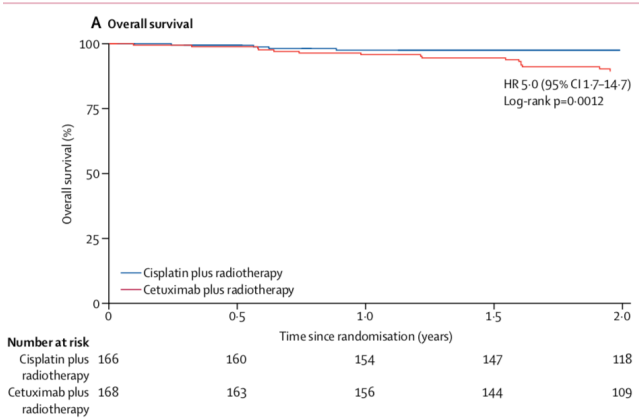
De-escalate: CRT superior to Cetuximab-RT



	Cisplatin plus radiotherapy (95% CI)	Cetuximab plus radiotherapy (95% CI)	p value
Primary outcome			
Overall			
Grade 3–5	4·81 (4·23–5·40)	4·82 (4·22–5·43)	0·98
All grades	29·15 (27·33–30·97)	30·05 (28·26–31·85)	0·49
Secondary outcomes			
Acute short-term toxicities			
Grade 3–5	4·43 (3·88–4·97)	4·35 (3·84–4·86)	0·84
All grades	19·96 (18·81–21·12)	20·35 (19·18–21·52)	0·64
Severe late toxicities			
Grade 3–5	0·41 (0·29–0·54)	0·48 (0·30–0·67)	0·53
All grades	9·44 (8·53–10·34)	9·87 (9·02–10·72)	0·49

t test used to compare treatment groups. No adjustments have been made for multiple testing. Toxicity assessed with Common Toxicity Criteria for Adverse Events, version 4.0.

Table 2: **Mean number of acute, late, and overall toxicity events per patient, by treatment group**

Mehanna et al. Lancet 2018

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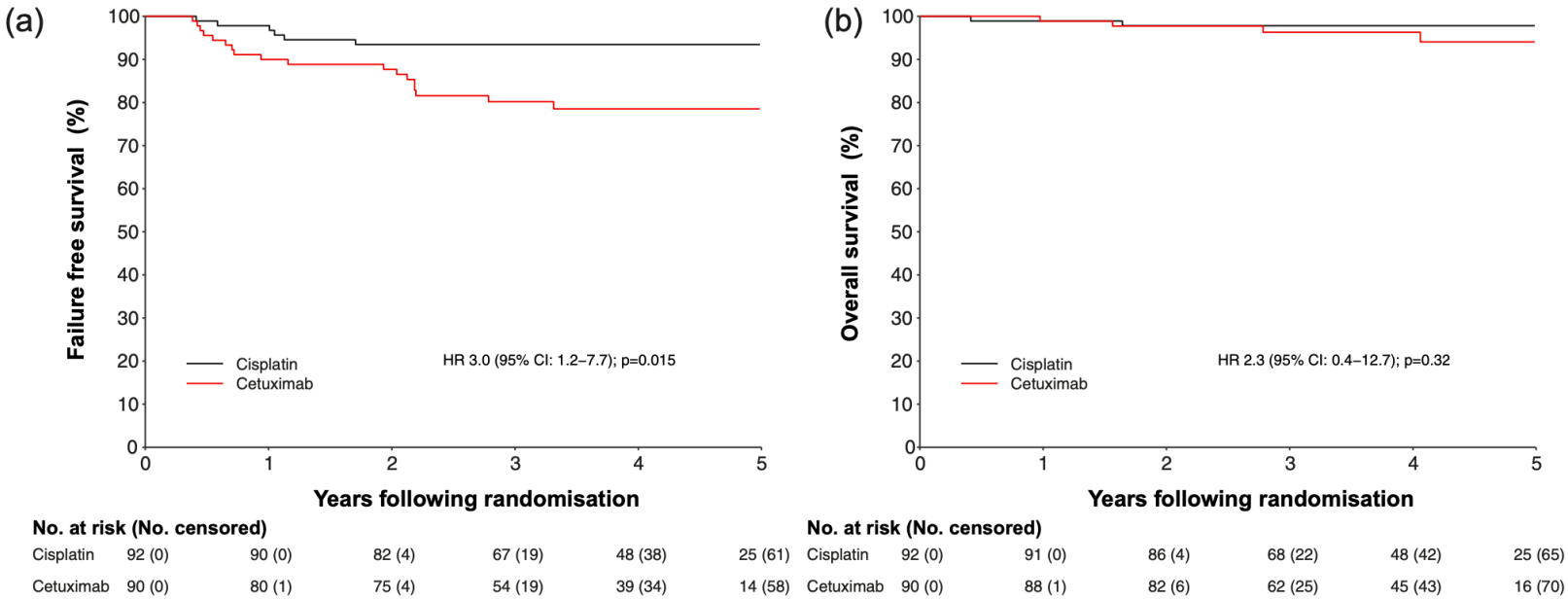
TROG 12.01: Cisplatin superior to Cetuximab



