How I Treat Locally Advanced Head and Neck Cancer, 2022

18th Annual California Cancer Consortium Conference

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In the past year or two, What data have emerged that have changed (or NOT) the way I approach SCCHN?

- TRANSORAL SURGERY TRIALS: ORATOR I, ORATOR II, ECOG 3311
- CDDP high vs low dose. Japanese adjuvant data vs TATA data
- HPV associated SCCHN : any progress in de- intensification?
- NPC induction plus adjuvant with capecitabine
- Biomarkers: cell free DNA for EBV, HPV.

What do non- surgeons need to know about what is going on with surgical trials?

- ORATOR
- ORATOR2
- ECOG 3311
- PATHOS

How should early stage p16+ oropharyngeal cancer be treated? Radiation – based or surgical?

What is done now:

"Currently, there is no level I evidence to favour one treatment strategy over the other. Instead, treatment selection is largely driven by institutional and patient biases with the majority of patients in the United States receiving surgery (82% of T1-T2 disease), while most patients receive primary RT in Canada."

From ORATOR II background section and Cancer 122:1523-32, 2016

original report

Randomized Trial of Radiotherapy Versus Transoral Robotic Surgery for Oropharyngeal Squamous Cell Carcinoma: Long-Term Results of the ORATOR Trial

T1-T2N0-2 p16-positive OPSCC

RT 70 Gy in 35 fractions (+ CDDP 100 mg/m2x 3 (96%) or cetuximab if N+)

versus

Trans oral resection + adjuvant XRT
60 Gy/30 fractions
if + margin or ENE, 64 Gy in 30 fractions + CDDP or cetuximab

J Clin Oncol 40:866-875. © 2022

MDADI: M.D. Anderson Dysphagia Inventory

20 questions such as:

My swallowing ability limits my day-to-day activities.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E2. I am embarrassed by my eating habits.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F1. People have difficulty cooking for me.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P2. Swallowing is more difficult at the end of the day.

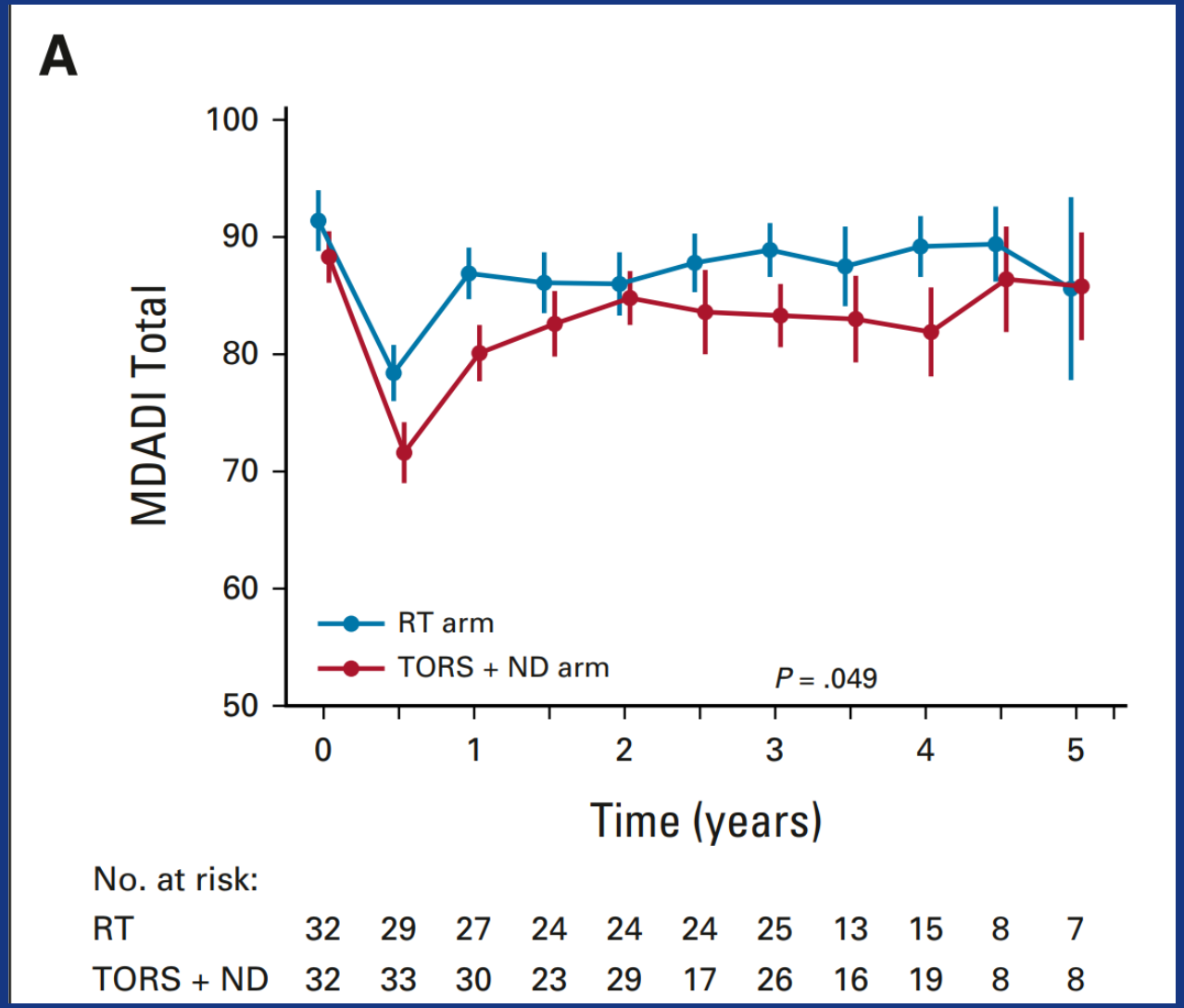
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E7. I do not feel self-conscious when I eat.

