Indian College of Radiation Oncology (ICRO)

Academic Wing of

Association of Radiation Oncologists of India (AROI)

50TH ICRO PG Teaching Program

30th & 31st August 2025

On

"Landmark Trials & Practice Changing Evidence in Breast, H & N, GI and Gynec Cancers "

Clinical trials on PORT: Early OSCC and dose fractionation, Node negative, OCAT, deintensification strategies: HPV +, MSKCC protocol: RO 30

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Adjuvant Therapy in Early Oral Cancers

Choice of Treatment

- Considerations of disease control: Site, extent, stage
- Anticipated functional and cosmetic outcomes
- Availability of resources and expertise

Early-Stage Oral Cavity: Need for Adjuvant Therapy

- Majority of early Stage I-II tumours have 5 year OS 75 – 85 %
- 15-25 % are aggressive tumours and require Adjuvant therapy
- Various High- risk factors have been shown to guide adjuvant therapy
- Recurrence is seen even in the absence of these high- risk factors: presence of histological parameters that have a bearing on DFS and OS

What information do we need .....

Pre-operative:
Ability to achieve an R0 resection

Cosmetic and functional excision

Extent of resection: Primary & Neck

Intra-operative:
Ability to achieve the above

Any surprises

Anticipated morbidity

Type of reconstruction

Post-operative:
Anticipated morbidity

Course & Stay in Hospital

Anticipated need for adjuvant therapy

What information do we need from: The Pathologist

Report Generated

Summary report

Category: **C** DMG: **DMG - HEAD & NECK(C)**

FINAL HISTOPATHOLOGY REPORT 19/05/2023

SUMMARY REPORT

Composite Resection - Left buccal mucosa and left segmental mandibulectomy :

Histology	: Squamous cell carcinoma, moderately differentiated
Tumor location	: Left buccal mucosa, left gingivobuccal sulcus, lower lip
Tumor epicentre	: Left buccal mucosa
Tumor size	: 4x3x2.5cm
Maximum depth of invasion	: 1.8cm
Predominant pattern of invasion	: Type 3
Worst pattern of invasion	: Type 4
Skin	: Invasive tumor involves epidermis with ulceration
Left Mandible	: Superficially eroded by tumor
Lymphatic emboli	: Absent
Vascular emboli	: Absent
Perineurial invasion	: Absent.

Margins:

All margins are free of tumor. Closest margin from the tumor is anterior mucocutaneous margin (0.8cm from tumor).

Lymph Nodes:

Left Modified radical neck dissection

- Cervical lymph node - Level Ia : Five lymph nodes, negative for metastasis (0/5).
- Cervical lymph node - Level Ib - Left : One out of three lymph nodes shows metastasis (1/3). Extranodal extension is present (Max. ENE dimension: 0.1cm). Largest size of metastasis is 1.6 cm.
- Cervical lymph node - Level IIa - Left : Nine lymph nodes, negative for metastasis (0/9).
- Cervical lymph node - Level IIb - Left : Six lymph nodes, negative for metastasis (0/6).
- Cervical lymph node - Level III - Left : Four lymph nodes, negative for metastasis (0/4).

The report relates only to the sample submitted.
All samples/slides/blocks submitted for evaluation will be retained by the hospital for 10 years only.
This report has been electronically verified and authorized for release.

1 of 6

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Final detailed report

Category: **C** DMG: **DMG - HEAD & NECK(C)**

FINAL HISTOPATHOLOGY REPORT 19/05/2023

Nature of Material Received: 12 Specimen
Pre-procedural therapy : Naive
Resection type : Primary

Gross Description:

Composite Resection - Left buccal mucosa and left segmental mandibulectomy :
Received oriented specimen of composite resection consisting of left buccal mucosa measuring 12x7cm and left segmental mandibulectomy measuring 10x6x6cm.
An ulceroproliferative and ulceroinfiltrative tumor is identified in the left buccal mucosa, left gingivobuccal sulcus and lower lip measuring 4x3x2.5cm.
The thickness of the tumor is 2.5cm.
The epicentre of the tumor is left buccal mucosa.
Skin is identified measuring 4x3cm and distance from tumour is 0.1cm. It is indurated.
Mandible is superficially eroded.
Margins : The distance of the various margins from the tumor are as follows :
-Anterior mucocutaneous margin: 0.8 cm; -Posterior Mucosal Margin: 1.5 cm; -Medial Mucosal Margin: 2 cm; -Lateral Mucosal Margin: 1.1 cm; -Skin margin: 1.2 cm; -Anterior Bony Margin: 1 cm; -Posterior Bony Margin: 1.6 cm

Lymph Nodes:
Left Modified radical neck dissection

- Cervical lymph node - Level Ia : Five nodes dissected largest measuring 0.6 cm.
- Cervical lymph node - Level Ib - Left : Three nodes dissected largest measuring 2.8 cm.
- Cervical lymph node - Level IIa - Left : Nine nodes dissected largest measuring 3 cm.
- Cervical lymph node - Level IIb - Left : No nodes identified. Fibrofatty tissue is submitted entirely.
- Cervical lymph node - Level III - Left : Five nodes dissected largest measuring 1 cm.
- Cervical lymph node - Level IV - Left : Six nodes dissected largest measuring 1 cm.
- Cervical lymph node - Level Va - Left : One node dissected measuring 1.5 cm.
- Cervical lymph node - Level Vb - Left : No nodes identified.
- Submandibular salivary gland - Left : Measures 3.5x2.8x2cm. Representative section is submitted.

Right Selective neck dissection

- Cervical lymph node - Level Ib - Right : Six nodes dissected largest measuring 1.1 cm.
- Cervical lymph node - Level IIa - Right : Three nodes dissected largest measuring 1.2 cm. Representative section

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This report has been electronically verified and authorized for release.

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Rationale for Adjuvant Therapy

- Sterilise subclinical/ microscopic disease
- Improve locoregional control
- Improve overall survival

Adjuvant Radiotherapy

- Why?- Rationale and evidence
- Who? – Indications and evidence
- What dose?- Rationale and evidence
- When?- Rationale and evidence

Histological Risk Factors to Aid in Adjuvant Therapy

Risk Factors for Adjuvant therapy

Other Adverse Factors
Perineural Invasion
Depth of Invasion
Lymphovascular Invasion
Worse Pattern of Invasion
Tumour Budding

The issue of “Adequate Margins”

- What constitutes adequate margins? 5 mm vs 2.2. mm
- Specimen driven vs Defect driven approach
- Utility of use of frozen section
- Evidence to suggest better performance with increasing volumes
- Need to revise positive margins & clinical implications
- Role of adjuvant RT: Especially in Early stage cancer

Does Clearance of Positive Margins Improve Local Control in Oral Cavity Cancer? A Meta-analysis

Mustafa G. Bulbul, MD[1,2], Osama Tarabichi, MD[1,2], Rosh K. Sethi, MD, MPH[1,2], Anuraag S. Parikh, MD[1,2], and Mark A. Varvares, MD[1,2]

Pooled LRFS data from 8 studies:

Patients in the R1 to R0 group had worse LRFS compared to the R0 group (hazard ratio [HR] = 2.897, P \ .001).

Patients in the R1 group were also found to have worse LRFS compared to the R0 group (HR = 3.795, P \.001).

Compared to final R1 group, the initially R1 to final R0 only showed a trend toward better LRFS.

Margin revision of initially positive margins to ‘‘clear’’ based on FS guidance does not equate to an initially negative margin

This does not significantly improve local control.

Calls into question the effectiveness of the current methodology of intraoperative FS in OCC resections

Mustafa G. Bulbul, Osama Tarabichi, Rosh K. Sethi, et al.
Otolaryngology– Head and Neck Surgery 1–10 DOI: 10.1177/0194599819839006

Perineural Invasion

Impact of Perineural Invasion in the Pathologically N0 Neck in Oral Cavity Squamous Cell Carcinoma

Steven B. Chinn, MD, MPH[1], Matthew E. Spector, MD[1], Emily L. Bellile, MS[2], John B. McHugh, MD[3], Thomas J. Gernon, MD[1,∞], Gregory T. Wolf, MD[1], Avraham Eisbruch, MD[4], and Douglas B. Chepeha, MD, MSPH[1,*]

- 88 patients of Oral cancer , with pN0 status
- All patients had undergone a minimum neck dissection of levels I-III
- 23 % were PNI +
- Of these 70 % underwent Adj RT
- Significant difference in local failure and not distant or regional failures in PNI+ vs PNI-
- PNI was seen to be associated with worse DFI and locoregional control & LVE with worse DFS
- Those PNI + patients who underwent Adj RT had significantly improved DFI (mean 6.5yrs v. 1.7yrs; p=0.014) and LRC (mean 6.7yrs v. 1.9yrs; p=0.047), not OS.
- PNI seen to be an **independent indicator for Adj RT** in the absence of positive nodal disease

Otolaryngol Head Neck Surg. 2013 December ; 149(6): 893–899

ORIGINAL ARTICLE

WILEY

Perineural invasion: Independent prognostic factor in oral cancer that warrants adjuvant treatment

Deepa Nair MS[1] | Manish Mair MCh[1] | Hitesh Singhvi MDS[1] | Aseem Mishra MS[1] | Sudhir Nair MCh[1] | Jaiprakash Agrawal MD[2] | Pankaj Chaturvedi MS[1]

Take home message:

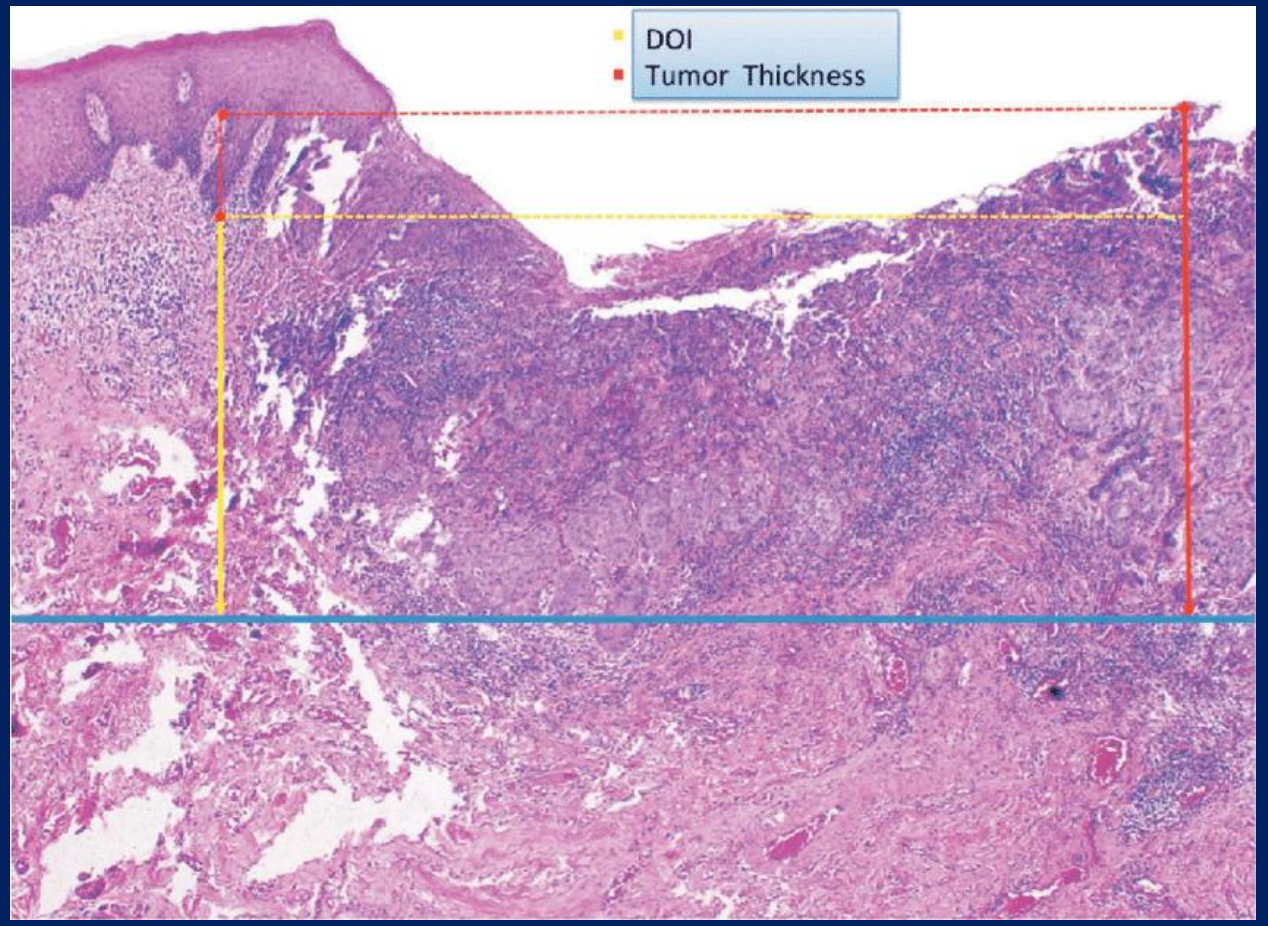
Presence of PNI:

- Higher T stage, Regional recurrence

- In the absence of other adverse features:
  - Size of nerve involved
  - Intra-tumoral, peripheral or extratumoral
  - Number of foci
- Discretion in the use as the sole adverse feature

Head & Neck. 2018;1–8.

What is DoI?



Tumor depth of invasion and prognosis of early-stage oral squamous cell carcinoma: A meta-analysis

Patrícia Carlos Caldeira[1] | Andrea María López Soto[2] |
Maria Cássia Ferreira de Aguiar[1] | Carolina Castro Martins[3]

Results: Twenty-seven studies were included (19 in the meta-analysis) with 2,404 patients with a mean of 60 years of age. High tumor DOI is associated with a greater chance of presenting lymph node metastasis, regardless of the cutoff point for DOI (13 meta-analysis; OR 1.69–53.08), recurrence (five meta-analysis; OR 1.22–3.83), and lower chance of survival (1 meta-analysis; OR 0.49). The certainty of evidence varied from very low to low.

Conclusions: Tumor DOI is a good prognosticator for early-stage OSCC. The findings of the current meta-analysis highlight the clinical relevance of DOI and corroborate its incorporation for staging OSCC.

Depth of invasion alone as an indication for postoperative radiotherapy in small oral squamous cell carcinomas: An International Collaborative Study

Methods: Retrospective analysis of DOI (<5, 5 to <10, ≥10 mm) and disease-specific survival (DSS) in a multi-institutional international cohort of 1409 patients with oral SCC ≤4 cm in size treated between 1990-2011.

Results: In patients without other adverse factors (nodal metastases; close [<5 mm] or involved margins), there was no association between DOI and DSS, with an excellent prognosis irrespective of depth. In the absence of PORT, the 5-year disease-specific mortality was 10% with DOI ≥10 mm, 8% with DOI 5-10 mm, and 6% with DOI <5 mm (P = .169), yielding an absolute risk difference of only 4%.

Conclusion: The deterioration in prognosis with increasing DOI largely reflects an association with other adverse features. In the absence of these, depth alone should not be an indication for PORT outside a clinical trial.

Primary Tumor Staging for Oral Cancer and a Proposed Modification Incorporating Depth of Invasion
An International Multicenter Retrospective Study

- Retrospective analysis of 3149 patients with oral squamous cell carcinoma
- Treated with curative intent at 11 comprehensive cancer centers (1990 -2011)
- Median follow-up of 40 months.

- No definite cut-off established
- Only evidence as adverse prognostic factor
- Impact of DoI in the presence of complete, adequate surgery & adequate neck dissection?

DOI was significantly associated with disease-specific survival ($P < .001$),
Demonstrated no institutional prognostic heterogeneity ($I2 = 6.3\%$; $P = .38$), and
Resulted in improved model fit compared with T category alone (lower AIC, $p < .001$).

JAMA Otolaryngol Head Neck Surg. 2014;140(12):1138-1148.

Lymphovascular Space Invasion

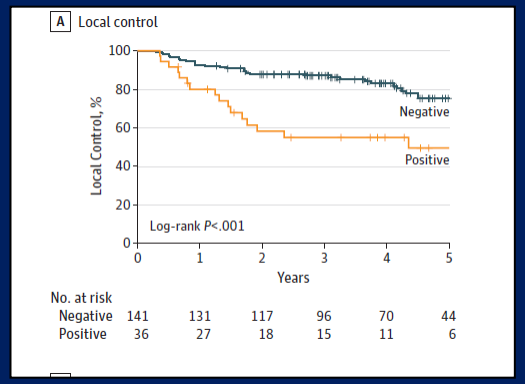
Research

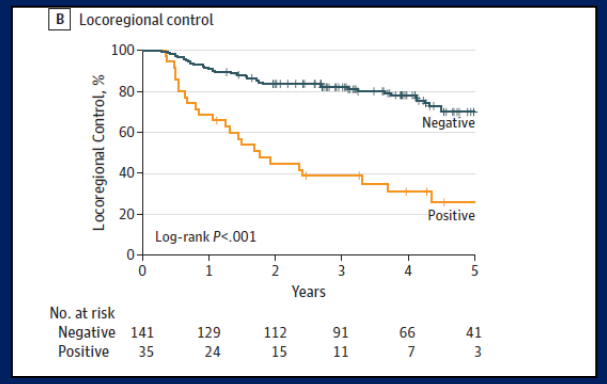
JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

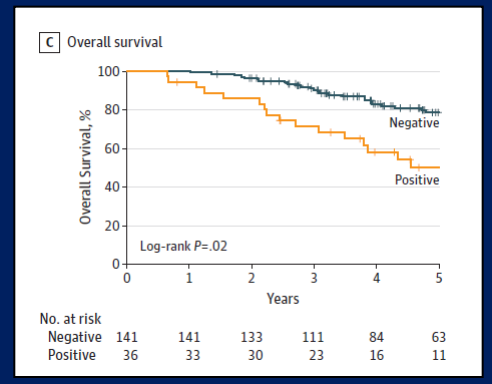
Association of Lymphovascular Space Invasion With Locoregional Failure and Survival in Patients With Node-Negative Oral Tongue Cancers

Richard J. Cassidy, MD; Jeffrey M. Switchenko, PhD; Naresh Jegadeesh, MD; Mutlay Sayan, MD; Matthew J. Ferris, MD; Bree R. Eaton, MD; Kristin A. Higgins, MD; Jeffrey T. Wadsworth; Kelly R. Magliocca, MD; Nabil F. Saba, MD; Jonathan J. Beitler, MD, MBA

- 180 patients, 2003 to 2013
- LVSI (OR, 0.06; *P* < .01): Worse LRC.
- Adj RT (OR, 7.74; *P* < .01) Improved LRC.
- 3-year LRC rates lower for patients with LVSI (38.8%) than those without
- LVSI (81.9%).
- 3 year OS significantly lower in patients with LVSI (71.3 %) than those without LVSI (90.3%)







CONCLUSIONS AND RELEVANCE Lymphovascular space invasion in patients with node-negative oral tongue cancer treated with upfront definitive surgery is associated with worse LRC and OS. Node-negative oral cavity cancers with LVSI warrant consideration of further adjuvant therapy, which should be further evaluated in a prospective setting.

Lympho vascular Invasion

- Significant associations between lymphatic and vascular invasion and overall stage tumor stage, nodal metastasis, extracapsular spread, perineural invasion, bone invasion, depth of invasion and pathologic differentiation.
- Statistically not associated with local recurrence, neck recurrence, and distant metastasis.
- **BUT** not an independent prognostic factor

Mohamed Adel, et al. Medicine Volume 94, Number 43, October 2015

ORIGINAL ARTICLE

Oral Squamous Cell Carcinoma

Histologic Risk Assessment, but Not Margin Status, Is Strongly Predictive of Local Disease-free and Overall Survival

Margaret Brandwein-Gensler, MD,† Miriam S. Teixeira, MD,* Carol Ming Lewis, MD, MPH,§ Bryant Lee, MD,* Linda Rolnitzky, MS,‡ Johannes J. Hille, DDS,‖ Eric Genden, MD,* Mark L. Urken, MD,* and Beverly Yiyao Wang, MD†*

- Developed a novel histological risk assessment system based on :
  - PNI
  - WPOI
  - Lymphocytic infiltrate
- Margin status was seen not to have an impact on survival in their cohort

TABLE 9. Proposed Risk Assessment for Oral Squamous Cell Carcinoma

	Point Assignment for Risk Scoring		
Histologic Variable	**0**	**1**	**3**
Perineural invasion	None	Small nerves	Large nerves
Lymphocytic infiltrate at interface	Continuous band	Large patches	Little or none
WPOI at interface	1 or 2 or 3	4	5

Risk Score (sum of all point assignments)	**Risk for local Recurrence**	**Overall Survival Probability**	**Adjuvant Treatment Recommendations**
Score = 0	Low	Good	No local disease-free benefit seen for adjuvant RT
1 or 2	Intermediate	Intermediate	No local disease-free benefit seen for adjuvant RT
3 to 9	High	Poor	RT regardless of 5 mm margins

Depth of invasion, tumor budding, and worst pattern of invasion: Prognostic indicators in early-stage oral tongue cancer

Alhadi Almangush, DDS,[1] Ibrahim O. Bello, BDS, PhD,[1,2] Harri Keski–Säntti, MD, PhD,[3] Laura K. Mäkinen, MD,[3] Joonas H. Kauppila, MD,[4] Matti Pukkila, MD, PhD,[5] Jaana Hagström, DDS, PhD,[1,6] Jussi Laranne, MD,[7] Satu Tommola, MD,[8] Outi Nieminen,[9] Ylermi Soini, MD, PhD,[10] Veli-Matti Kosma, MD, PhD,[10] Petri Koivunen, MD, PhD,[11] Reidar Grénman, MD, PhD,[12] Ilmo Leivo, MD, PhD,[1,9] Tuula Salo, DDS, PhD[13,14*]

233 cases of T1/T2 N0 tongue cancers – following histological parameters assessed

1. Tumour budding
2. Depth of Invasion
3. Histological Risk Assessment (WPOI/ Lymphocytic Response /PNI)
4. Cancer associated Fibroblasts

On Multivariate analysis:
Depth > 4 mm , Tumour budding > 5 cells at the invasive front along with WPOI: significant predictors of Disease Specific Survival: **need Treatment Intensification**

Head Neck 36: 811– 818, 2014

Published literature on impact of adverse histological features in early OSCC.