Rischin et al. Int J Radiation Oncol Biol Phys 2021

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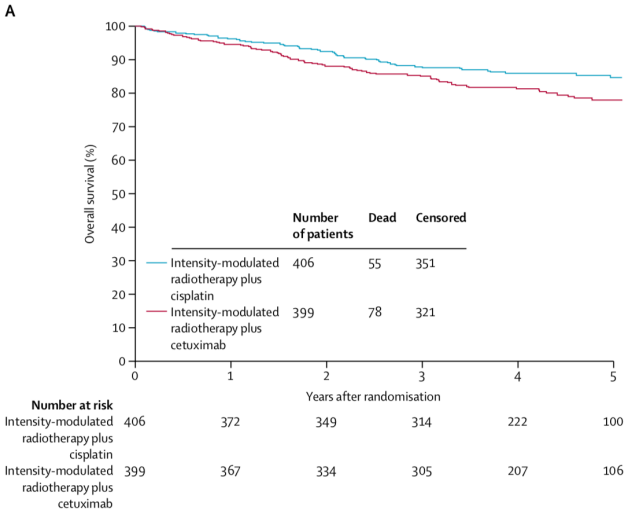
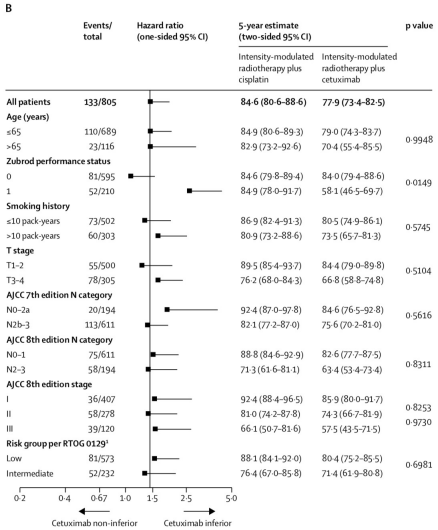
RTOG 1016: CRT superior to Cetuximab-RT