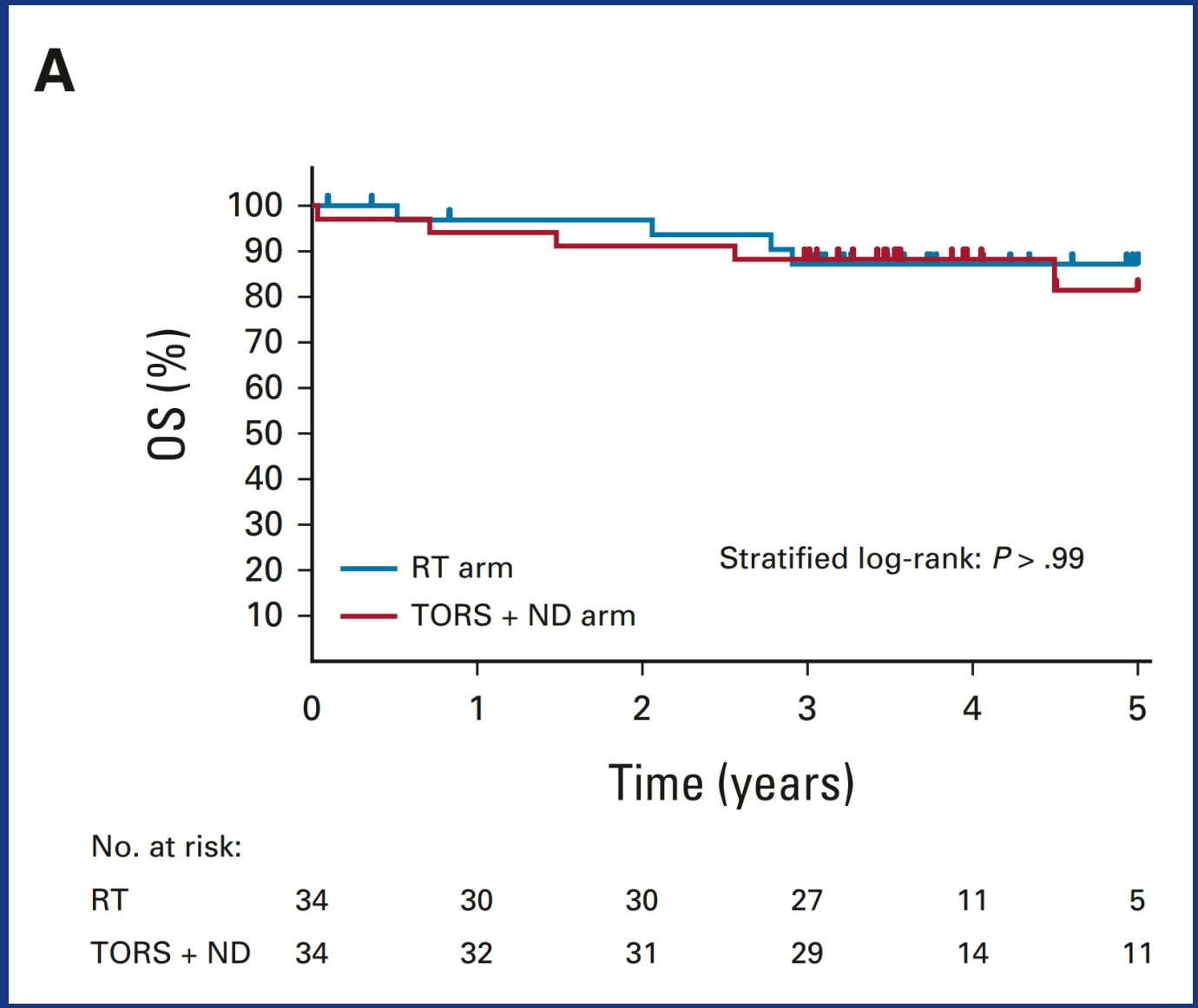
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

Arch Otolaryngol Head Neck Surg. 2001;127(7):870-876

Primary endpoint in ORATOR: direct comparison of MDADI, assuming 10% improvement with TORS



ORATOR secondary endpoint : OS



JAMA Oncology | Original Investigation

Assessment of Toxic Effects and Survival in Treatment Deescalation With Radiotherapy vs Transoral Surgery for HPV-Associated Oropharyngeal Squamous Cell Carcinoma

The ORATOR2 Phase 2 Randomized Clinical Trial

T1-T2N0-2 p16-positive OPSCC

RT 60 Gy in 30 fractions (+ weekly CDDP 40mg/m2 if N+)

versus

Trans oral resection + adjuvant XRT
50 Gy/25 fractions
if + margin or ENE, 60 Gy in 30 fractions

JAMA Oncol. doi:10.1001/jamaoncol.2022.0615
Published online April 28, 2022.

Surgical credentialling

- Head and Neck Surgery with fellowship
- > 30 neck dissections/ year
- >20 TORS procedures/year
- >20 TORS for OPSCC as primary surgeon
- >5 TORS in past year

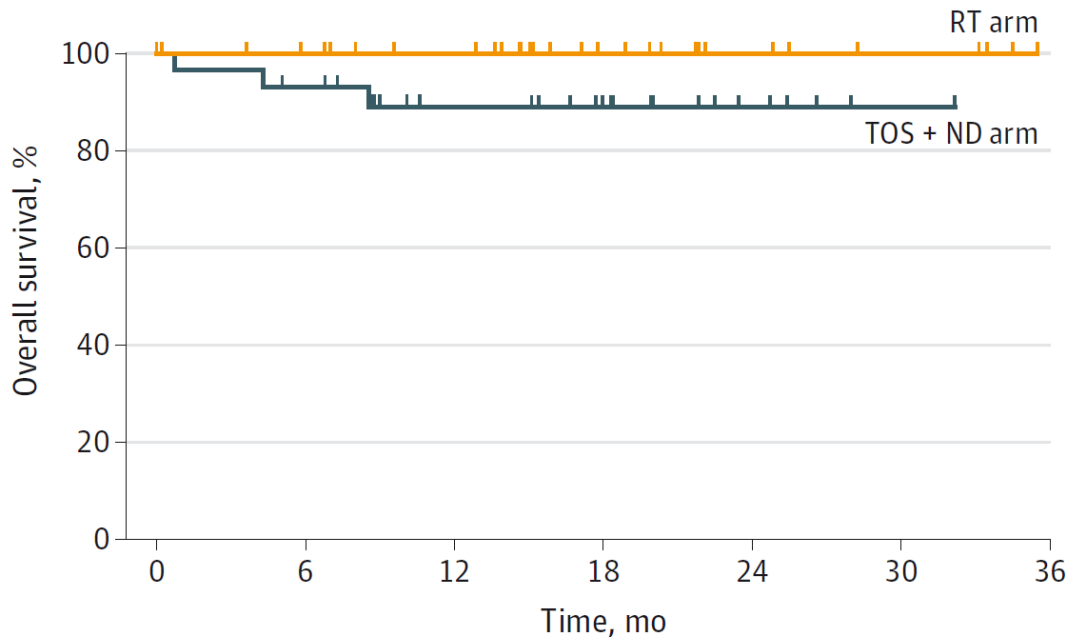
Trial design plan: PHASE 2, no di
comparison