Year	Author	No. of patients	Conclusions	Remarks
LVE/LVSI				
2017	Cassidy	180	LVSI associated with worse OS on MVA (HR = 2.20; 95% CI, 1.19–4.06; p = 0.01)	Overall LVSI present in only 20% patients
2013	Chen	442	No significant differences in the [illegible].2%, p = 0.51) and OS (90.9 vs 85.2%, p = 0.18) No impact of LVE/PNI on MVA	Only 82 patients had LVE/PNI
PNI				
2018	Nair	1524	PNI higher in tongue cancers The PNI significantly affected both DFS(DFS HR= 1.84) and OS(OS; HR = 1.7). Patients with early p N0 disease and PNI more likely to develop recurrences and have mortality (HR = 2.79 for DFS; H[illegible] these patients showed association improvement in surv[illegible]	-Population predominantly gingivo – buccal cancers(65%) – 41% of patients with T3-T4 primaries
2017	Thiagarajan	322	Statistically significant reduction[illegible]NI (60 months vs 26 months, p = 0.027)	70 patients met criteria for inclusion PNI present in only 6 patients overall
2012	Tai	307	PNI predicted for Neck metastasis (p < 0.001,HR = 3.36,95% CI-1.85–6.1) Neck recurrence (p < 0.001, HR – 4.25,95% CI-2.01–8.98) DSS (p = 0.027,HR – 2.08,1.09–3.99) Elective neck dissection contributed to a significantly better 5-year DSS only incN0 patients with PNI-positive tumors (p = 0.0071	PNI Present in 27% patients (84 patients)
Close Margin				
2013	Ch'ng	144	LC with surgery alone-91% DSS with surgery alone 84% (5 years). No pattern of worse LC or DSS with ordered stratification of close margins.	-POI unknown in 10% of patients and pushing in 10% of patients – 27% patients WDSCC
2017	Tasche	443	Local recurrence rates (%) by distance from invasive tumor (in mm) < 1–44 2–28 3–17 4–13 5–13 ≥5–14	No history of tobacco usage 41% female patients (likely preponderance of HPV positive disease and lesser relevance of positive margins)
2018	Fridman	1257	5 yr OS Clear margin (995)-80% Close margin (n = 205)- 52% Close margins associated with > 2 fold recurrence (p < 0.0001) Adjuvant therapy significantly improved outcomes for close/positive margins (p = 0.002–0.03)	-No indication of subsites (tongue vs.gingivo- buccal) -Close and positive margins clubbed together

Equivocal

Unequivocal

Unequivocal

Oral Oncology 104 (2020) 104627

Importance of POI

Head and Neck Pathology
https://doi.org/10.1007/s12105-023-01571-9

RESEARCH

Significance of Worst Pattern of Invasion-5 in Early-Stage Oral Cavity Squamous Cell Carcinoma

Shima Mohamed[1,5] · Hadeel Jawad[1,6] · Ryan O' Sullivan[2] · Deirdre Callanan[2,4] · Patrick Sheahan[2,3,4] · Linda Feeley[1,4]

WPOI: defined by the presence of satellite nodules, extratumoural perineural invasion (PNI) and/or extratumoural lymphovascular space invasion (LVI) in low-stage, node negative OCSCC.

Prognostic implication of WPOI5

160 patients with T1/T2N0 tumours staged using TNM7 treated surgically.
Histology of the primary tumour was re-reviewed to assess for the presence of WPOI-5 parameters.

Univariate analysis: WPOI-5 and its 3 constituent components of satellite nodules, extratumoural PNI & extratumoural LVI were all significantly associated with disease-specific survival (DSS) and overall survival (OS).

Multivariate analysis:

Satellite nodules (odds ratio 6.61, 95% CI 2.83–15.44, $p < 0.0001$) and extratumoural LVI (odds ratio 9.97, 95% CI 2.19–45.35, $p = 0.003$) were independently associated with OS.
Postoperative radiotherapy (odds ratio 0.40, 95% CI 0.19–0.87, $p = 0.02$) and non-tongue subsite (odds ratio 3.03, 95% CI 1.70–5.39, $p = 0.0002$) were also significantly associated with OS.

Conclusion: Satellite nodules and extratumoural LVI correlated significantly with survival outcomes in early-stage OSCC.

Table 2 Univariate analysis of impact of pathological features and postoperative radiotherapy on DSS and OS

	LRR OR (95% CI)	LRR p-value	DSS OR (95% CI)	DSS p-value	OS OR (95% CI)	OS p-value
Non-tongue primary site (vs tongue)	0.75 (0.36, 1.53)	0.43	0.92 (0.33, 2.54)	0.78	2.01 (1,17–3.47)	0.01
> 5 mm depth of invasion	1.60 (0.75, 3.40)	0.23	2.26 (0.72–7.09)	0.16	0.91 (0.54–1.53)	0.71
> 10 mm depth of invasion	1.52 (0.65, 3.55)	0.33	3.04 (1.03–8.97)	0.04	1.18 (0.58–2.41)	0.65
> 20 mm diameter	1.00 (0.45, 2.24)	0.99	2.14 (0.76–6.05)	0.15	1.27 (0.71–2.26)	0.42
Non-cohesive pattern of invasion	2.09 (1.02, 4.30)	0.04	4.22 (1.48–12.09)	0.007	1.62 (0.94–2.79)	0.08
Involved margins (RCPath)	0.84 (0.34, 2.07)	0.71	0.80 (0.22–2.87)	0.73	0.50 (0.23–1.06)	0.07
Involved margins (CAP)	0.98 (0.34, 2.84)	0.97	0.46 (0.06–3.56)	0.46	0.49 (0.18–1.36)	0.17
Any PNI	4.46 (2.14, 9.30)	< 0.0001	10.23 (3.29–31.84)	< 0.0001	1.97 (1.06–3.66)	0.03
Extratumoral PNI	8.01 (2.30, 27.83)	0.001	14.46 (3.69–56.70)	0.0001	5.30 (1.84–15.22)	0.002
Intratumoral PNI	3.96 (1.89, 8.27)	0.0003	7.62 (2.55–22.75)	0.0001	1.81 (0.96–3.43)	0.07
Any LVI	2.09 (0.63, 6.91)	0.23	4.73 (1.33–16.79)	0.02	1.88 (0.75–4.72)	0.18
Extratumoral LVI	23.46 (6.35, 86.62)	< 0.0001	73.50 (14.61–369.80)	< 0.0001	22.65 (6.17–83.1)	< 0.0001
Intratumoral LVI	1.36 (0.32, 5.74)	0.67	2.93 (0.66–13.01)	0.16	1.48 (0.54–4.10)	0.45
Satellite nodules	6.53 (2.71, 15.72)	< 0.0001	18.32 (5.53–60.67)	< 0.0001	5.45 (2.66–11.15)	< 0.0001
WPOI-5	6.77 (2.89, 15.84)	< 0.0001	22.68 (6.54–78.68)	< 0.0001	5.31 (2.64–10.65)	< 0.0001
Postoperative radiotherapy	1.05 (0.49, 2.26)	0.90	0.37 (0.08–1.65)	0.19	0.41 (0.20–0.85)	0.02

The impact of worst pattern of invasion on the extension of surgical margins in oral squamous cell carcinoma

DOI: 10.1002/hed.26956

Hugo F
Clóvis
Ivete F
PhD[1,3]

Abstract

Background: To evaluate margins for oral carcinoma according to types of invasion front.

Methods: Retrospective cohort of 772 patients with worst pattern of invasion (WPOI) graded 1–5. Local recurrence was the outcome of interest.

Results: Local recurrences occurred in 164 patients (21.2%) and was affected by WPOI type 4/5, margin distance, perineural invasion, and adjuvant radiotherapy. In patients with WPOI types 1/2/3, a cutoff of 1.7 mm was considered ideal margin extent and in patients with WPOI types 4/5, the cutoff was 7.8 mm. Patients below these thresholds had a significantly higher incidence of local recurrence.

Conclusions: Different WPOI determine the ideal extent of surgical margins as 1.7 mm for patients with types 1–3, and 7.8 mm in patients with types 4/5.

- Most literature talks about the poor prognosis of these adverse features
- Sparse literature on the impact of PORT on outcomes

Impact of Postoperative Radiotherapy on the Prognosis of Early-Stage (pT1-2N0M0) Oral Tongue Squamous Cell Carcinoma

J Clin Oncol 00:1-12

Qiaoying Tian, MD[1,2,3]; Lin Jiang, MD[1,4,5]; Dongjun Dai, MD[1,3]; Lihong Liu, MD[1,3]; Xiaomeng Shi, MD[6]; Yinglu Guo, MD[1,3]; Dang Wu, MD[1,2,3]; Jia Yang, MD[1,2,3]; Jing Xu, MD[1,2,3]; Zhuoying Cai, MD[7]; Zhimin Ye, MD[8]; Yun Xi, MD[9]; Zengguang Zheng, MD[9]; Huimin Li, MD[9]; Yongjie Shui, MD[1,2,3]; Yanming Liu, MD[7]; Jinbiao Shang, MD[4,5]; Shumei Wei, MD[10]; and Qichun Wei, MD[1,2,3]

PA

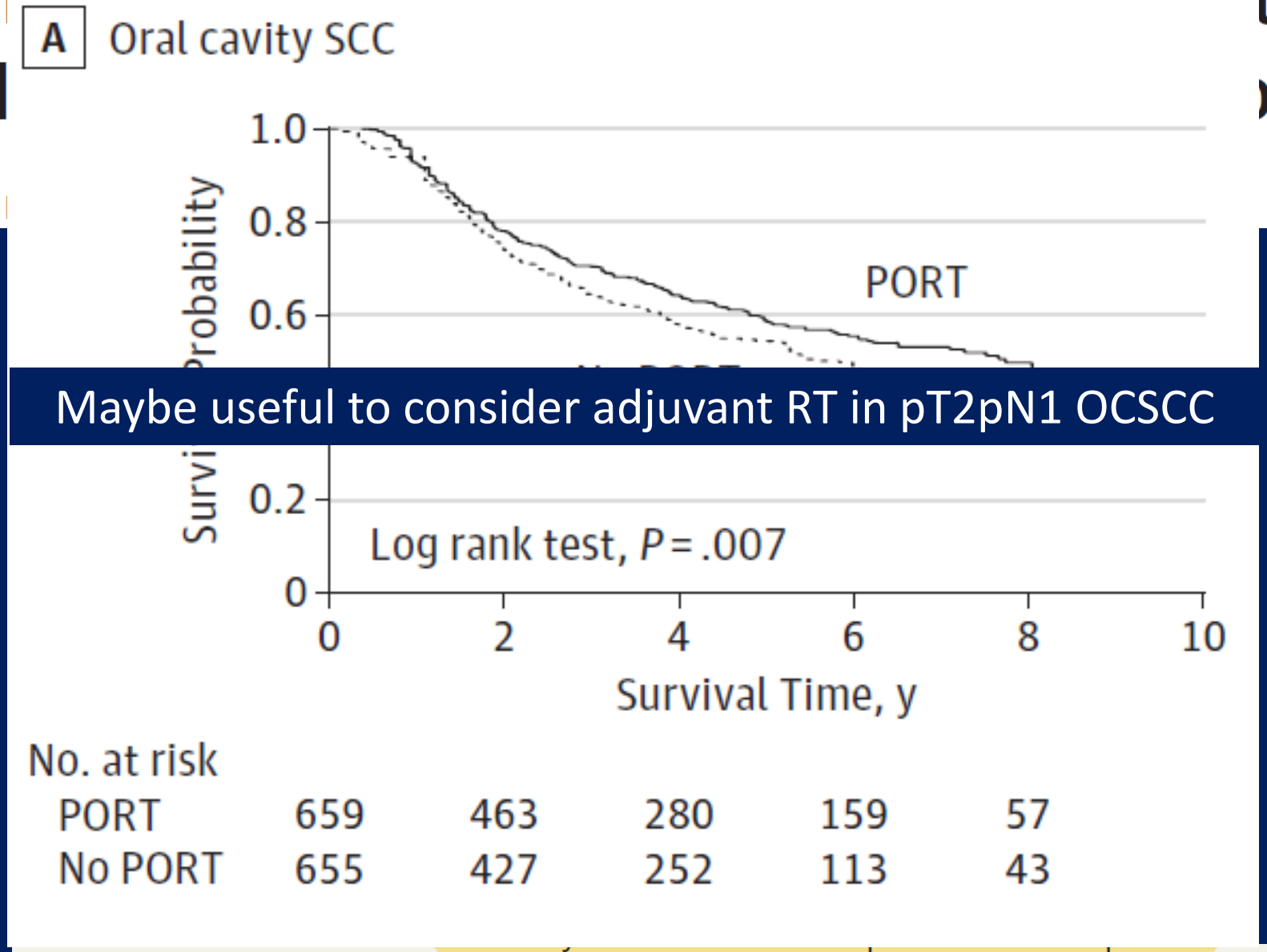
In conclusion, patients with moderately-to-poorly differentiated early-stage (pT1-2N0M0) OTSCC benefited from PORT. Our study provided robust evidence that patients with PNI and/or LVI who underwent PORT had improved survival. PORT also offered DFS benefit among patients with DOI >5 mm. These findings, derived from a large sample size, suggest a reconsideration of the current guidelines regarding the application of PORT in patients with early-stage (pT1-2N0M0) OTSCC.

81% *v* 58%; *P* = .022; DFS, 76% *v* 47%; *P* = .002). In subgroups with DOI >5 mm or close margins, PORT contributed to improved DFS (80% *v* 64%; *P* = .006; 92% *v* 66%; *P* = .049) but did not significantly affect OS.

Contentious Issues???

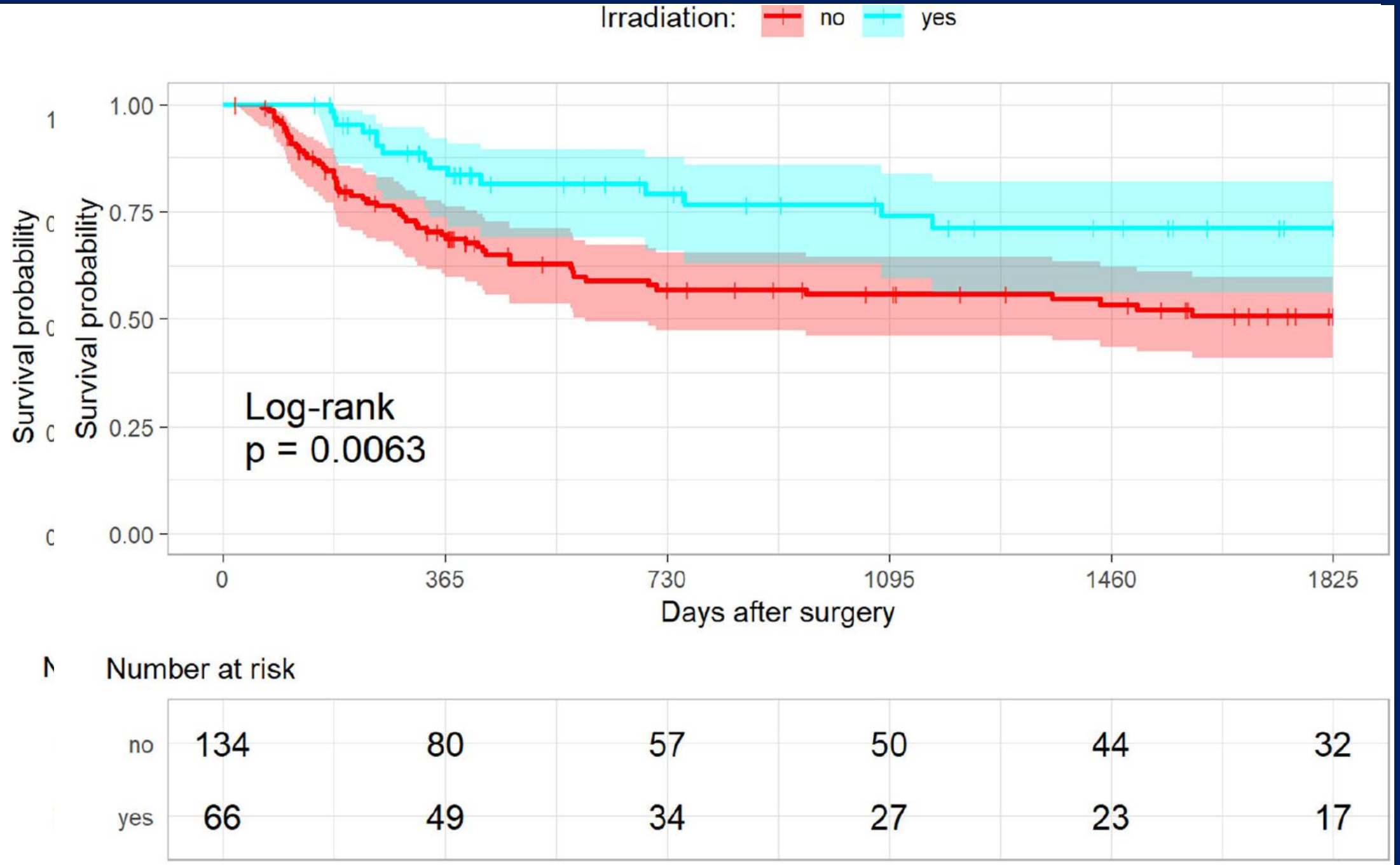
1. Role of Adj RT in pN1 OCSCCC?

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study identified 1467 adult patients with OC SCC and 790 patients with OP SCC with pT1N1 or pT2N1 disease in the



Maybe useful to consider adjuvant RT in pT2pN1 OCSCC

with pN1 OC and OP SCC, especially in those younger than 70 years or those with pT2 disease.



three years after therapy compared to the observation group.

Conclusions

- Adjuvant radiotherapy: improves post-operative locoregional control in patients with early-stage cancer in the presence of adverse features: PNI, Close margins, combination
- However, it is essential to standardise the reporting guidelines for these parameters
- Treatment intensification in the presence of above HR features should be weighed judiciously: In combination, by themselves alone
- Further clinical validation of their impact is essential: Various nomograms available
- Use of adjuvant RT has to be weighed in the light of disease related outcomes & toxicity

Radiotherapy and Oncology 177 (2022) 95–104

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review Article

AIRO GORTEC consensus on postoperative radiotherapy (PORT) in low-intermediate risk early stages oral squamous cell cancers (OSCC)

Anna Merlotti [a,*], Daniela Alterio [b], Ester Orlandi [c], Séverine Racadot [d], Pierluigi Bonomo [e], Pierfrancesco Franco [f], Elisa D'Angelo [g], Stefano Ursino [h], Yoann Pointreau [i], Michel Lapeyre [j], Pierre Graff [k], Alessia Di Rito [l], Angela Argenone [m], Daniela Musio [n], Francesca De Felice [o], Francesco Dionisi [p], Giuseppe Fanetti [q], Ida D'Onofrio [r], Liliana Belgioia [s], Marta Maddalo [t], Melissa Scricciolo [u], Jean Bourhis [v], Elvio Russi [a], Juliette Thariat [w]

Locally Advanced Cancers

Why? Adjuvant Radiotherapy

- Most patients present with advanced stage disease
  - Stage I 0%, stage II 11.53%, stage III 82.37% & stage IV 6.1%
    (Shenoi R et al (Indian J Cancer, 2012 49(1):21-6)
- Single modality treatment is ineffective
- Can reduce local and locoregional recurrences
- Well studied in several series

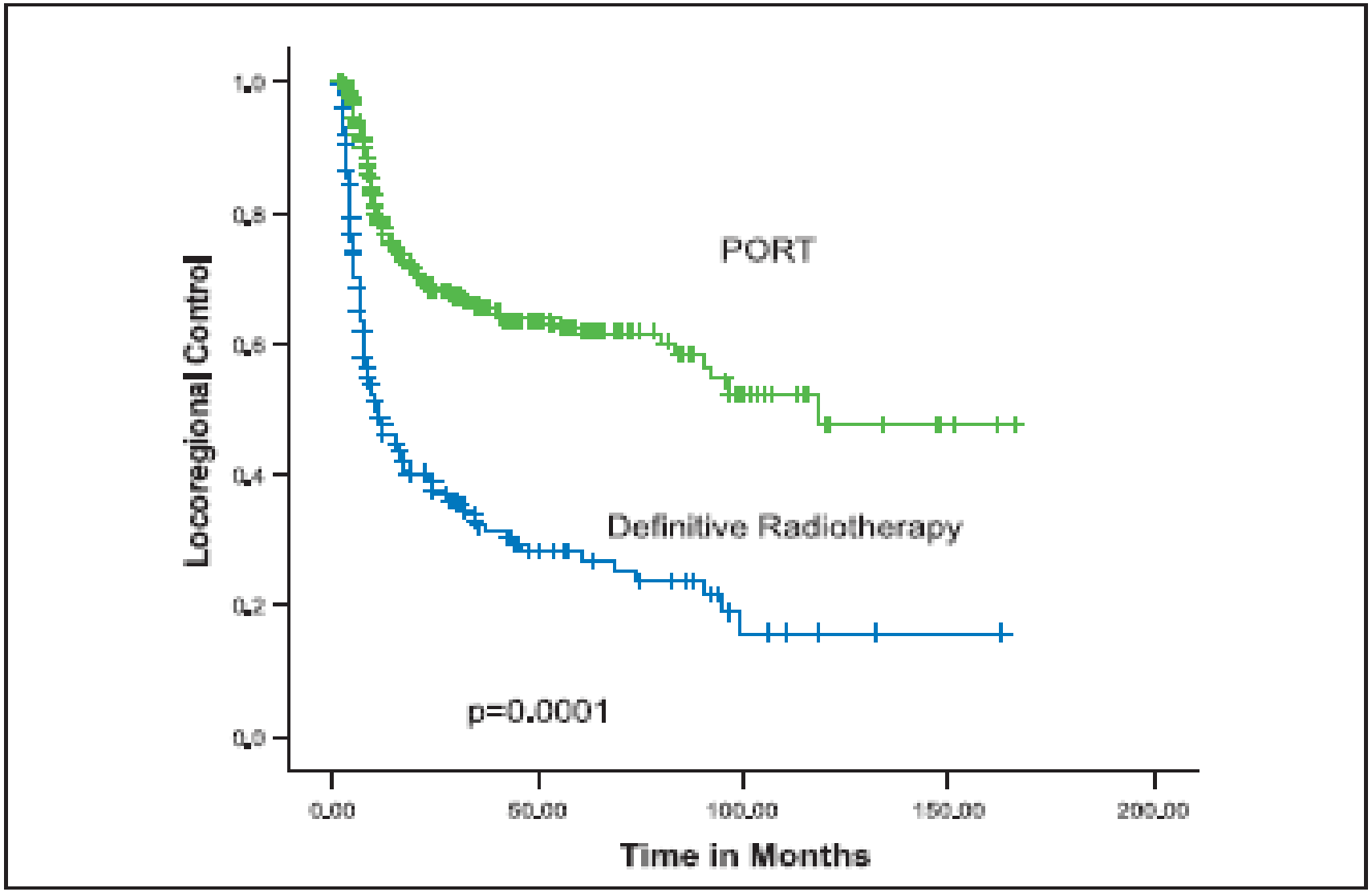


Figure 1: Kaplan Meier curves of the locoregional control by the treatment modality PORT: Postoperative Radiotherapy

Surgery Vs Surgery + Post op RT

Author/Group	No. of pts.	Stage	Results
Kokal et al (Virginia1988) (Randomised)	46 Sx (27) Sx + PORT (24)	III, IV	Rate of relapse was 37% Vs 68 % (P value- NS). 3 yr OS rate 58.5% and 46.5 %
Huang et al (Virginia 1992)	125(High risk factors) Sx (71) Sx+ PORT (54)	LA	LRC - 59 Vs 31% (P value- S) OS- 50 Vs 30% (P value -S)
Fletcher (M.D Anderson1977)	169	IV	Rate of failure above the clavicles 24 Vs 13%
Badawi et al (1982)	328	III, IV	Rate of failure above the clavicles 48 Vs 16% and OS - 40 Vs 25%
Francheschi D MSKCC (1992)	297	Oral tongue ca III ,IV	LRR 43 Vs 29% Neck rec. 29 Vs 13%
Mishra et al India 1996	140 Sx- 52 PORT- 70	LA Ca BM	DFS 68 % Vs 38 %. OS 94% Vs 84%

TNM	Surg alone	Surg + PORT	
T3–4 N0M0	35 (58)	24 (30)	$P<0.05$
T3–4N1–2bM0	25 (41.6)	56 (70)	$P<0.05$

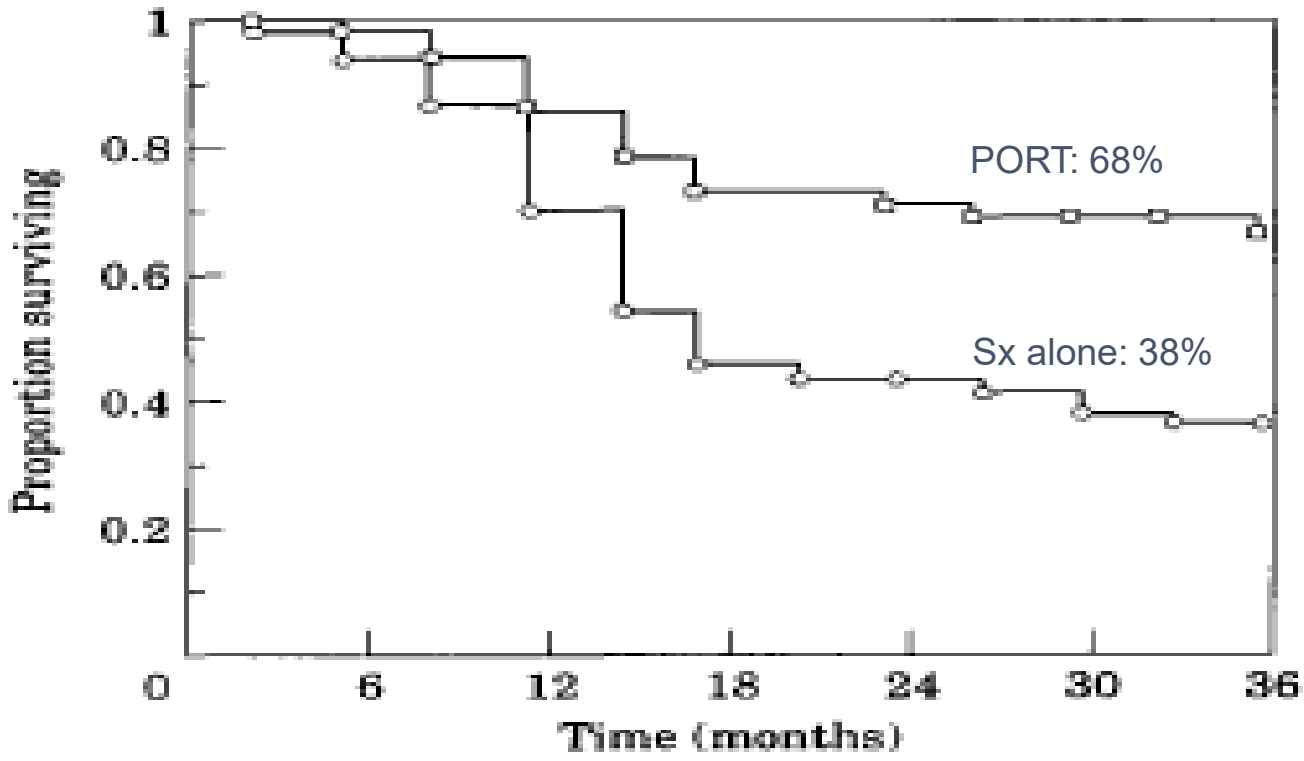


Fig. 1. Actuarial disease-free survival rates in the surgery alone (○) and post-operative radiotherapy (□) groups.