Gillison et al. Lancet 2018

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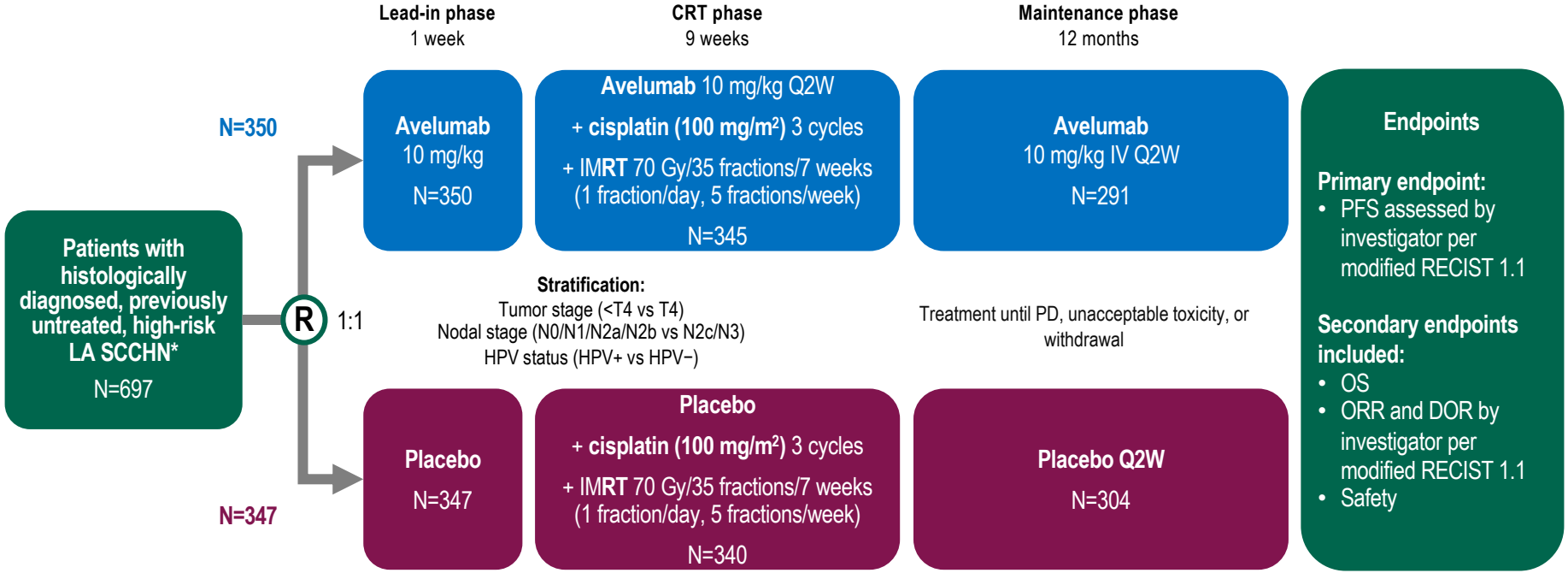
JAVELIN Head & Neck 100: study design

Randomized, placebo-controlled, double-blind, phase 3 trial

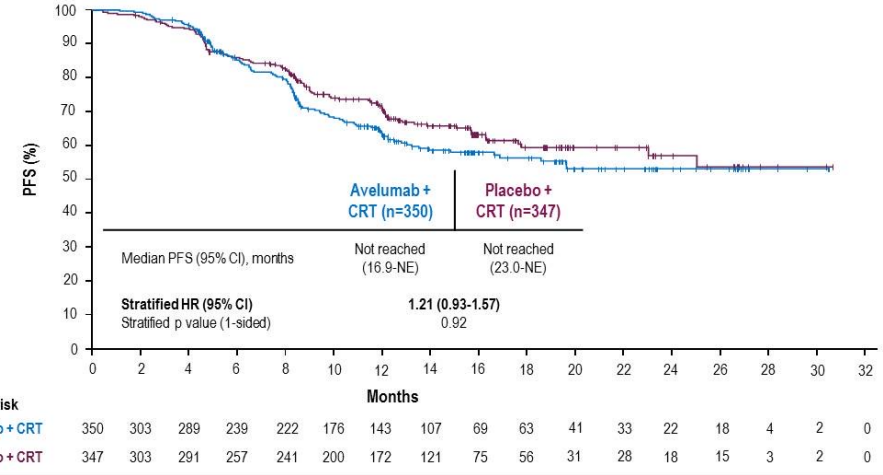


DOR, duration of response; **HPV**, human papillomavirus; **IMRT**, intensity-modulated radiation therapy; **IV**, intravenously; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **Q2W**, every 2 weeks; **R**, randomized; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1.

