Laryngeal Preservation Therapy for Laryngeal Cancer

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Midwest Radiation Oncology Symposium 8/18/2023

No conflict of interest to disclose

University of Nebraska Medical Center

Objectives:

- Discuss the role of radiation therapy in management laryngeal cancer
- Discuss the challenges in selecting the appropriate patients for laryngeal preservation
- Discuss LPT; QOL, and new clinical trials

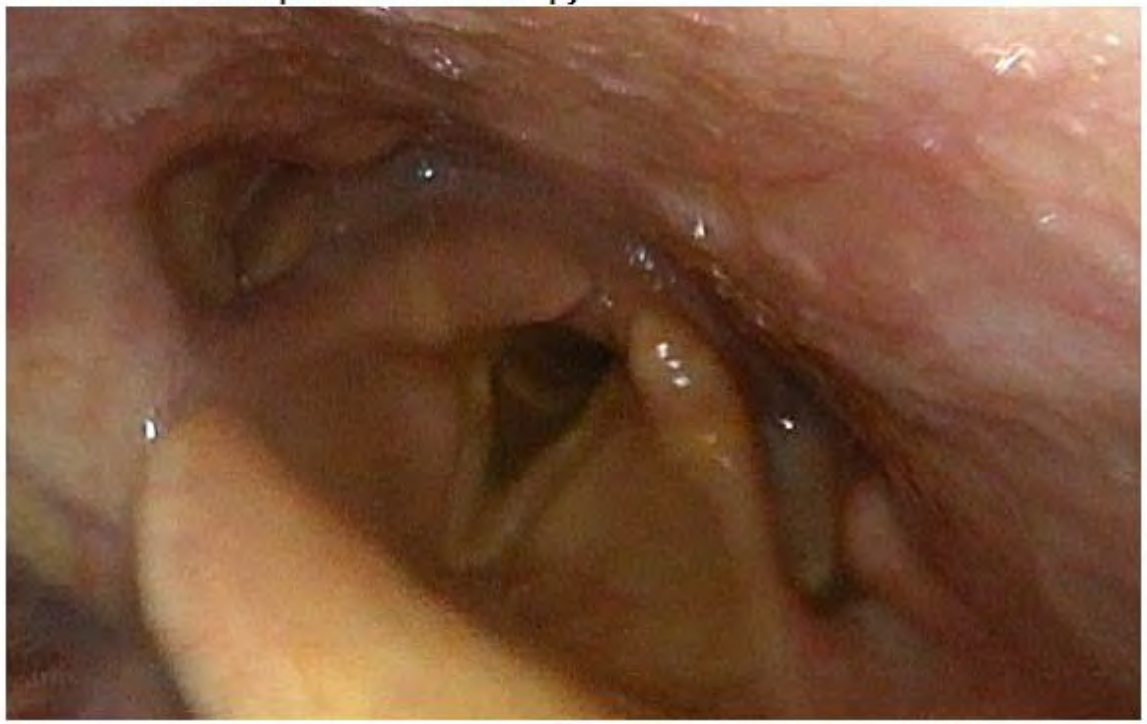
Laryngeal Cancer Treatment Approaches

Stage	Treatment options
T1/T2 and N0/N1	Surgery Definitive radiotherapy
T3/T4 or N2/N3	Combined Modality Surgery, RT, CT
Recurrent or M1	Combined modality Or palliative therapy CT, CT/IO, IO

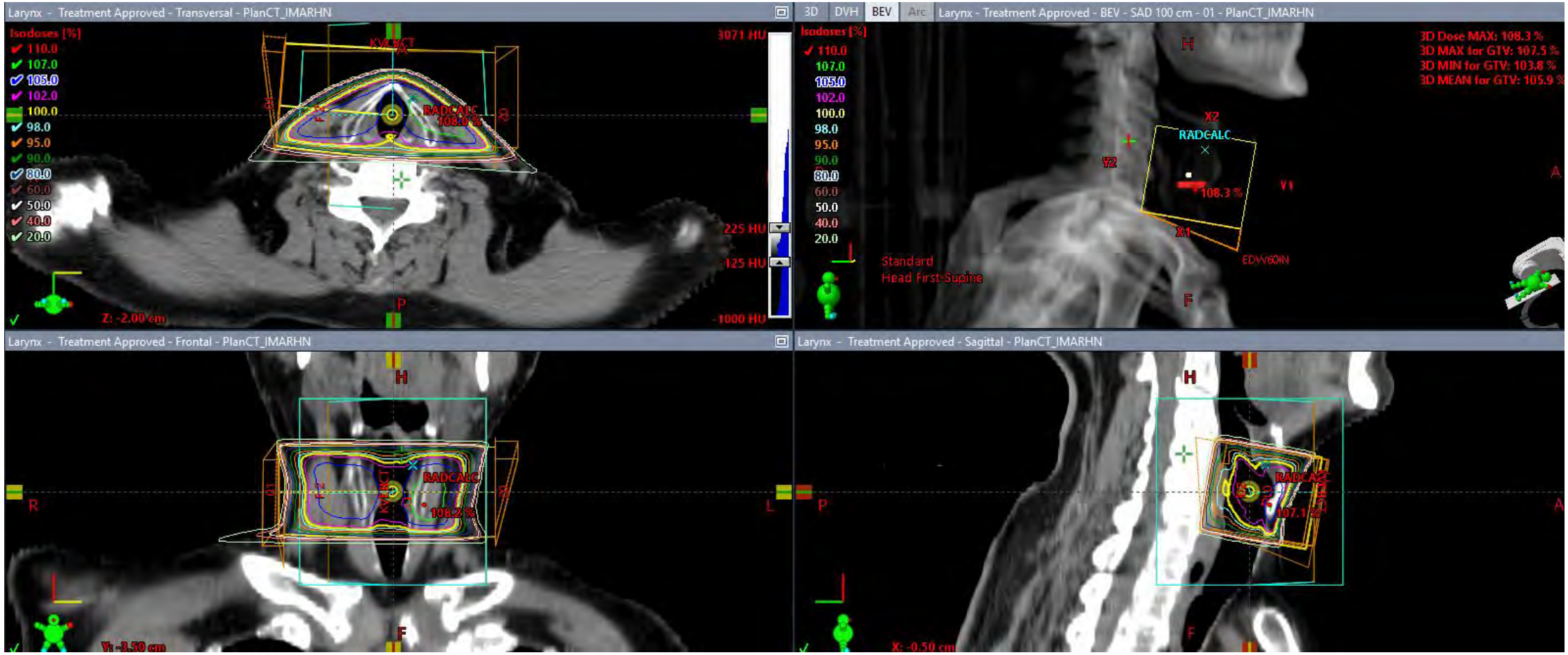
An 85 y.o. male with progressive hoarseness is diagnosed with a moderately differentiated SCC involving the left vocal fold and anterior commissure. Received 63Gyin 28 fractions