- Primary endpoint: 2 ye
- One sided one
- **To te**
- “
- 80
- 140

Accrual was halted because of excessive toxic effects in the TOS and ND arm

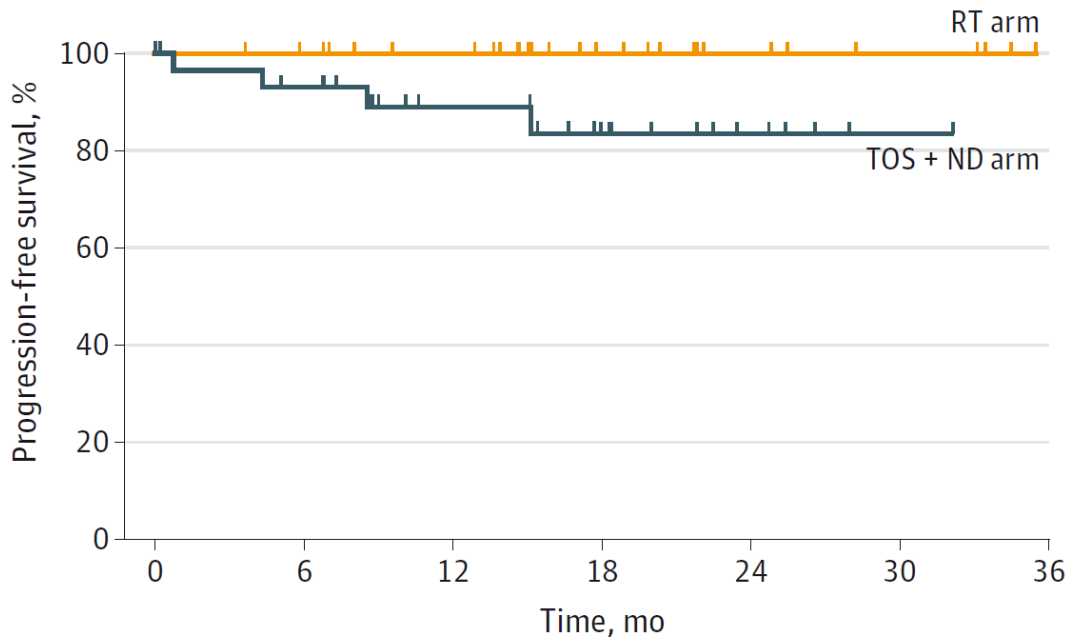
ORATOR II primary endpoint: OVERALL SURVIVAL

A Overall survival stratified by treatment arm



No. at risk						
RT arm	30	27	23	13	7	4
TOS + ND arm	31	26	17	12	5	1

B Progression-free survival stratified by treatment arm



No. at risk						
RT arm	30	27	23	13	7	4
TOS + ND arm	31	26	17	11	5	1

RT indicates radiotherapy; TOS + ND, transoral surgery and neck dissection

ECOG 3311:Look closely at the question being asked.

original reports

Phase II Randomized Trial of Transoral Surgery and Low-Dose Intensity Modulated Radiation Therapy in Resectable p16+ Locally Advanced Oropharynx Cancer: An ECOG-ACRIN Cancer Research Group Trial (E3311)

T1-2 p16 positive OPSCC no matted LN
All patients underwent TORS

Primary endpoint: estimation of 2 year PFS for intermediate risk patients (ARMS B and C)

Each arm worthy of **further study if "**the upper limit of the exact 90% binomial CI exceeded 85%

J Clin Oncol 40:138-149. © 2021

ECOG 3311 assignments

TABLE 1: Adjuvant De-escalation After TORS From ECOG-ACRIN 3311

Study Arm	Pathology	Study Intervention
A	Negative margins (> 3 mm), N0–N1, no ENE	Observation
B	Close margins (< 3 mm), 2–4 LN, ≤ 1 mm ENE, PNI/LVI	IMRT 50 Gy/25 Fx
C		IMRT 60 Gy/30 Fx
D	Positive margin, > 1 mm ENE, ≥ 5 LN	IMRT 66 Gy/33 Fx + cisplatin 40 mg/m² weekly