Who should receive Adjuvant Radiotherapy?
Defining risk groups

Who should receive Adjuvant Radiotherapy?
Adverse features

Primary

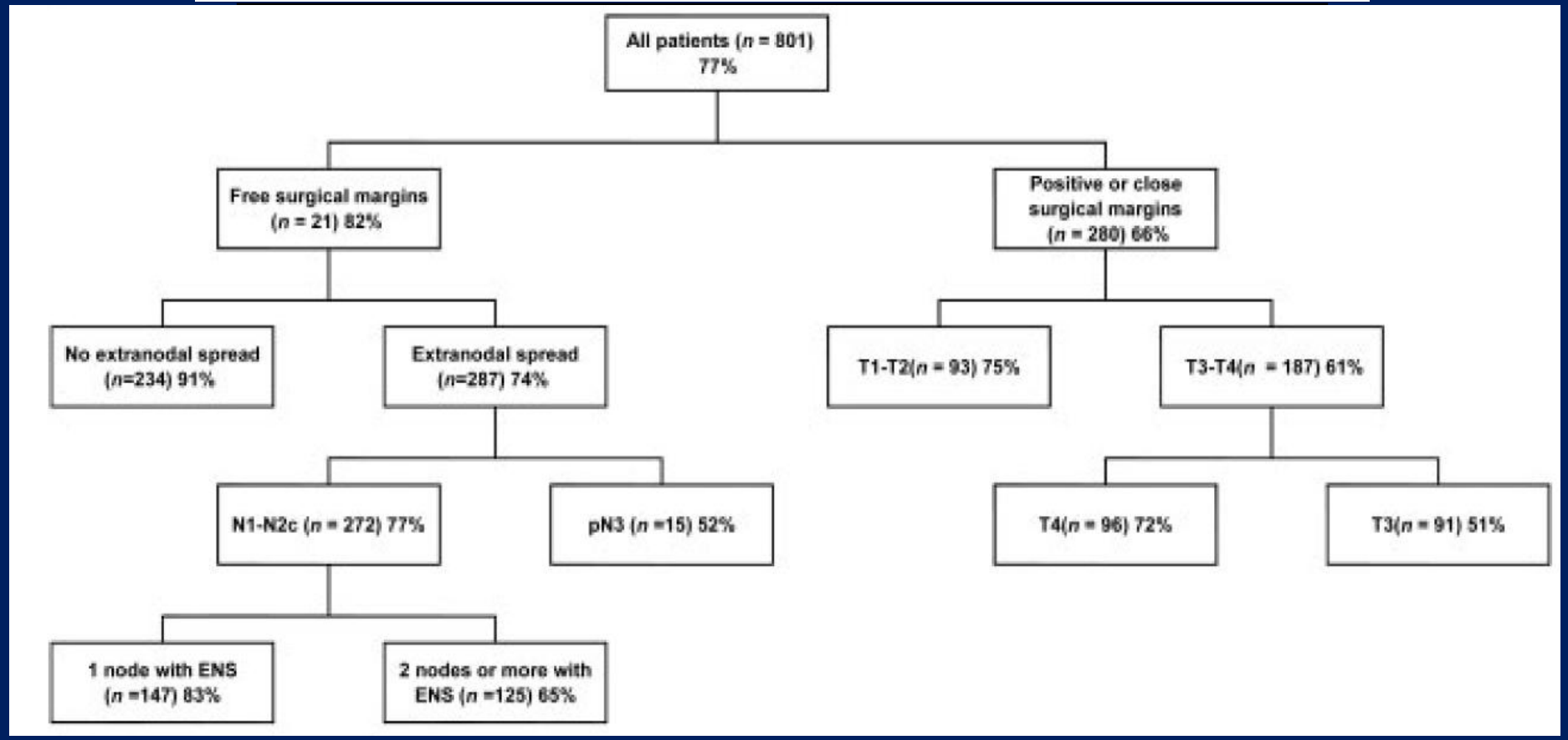
- **Microscopically +ve surgical margins**
- T stage
- Lymphovascular invasion (LVI)
- Peri neural spread (PNI)
- Recurrent disease
- Tumor spillage
- Depth of tumor invasion
- Oral cavity primary site.

Node

- **Extra capsular extension (ECE)**
- ≥ 2 involved neck nodes
- > 1 positive nodal group,
- Nodal diameter>3 cm,

Risk Level	RTOG 85-03[4]	M.D. Anderson Cancer Center[5]	University of Pennsylvania[6]	UZ Amsterdam[7]	EORTC/RTOG[3]
Highest risk	Margins	ECS; 2+ factors	ECS; margins; 2+ LNs	ECS in 2+ LNs; T3 (with margins); pN3	ECS; margins
Intermediate or high risk	2+ LNs; ECS	1 risk factor	1 risk factor	ECS in 1 LN; T1-2,T4; with margins	Perineural invasion; LN+ at levels 4-5 in oropharynx and oral cavity cancer patients; vascular embolisms; and stage III-IV

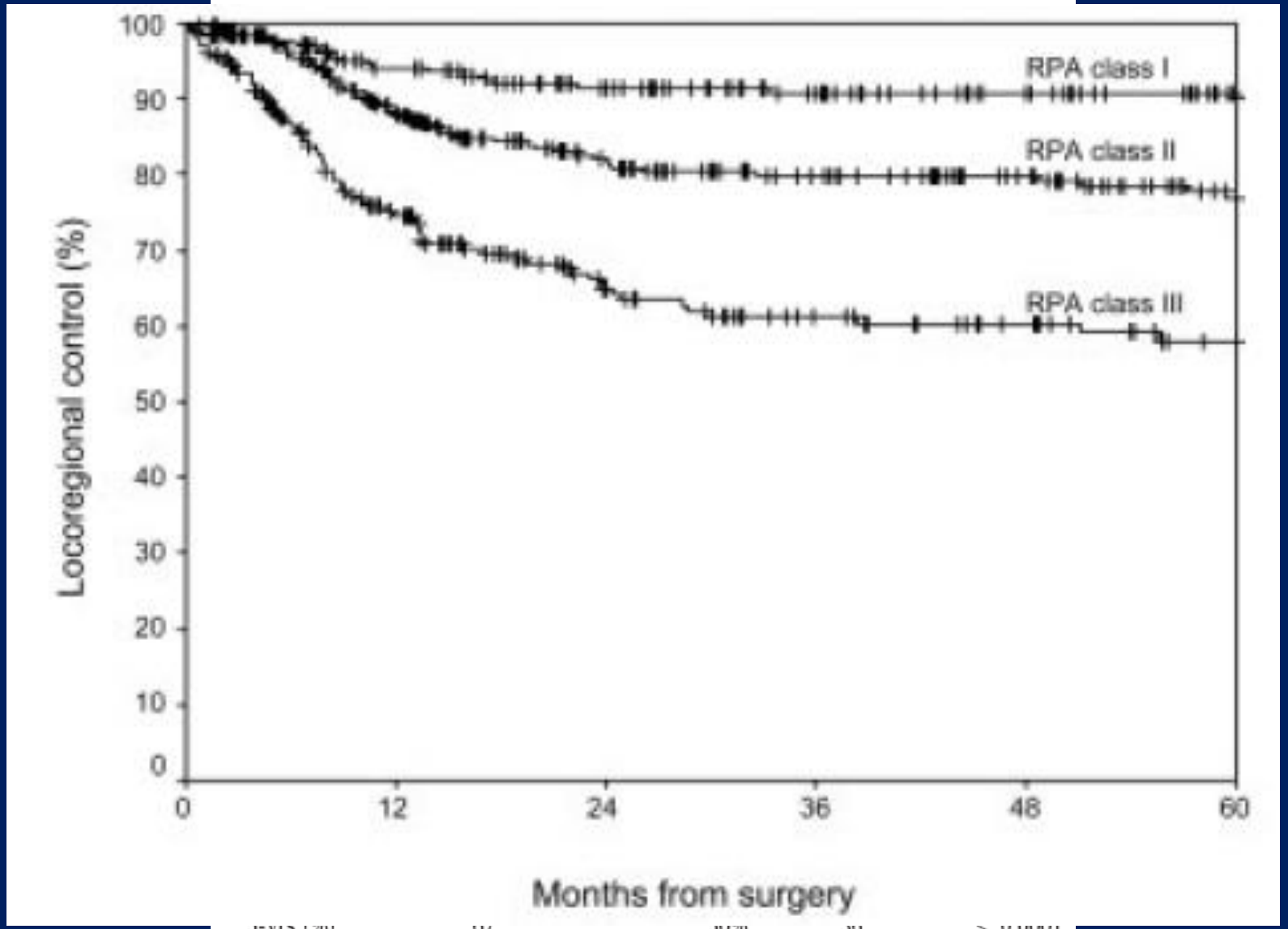
Risk-Group Definition by Recursive Partitioning Analysis of Patients with Squamous Cell Head and Neck Carcinoma Treated with Surgery and Postoperative Radiotherapy



CANCER October 1, 2005 / Volume 104 / Number 7

Recursive Partitioning Analysis Classes and Outcome

...inoma/Langendijk et al.



5-yrs (%)	67	36%	36	< 0.0001
HR	1.00	1.49	2.35	
95%CI	—	1.56–1.91	1.81–3.04	

CANCER October 1, 2005 / Volume 104 / Number 7

Adjuvant Radiotherapy: What dose?

- Several retrospective studies: 60-65Gy in 6-7 wks
- No definite dose response relationship beyond 57.6Gy except for patients with extranodal extension (dose response till 63 Gy)
- Hence, for patients with high risk features higher doses >60 Gy recommended.

Peters.L.J.et al. Int J Radiat Oncol Biol Phys. 26(1):3-11(1993)

Head & Neck Cancers

Adjuvant Radiotherapy: Timing/ OTT

- Parsons et al showed that irradiation should begin within about 6 weeks after surgery.*
- Local control was better when overall treatment time from date of Sx to RT completion was less than 100 days.*
- Short OTT of radiation was found to be associated with higher rates for LRC, DFS, and OS.**
- LRC worsened by 9% with every week's prolongation of OTT.**

* Parsons et al IJROBP Vol 39; 1;137-148;1997

**Langendijk et al IJROBP., Vol. 57, No.3 693–700,2003

Influence of Treatment Package Time on outcomes in High-Risk Oral Cavity Carcinoma in patients receiving Adjuvant Radiation and Concurrent Systemic Therapy: A Multi-Institutional Oral Cavity Collaborative study☆

Objectives: To explore the influence of treatment package time(TPT) in high-risk oral cavity squamous cell carcinoma(OCSCC) receiving adjuvant radiotherapy with concurrent chemotherapy(CRT).

Materials and Methods: We queried our multi-institutional OCSCC collaborative database for cases diagnosed between 2005 and 2015 who underwent surgery followed by adjuvant CRT. All patients had high-risk features: extranodal extension(ENE) and/or positive surgical margin(PM). TPT was days between surgery to last radiotherapy fraction. Kaplan-Meier curves, log-rank p-values and multivariate analysis(MVA) were used to investigate the impact of TPT on overall(OS), disease-free(DFS), locoregional failure-free(LRFS) and distant metastases-free(DMFS) survival.

Results: We identified 187 cases: median age 58 (range, 24–87 years), males 66%, and ever smokers 69%. ENE and PM were detected in 85% and 32%, and oral tongue and floor of the mouth constituted 49% and 18%, respectively. Median radiotherapy and cisplatin doses received were 66 Gy and 200 mg/m2. Overall, median TPT was 98 (range, 63–162 days). OS was worse for TPT > 90-days (n = 134) than TPT ≤ 90 (n = 53) at two-(65% vs. 71%) and five-years (45% vs. 62%); $p = 0.05$, with similar results for DFS. No influence on LRFS or DMFS was noted. More lymph nodes(LN) dissected($P = 0.039$), T3-4 disease($P = 0.017$), and unplanned reoperations($P = 0.037$) occurred with TPT > 90-days. On MVA, TPT in 10-day increments was independently detrimental for OS (Hazard Ratio: 1.14; 95 %Confidence Interval [1–1.28]; $P = 0.043$), perineural invasion, age and positive LN ($p < 0.05$ for all).

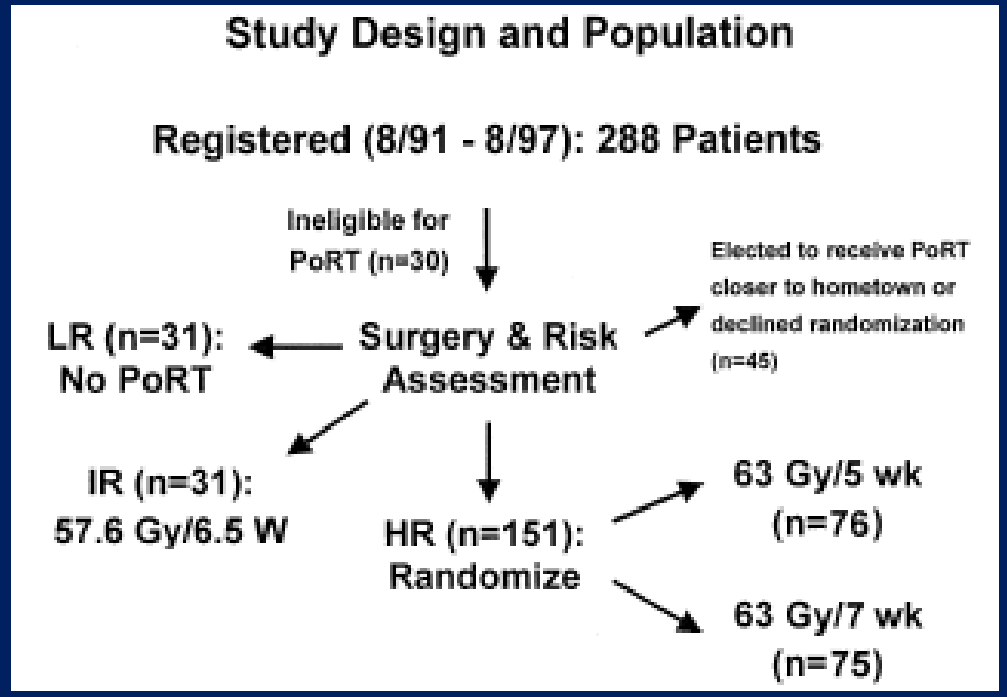
Conclusion: In one of the largest multi-institutional cohorts, TPT > 90-days predicted worse OS for high-risk OCSCC receiving adjuvant CRT. All efforts are needed to optimize perioperative care and baseline conditions for favorable outcomes.

Ghanem et al., Oral Oncology 126 (2022) 105781

RANDOMIZED TRIAL ADDRESSING RISK FEATURES AND TIME FACTORS OF SURGERY PLUS RADIOTHERAPY IN ADVANCED HEAD-AND-NECK CANCER

K. Kian Ang, M.D.,* Andy Trotti, M.D.,† Barry W. Brown, Ph.D.,‡ Adam S. Garden, M.D.,* Robert L. Foote, M.D.,§ William H. Morrison, M.D.,* Fady B. Geara, M.D.,*[1] Douglas W. Klotch, M.D.,‖ Helmuth Goepfert, M.D.,¶ and Lester J. Peters, M.D.*

Purpose: A multi-institutional, prospective, randomized trial was undertaken in patients with advanced head-and-neck squamous cell carcinoma to address (*1*) the validity of using pathologic risk features, established from a previous study, to determine the need for, and dose of, postoperative radiotherapy (PORT); (*2*) the impact of accelerating PORT using a concomitant boost schedule; and (*3*) the importance of the overall combined treatment duration on the treatment outcome.



Methods and Materials: Of 288 consecutive patients with advanced disease registered preoperatively, 213 fulfilled the trial criteria and went on to receive therapy predicated on a set of pathologic risk features: no PORT for the low-risk group (n = 31); 57.6 Gy during 6.5 weeks for the intermediate-risk group (n = 31); and, by random assignment, 63 Gy during 5 weeks (n = 76) or 7 weeks (n = 75) for the high-risk group. Patients were irradiated with standard techniques appropriate to the site of disease and likely areas of spread. The study end points were locoregional control (LRC), survival, and morbidity.

	Intermediate risk	High risk	
Side effect	57.6 Gy/6.5 wk (n = 31)	63 Gy/5 wk (n = 76)	63 Gy/7 wk (n = 75)
Acute reactions (%)			
Confluent mucositis	5 (16)	47 (62)	27 (36)
Tube feeding*	12 (39)	39 (51)	35 (47)
Grade 3–4 late morbidity			
Ulcer/soft tissue necrosis	—	2	2
Fibrosis	1	19	13
Dysphagia	4	16	13
Fistula	—	2	5
Osteonecrosis requiring surgery	—	1	2
Chondritis	—	0	1
Total no. of complications	5	40	36
Patients with complications (n)	5	26	25
2-and 5-year actuarial rates (%)	17, 17	36, 38	36, 42

Is there Evidence for Dose Escalation in the Adjuvant Setting?

Final Report of a Prospective Randomized Trial to

Recurrence risk at primary site

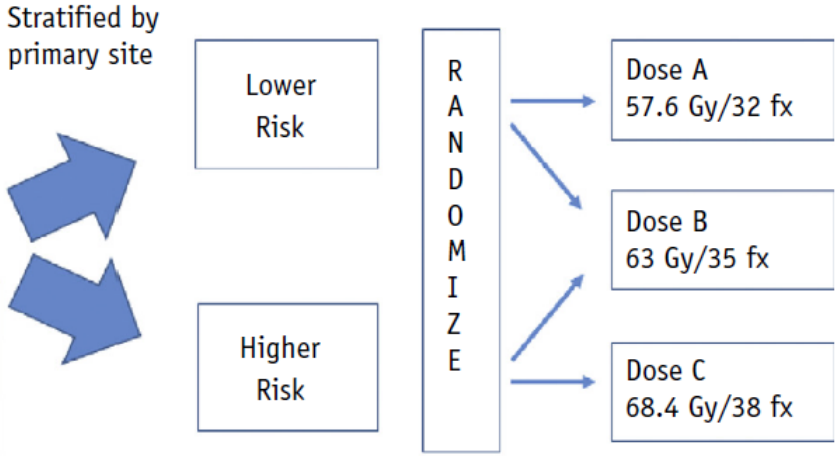
Criteria	Points				
	0	1	2	3	4
Stage	T1-T2	–	T3	–	T4
Margins	-ve	–	Mucosa +ve-> -ve	Deep +ve -> -ve	Close final margins (< 5 mm)
Nerve invasion	-ve	–	Minor nerve(s) +ve	Minor nerve(s) +ve	Major nerve +ve
Neck nodes	N0	N1	≥N2	–	–

Recurrence risk in the neck

Criteria	Points				
	0	1	2	3	4
N. Of nodes	0	1	2-3	≥4 or matted	–
N. Of nodal groups	0-1	2	3	≥4	–
Size/ECE	–	<3 cm without ECE	>3 cm without ECE	<3 cm with ECE	3-6 cm with ECE
Direct invasion	–	–	–	Muscle; skin; nerve; vein	Carotid; base of skull

Point range = 0- 14; Low risk = 1-6; High risk 7- 14

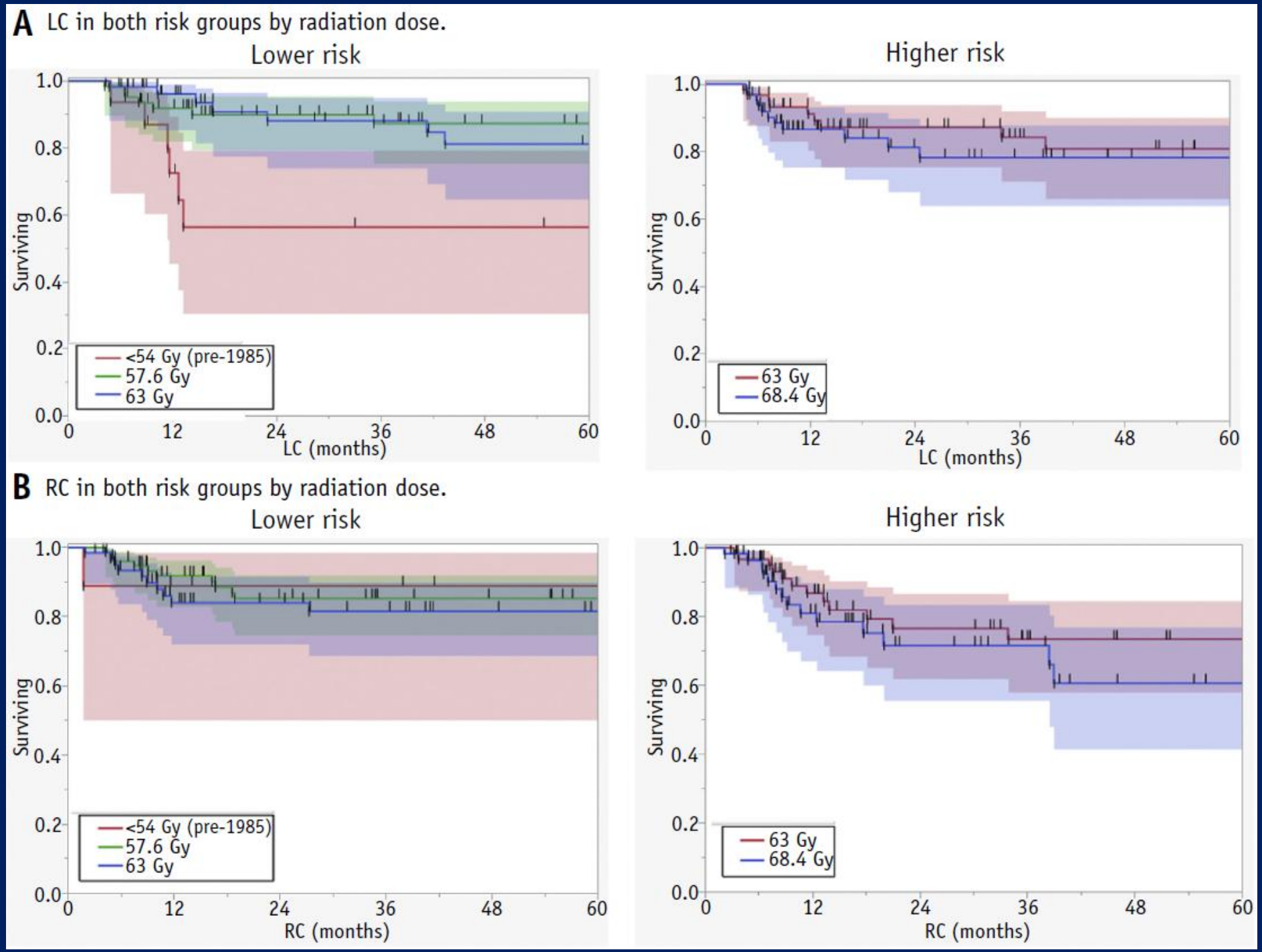
Any final positive margin automatically connotes high risk



Int J Radiation Oncol Biol Phys, Vol. 98, No. 5, pp. 1002–1011, 2017

Results: A total of 264 patients were included. The actuarial 5-year locoregional control rate was 67%. A second primary cancer was documented in 27% of patients. The 5- and 10-year freedom—from—distant metastasis rates were 64% and 60%, respectively, whereas the 5- and 10-year overall survival rates were 32% and 20%, respectively. There was no statistically significant difference in tumor control between different dose levels in both the lower- and higher-risk groups. On multivariate analysis, nonwhite race ($P = .0003$), positive surgical margins ($P = .009$), extracapsular extension (ECE, $P = .01$), and treatment package time (TPT) $\geq$85 days ($P = .002$) were independent correlates of worse locoregional control, whereas age $\geq$57 years ($P < .0001$), positive surgical margins ($P = .01$), ECE ($P = .026$), and TPT $\geq$85 days ($P = .003$) were independently associated with worse overall survival.