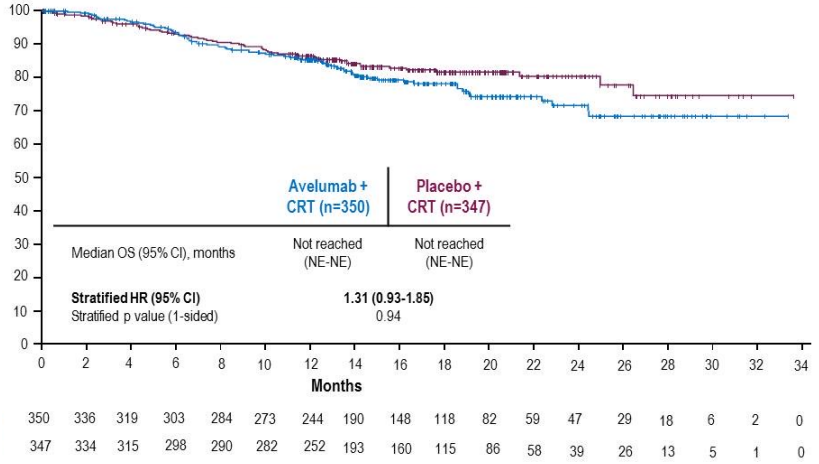
* High-risk LA SCCHN (oral cavity, oropharynx, larynx, or hypopharynx): HPV-negative disease stage III, IVa, IVb; nonoropharyngeal HPV-positive disease stage III, IVa, IVb; HPV-positive oropharyngeal disease T4 or N2c or N3 (TNM staging per AJCC, 7th edition).

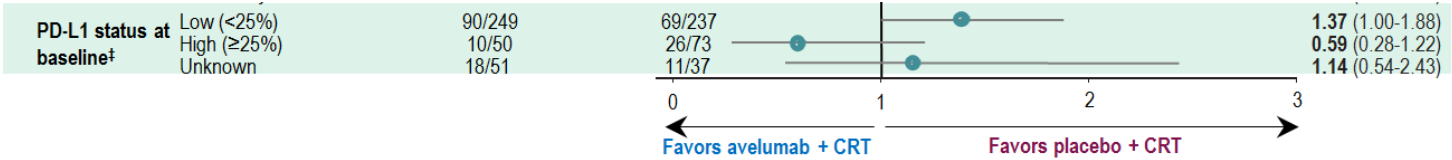
Addition of avelumab to CRT does not improve outcome

PFS



OS





Why de-intensification/de-escalation?

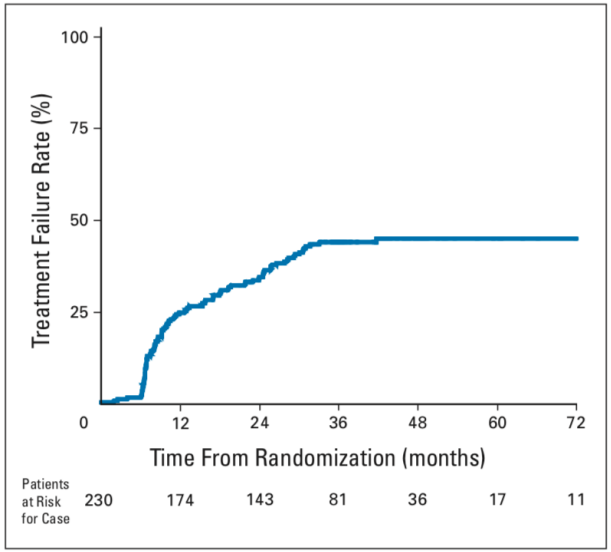


Fig 1. Time to severe late toxicity (shown in the graph as Treatment Failure Rates): all assessable patients.