ECOG 3311 PRIMARY ENDPOINT: 2 YEAR PFS

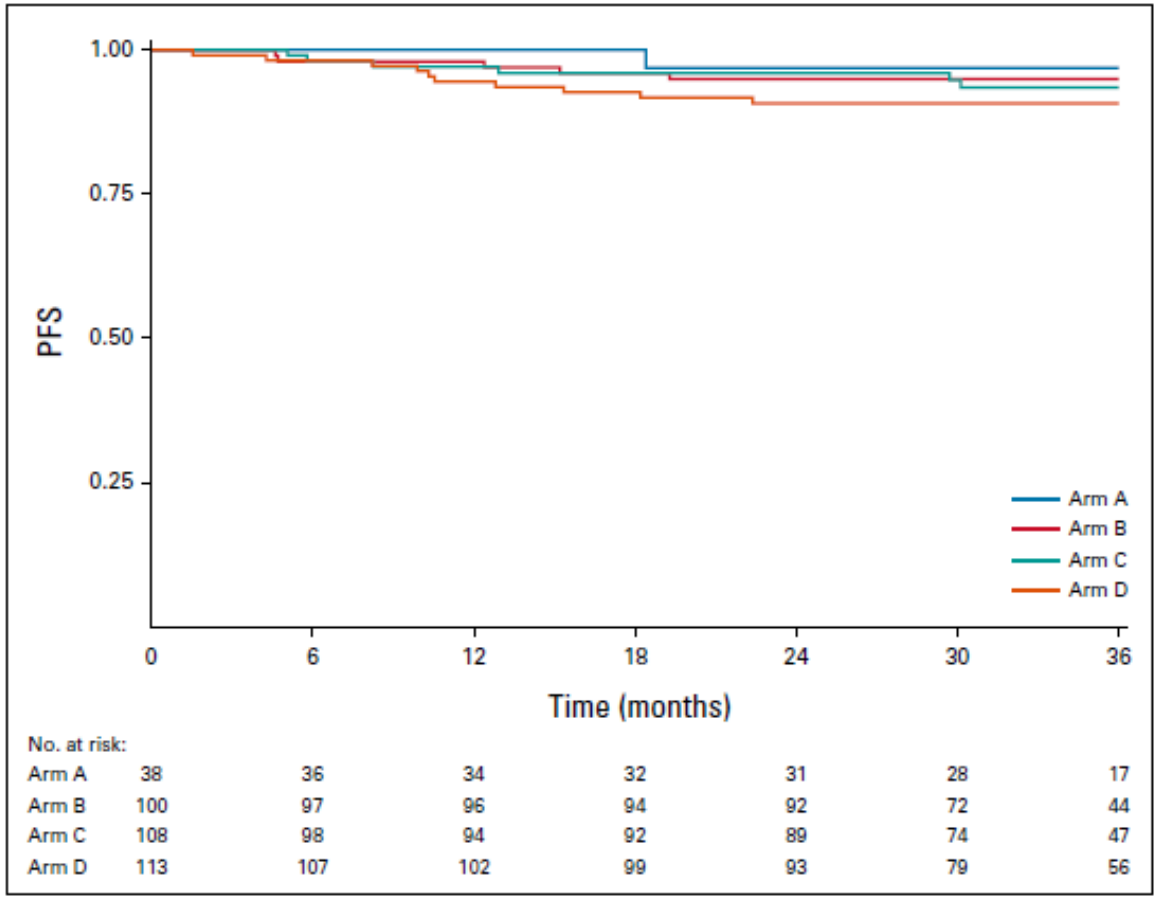


FIG 2. Kaplan-Meier estimates of PFS by arm for 359 evaluable patients. PFS, progression-free survival.

TABLE 2. 2-Year PFS, Overall PFS Events, and Sites of Recurrence

Arm	Patients (No.)	2-Year PFS (%)	90% CI
A	38	96.9	91.9 to 100
B	100	94.9	91.3 to 98.6
C	108	96.0	92.8 to 99.3
D	113	90.7	86.2 to 95.4

Exactly what questions did ECOG 3311 answer?

What ECOG 3311 tells us:

PFS is OK across all treatments using pathological staging from TOS as a selector

What it DOES NOT tell uis:

Whether this is any better than a de- escalation using TOS is better than what can be done with clinical l(nonsurgical) info alone.

What is the basis for lowering radiation doses as a comparator with surgery? Are there any high level data , controlled against definitive doses as prescribed in ORATOR I?

Translation to med onc:

Imagine this phase 2 trial:

in HPV pos SCCHN, T1-2, N1-2:

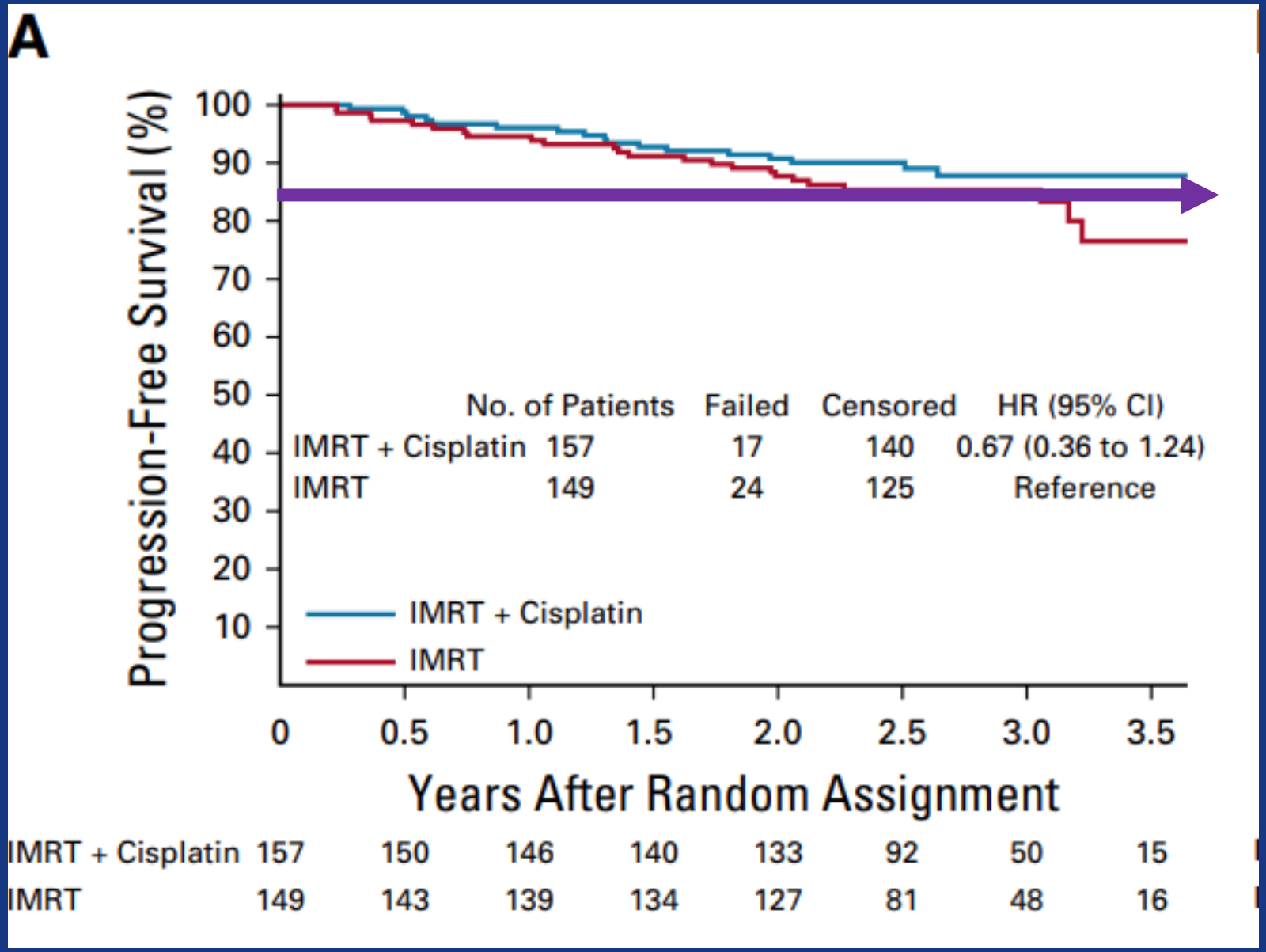
70 GY XRT with either concurrent ICI or 34 mg/m2 CDDP weekly

NRG HN002

- Randomized phase 2
- p16-positive, T1-T2 N1-N2b M0, or T3 N0-N2b M0 OPSCC
- 60 Gy IMRT over 6 weeks + CDDP 40mg/m2 weekly
- 60 Gy IMRT over 5 weeks

- Primary endpoint. NONCOMARATIVE
  - 2 year PFS must be > 85%

•. 2021 Mar 20;39(9):956-965.
•. 2021 Mar 20;39(9):956-965.