Conclusions: This long-term report of PORT delivered at 1.8 Gy/d to total doses of 57.6 to 68.4 Gy without chemotherapy for head and neck squamous cell carcinoma demonstrated that increasing dose did not significantly improve tumor control. On multivariate analysis, the only significant treatment variable was TPT. The results confirm that positive surgical margins and/or nodal ECE remains the most significant predictive pathologic factors.


A LC in both risk groups by radiation dose.
Lower risk
Higher risk
Surviving
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
LC (months)
<54 Gy (pre-1985)
57.6 Gy
63 Gy
63 Gy
68.4 Gy
B RC in both risk groups by radiation dose.
Lower risk
Higher risk
RC (months)

Adjuvant Radiotherapy

- Local failures-25-50%
- Distant failures- 25%
- 5 yr survival rate- 30 - 94%
- Despite adjuvant radiation results are poor, esp. in patients with high risk features

- **Extranodal extension**
- **Positive margins of resection**
- **? Multiple nodal Involvement**
- **? Combination of several adverse features**

- Hence, the need for **Treatment Intensification**

Methods of Intensification of Adjuvant Therapy

- Adjuvant Concurrent chemoradiotherapy
- Altered fractionation Radiotherapy
- Concurrent RT with targeted therapy

Adjuvant Chemo-Radiotherapy in HN Cancers: Adjuvant RT Intensification

Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer

Jacques Bernier, M.D., Ph.D., Christian Domenge, M.D.,

The NEW ENGLAND JOURNAL of MEDICINE

EORTC 22931

- Aim – To compare concomitant cisplatin + RT vs RT alone as adjuvant treatment for stage III / IV head and neck cancer.
- Arms – RT alone Vs CTRT (cisplatin 3 weekly)
- 66 Gy over a period of 6.5wk with concurrent cisplatin(100mg/m2 on day 1,22,43)
- 167 patients in each arm
- Hypothesis : CTRT improves PFS, OS, LRC
- Primary Endpoint: Progression-Free Surviv
- Secondary Endpoints: Overall survival, loca
- MFU – 60 months

High risk patients

- positive margins
- ENE
- multiple nodes
- perineural/vascular invasion

PORT alone

PORT + Chemotherapy

Published May 6, 2004, N Engl J Med 2004;350:1945-1952, DOI: 10.1056/NEJMoa032641 VOL. 350 NO. 19

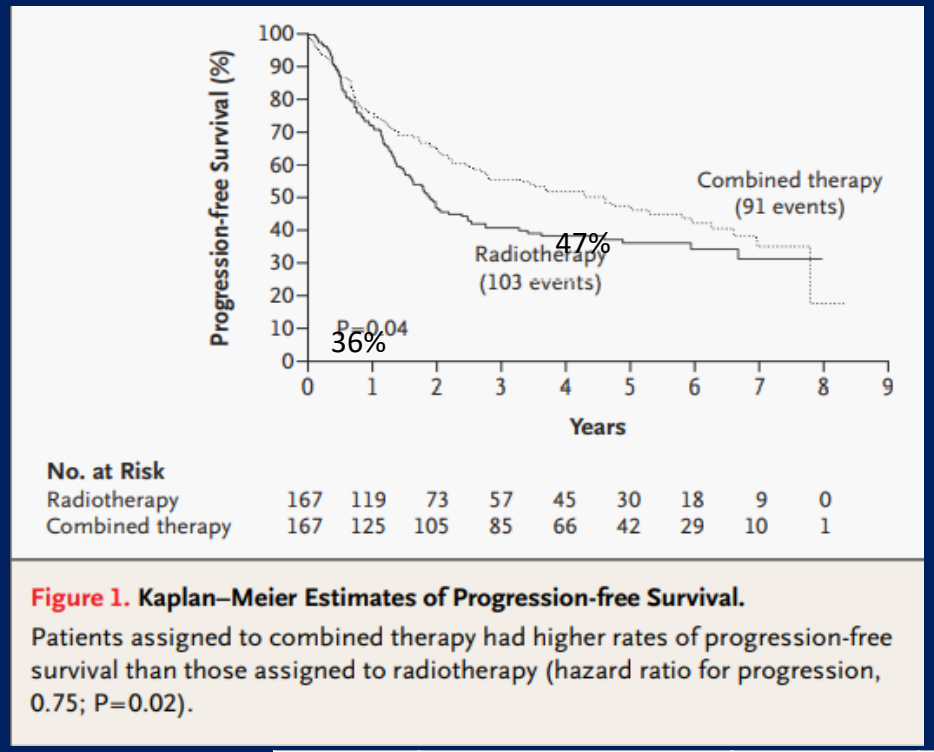


Figure 1. Kaplan–Meier Estimates of Progression-free Survival.

Patients assigned to combined therapy had higher rates of progression-free survival than those assigned to radiotherapy (hazard ratio for progression, 0.75; P=0.02).

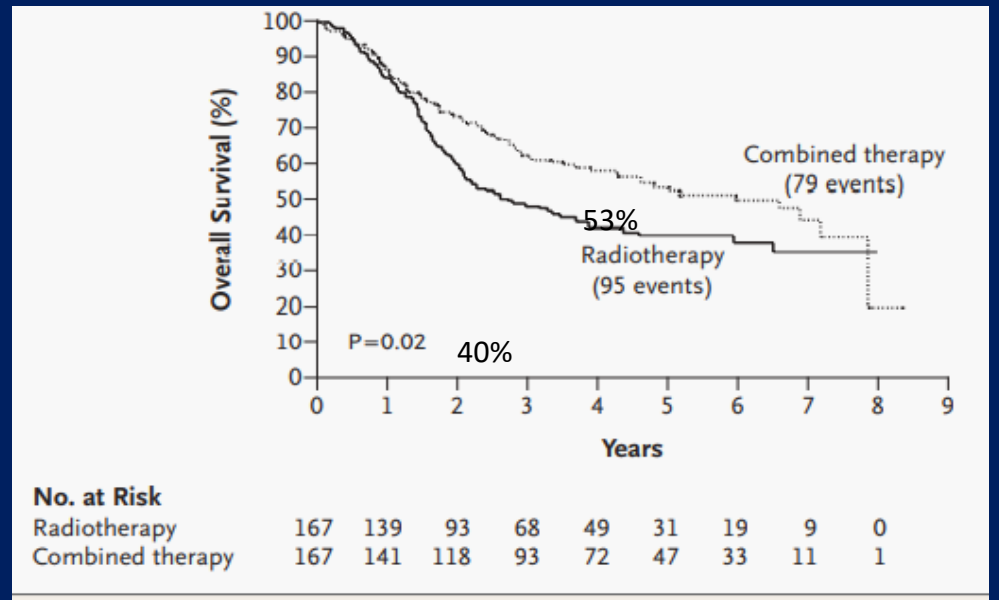


Figure 2. Kaplan–Meier Estimates of Overall Survival.

Patients assigned to combined therapy had higher survival rates than those assigned to radiotherapy (hazard ratio for death, 0.70; P=0.04).

S.No	Outcome	RT	RT + Chemo	
1.	PFS at 5yrs	36%	47%	HR 0.75; *P=0.04*
2.	OS at 5yrs	40%	53%	HR 0.70; *P=0.02*
3.	LRF	31%	18%	*P=0.007*

- Results – PFS, OS better in CTRT arm with similar acute and late toxicities
- Significant survival improvement with addition of cisplatin
- Conclusion - Postoperative concurrent administration of high-dose cisplatin with radiotherapy is more efficacious than radiotherapy alone

Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamous-Cell Carcinoma of the Head and Neck

Jay S. Cooper, M.D., Thomas F. Pajak, Ph.D., Arlene A. Forastiere, M.D., John Jacobs, M.D.,

- Hypothesis - Concurrent postoperative administration of cisplatin and radiotherapy would improve the local and regional control
- Sample size – 439
- Arms – RT alone (60 to 66 Gy in 30 to 33 fractions over a period of 6 to 6.6 weeks) Vs RT + 3 weekly cisplatin (100 mg per sq meter of BSA) after surgery
- MFU – 45.9 months

Published May 6, 2004, N Engl J Med 2004;350:1937-1944, DOI: 10.1056/NEJMoa032646, VOL. 350 NO. 19

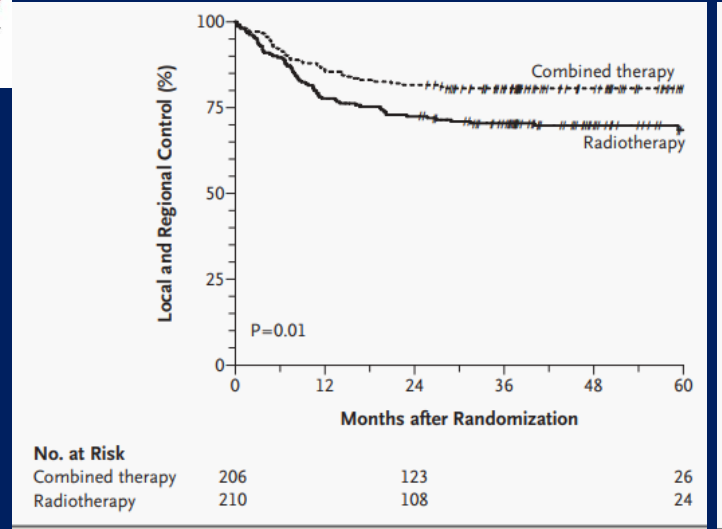


Figure 1. Rates of Local and Regional Control.
Patients assigned to receive radiotherapy and concurrent chemotherapy had a higher rate of local and regional control than patients assigned to receive radiotherapy alone (P=0.01 by Gray's test). Tick marks indicate censored data.

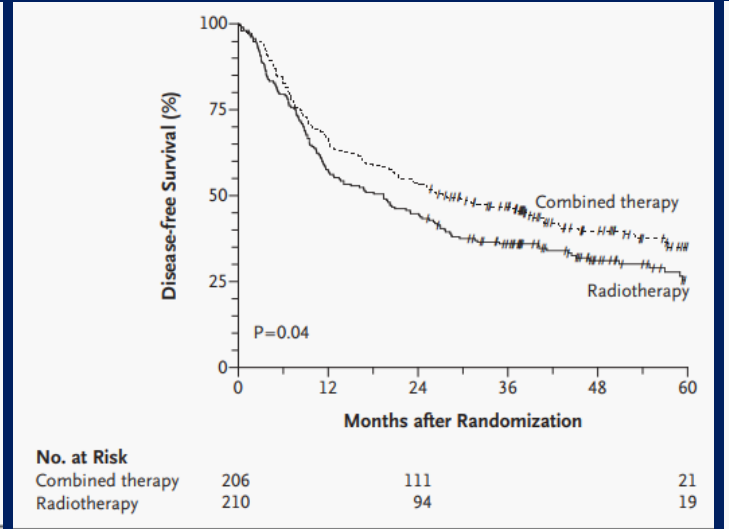


Figure 2. Kaplan–Meier Estimates of Disease-free Survival.
Patients assigned to receive radiotherapy and concurrent chemotherapy had a higher rate of disease-free survival than patients assigned to receive radiotherapy alone (P=0.04 by the log-rank test). Tick marks indicate censored data.

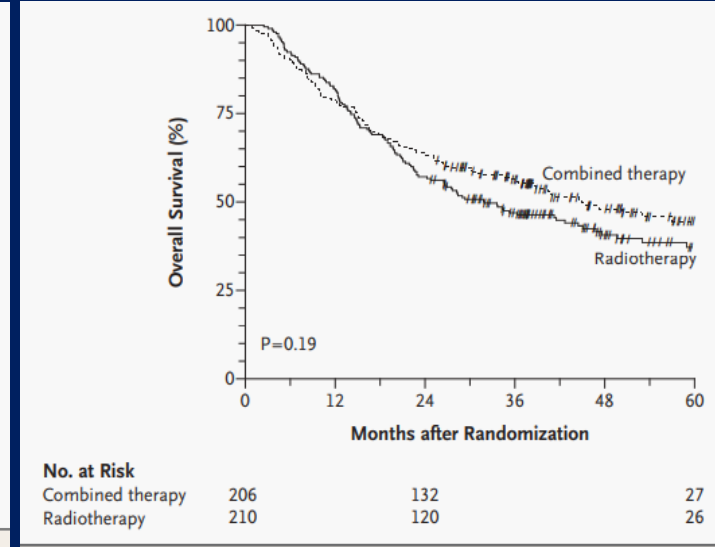


Figure 3. Kaplan–Meier Estimates of Overall Survival.
Overall survival did not differ significantly between groups (P=0.19 by the log-rank test). Tick marks indicate censored data.

Results –

LRC 82 % vs 72 %

DFS better in CTRT (HR 0.78, p =0.04)

OS comparable (HR 0.84, p=0.19)

Acute toxicity >grade 3 more in CTRT (77 % vs 34 %, p < 0.001)

Conclusion - patients with resected head and neck cancer, concurrent postoperative chemotherapy and radiotherapy significantly improve the rates of local and regional control and disease-free survival.

However, the combined treatment is associated with a substantial increase in adverse effects.

S.No	Features	RTOG 9501	EORTC 22931
1	Primary Endpoints	LRC	PFS
2	Eligibility Criteria and high risk features	Strict high-risk features • ≥2 nodes • ENE • positive margins	Stage III/IV + High risk pathology • Multiple nodes • ENE • Positive margins • vascular/perineural invasion More inclusive criteria in EORTC
3	Treatment Regimens	Similar	Similar
4	Locoregional Control (2–5 yrs)	↑ with CRT (82% vs 72%, *P=0.01*)	↑ with CRT (18% vs 31% failures, *P=0.007*)
5	Progression-Free Survival	Improved (HR 0.78; *P=0.04*)	Improved (5-yr PFS: 47% vs 36%; HR 0.75; *P=0.04*)
6	Overall Survival	Not significant (HR 0.84; *P=0.19*)	Significant (5-yr OS: 53% vs 40%; HR 0.70; *P=0.02*)
7	Distant Metastasis	No difference	No difference

Adjuvant Chemoradiotherapy Meta-Analysis

Table 2. Efficacy data: randomized trials of chemoradiotherapy versus radiotherapy alone.

Author/year, ref.	No. of pts.	Treatment arms	Point in time*	Locoregional recurrence	Progression-free survival	Disease-free survival	Overall survival	Median survival, mo
Bernier et al, 2004[11]	167	CT/RT	5 y	18%	47%	NR	53%	72
	167	RT		31%	36%	NR	40%	32
				$p = .007$	$p =$ NR		$p =$ NR	$p =$ NR
			Overall	NR	HR = 0.75, $p = .04$	NR	HR = 0.70, $p = .02$	
				NR	95% CI = 0.56–0.99	NR	95% CI = 0.52–0.95	
Cooper et al, 2004[12]	206	CT/RT	3.8 y	19%	NR	40%	50%	45
	210	RT		30%	NR	30%	41%	32
				$p =$ NR		$p =$ NR	$p =$ NR	$p =$ NS
			Overall	HR = 0.61, $p = .01$	NR	HR = 0.78, $p = .04$	HR = 0.84, $p = .19$	
				95% CI = 0.41–0.91	NR	95% CI = 0.61–0.99	95% CI = 0.65–1.09	
Bachaud et al, 1996[13]	39	CT/RT	5 y	23%	NR	45%	36%†	40
	44	RT		41%	NR	23%	13%	22
				$p = .08$		$p < .02$	$p < .01$	$p =$ NR
			Overall	NR	NR	NR	NR	
				NR	NR	NR	NR	
Šmid et al, 2003[14]	59	CT/RT	2 y	14%	NR	78%‡	74%	> 48‡
	55	RT		31%	NR	60%	64%	32
				$p = .037$		$p = .099$	$p = .036$	$p =$ NR
			Overall	NR	NR	NR	NR	
				NR	NR	NR	NR	

Abbreviations: pts., patients; CT/RT, chemotherapy plus radiotherapy; RT, radiotherapy; NR, not reported; HR, hazard ratio; CI, confidence interval; NS, not statistically significant; Y, years.
**Percentiles reflect the point in time that outcomes were measured; overall data reflect hazard ratios from Kaplan–Meier curves.*
†Survival corrected by deaths of intercurrent disease was 47% with chemoradiotherapy and 23% for radiotherapy alone.
‡Data extracted from survival curves by reviewer.

HEAD & NECK—DOI 10.1002/hed January 2007

DEFINING RISK LEVELS IN LOCALLY ADVANCED HEAD AND NECK CANCERS: A COMPARATIVE ANALYSIS OF CONCURRENT POSTOPERATIVE RADIATION PLUS CHEMOTHERAPY TRIALS OF THE EORTC (#22931) AND RTOG (#9501)

Jacques Bernier, MD, PhD,[1] Jay S. Cooper, MD,[2] T. F. Pajak, PhD,[3] M. van Glabbeke, Ir,[4]

- Significant factors for CTRT: ECE, positive margins
- Trend in favor of CTRT: Stage III– IV disease, LVE, PNI, clinically enlarged level IV –V lymph nodes.
- No benefit of CTRT: 2 or more positive lymph nodes without ENE
- **Conclusion**: The margin status and ENE as indicators for CTRT were established by this pooled analysis

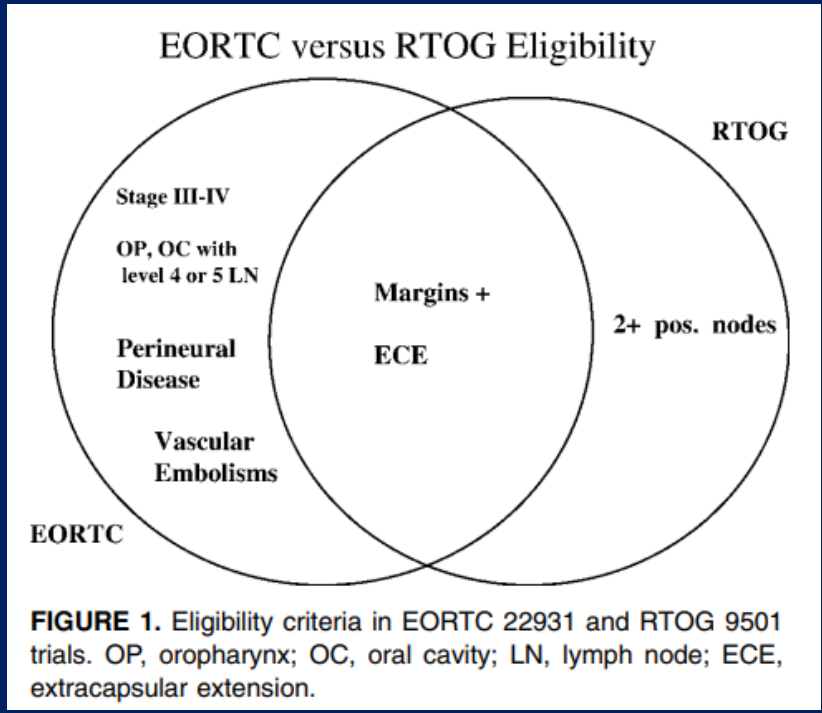


FIGURE 1. Eligibility criteria in EORTC 22931 and RTOG 9501 trials. OP, oropharynx; OC, oral cavity; LN, lymph node; ECE, extracapsular extension.