Table 3. Types of Late Toxicity Events Seen by Trial

Variable	91-11	97-03	99-14	Total
Feeding tube dependence > 2 years post-radiation therapy	—*	29*		29
RTOG late toxicity criteria, grade 3+				
Pharyngeal dysfunction	16	28	19	63
Laryngeal dysfunction	22	6	0	28
Death	11	9	2	22
Other (eg, infection, fistula)	3	0	1	4
Any	38†	40†	21†	99†
No severe late toxicity event (controls)	50	62	19	13

Abbreviation: RTOG, Radiation Therapy Oncology Group.
*Feeding tube data were not collected at all in RTOG study 91-11.
†Numbers do not always add up along columns, due to some patients having more than one toxicity event.

18,2% 47,5%
27,5%

Machtay et al. JCO 2008

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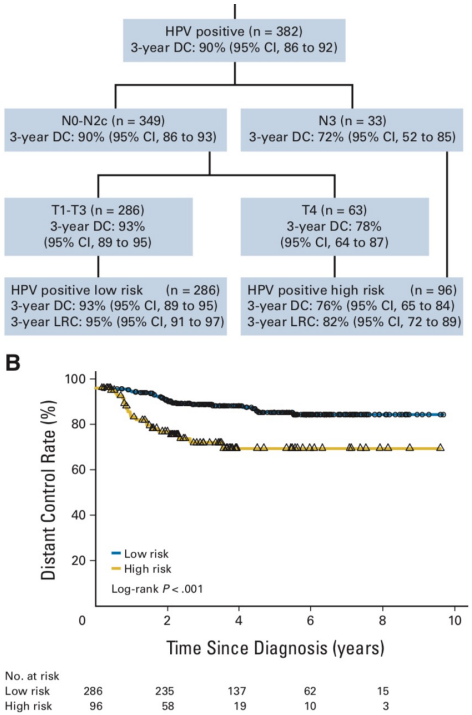
De-escalation is not for everybody



T1-3 N0-2b

AJCC 7th classification

O'Sullivan et al. JCO 2013

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Strategies of de-escalation

- De-intensification of chemotherapy
- De-intensification of CRT
- Reduced RT after induction response
- De-intensification of adjuvant CRT

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Benefit of de-intensification

TABLE 2 Subgroup analysis for overall survival

Subgroups	N° of studies	HR (95%CI)	*p*	I^2 (*p* for heterogeneity)	Type of analysis
Strategy:	8	1.42 (1.16–1.75)	<0.01	44.7 (0.08)	Random
• CTRT vs. RT (curative)	5	0.58 (0.32–1.06)	0.07	70 (<0.01)	Random
• S + RT vs. S + CTRT (adjuvant)	3	1.61 (0.78–3.33)	0.07	60 (0.08)	Random
• S + CTRT vs. S					
Systemic therapy or RT:	6	3.47 (1.67–7.2)	<0.01	70.4 (<0.01)	Random
• RT + CDDP vs. RT + CET (curative)	6	1.64 (1.3–2.08)	<0.01	43 (0.11)	Fixed
• RT + CDDP vs. RT + other CT/schedules	6	0.98 (0.75–1.29)	0.91	0 (0.74)	Fixed
• RT vs. different RT doses/schedules					
Setting:	40	1.39 (1.21–1.59)	<0.01	73.3 (<0.01)	Random
• Definitive	9	0.88 (0.55–1.39)	0.59	70 (<0.01)	Random
• Adjuvant					
Type of study:	10	1.39 (1.04–1.89)	<0.01	59.8 (<0.01)	Random
• Randomized	39	1.28 (1.11–1.48)	0.023	70 (<0.01)	Random
• Nonrandomized					
Quality of studies:	10	1.23 (0.87–1.73)	0.23	73 (<0.01)	Random
• Low	39	1.32 (1.14–1.53)	<0.01	73 (<0.01)	Random
• Moderate-high					

Note: HR > 1 indicated better outcome for standard (nondeescalated) arms.

Pettrelli et al. Head and neck 2022

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Thank you for your attention

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