JCO 2021 Mar 20;39(9):956-965.

NRG HN 002

- PFS:
  - IMRT + C was 90.5%
  - IMRT, 2-year PFS was 87.6%

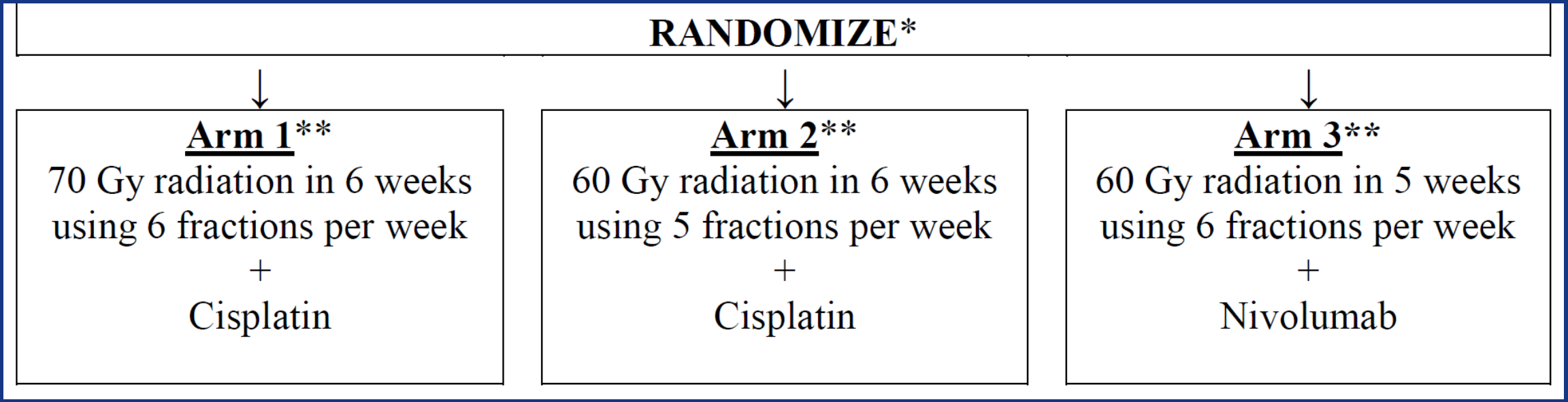
Conclusion:

The IMRT + C arm met both prespecified end points justifying advancement to a phase III study

Question: What would you set as noninferiority boundary for a phase 3?

HN005 :De-intensified Radiation Therapy With Chemotherapy (Cisplatin) or Immunotherapy (Nivolumab) in Treating Patients With Early-Stage, HPV-Positive, Non-Smoking Associated Oropharyngeal Cancer

- T1-2 N1 or T3 N0-1 p16 pos OPSCC
- Primary endpoint: To demonstrate co-primary endpoints of non-inferiority of PFS and superiority of quality of life (QOL) as measured by the MDADI
- CDDP 100 mg/m2 x 2 doses



HN005 statistics, Phase 3 po

The null hypothesis for each
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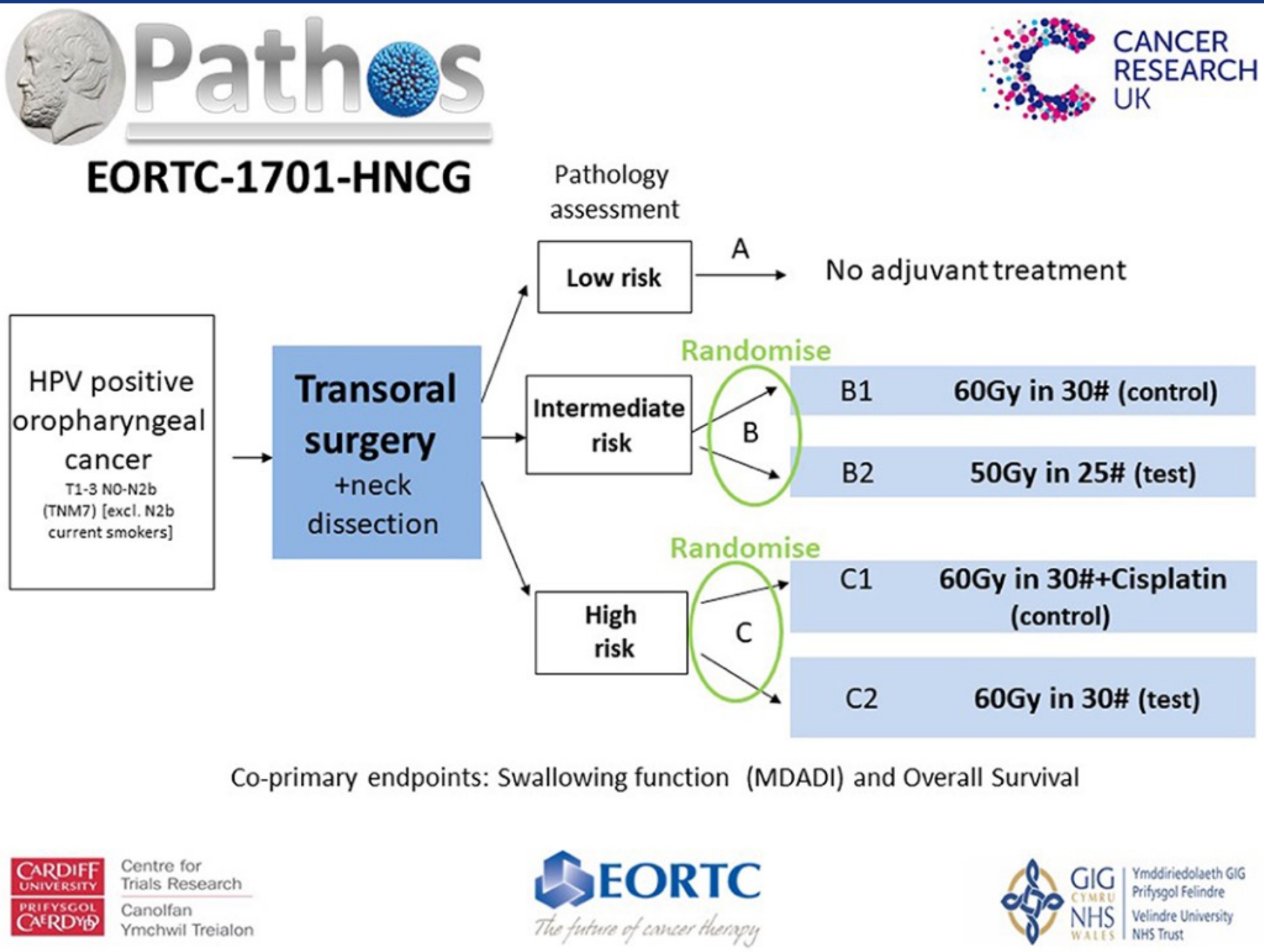
2 year PFS of 92.3% for the
ear PFS for the experimental arms will

b

Is 87% PFS OK if the control is 92%?