First published: 13 September 2005, https://doi.org/10.1002/hed.20279

Long-Term Follow-Up of the RTOG 9501/Intergroup Phase III Trial: Postoperative Concurrent Radiation Therapy and Chemotherapy in High-Risk Squamous Cell Carcinoma of the Head & Neck

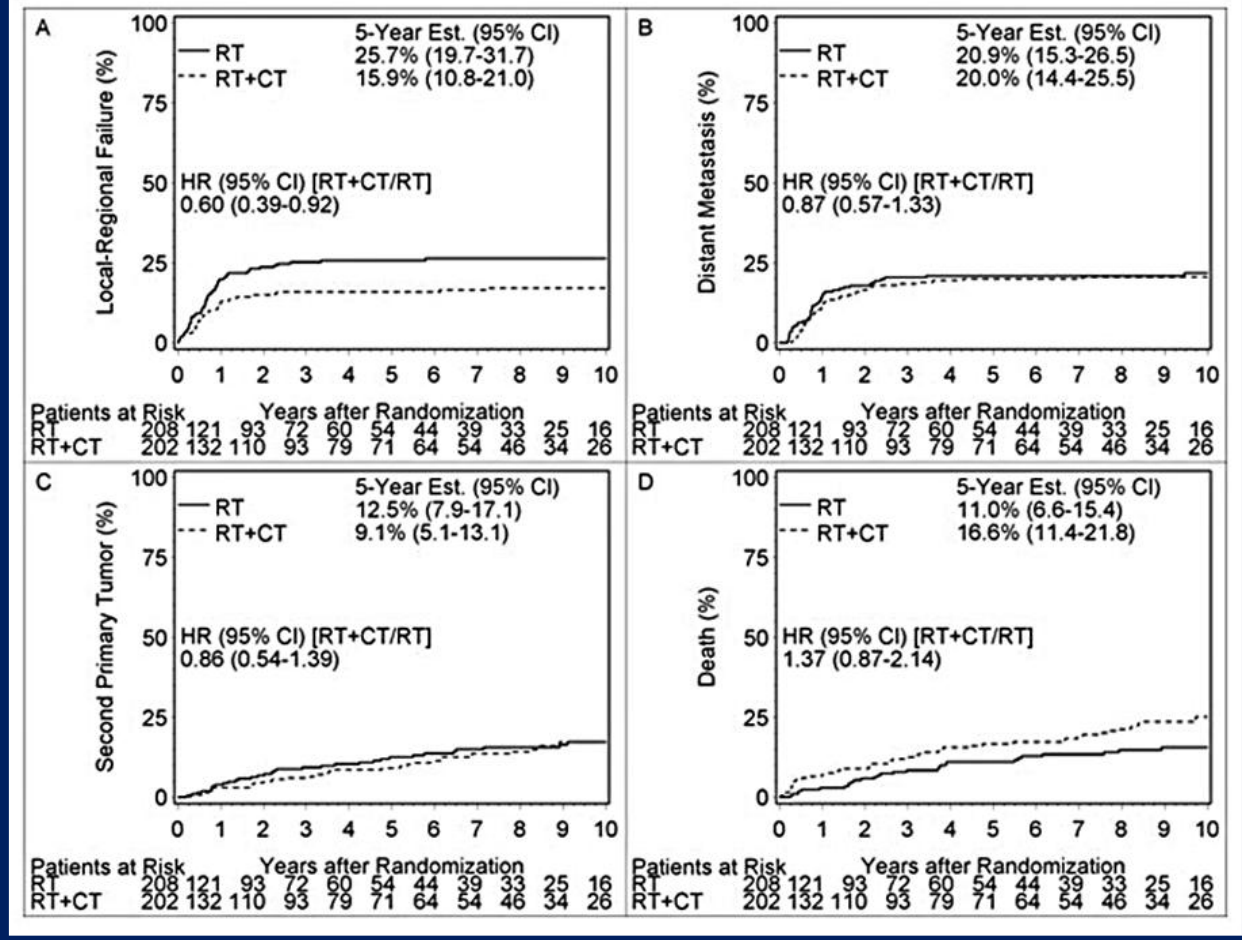
Jay S. Cooper, MD,
Maimonides Cancer Center, New York, NY

- **Patient Characteristics**
- Total: 459 patients
  - RT: 232
  - CRT: 227
- Balanced demographics between groups
- Median follow-up: ~10 years

PMID: 22749632, PMCID: PMC3465463, DOI: 10.1016/j.ijrobp.2012.05.008

Outcomes

S.No	Outcome	CRT	RT	P-value
1.	10y LRC	81%	69%	0.01
2.	10y DFS	43%	34%	0.02 (HR – 0.76)
3.	10y OS	43%	40%	0.19 (HR – 0.84)



- Subgroup Analysis:
- Greatest benefit in patients with: ECE and/or positive margins
- These patients had improved OS with CRT (HR = 0.59, p = 0.014)

Toxicity

- CRT associated with more acute toxicity:
- Grade 3+ mucositis
- hematologic toxicity
- Late toxicity: xerostomia, dysphagia also more common in CRT arm

Conclusions

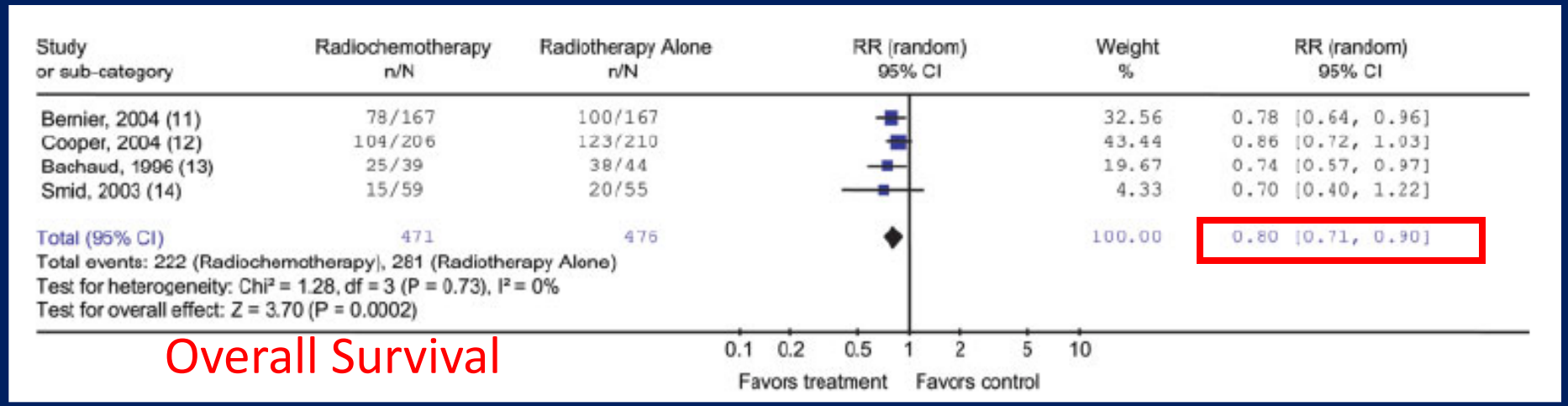
- CRT improves LRC and DFS in high-risk patients
- OS benefit observed in ECE/positive margin subgroup
- CRT should be standard for high-risk resected HNC

Limitations & Considerations

- Conducted before routine HPV testing
- Comorbidities not fully accounted for
- Benefit should be weighed against toxicity, especially in older/frail patients

- Clinical Implications:
- Affirmation of CRT for ECE/positive margin patients
- Importance of multidisciplinary care
- Ongoing need for biomarkers to refine selection

Adjuvant Chemoradiotherapy Meta-Analysis



12.5% absolute improvement in OS (NNT=8)

Grade III/IV mucositis- 70% vs. 34%

Treatment related deaths-1-2%

HEAD & NECK—DOI 10.1002/hed January 2007

Adjuvant Chemoradiotherapy Meta-Analysis

Conclusions:

- Chemoradiotherapy beneficial for high risk factors :
  - Extranodal extension
  - Positive Cut margins
- Beneficial < 70 years of age
- Significant toxicity
- Need for intense supportive care

Long-term Follow-up of the RTOG 9501/Intergroup Phase III Trial: Postoperative Concurrent Radiation Therapy and Chemotherapy in High-Risk Squamous Cell Carcinoma of the Head and Neck

Results: At 10 years, the local-regional failure rates were 28.8% vs 22.3% ($P = .10$), disease-free survival was 19.1% vs 20.1% ($P = .25$), and overall survival was 27.0% vs 29.1% ($P = .31$) for patients treated by RT vs RT + CT, respectively. In the unplanned subset analysis limited to patients who had microscopically involved resection margins and/or extracapsular spread of disease, local-regional failure occurred in 33.1% vs 21.0% ($P = .02$), disease-free survival was 12.3% vs 18.4% ($P = .05$), and overall survival was 19.6% vs 27.1% ($P = .07$), respectively.

Conclusion: At a median follow-up of 9.4 years for surviving patients, no significant differences in outcome were observed in the analysis of all randomized eligible patients. However, analysis of the subgroup of patients who had either microscopically involved resection margins and/or extracapsular spread of disease showed improved local-regional control and disease-free survival with concurrent administration of chemotherapy. The remaining subgroup of patients who were enrolled only because they had tumor in 2 or more lymph nodes did not benefit from the addition of CT to RT.

Original Article

Re-examining Post-operative Chemoradiotherapy in Head and Neck Cancer: An Updated Long-Term Combined Analysis of RTOG 9501/EORTC 22931

Z.S. Zumsteg [1], M. Luu [2], C. Fortpied [3], J.K. Jang [1], M.M. Chen [4], J. Mallen-St. Clair [5], E. Walgama [5], Q.T. Le [6], M. Machtay [7], S. Tribius [8], A. Forastiere [9], S. Wong [10], E. Mahmut Ozsahin [11], V. Gregoire [12], J.B. Vermorken [13], A.S. Ho [6], S.S. Yom [14]

- **Rationale for Updated Analysis**

  - The original pooled analysis was **post-hoc** and did not perform formal *treatment-by-marker interaction* tests. Without interaction testing, one cannot conclude that ENE/margin status is a true predictive biomarker of CRT benefit.

  - Updated follow-up data (median 6.9 years) are now available for all patients, allowing re-assessment of outcomes.

A predictive biomarker is a biological characteristic used to identify individuals who are more likely to respond positively or negatively to a specific treatment
Eg: PD-L1 expression: Predicts response to immune checkpoint inhibitors in various cancers.

Zumsteg *et al.*, *Annals of Oncology* (2025)

- The current study re-examines whether CRT's benefit truly differs between subgroups and evaluates cancer-specific vs other-cause mortality.

- **Predictive vs prognostic:**

  - Identifying subgroups with/without significant benefit is insufficient.

  - A *predictive* factor requires a statistically significant interaction (difference in treatment effect) between subgroups.

- **Patient population:**
  - 744 patients (410 from RTOG 9501, 334 from EORTC 22931) treated between 1994–2004.
  - 91% (680/744) met eligibility for both trials.
  - Median age 55; only 3.5% were >70. 55% had ENE; 18% had positive margins.

- **Treatment:** Post-operative radiation (60–66 Gy) with or without concurrent cisplatin (100 mg/m² Q3weeks×3). Both trials used similar regimens.

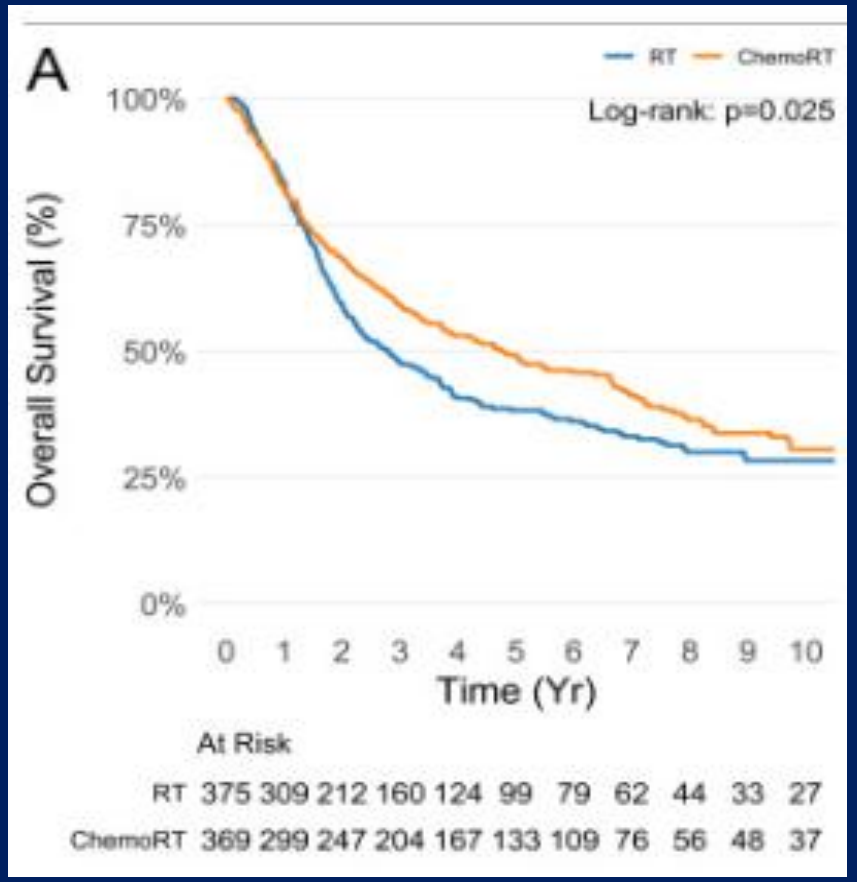
- Characteristics were balanced between RT and CRT arms.
- Median follow-up 6.9 years (5.0 EORTC, 10.0 RTOG).
- **Between trials**: RTOG patients were slightly older, more often oropharyngeal, higher N2-3 and PNI rates
- EORTC had more margin-positive cases. (Importantly, no systematic bias in randomization was noted.)

- **Statistics:**
  - Overall survival (OS) by Kaplan-Meier and Cox regression.
  - Cancer-specific mortality (CSM), other-cause mortality (OCM), locoregional recurrence (LRR), and distant metastasis (DM) analyzed via cumulative-incidence with Fine-Gray competing-risks models.

- **Interaction testing:**
  - Interaction terms (treatment×covariate) were tested in Cox and Fine-Gray models by likelihood-ratio test.
  - Bonferroni correction for multiple interactions ($p<0.006$ considered significant) was applied.
  - Sensitivity analyses stratified by trial and censored at 5 years were also performed.

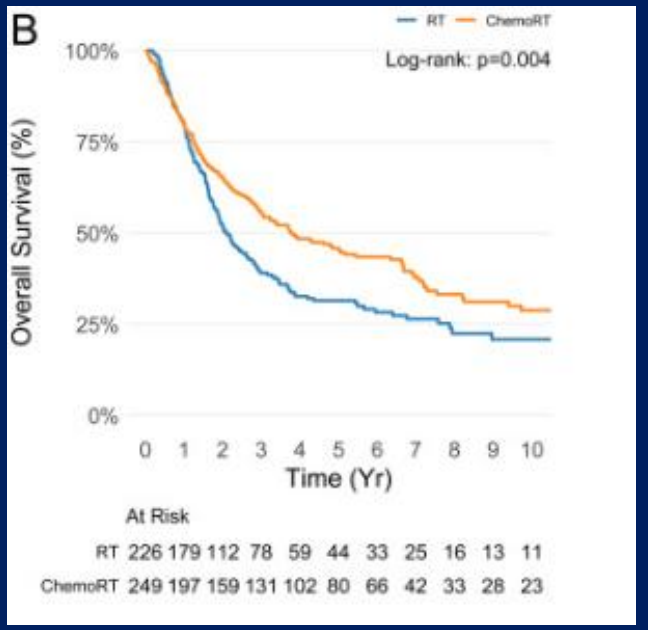
OS

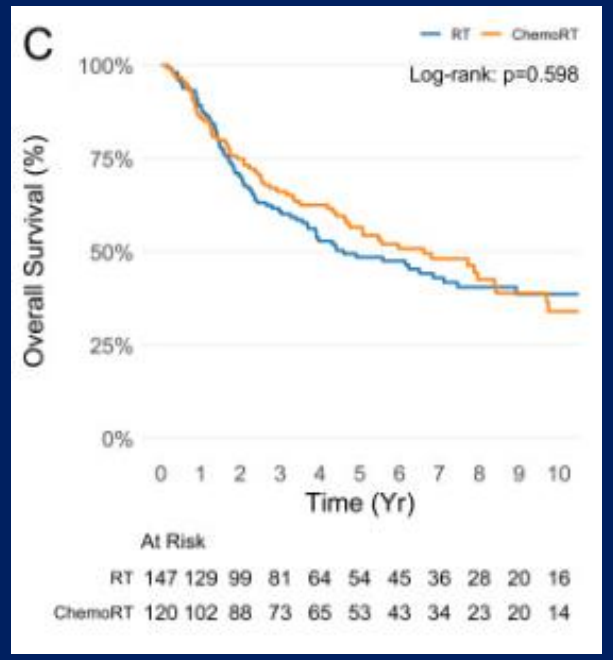
- **Overall Survival (OS) – All Patients**
- **OS benefit:** CRT significantly improved OS in the combined cohort. 7-year OS was 41% with CRT vs 33% with RT.
- **Hazard ratio:** CRT vs RT yielded OS HR=0.81 (95% CI 0.68–0.97, p=0.026).
- **Across trials:** No significant heterogeneity in CRT effect on OS between RTOG and EORTC (consistent benefit).



Overall Survival – ENE/Margin

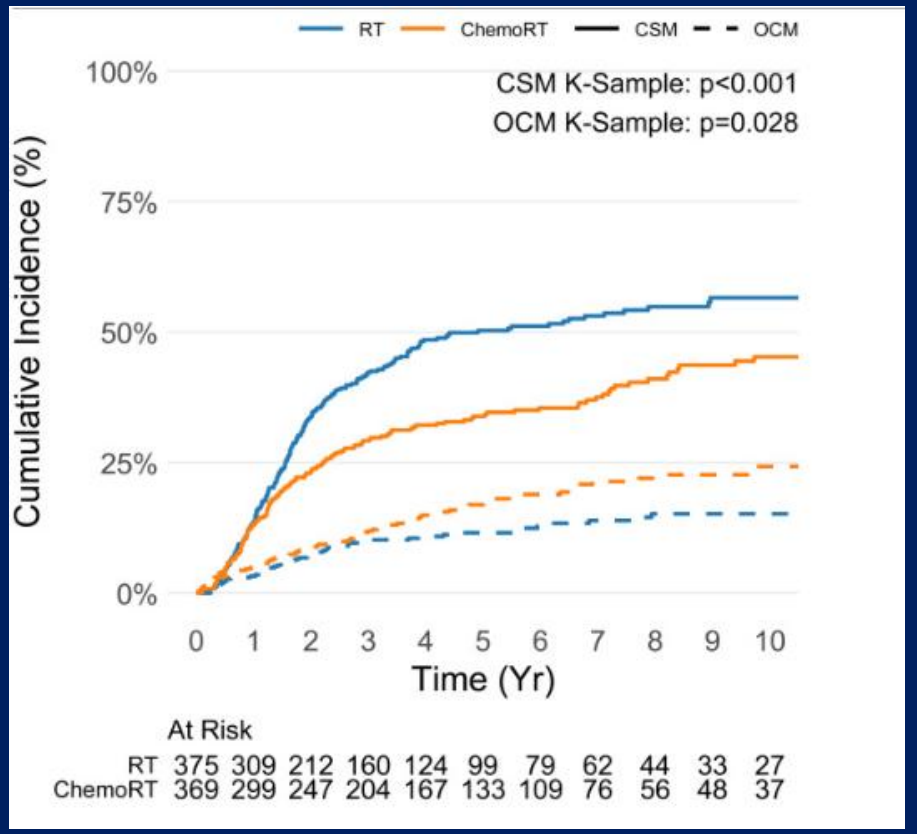
- High-risk subgroup:
- CRT improved OS (HR=0.71, 95% CI 0.57–0.89, p=0.003) in patients with ENE or positive margins.
- 7-year OS ~44% vs 31%.
- Low-risk subgroup (no ENE, negative margins): No significant OS benefit (HR=0.94, 95% CI 0.68–1.30, p=0.70). 7-year OS ~37% vs 33%.
- Interaction test: The treatment-by-(ENE/margin) interaction p=0.17 (not significant).
- This means ENE and/or positive margins are not predictive biomarkers for benefit from CRT, and even patients without these features may benefit.





Cancer-specific vs Other-cause Mortality

- **Cancer-specific mortality (CSM):** CRT significantly reduced CSM. 10-year CSM HR=0.68 (95% CI 0.55–0.83, p<0.001).
- **Other-cause mortality (OCM):** CRT **increased** OCM. 10-year OCM HR=1.51 (95% CI 1.07–2.12, p=0.018).
- **Competing-risk curves:** The cumulative incidence curves show that by year 10, the CRT arm has a higher fraction of other-cause deaths (suggesting treatment-related toxicity or comorbidities) that partially offsets the cancer survival benefit. (K-sample tests: CSM p<0.001, OCM p=0.028.)
- **Implication:** While CRT prolongs life by preventing cancer deaths, it also adds non-cancer risks (toxicity, comorbid events) that clinicians must weigh, especially in older/frail patients.



Patterns of Failure

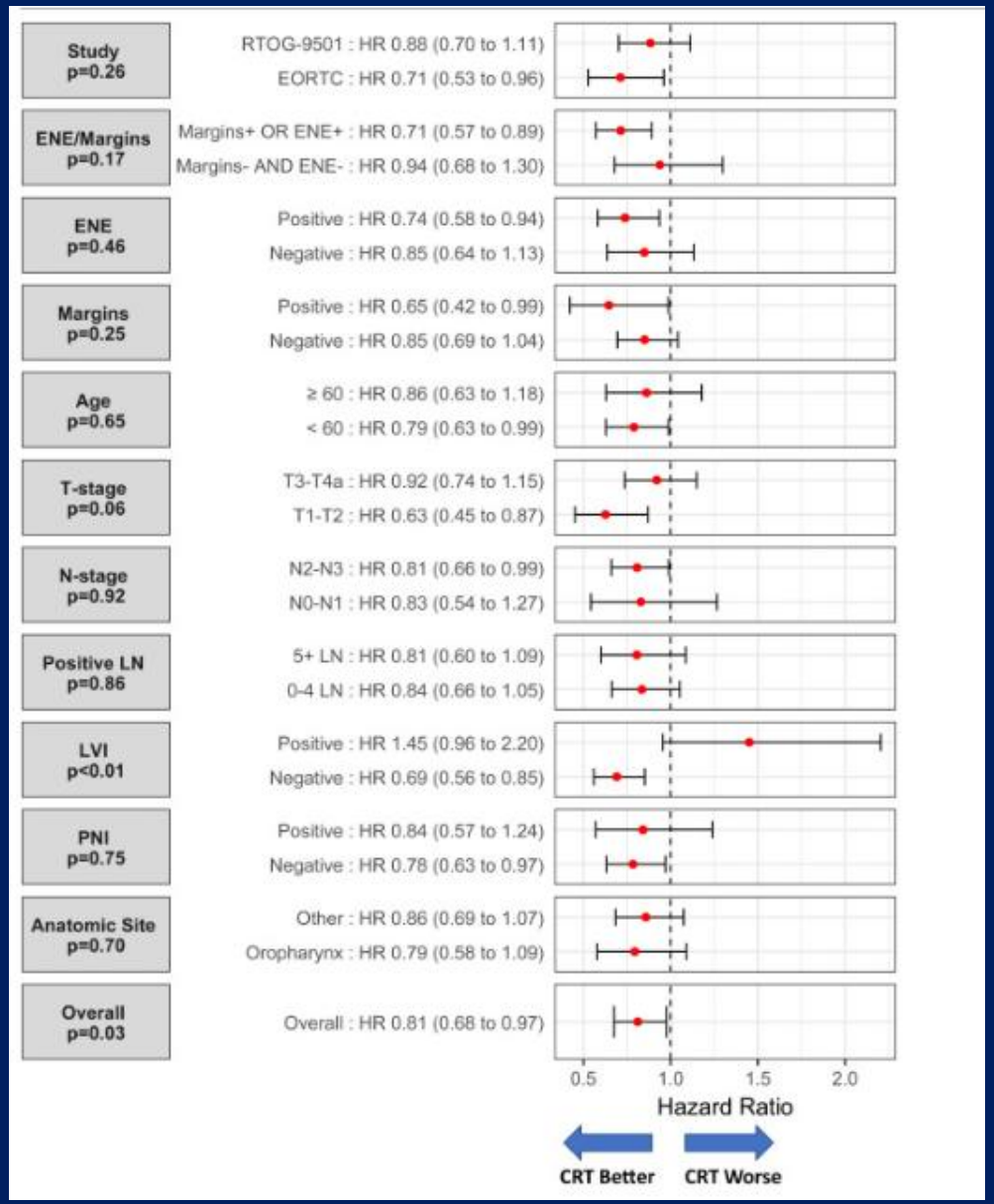
- **Locoregional recurrence (LRR):** Post-op CRT significantly reduced LRR. HR=0.64 (95% CI 0.48–0.85, p=0.002).
- **7-year LRR rates:** 20% with CRT vs 31% with RT (p=0.003).

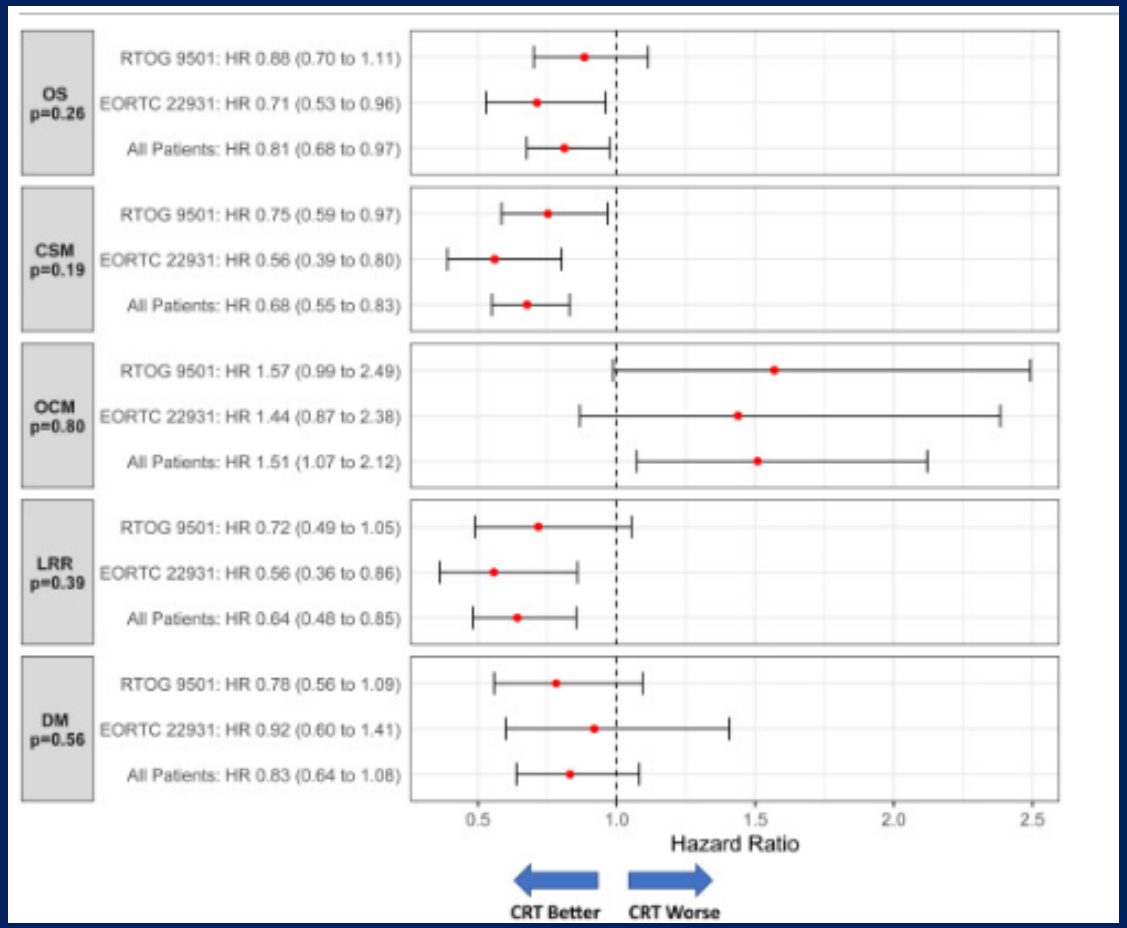
- **Distant metastasis (DM):** No statistically significant difference in DM. HR=0.83 (95% CI 0.64–1.08, p=0.17).
- **7-year DM rates:** 26% with CRT vs 31% with RT (p=0.20).

- **Interpretation:** CRT's main impact is on reducing local-regional relapse; it has little effect on distant spread in this setting.

Subgroup Analysis (Other Factors)

- **Age:** Patients <60 vs ≥60: CRT reduced OS risk in both (<60: HR≈0.79; ≥60: HR≈0.86). Interaction p=0.65 (not significant).
- Trends (pre-correction): CRT slightly increased OCM in older patients (p_int=0.02).
- **Tumor stage (T/N):** Benefit seen across T1-2 and T3-4a (HR ~0.63 and 0.92).
- **LVI and PNI:** in LVI- pts, CRT was beneficial (HR≈0.69), in LVI+ patients CRT had higher HR≈1.45 (i.e. possible harm).
- PNI+ had no benefit (HR≈0.84) while PNI- did (HR≈0.78). These patterns suggest prognostic heterogeneity but none reached significance after multiple-testing.
- **Summary:** No subgroup effect met the stringent **interaction threshold** (p<0.006) for OS or other endpoints.


Study p=0.26
RTOG-9501 : HR 0.88 (0.70 to 1.11)
EORTC : HR 0.71 (0.53 to 0.96)
ENE/Margins p=0.17
Margins+ OR ENE+ : HR 0.71 (0.57 to 0.89)
Margins- AND ENE- : HR 0.94 (0.68 to 1.30)
ENE p=0.46
Positive : HR 0.74 (0.58 to 0.94)
Negative : HR 0.85 (0.64 to 1.13)
Margins p=0.25
Positive : HR 0.65 (0.42 to 0.99)
Negative : HR 0.85 (0.69 to 1.04)
Age p=0.65
≥ 60 : HR 0.86 (0.63 to 1.18)
< 60 : HR 0.79 (0.63 to 0.99)
T-stage p=0.06
T3-T4a : HR 0.92 (0.74 to 1.15)
T1-T2 : HR 0.63 (0.45 to 0.87)
N-stage p=0.92
N2-N3 : HR 0.81 (0.66 to 0.99)
N0-N1 : HR 0.83 (0.54 to 1.27)
Positive LN p=0.86
5+ LN : HR 0.81 (0.60 to 1.09)
0-4 LN : HR 0.84 (0.66 to 1.05)
LVI p<0.01
Positive : HR 1.45 (0.96 to 2.20)
Negative : HR 0.69 (0.56 to 0.85)
PNI p=0.75
Positive : HR 0.84 (0.57 to 1.24)
Negative : HR 0.78 (0.63 to 0.97)
Anatomic Site p=0.70
Other : HR 0.86 (0.69 to 1.07)
Oropharynx : HR 0.79 (0.58 to 1.09)
Overall p=0.03
Overall : HR 0.81 (0.68 to 0.97)
0.5
1.0
1.5
2.0
Hazard Ratio
CRT Better
CRT Worse


OS p=0.26
RTOG 9501: HR 0.88 (0.70 to 1.11)
EORTC 22931: HR 0.71 (0.53 to 0.96)
All Patients: HR 0.81 (0.68 to 0.97)
CSM p=0.19
RTOG 9501: HR 0.75 (0.59 to 0.97)
EORTC 22931: HR 0.56 (0.39 to 0.80)
All Patients: HR 0.68 (0.55 to 0.83)
OCM p=0.80
RTOG 9501: HR 1.57 (0.99 to 2.49)
EORTC 22931: HR 1.44 (0.87 to 2.38)
All Patients: HR 1.51 (1.07 to 2.12)
LRR p=0.39
RTOG 9501: HR 0.72 (0.49 to 1.05)
EORTC 22931: HR 0.56 (0.36 to 0.86)
All Patients: HR 0.64 (0.48 to 0.85)
DM p=0.56
RTOG 9501: HR 0.78 (0.56 to 1.09)
EORTC 22931: HR 0.92 (0.60 to 1.41)
All Patients: HR 0.83 (0.64 to 1.08)
0.5
1.0
1.5
2.0
2.5
Hazard Ratio
CRT Better
CRT Worse

Statistical Interpretation

- **Predictive vs Prognostic:** ENE and margin positivity are **prognostic** (indicating higher baseline risk) but were *not proven predictive* of CRT benefit in this analysis.

- **Interaction requirement:** A subgroup showing significant benefit while another does not is *not enough* to claim predictive value. One must show that the treatment effect is statistically different between subgroups (interaction test). In this study, interactions were non-significant.

- **Confidence intervals:** The overlap of 95% CIs between subgroups (e.g. ENE+ vs ENE–) indicates uncertainty about true differences. A point estimate HR<1 in one group vs ≈1 in another could simply reflect sample size/power differences.

Clinical Implications

Broad benefit of CRT:

- The updated analysis supports offering concurrent CRT after surgery to *all* high-risk patients, not only those with ENE or positive margins.
- Patients without those classic features still had point-estimate OS improvement.

Patient selection:

- Decisions should incorporate overall health and comorbidity. Because CRT raises OCM, elderly or frail patients may have less net benefit.
- In practice, a 65-year-old with multiple comorbidities might opt for RT alone, whereas a fit patient even without ENE/margin would still likely get CRT.

Clinical Implications

Guidelines:

- Current NCCN guidelines already level-1 endorse CRT for ENE/margin+.
- This analysis suggests we should *not* categorically omit CRT in patients deemed "intermediate risk" (e.g. LVI+, PNI+, close but negative margins) without further evidence.

Shared decision-making:

- Discuss potential benefit vs toxicity.
- Inform patients that CRT reduces cancer death/recurrence but increases risk of non-cancer complications.

- It is important to interpret these results in light of the RTOG 0920

Conclusions

- Post-operative CRT provides a **significant OS benefit** in combined RTOG 9501/EORTC 22931 cohort, primarily by reducing cancer-specific death and locoregional recurrence.
- The **classic high-risk factors (ENE, positive margin)** were *not* confirmed as predictive biomarkers of CRT benefit – patients without them may still gain from CRT.
- OCAT trial's **High-Risk Profile (HRP) subgroup** (defined as T3–T4 + N2–N3 **+ ECE**), Statistically significant difference in **DFS** and **OS** in intensification arms.
- RTOG 0920 - Showed DFS benefit but no OS benefit, for intermediate risk factors
- CRT was offset by increased other-cause mortality, highlighting the importance of **patient selection.**
- In practice, a case-by-case approach remains key: CRT for all eligible high-risk patients, with careful consideration of **comorbidity and patient preference**.
- Future work: **biomarker-driven personalization** and geriatric oncology are high priorities, given these findings.

Biological optimization

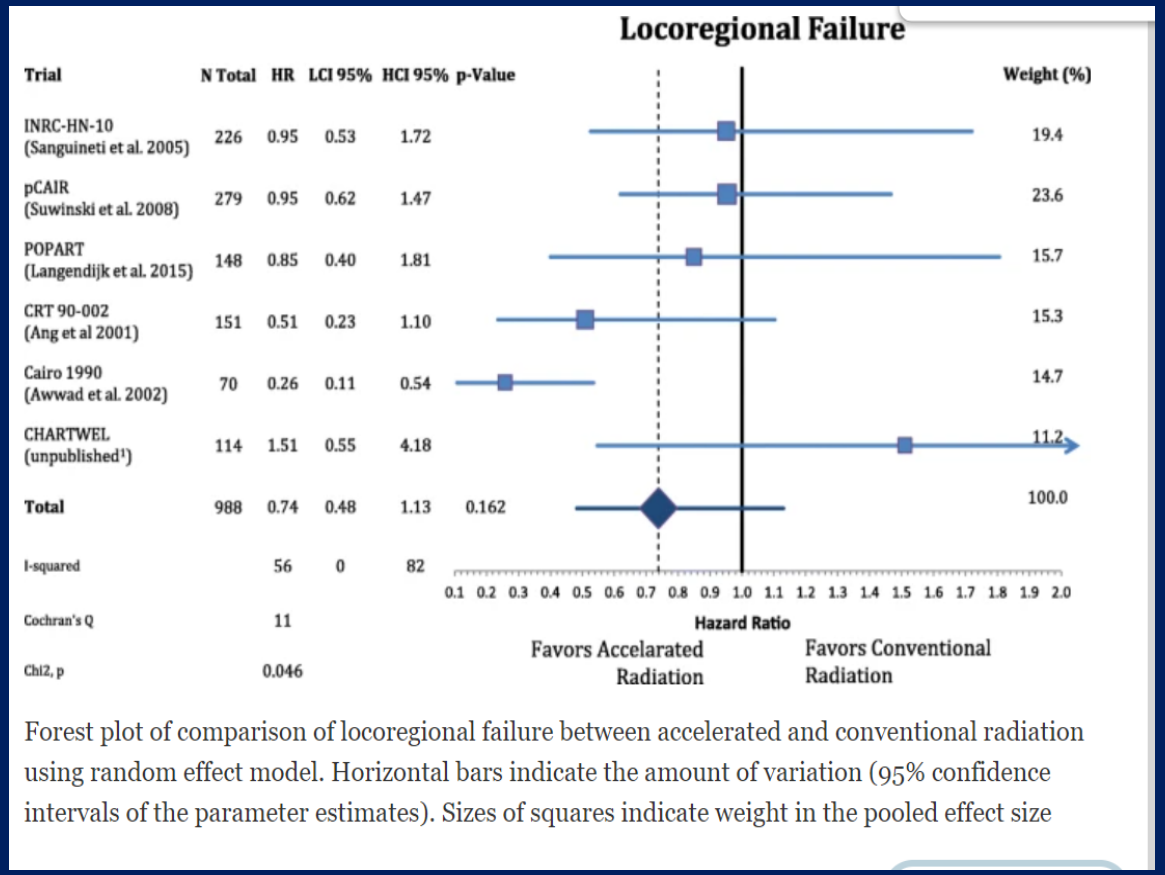
- Altered fractionation
- Biological response modifiers
- Targeted therapies

Research | Open Access | Published: 04 October 2018

Accelerated vs. conventionally fractionated adjuvant radiotherapy in high-risk head and neck cancer: a meta-analysis

Christiane Matuschek, Jan Haussmann, Edwin Bölke, Stephan Gripp, Patrick J. Schuler, Bálint Tamaskovics, Peter Arne Gerber, Freddy-Joel Djiepmo-Njanang, Kai Kammers, Christian Plettenberg, Bahar Anooshahr, Klaus Orth & Wilfried Budach

- Metanalysis of 6 Trials and 988 Patients
- Accelerated Adjuvant RT did not improve outcomes significantly as compared standard conventional RT
- Significantly Higher Acute toxicities with conventional RT
- Late toxicities similar in both cohort



Forest plot of comparison of locoregional failure between accelerated and conventional radiation using random effect model. Horizontal bars indicate the amount of variation (95% confidence intervals of the parameter estimates). Sizes of squares indicate weight in the pooled effect size

Oral cavity adjuvant therapy (OCAT) -a phase III, randomized controlled trial of surgery followed by conventional RT (5 fr/wk) versus concurrent CT-RT versus accelerated RT (6fr/wk) in locally advanced, resectable, squamous cell carcinoma of oral cavity

Sarbani G. Laskar [a,*], Devendra Chaukar [b], Mandar Deshpande [c], Abhishek Chatterjee [a], Shwetabh Sinha [a], Santam Chakraborty [d], Jai P. Agarwal [a], Tejpal Gupta [a], Ashwini Budrukkar [a], Vedang Murthy [a], Prathamesh Pai [b], Pankaj Chaturvedi [b], Gouri Pantvaidya [b], Anuja Deshmukh [b], Deepa Nair [b], Sudhir Nair [b], Kumar Prabhash [e], Monali Swain [a], Anuj Kumar [a], Vanita Noronha [e], Vijay Patil [e], Amit Joshi [e], Anil DCruz [f]

European Journal of Cancer 181 (2023) 179–187

Objectives

Primary

- Efficacy of addition of **Concurrent chemotherapy** to post-operative adjuvant radiotherapy in improving local-regional control (LRC)
- Shortening of duration of post-operative radiotherapy, by administering **6 fr / week** instead of 5 fr / week, could improve LRC

Secondary

- Overall Survival (OS)
- Quality of life (QOL)
- Patient compliance
- Treatment related toxicity

Inclusion criteria

Previously untreated, resectable, locally advanced stage III/ IV non-metastatic, biopsy proven, OCC

One or more of the following must be present

- Extracapsular nodal extension (ECE)
- Involvement of $\geq$ 2 regional LN
- Margin of resection with invasive cancer

- Extensive ST &/ skin infiltration requiring major reconstruction
- Perineural Invasion (PNI)
- Lymphovascular Emboli (LVE)

Protocol treatment to begin within **8 weeks of surgery**

Trial Design

Adequate surgery with appropriate reconstruction
(Stratification: T stage: T1-2/ T3-4, N stage: N0-1/ N2-3**)**

RANDOMISATION (900)

1:1:1

Control	Test Arm 1	Test Arm 2
5DRT (299)	CTRT (300)	6DRT (301)

- 5DRT: 5 fractions of Radiotherapy (RT)/ week
- CTRT: Concurrent Chemotherapy (CT) with RT
- 6DRT: 6 fractions of RT / week

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Patterns of Failure

Median FU: 95.9 months (IQR: 76.1-122.4 months)

Characteristics	5D RT arm (n=299)	CTRT arm (n=300)	6D RT arm (n=301)
Any recurrence	**135 (45.1%)**	**131 (43.7%)**	**140 (46.5%)**
Local Recurrence	46 (34.1%)	44 (33.6%)	51 (36.4%)
Regional Recurrence	24 (17.8%)	23 (17.6%)	27 (19.3%)
Locoregional Recurrence	19 (14.1%)	16 (12.2%)	20 (14.3%)
Locoregional +Distant Metastases	22 (16.2%)	34 (25.9%)	20 (14.3%)
Distant Metastases	24 (17.8%)	14 (10.7%)	22 (15.7%)

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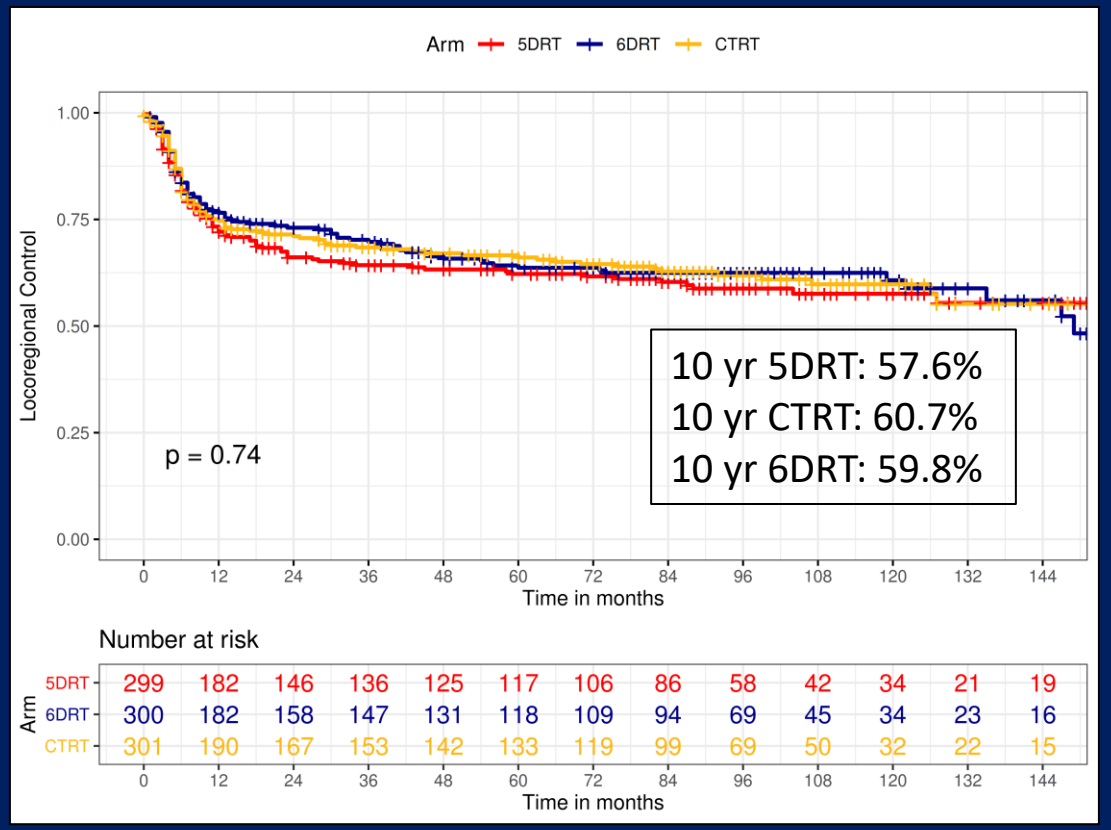
Overall Trial Population