European colleagues' ongoing trials:

- **EORTC-1420-HNCG-ROG**
  - TOS versus IMRT for T1-2, N1-1, Oropharynx squamous cell carcinoma p16+/
  - 112 patients
  - Primary endpoint: MDADI
- **PATHOS**
  - **ECOG 3311 redux?**
  - **1100 patients**



Margin
< 1mm
or ECS

Who is a good TOS surgeon and does it matter?

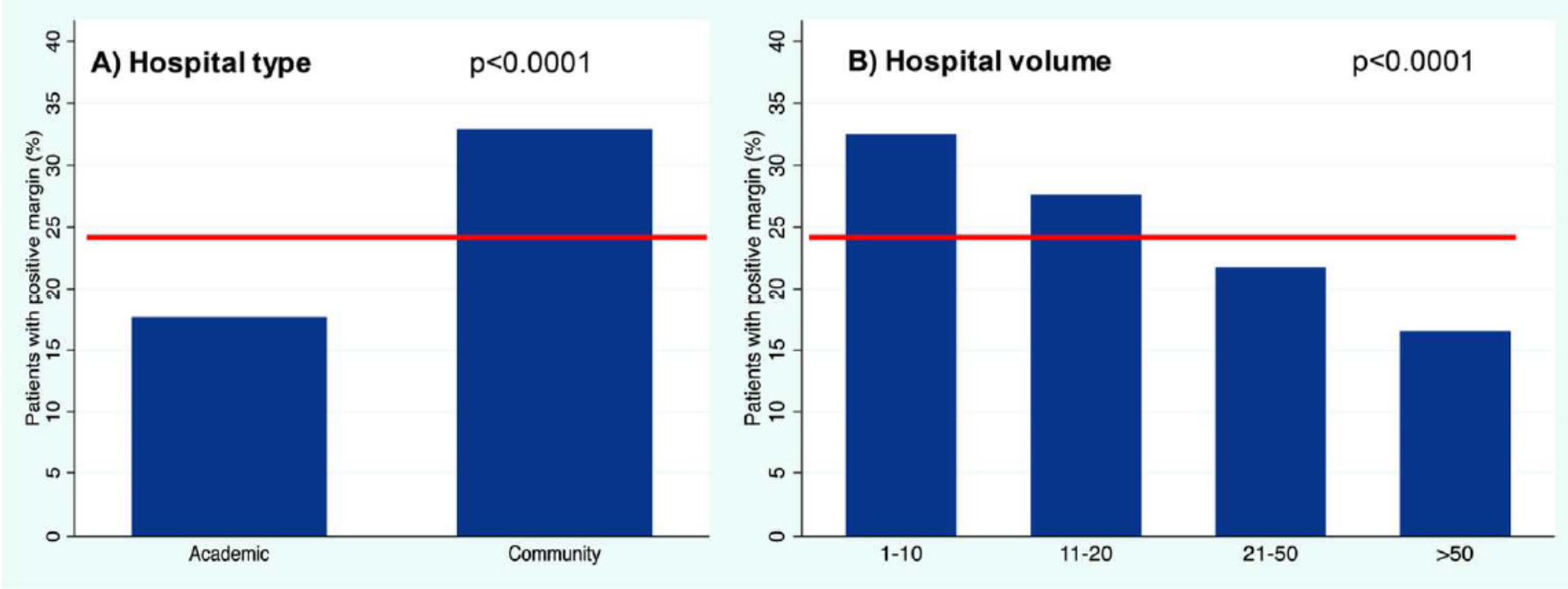


Figure 4. Margin positivity by hospital characteristics. A. Positive margins by hospital type. B. Positive margins by hospital volume. The line represents overall positive margin percentage. P-values are via chi-square statistic.
64x24mm (600 x 600 DPI)

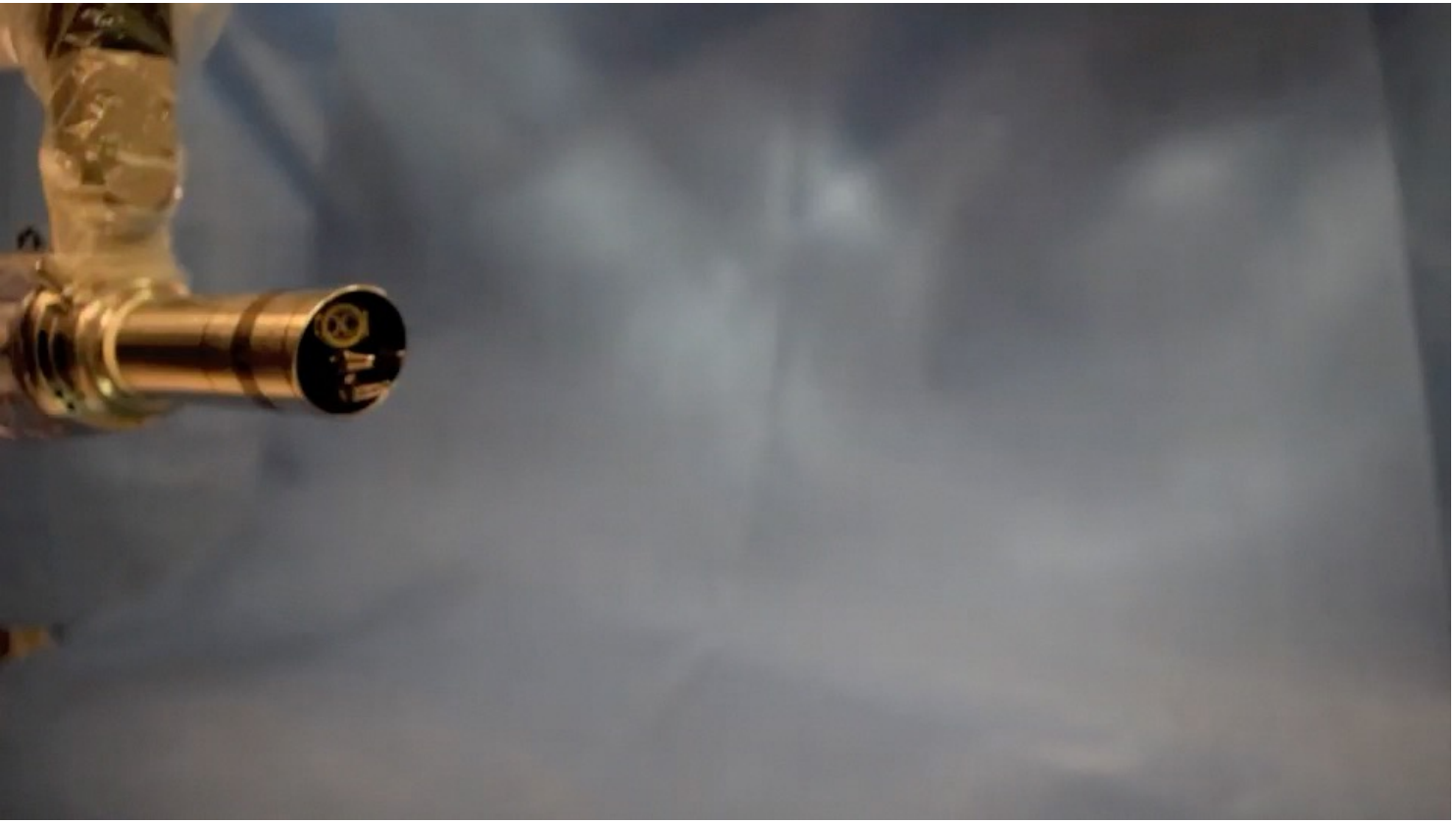
Cancer 122:1523-32, 2016

PRESIDENTIAL ADDRESS

We Show Pictures, They Show Curves

John A. Ridge, MD, PhD

ARCH OTOLARYNGOL HEAD NECK SURG/VOL 136 (NO. 12), DEC 2010



The Laryngoscope

A Flexible, Single-Arm Robotic Surgical System for Transoral Resection of the Tonsil and Lateral Pharyngeal Wall: Next-Generation Robotic Head and Neck Surgery

F. Christopher Holsinger, MD, FACS

Objectives/Hypothesis: To describe the application of a novel flexible robotic surgical system to transoral endoscopic head and neck surgery of the tonsillar fossa and lateral oropharyngeal wall.

Study Design: Preclinical anatomic study using three human cadavers.

Methods: Transoral resection of the lateral oropharyngeal wall with mucosal and muscular resection of the tonsillar fossa.

Results: This single-port flexible robotic system could be used to successfully perform transoral resection of this region. The optimal angle to dock the patient-side cart was at a 90-degree angle to the operating room table. The placement of the remote center of the robotic instrument arm was evaluated in three positions. When the cannula tip was placed at 10 to 15 cm, all instruments could be deployed past the first and second joggle joint settings, without collision or restriction of arm movement. Using this position and docking location, all four arms were deployed inside the oral cavity without collision or restriction of movement in all three cadavers. The Da Vinci SP (Intuitive Surgical, Inc., Sunnyvale, CA) provided sufficient access, reach, and visualization in order to complete a transoral lateral oropharyngectomy.

Conclusion: The first preclinical feasibility study of a novel, flexible, single-arm robotic surgical system is presented for its use in transoral endoscopic head and neck surgery.

Key Words: Transoral endoscopic head and neck surgery, transoral robotic surgery, oropharyngeal carcinoma, tonsil.

Level of Evidence: N/A.