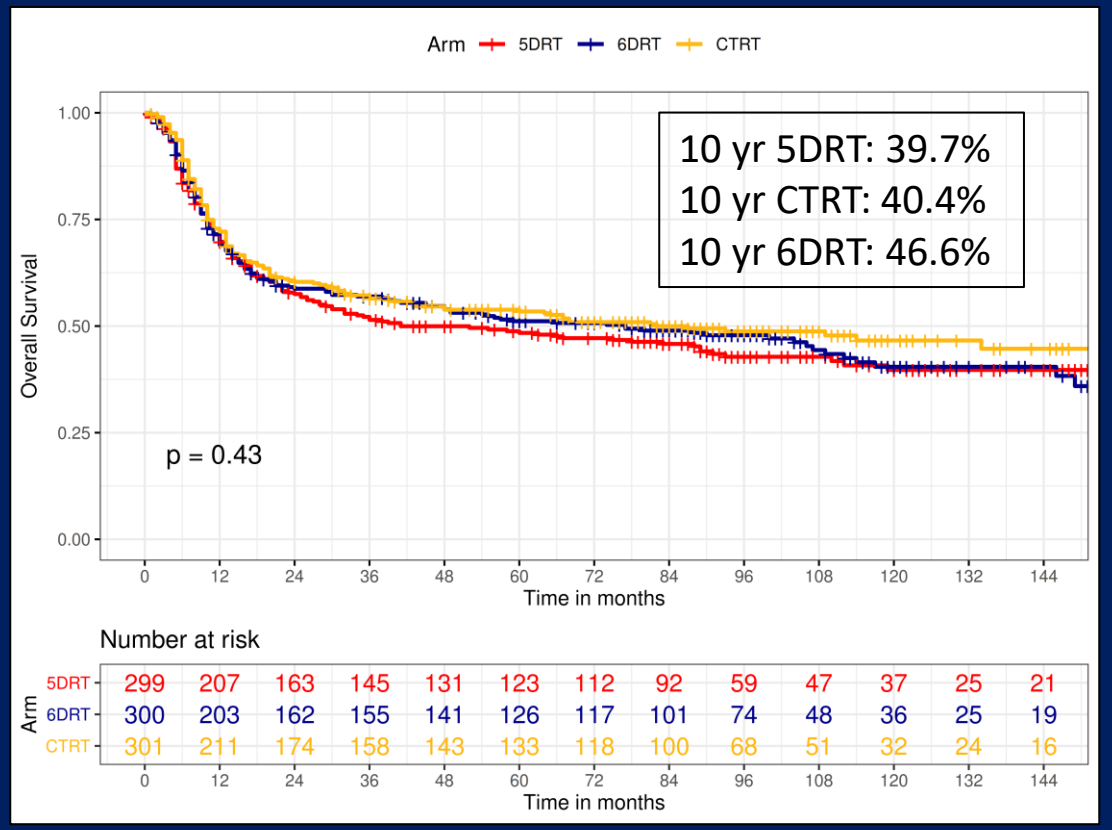
Locoregional Control



CTRT vs. 5DRT: p=0.49, HR=0.90 , 95% CI=0.69-1.19

6DRT vs.5DRT: p=0.53, HR=0.91, 95% CI=0.69-1.20

Overall Survival



CTRT vs. 5DRT: p= 0.63, HR=0.95, 95% CI=0.76-1.18

6DRT vs.5DRT: p=0.20,HR=0.86, 95% CI=0.69-1.08

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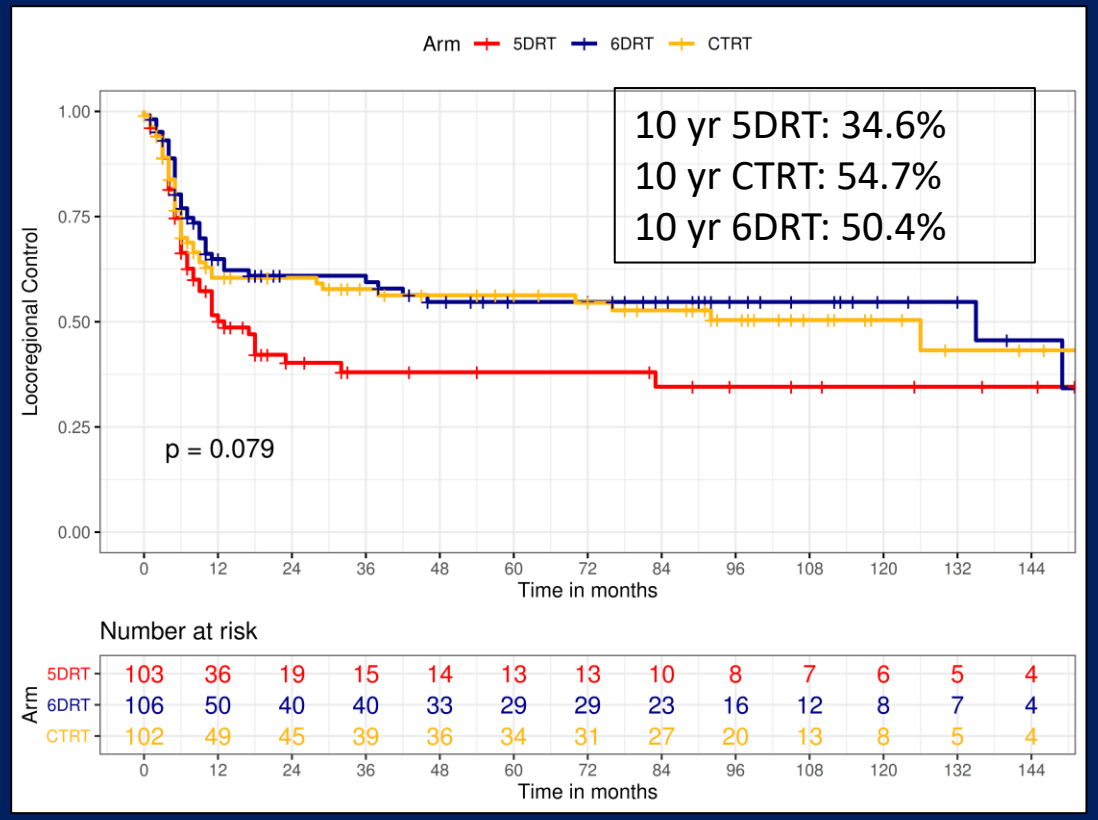
High Risk Group: T3-4+N2-3+ECE



CTRT vs. 5DRT :p=0.04,HR=0.64,95% CI=0.43-0.97
6DRT vs.5DRT :p=0.10,HR=0.84,95% CI=0.70-1.0

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Conclusions

- All Locally Advanced Oral Cavity Squamous Carcinoma are not High Risk
- With negative resection margins:
  Treatment intensification loses its impact

EXCEPT IN

- A high-risk group with a combination of T3/4, N2/3 with ENE.
- No difference in acute toxicity or compliance to RT between arms

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Conclusions

- Adjuvant radiotherapy: improves post-operative locoregional control in patients with early stage cancer in the presence of adverse features: PNI, Close margins, combination
- Post-operative chemoradiotherapy: superior locoregional control, progression-free survival, and in some studies, overall survival for high-risk patients with involved surgical margins as well as those with extranodal tumor spread
- Treatment intensification in the absence of above HR features should be weighed judiciously
- Post-operative radiotherapy treatment volumes: based on the risk of recurrence and clinically occult involvement of head and neck subsites and nodal regions

Postoperative Radiotherapy ± Cetuximab for Intermediate-Risk Head and Neck Cancer

Mitchell Machtay, MD[1]; Pedro A. Torres-Saavedra, PhD[2,3]; Wade Thorstad, MD[4]; Phuc Felix Nguyen-Tân, MD[5]; Lillian L. Siu, MD[6]; F. Christopher Holsinger, MD[7]; Adel El-Naggar, MD, PhD[8]; Christine Chung, MD[9]; Anthony Cmelak, MD[10]; Barbara Burtness, MD[11]; Greg Bednarz, PhD[12]; Harry Quon, MD[13]; Stephen L. Breen, PhD[14]; Clement K. Gwede, PhD, RN[9]; Adam P. Dicker, MD, PhD[15]; Min Yao, MD, PhD[1]; Richard C. Jordan, PhD, DDS[16]; Jennifer Dorth, MD[17]; Nancy Lee, MD[18]; Jason W. Chan, MD[19]; Neal Dunlap, MD[20]; Voichita Bar-Ad, MD[15]; William A. Stokes, MD[21]; Arnab Chakravarti, MD[22]; David Sher, MD[23]; Shyam Rao, MD, PhD[24]; Jonathan Harris, MS[3,25]; Sue S. Yom, MD, PhD[19]; and Quynh-Thu Le, MD[7]; on behalf of NRG Oncology RTOG 0920 Collaborating Team

- **Phase III**, multicenter, randomized controlled trial
- Planned accrual: ~700 patients.
- Enrolled: 702 (577 eligible for analysis).
- Accrual: 2009–2018.
- **Primary Endpoint: Overall survival (OS)**
- **Secondary Endpoints: Disease-free survival (DFS)**

Journal of Clinical Oncology Volume 43, Number 12 https://doi.org/10.1200/JCO-24-01829

Eligibility Criteria

- Inclusion criteria: Completely resected squamous cell carcinoma of the head and neck (oral cavity, oropha adjuvant radiotherapy.
- Patients had clear surgical margins an pathology.
- Pathologic Stage: Eligible tumors were nodal stage N0–N2, M0.
- **Intermediate-Risk" Features:** All patie warranting postoperative RT (but **not** mandate chemo).

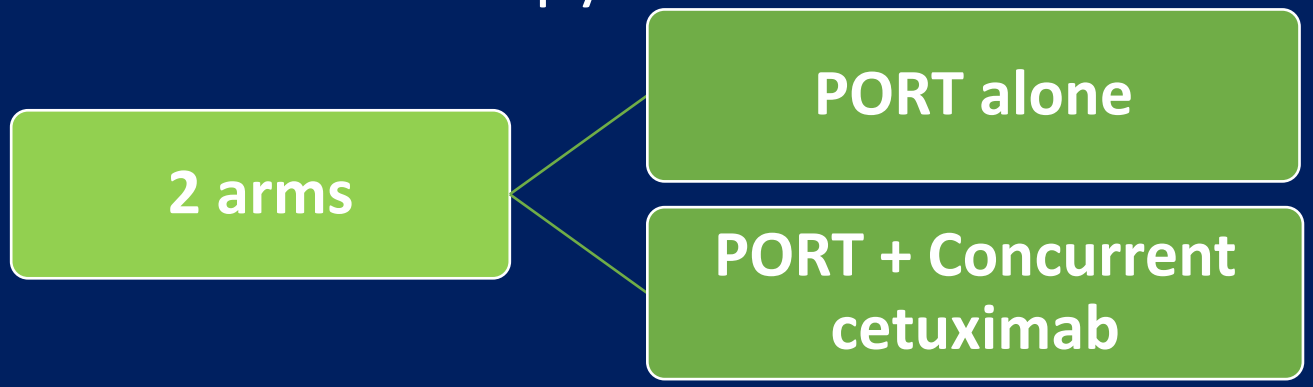
S.No	Intermediate risk factors
1	Perineural invasion
2	Lymphovascular invasion
3	Single lymph node > 3 cm or ≥ 2 lymph nodes (all < 6 cm) without ECE
4	Close surgical margins (cancer extending to within 5 mm of margin)
5	T3 or T4a primary tumor
6	T2 oral cavity cancer with DOI > 5 mm

Eligibility Criteria

- **Exclusion Criteria:**
- Patients with **positive margins** or **extracapsular spread (ENE)** were **excluded** (such patients fall into a high-risk category that typically receives cisplatin chemoradiation).
- Pts with Ca Hypopharynx and distant metastatic disease.

Trial Schema

- **Randomization:** After surgery, eligible patients were stratified and then randomized **1:1** to one of two postoperative treatment arms:
- **Arm 1 – IMRT Alone:** Adjuvant intensity-modulated radiotherapy **(IMRT)** to 60–66 Gy over ~6 weeks (2 Gy/fraction). No concurrent systemic therapy.
- **Arm 2 – IMRT + Cetuximab:** Adjuvant IMRT (60–66 Gy) *with concurrent **cetuximab*** therapy.



Results

- Enrolled **702 patients** for **screening**
- **577** were randomly assigned/**eligible**
- **287 in RT alone arm and 290 patients in RT + conc cetuximab arm**
- From **November 2009** to **March 2018**
- Most patients (**61.2%**) had pathologic stage **IVA** cancer
- Most (**63.6%**) had **oral cavity cancer**
- Most (**84.6%**) had **high EGFR expression**
- In the **HPV-negative** subgroup, **88.6%** had high EGFR expression compared with **71.2%** in the **HPV-positive** subgroup ($P < .0001$)

Outcomes

- At median 7.2-year follow-up
- cetuximab did not significantly impact OS in the overall cohort.
- **DFS** was significantly improved by adding cetuximab.

S.No	Outcome	RT + C	RT	P-value
1	5y-OS	76.5%	68.7%	0.07
2	5y-DFS	71.7%	63.6%	0.0168

Subgroup Finding

- **Subgroup Finding: T**he DFS benefit was **observed mainly in HPV-negative** patients (who comprised ~80% of the trial).
- In the smaller subset of HPV-positive oropharyngeal patients, adding cetuximab did not appear to improve outcomes (no significant benefit in that subgroup).
- This implies patient biology (HPV status) influenced efficacy.

Toxicities

- **Acute toxicities** were significantly higher with cetuximab.
- **No treatment-related deaths** (Grade 5 toxicity) occurred in either group.
- Patient-reported quality of life (QOL) analyses showed no persistent QOL detriment from cetuximab.

S.No	Toxicities	RT + C	RT	P-value
1	Acute Gr 3-4	70.3%	39.7%	<0.001
2	Late Gr ≥3	33.2%	29%	0.3101

Conclusion

- Given the lack of an OS improvement, postoperative RT alone remains the standard for most intermediate-risk patients. Unlike high-risk patients (who receive cisplatin chemoradiation per historic trials), those with intermediate-risk features are not routinely recommended to receive concurrent cetuximab – the trial did not establish it as a new standard of care.
- However, the positive DFS signal suggests that adding cetuximab may be considered on a case-by-case basis. Specifically, carefully selected HPV-negative patients with multiple adverse features (who have substantial recurrence risk) and who cannot receive cisplatin might benefit from RT+cetuximab

S.NO	Study	Results	
1.	EORTC 22931	PFS, OS better in CTRT arm with similar acute and late toxicities	Establised Margin status and ENE ad indications for CTRT
2.	RTOG 9501	DFS and LRC better in CTRT arm, No OS benefit	
3.	RTOG 0920	DFS benefit, No OS benefit	In Intermediate risk factors
4.	OCAT	**DFS** and **OS** benefit in intensification arms	High-Risk Profile subgroup (defined as T3–T4 + N2–N3 + ECE)
5	Trifiletti et al., 2017	OS benefit	Highest for pts with 2-4 LNs +
6	Zumsteg et al., 2019	OS benefit	Highest for pts with > 6 LNs
7	This Analysis	CTRT has Survival benefit, but more OCM	Pts with out ENE and Positive margins may benefit from CTRT

Adjuvant Radiotherapy in HN Cancers (HPV associated cancers)

PATHOS

- PATHOS - Post-operative Adjuvant Treatment for HPV-positive Tumors, a clinical study in head-and-neck.
- .Main Objective: PATHOS is designed to determine whether reducing the intensity of adjuvant therapy (less radiation and/or avoiding chemotherapy) after surgery can improve long-term swallowing function while maintaining excellent tumor control and survival outcomes.
- It aims to de-escalate treatment safely, minimizing side effects without compromising cure rates.

Study Design

- **multicenter Phase II/III randomized controlled trial** (adaptive design).
- Approximately **1,100 patients** with **HPV-positive OPSCC** (tumor stage T1–T3, N0–N2b under AJCC 7th edition) are enrolled
- All patients undergo **minimally invasive transoral surgery** (Transoral Robotic Surgery or laser microsurgery) plus neck dissection as initial treatment, prior to adjuvant therapy assignment.
- Eligible patients must have resectable disease and confirmed HPV-positive tumor status (p16 positive)

Risk Stratification

- After surgery, patients are stratified into three risk groups based on pathology:

Low-risk

no adverse features (clear margins, no extracapsular spread, etc.) –

no adjuvant therapy (observation only), per standard practice.

Intermediate-risk

close margins (1–5 mm), perineural or lymphovascular invasion (PNI/LVI), or

limited nodal involvement (e.g. N2a/N2b) –

randomized to either (~60 Gy, control) or (~50 Gy, Test)

High-risk

positive margin (<1 mm) or extranodal extension (ENE) in lymph nodes **randomized** to 60 Gy + concurrent cisplatin, control or 60 Gy without chemotherapy.

- End points
- The Phase II portion primarily evaluated **swallowing function at 1 year** post-treatment, measured by the MD Anderson Dysphagia Inventory (MDADI) patient-reported.
- The Phase III portion is powered as a **non-inferiority trial** for **overall survival** (OS) as the primary endpoint, with long-term **swallowing quality-of-life** (MDADI) as a co-primary endpoint.

- Results: Awaited

E 3311

- Use **Transoral Robotic Surgery (TORS) ± Neck Dissection** → guide **risk-adapted adjuvant therapy**.
- Phase II Randomized Trial (n ≈ 495 HPV+ OPC pts)
- Risk Stratification after Surgery:
- Low risk: Negative margins, N0–N1, no ENE → Observation only
- Intermediate risk: Close margins, ≤4 nodes, minimal ENE → Randomized Arm B: 50 Gy PORT, Arm C: 60 Gy PORT
- High risk: Positive margins, ENE >1 mm, ≥5 nodes → 66 Gy PORT + cisplatin
- Primary endpoint: 2-yr Progression-Free Survival (PFS)

Ferris et al, JCO, 2021

Results

- 2-yr PFS:
- Observation (low risk): ~96%
- 50 Gy PORT: ~95%; 60 Gy PORT: ~96%
- High-risk CRT: ~90%
- Functional outcomes: 50 Gy PORT had better swallowing/QoL vs 60 Gy.
- Conclusion: TORS + risk-adapted adjuvant therapy is safe.PORT dose reduction to 50 Gy in intermediate risk is effective & less toxic. Confirms de-escalation feasibility in HPV+ OPC.

Long-Term Follow-Up of E3311, an ECOG-ACRIN Cancer Research Group Phase II Trial of Transoral Surgery and Risk-Based Adjuvant Treatment in Human Papillomavirus–Initiated Oropharynx Cancer

Barbara Burtness, MD[1]; Yael Flamand, MS[2]; Harry Quon, MD[3]; Gregory S. Weinstein, MD[4]; Ranee Mehra, MD[5]; Joaquin J. Garcia, MD[6]; Seungwon Kim, MD[7]; Bert W. O'Malley Jr, MD[4,8]; Enver Ozer, MD[9]; Chukwuemeka Ikpeazu, MD, PhD[10]; Wayne M. Koch, MD[11]; Neil D. Gross, MD[12]; R. Bryan Bell, MD[13]; Mihir Patel, MD[14]; Miriam N. Lango, MD[12]; Luc G. Morris, MD[15]; Russell Smith, MD[16]; Daniel Karakla, MD[17]; Jeremy D. Richmon, MD[18]; Floyd C. Holsinger, MD[19]; and Robert L. Ferris, MD, PhD[20]

- First large cooperative group trial testing **deintensified PORT** strategies in surgically managed p16+ OPC
- Population: Resectable p16+ cT1–T2 OPC, AJCC 7th, no matted nodes.
- Sample size: 359 evaluable patients.
- Male predominance: 89%
- Primary site: Tonsil (66%), base of tongue (31%)
- Smoking: 70% ≤10 pack-years
- Stage: Mostly T1–T2; 84% N1 or N2b

DOI https://doi.org/10.1200/JCO-24-02550

Inclusion criteria

- Inclusion Criteria:
- Newly diagnosed, p16+ (HPV-associated) oropharyngeal squamous cell carcinoma (OPC).
- Tumor stage: T1–T2 (AJCC 7th edition).
- Nodal status: No matted neck nodes.
- Resectability: Tumors had to be resectable with transoral surgery (TOS) and neck dissection.
- Performance status: ECOG 0–1.
- Adequate organ function (labs within protocol-defined limits).
- No distant metastases (M0).

Exclusion criteria

- Step -1 - Before surgery
- Clinical T3 disease at baseline.
- N2c or N3 nodal stage at baseline.
- Matted nodes in the neck.
- Primary tumor not clinically measurable.
- Inadequate baseline work-up:
  - Required labs or scans not done within 4 weeks before registration.
  - Creatinine clearance < 60 mL/min.
  - Total bilirubin > ULN.
  - Missing baseline pathology report.

- Step - 2 - post-surgery, before risk assignment
- Surgery delayed > 4 weeks from Step 1 registration. Registration to Step 2 > 7 weeks aftersurgery.
- Incorrect risk assignment (misclassification by pathology).

Risk Stratification

- After TOS + neck dissection:
- Arm A (low-risk): Clear margins, 0–1 LN, no ENE → Observation
- Arm B (intermediate): 2–4 LN or ENE ≤1 mm → 50 Gy PORT
- Arm C (intermediate): 2–4 LN or ENE ≤1 mm → 60 Gy PORT
- Arm D (high-risk): >4 LN, >1 mm ENE, positive margin → 60–66 Gy + cisplatin
- Primary endpoints: Feasibility; 2-yr PFS in intermediate-risk group.

Key Outcomes

S.No	Outcomes	Overall	Arm A	Arm B	Arm C	Arm D
1	54-month PFS	90.6 %	93.2 % (but 4 recurrences, all N1)	94.9 %	90.2 %	85.5 %
2	54-month OS	95.3 %	97.1 %	97.9 %	95.1 %	92.5 %

No difference by **RT dose (50 vs 60 Gy)**, smoking history, or subsite

Conclusions & Implications

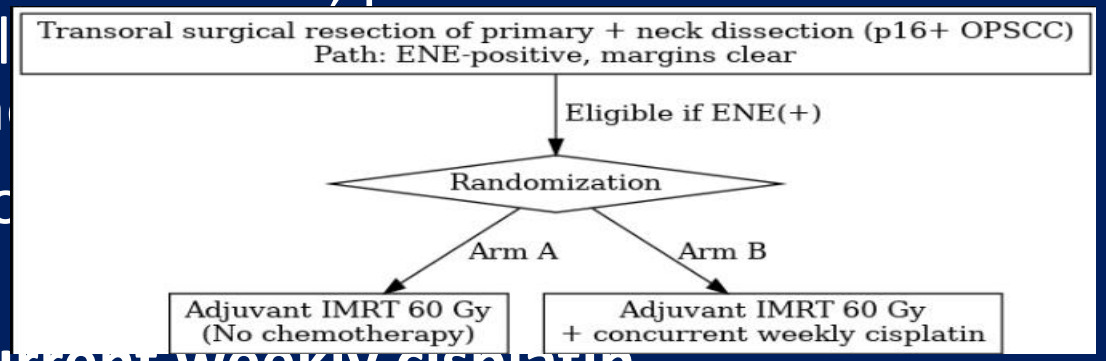
- TOS + risk-based adjuvant therapy is feasible in multicenter setting.
- Excellent long-term outcomes across risk groups.
- Dose de-escalation (50 Gy) safe for intermediate-risk patients.
- Observation safe in low-risk, but N1 subset may relapse late.
- Supports Phase III testing of surgical approach vs standard CRT.
- Potential practice-changing pathway for HPV+ OPC deintensification

ADEPT

- Adjuvant De-escalation, Extracapsular Spread, P16+, Transoral (ADEPT) Trial
- a Phase III study led by Washington Univ., examining reduced-intensity adjuvant therapy in HPV-positive oropharyngeal SCC.
- Objective: Test if radiotherapy (RT) alone after transoral surgery is non-inferior to standard cisplatin-based chemoradiotherapy (CRT) in p16+ OPSCC with extracapsular nodal extension (ENE)
- Primary endpoints: disease-free survival (DFS) and locoregional control (LRC)
- Rationale: HPV-positive oropharyngeal cancers have better prognosis and survivors suffer significant long-term toxicity from CRT.
- Standard adjuvant therapy adds cisplatin for ENE (high-risk feature) to improve control. However, retrospective data suggested no DFS benefit to chemo in HPV+ ENE patients (3-yr DFS ~91.8% with CRT vs 94.5% with RT alone, $p = 0.74$), providing a strong rationale to de-intensify adjuvant treatment in this setting.

Trial Design & Schema

- After transoral primary resection and neck dissection, patients with **HPV+ OPSCC** who had **ENE-positive** nodal
were **randomized** to two adjuvant treatm
- **Arm A:** Postoperative IMRT **60 Gy** to tumo
chemotherapy.
- **Arm B:** Postoperative IMRT **60 Gy + concurrent weekly cisplatin (40 mg/m²)**.
- Stratification was by T-stage (T1–2 vs T3–4) and smoking history (≤10 vs >10 pack-years).
- The trial was designed to enroll ~500 patients (1:1) to detect ≤5% DFS difference (powered for non-inferiority).



Inclusion & Exclusion Criteria

- **Inclusion:** Histologically confirmed **p16-positive OPSCC** of tonsil/base-of-tongue. Tumor stage T1–T4a, **resectable via transoral surgery** (TORS/TLM) with **negative margins** after resection.
- Pathologically **node-positive** disease with **extracapsular spread (ENE)** in ≥1 lymph node on final pathology.
- Age ≥ 21
- ECOG ≤ 2
- Adequate organ function to tolerate cisplatin (renal, hepatic, marrow parameters within normal limits).