***Laryngoscope*, 126:864–869, 2016**

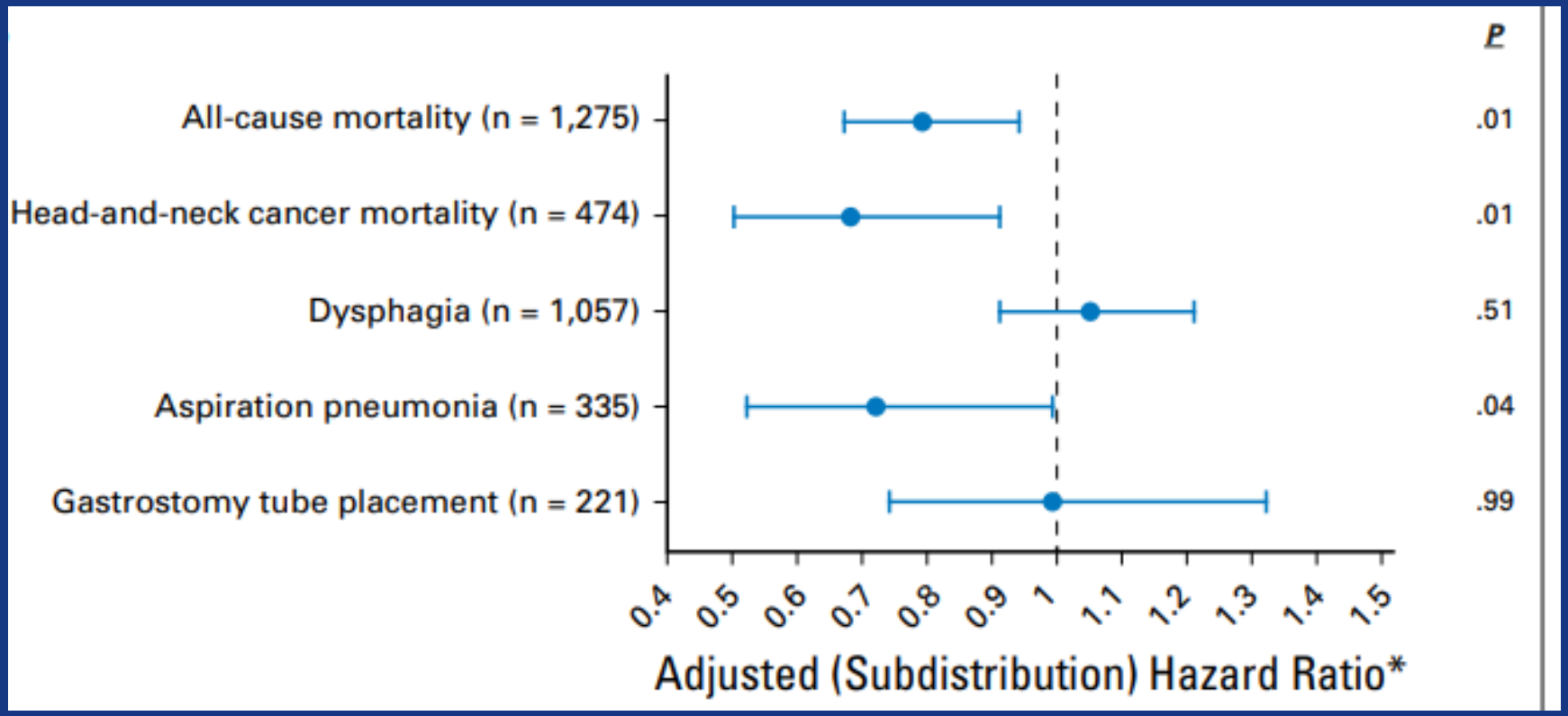
THE Laryngoscope
FOUNDED IN 1896

The Triological Society
UPHOLDING THE NOBLE LEGACY

Single-port Robotics: A Fundamentally New Architecture

Who is a good radiation oncologist and does it matter?

Outcome impact of radiation oncologist patient volume for patients treated with IMRT. SEER data evaluation



"for every five additional patients treated per provider per year, the risk of all-cause mortality decreased by 21%"

J Clin Oncol 34:684-690. © 2016

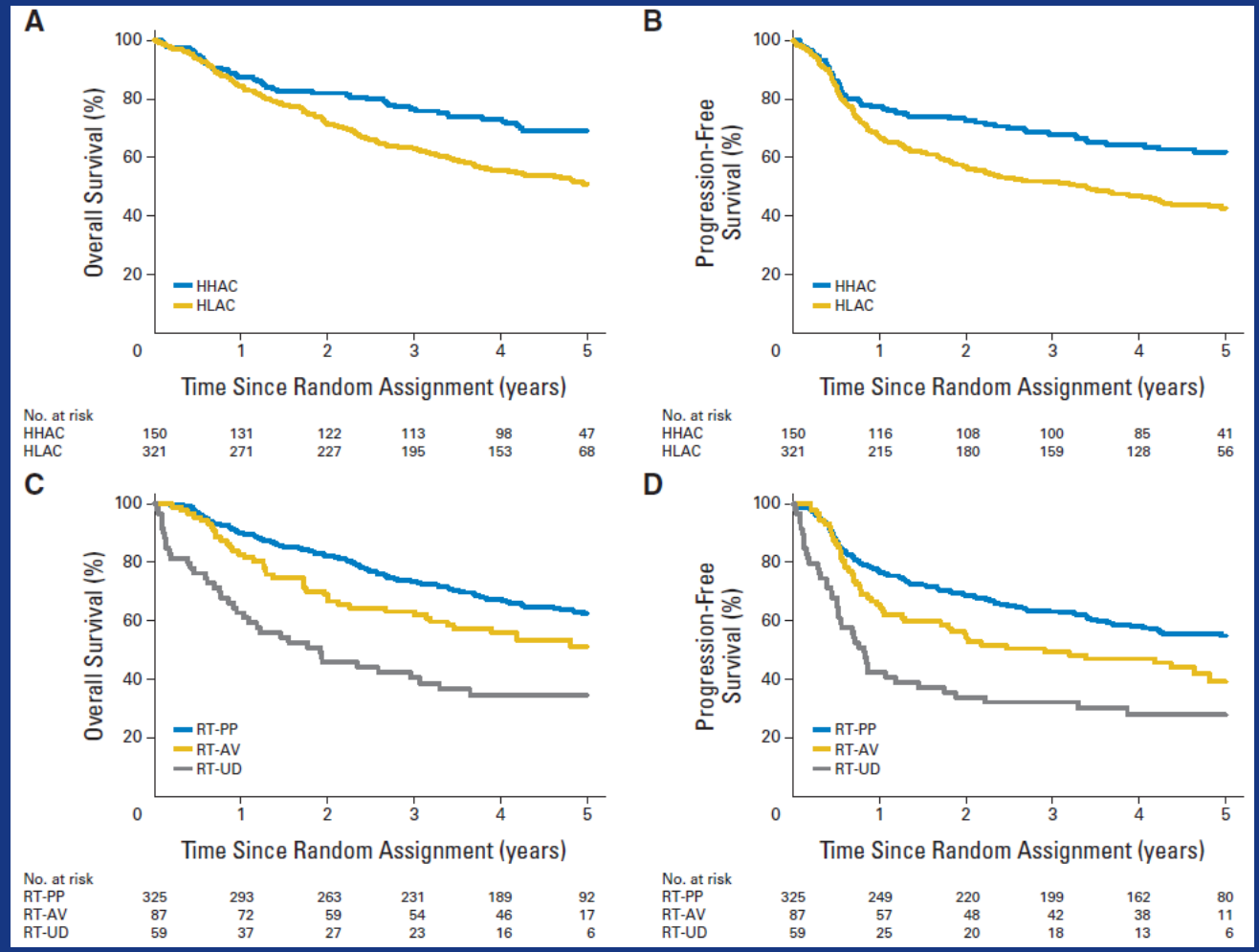
Should quality be compared by person or program? Patients treated "uniformly" on RTOG,0129, accelerated versus standard fractionation

Institutional Clinical Trial Accrual Volume and Survival of Patients With Head and Neck Cancer

HLAC: Historically low accrual center

HHAC: Historically high accrual center

PP: per protocol
AV: acceptable variation
UD: unacceptable deviation



J Clin Oncol 33:156-164. © 2014

Should all insured patients have options for treatment providers?

SB-987 California Cancer Care Equity Act proposal:

This bill would require a Medi-Cal managed care plan to make a good-faith effort to include in its contracted provider network at least one **National Cancer Institute (NCI)-designated comprehensive cancer center, site affiliated with the NCI Community Oncology Research Program (NCORP), or qualifying academic cancer center**, as defined, located within the beneficiary's county of residence or as otherwise specified, and **ensure that any beneficiary diagnosed with a complex cancer diagnosis, as defined, is referred eligible to request a referral to any of those centers** within 15 business days of the diagnosis…

Medical oncologist patient volume and outcomes in head and neck cancer patients

END