- **Exclusion: Node-negative (pN0)** disease (no adjuvant therapy needed).
- **Distant metastases** at presentation.
- **Positive or close margins** or unresected residual disease after surgery (required re-resection – such patients not eligible for de-escalation).
- Patients who did not undergo TORS for T3–T4 tumors (open surgery cases) were excluded to ensure a uniform minimally-invasive cohort. No prior head/neck radiation or concurrent investigational therapy.
- No other active invasive malignancy (within 3 years) except non-melanoma skin cancer

Preliminary Results & Early Closure

- Enrollment & Early Closure: The trial accrued only 23 patients (20 randomized) from 2013–2019 and was terminated early in 2020 due to slow accrual and funding issues
- Planned accrual (~496) was not met, so no definitive conclusions could be drawn (study underpowered).
- No peer-reviewed publication ensued; results were posted in summary form.

- **Efficacy Outcomes:** With limited numbers and follow-up,
- **2-year locoregional control** and **overall survival** appeared **similar** between RT-alone vs CRT arms in preliminary analysis (no obvious LRC detriment without chemo in this small sample).
- However, a **trend toward lower 2-year DFS** (or progression-free survival) was observed in the **RT-alone arm** (~mid-80% range) compared to CRT (approaching ~95%).
- This aligns with other de-escalation data showing higher relapse rates when chemo is omitted in high-risk patients.

- **Toxicity:** As expected, **acute toxicity was lower with RT alone**. The RT-only group had markedly fewer ≥Grade 3 adverse events and feeding tube placements during treatment.
- Patients receiving RT-alone reported milder acute dysphagia and faster post-treatment quality-of-life recovery, whereas CRT patients experienced more significant mucositis, swallowing difficulty, and weight loss.
- **No unexpected safety concerns** were noted in either arm before closure.

Interpretation & Clinical Implications

- **Significance of Testing RT Alone in ENE(+) HPV+ Disease**
- ADEPT is the first randomized trial to directly challenge the necessity of chemotherapy for **ENE-positive** HPV-associated OPSCC, a subset traditionally managed with trimodality therapy.
- This test is pivotal because HPV+ patients generally have favorable tumor biology, raising the question of whether **cisplatin's added benefit (established in HPV– disease) applies equally to HPV+ tumors**

- The early halt (and similar trials' data) suggest caution in omitting chemotherapy for ENE-positive patients.
- While de-intensification succeeded for intermediate-risk, ENE-negative cases (e.g. E3311, SIRS showed excellent outcomes with lower RT doses alone), the high-risk ENE+ cohort appears to derive a tangible DFS benefit from chemotherapy.

MSKCC PROTOCOL: RO 30

Precision Radiotherapy: Reduction in Radiation for Oropharyngeal Cancer in the 30 ROC Trial

Nadeem Riaz, MD,[1,2,‡] Eric Sherman, MD,[3,‡] Xin Pei, PhD,[1,‡] Heiko Schöder, MD,[4] Milan Grkovski, PhD,[5] Ramesh Paudyal, PhD,[5] Nora Katabi, MD,[6] Pier Selenica, BSc,[6] Takafumi N. Yamaguchi, PhD,[7,8,9] Daniel Ma, MD,[10] Simon K. Lee, MSc,[6] Rachna Shah, BSc,[1] Rahul Kumar, PhD,[11] Fengshen Kuo, PhD,[2] Abhirami Ratnakumar, PhD,[1] Nathan Aleynick, BSc,[6] David Brown, PhD,[11] Zhigang Zhang, PhD,[12] Vaios Hatzoglou, MD,[4] Lydia Y. Liu, PhD,[7,8,9,13,14] Adriana Salcedo, PhD,[8,13] Chiaojung J. Tsai, MD,[1] Sean McBride, MD,[1] Luc G. T. Morris, MD,[2,15] Jay Boyle, MD,[15] Bhuvanesh Singh, MD, PhD,[15] Daniel S. Higginson, MD,[1] Rama R. Damerla, PhD,[1] Arnaud da Cruz Paula, BSc,[6] Katharine Price, MD,[16] Eric J. Moore, MD,[17] Joaquin J. Garcia, MD,[18] Robert Foote, MD,[10] Alan Ho, MD, PhD,[3] Richard J. Wong, MD,[15] Timothy A. Chan, MD, PhD,[1,2,19] Simon N. Powell, MD, PhD,[1] Paul C. Boutros, PhD,[7,8,9,13,20,21,22] John L. Humm, PhD,[5] Amita Shukla-Dave, PhD,[4,5] David Pfister, MD,[3] Jorge S. Reis-Filho, MD, PhD,[6,19,*] Nancy Lee, MD[1,*]

- **Phase II, prospective, single-institution trial** conducted at MSKCC.
- To determine whether **PET/MRI-guided adaptive de-escalation to 30 Gy chemoradiation** can safely maintain high cure rates in HPV+ OPSCC patients, while **significantly reducing treatment-related toxicity**.

Riaz N. *et al.* **Precision Radiotherapy: Reduction in Radiation for Oropharyngeal Cancer in the 30 ROC Trial**. *J. Natl. Cancer Inst.* 2021;113(6):742-751pubmed.ncbi.nlm.nih.govpmc.ncbi.nlm.nih.gov. (Primary publication of 30 ROC trial results)

Clinical Background & Rationale for De-escalation

- HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) has a distinct biology and affects younger patients, often with few comorbidities.
- Crucially, HPV-related OPSCC carries an **excellent prognosis** under standard therapy. However, conventional chemoradiotherapy (70 Gy with concurrent cisplatin) can cause **significant acute and long-term toxicities**.
- The **rationale for de-escalation** is to maintain the high cure rates while reducing treatment intensity and side effects.

- Laboratory and clinical evidence suggest HPV-associated tumors are more radiosensitive (due in part to HPV oncoproteins like E7 impairing DNA repair), raising the possibility that **lower radiation doses** could suffice for cure.

- This has spurred trials to **“de-intensify”** therapy in favorable HPV-positive OPSCC, using biomarkers to select patients who might be safely treated with reduced radiation dose while preserving excellent oncologic outcomes.

30 ROC Trial – Hypothesis

- Functional imaging could identify patients whose tumors are so responsive that **30 Gy** of chemoradiation would be sufficient for cure In other words, using an **adaptive approach** guided by intra-treatment imaging (tumor hypoxia on PET), one could select patients for a ~60% dose reduction (70→30 Gy) without compromising outcomes.

- **Design: Phase II, prospective, single-institution trial** conducted at MSKCC.
- Sample size: 19
- Time Period: 2015–2016.
- Eligibility criteria:

➢Newly diagnosed, untreated, histologically confirmed HPV-positive oropharyngeal squamous cell carcinoma (OPSCC).

➢Stage: AJCC 8th edition stage I–II, non-bulky disease.

➢ECOG performance 0–1.

➢No prior head & neck RT, no metastasis.

- Imaging Assessment:

➢Pretreatment 18F-FMISO PET (to detect hypoxia).

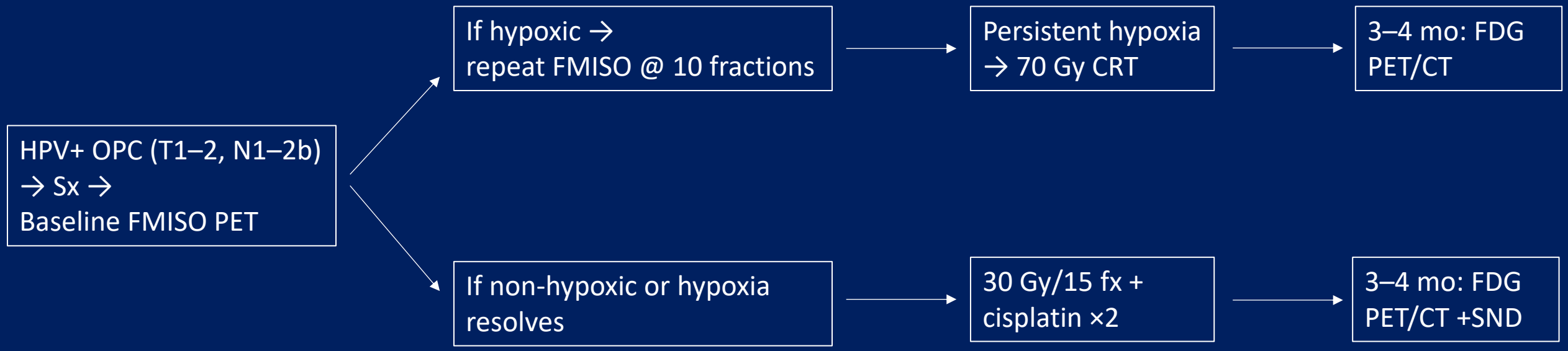
➢Intratreatment FMISO PET after ~10 fractions (20 Gy) of RT. Multiparametric MRI used as a correlative imaging biomarker.

- Adaptive Randomization Based on Hypoxia:

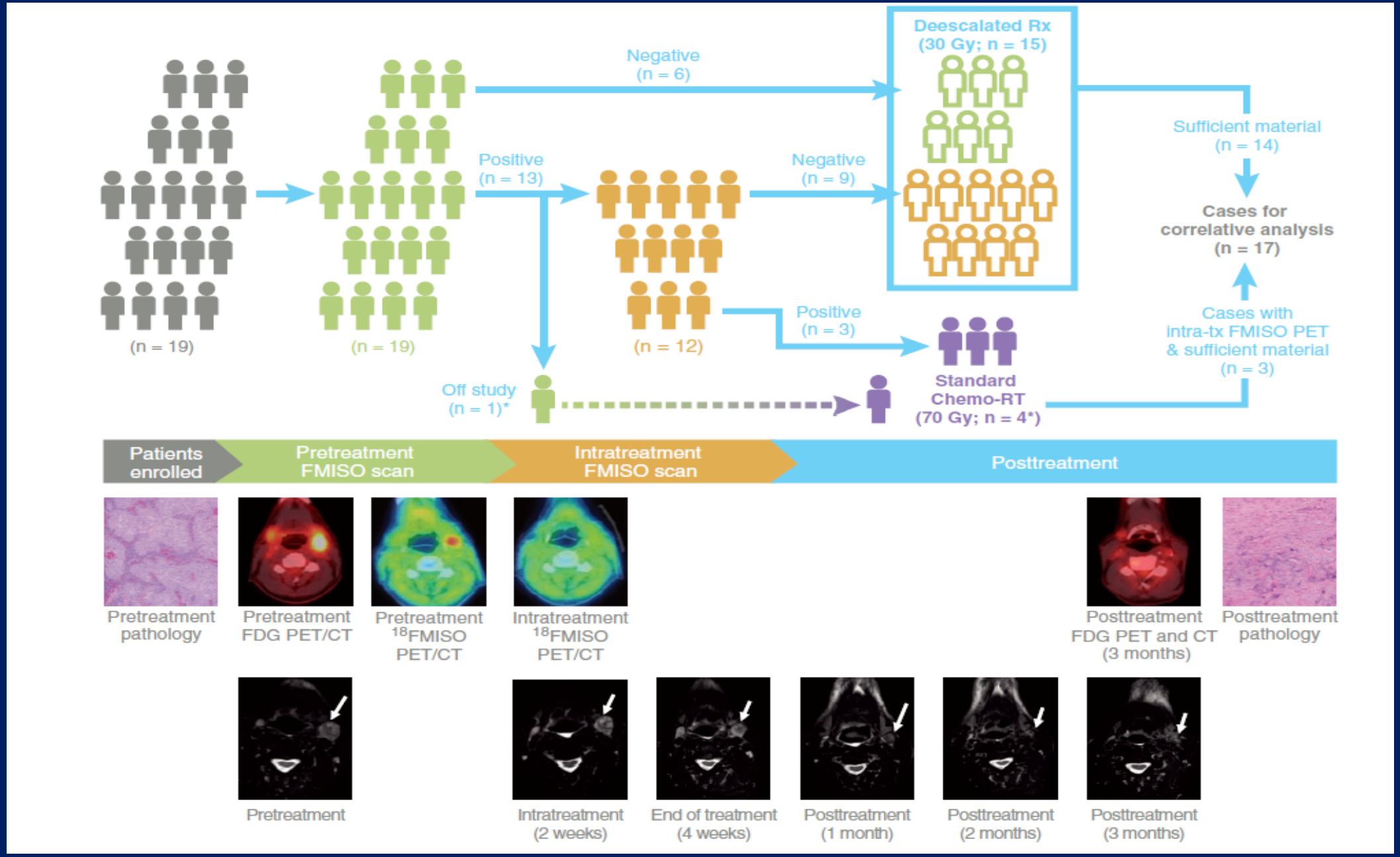
➢No hypoxia at baseline OR resolution of hypoxia at fraction 10 → De-escalated RT: 30 Gy in 15 fractions + concurrent chemotherapy.

➢Persistent hypoxia at fraction 10 → Standard RT: 70 Gy in 35 fractions + concurrent chemotherapy.

Trial Schema



- **Primary Endpoint**:
  - **Pathological complete response (pCR)** at resection or radiographic/metabolic complete response if no surgery.
- **Secondary Endpoints**:
  - **Locoregional control (LRC)**
  - **Overall survival (OS)**
  - **Acute and late toxicities**
  - **Quality of life (QOL)**
  - **Correlative imaging and genomic biomarkers** (DNA repair defects, immune signatures).


Deescalated Rx
(30 Gy; n = 15)
Negative
(n = 6)
Positive
(n = 13)
Negative
(n = 9)
Positive
(n = 3)
Off study
(n = 1)*
Standard
Chemo-RT
(70 Gy; n = 4*)
Sufficient material
(n = 14)
Cases for
correlative analysis
(n = 17)
Cases with
intra-tx FMISO PET
& sufficient material
(n = 3)
(n = 19)
(n = 19)
(n = 12)
Patients enrolled
Pretreatment FMISO scan
Intratreatment FMISO scan
Posttreatment
Pretreatment pathology
Pretreatment FDG PET/CT
Pretreatment 18FMISO PET/CT
Intratreatment 18FMISO PET/CT
Posttreatment FDG PET and CT (3 months)
Posttreatment pathology
Pretreatment
Intratreatment (2 weeks)
End of treatment (4 weeks)
Posttreatment (1 month)
Posttreatment (2 months)
Posttreatment (3 months)

Treatment Details

- **De-escalation arm (30 Gy): 30 Gy** in 15 daily fractions over 3 weeks.
- Covering the postop primary tumor bed, gross nodal disease, and all at-risk regional nodal level
- Concurrent chemotherapy was given to enhance radiosensitivity: cisplatin 100 mg/m² IV on days 1 and 22 (two cycles during the 3-week RT)
- Patients ineligible for cisplatin received carboplatin (AUC 5) plus 5-fluorouracil (2400 mg/m² over 4 days), also administered on days 1 and 22 (no chemotherapy dose reductions were allowed)

- **Standard arm (70 Gy): 70 Gy** in 35 fractions over 7 weeks
- covering gross disease and elective volumes per usual practice.
- concurrent cisplatin schedule (100 mg/m² every 3 weeks, for 3 cycles)

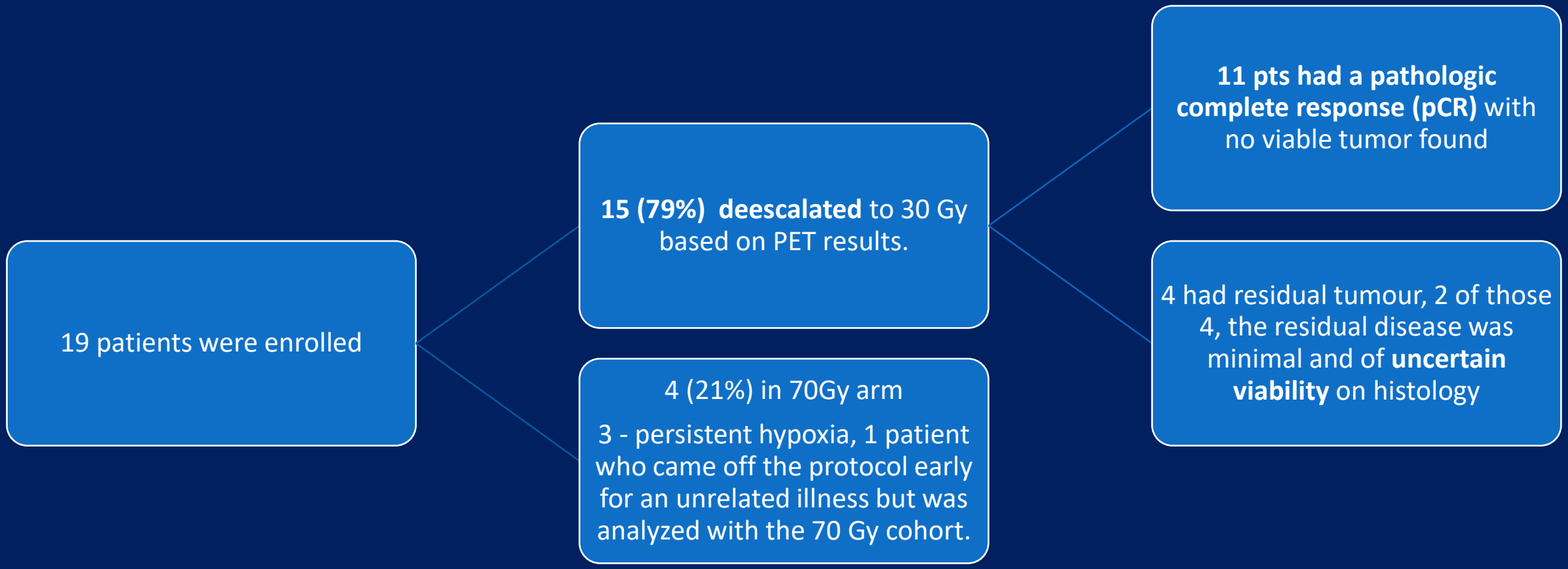
There was no randomization between 30 Gy vs 70 Gy; **treatment allocation was biologically determined** by the PET results.

Patient Characteristics

Table 1. Patient characteristics (n = 19)[a]

Characteristic	No. (%)
Sex	
Male	16 (84.2)
Female	3 (15.8)
Age, median (range), y	57 (44-70)
Smoking	
Never	11 (57.9)
<10 pack-years	6 (31.6)
>10 pack-years	2 (10.5)
Primary site	
Tonsil	11 (57.9)
Base of tongue	5 (26.3)
Unknown primary	3 (15.8)
T class	
1	11 (57.9)
2	5 (26.3)
X	3 (15.8)
N class	
1	5 (26.3)
2a	3 (15.8)
2b	11 (57.9)
Stage	
III	5 (26.3)
IVa	14 (73.7)

RESULTS



Only 1 patient in the de-escalation arm had a in-field failure, It was noted this patient deviated from protocol—suggesting some compliance or treatment issue

Outcomes

- At a median follow-up of ~34 months
- **2y LRC (30Gy protocol): 100%, 2y LRC (whole cohort): 94.4 % (including 1 protocol deviated pt)**
- **2y OS: 94.7%**
- 2y DFS: 100%.
- **2y PFS:** 89–93%.
- These high survival rates reflect both the favorable biology of HPV-associated cancer and the effectiveness of therapy even at the reduced dose.

Acute Toxicity

Toxicity	CTCAE v4.0 toxicity, No. (%)			
	0	1	2	3-5
Mucositis	5 (33.3)	8 (53.3)	2 (13.3)	0
Dysphagia	4 (26.6)	10 (66.6)	1 (6.6)	0
Dermatitis	3 (20.0)	12 (80.0)	0	0

[a]CTCAE = Common Terminology Criteria for Adverse Events.

- **No acute Grade ≥3 radiation toxicities** were observed in de-escalated patients. **0% experienced Grade 3 mucositis, dysphagia, or dermatitis** in the 30 Gy cohort.
- **mucositis was mostly Grade 1–2** (mild to moderate) in the 30 Gy group. Average **weight loss during therapy was only 4.3%** of body weight.
- **No patient required a feeding tube** for nutritional support– a remarkable outcome given that 20–30% of patients need PEG tubes with standard chemoradiation.
- Patients generally managed oral intake throughout the 3-week regimen, owing to the milder mucosal injury from halved radiation dose.

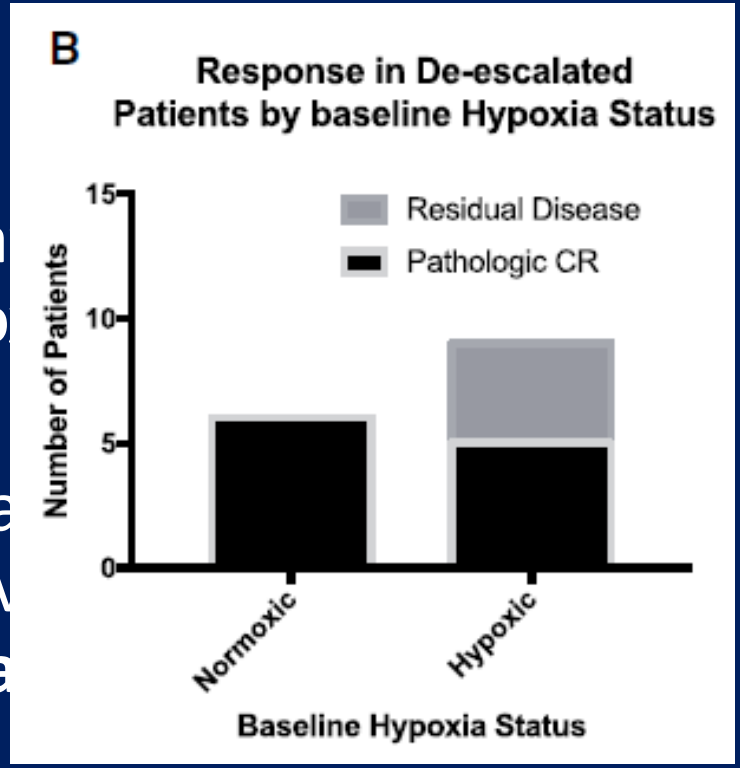
Quality of Life Outcomes

- **swallowing function was largely preserved** with de-escalation.
- some dryness of mouth did occur, but to a lesser degree than expected with full-dose RT, and there was partial recovery over time.
- Importantly, these de-escalated patients avoided many of the chronic issues like feeding tube dependence and severe swallowing dysfunction that can plague survivors of 70 Gy treatment

S.No		At 4m post therapy	At 2y post therapy
1	Dysphagia (MDADI)	6.6 point drop from pre treatment	2.8 point drop from pre treatment
2	Xerostomia	18.6 point increase	12.3 point increase

Correlative Imaging Findings (PET/MRI Biomarkers)

- **Baseline hypoxia PET:**
- All 6 patients with **no uptake on baseline FMISO** achieved a pathologic complete response (pCR) a rate), whereas 4 of 9 patients with **baseline hypo** disease.
- Thus, absence of hypoxia upfront strongly associa Baseline PET hypoxia was not statistically definitiv N), but the trend suggests **pretreatment oxygena influences outcome**.



Study Limitations

- Small sample size
- Single-arm design
- Surgery as part of protocol
- Follow-up duration
- Specialized imaging and logistics
- Chemotherapy differences

Clinical Implications

- Demonstration of Feasibility
- Patient Quality of Life
- Biomarker-Driven Treatment
- Reduction of Healthcare Costs and Burden
- Biology as a Therapeutic Guide

Summary

if the 30 Gy approach is confirmed in larger trials, the **clinical practice for HPV-associated oropharyngeal cancer could shift** from a maximal treatment for all to a **risk-adapted strategy**.

Many patients might be cured with much less treatment (and toxicity) – a win for patients' survival *and* quality of survivorship.

The trial's success lays the groundwork for future treatment paradigms where **"less can be more,"** using precision tools to maintain efficacy while sparing patients unnecessary harm.

THANK YOU

QUESTIONS??????