Image prior to the radiation therapy

8/19/2020 9 months post radiation therapy



Radiation for T1 Glottic Larynx Cancer



ELSEVIER

International Journal of Radiation Oncology*Biology*Physics

Volume 90, Issue 2, 1 October 2014, Pages 255-260

Clinical Investigation

Voice Quality After Treatment of Early Vocal Cord Cancer: A Randomized Trial Comparing Laser Surgery With Radiation Therapy

Leena-Maija Aaltonen MD, PhD [*], Noora Rautiainen MA [†], Jaana Sellman PhD [†], Kauko Saarilahti MD, PhD [‡], Antti Mäkitie MD [*], Heikki Rihkanen MD, PhD [*], Jussi Laranne MD, PhD [§], Leenamaija Kleemola MD, PhD [§], Tuija Wigren MD, PhD [‖], Eeva Sala MD, PhD [¶], Paula Lindholm MD, PhD [#], Reidar Grenman MD [¶], Heikki Joensuu MD [‡]

Table2. Expert-rated voice quality

Measurement	Transoral laser surgery				Radiation therapy				
	Baseline	6 months	24months	P*	Baseline	6 months	24months	P*	P†
Grade	1.61 (0.94)	1.78 (0.16)	1.61 (0.17)	.537	1.44 (0.92)	1.56 (0.18)	1.39 (0.19)	.614	.967
Roughness	1.30 (0.88)	1.13 (0.92)	1.26 (0.86)	.699	1.22 (0,73)	1.56 (0.92)	1.39 (0.61)	.284	.248
Breathiness	1.35 (0.89)	1.48 (0.90)	1.52 (0.95)	.617	1.17 (0.79)	0.44 (0.62)	0.28 (0.58)	<.001	<.001
Asthenia	0.61 (0.66)	0.75 (0.68)	0.74 (0.69)	.599	0.56 (0.51)	0.06 (0.24)	0.11 (0.32)	.001	.003
Strain	0.96 (0.71)	0.83 (0.72)	0.78 (0.80)	.532	0.83 (0.92)	0.89 (0.68)	1.06 (0.80)	.498	.288

Table 3. Self-rated voice quality

Measurement	Transoral laser surgery				Radiation therapy				
	Baseline	6 months	24 months	P*	Baseline	6 months	24 months	P*	P†
Hoarseness	59.0 (19,0)	50.7 (28.9)	43.1 (27.1)	.040	53.1 (22.0)	34.1 (24.3)	35.4 (26.7)	.026	.144
Impact on everyday life	44.6 (26.5)	31.4 (25.9)	32.4 (25.3)	.089	32.1 (25.7)	14.4 (18.8)	8.40 (9.3)	.001	.007

The data are mean values (standard deviations) evaluated on a visual analogue scale (VAS) scored from 0 to 100. The higher scores indicate worse subjective impression of the quality of voice. The baseline VAS was missing from 5 patients in the laser surgery group and from 1 patient in the radiation therapy group, and the 6-month sample from 7 and 3 patients, and the 24-month sample from 6 and 8 patients, respectively.

In conclusion:

- Radiation therapy results in less breathy voice than TLS, but the overall voice quality is similar.
- Radiation therapy may be the treatment of choice when the requirements for the voice quality are demanding.
- An anterior tumor location in the vocal cord is associated with a breathy voice when cancer is treated with TLS.
- TLS has the advantage of being completed within 1 day, which may also influence patient preference.
- A larger study is warranted to compare the effects on survival.

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Volume 90, Issue 2, 1 October 2014, Pages 255-260

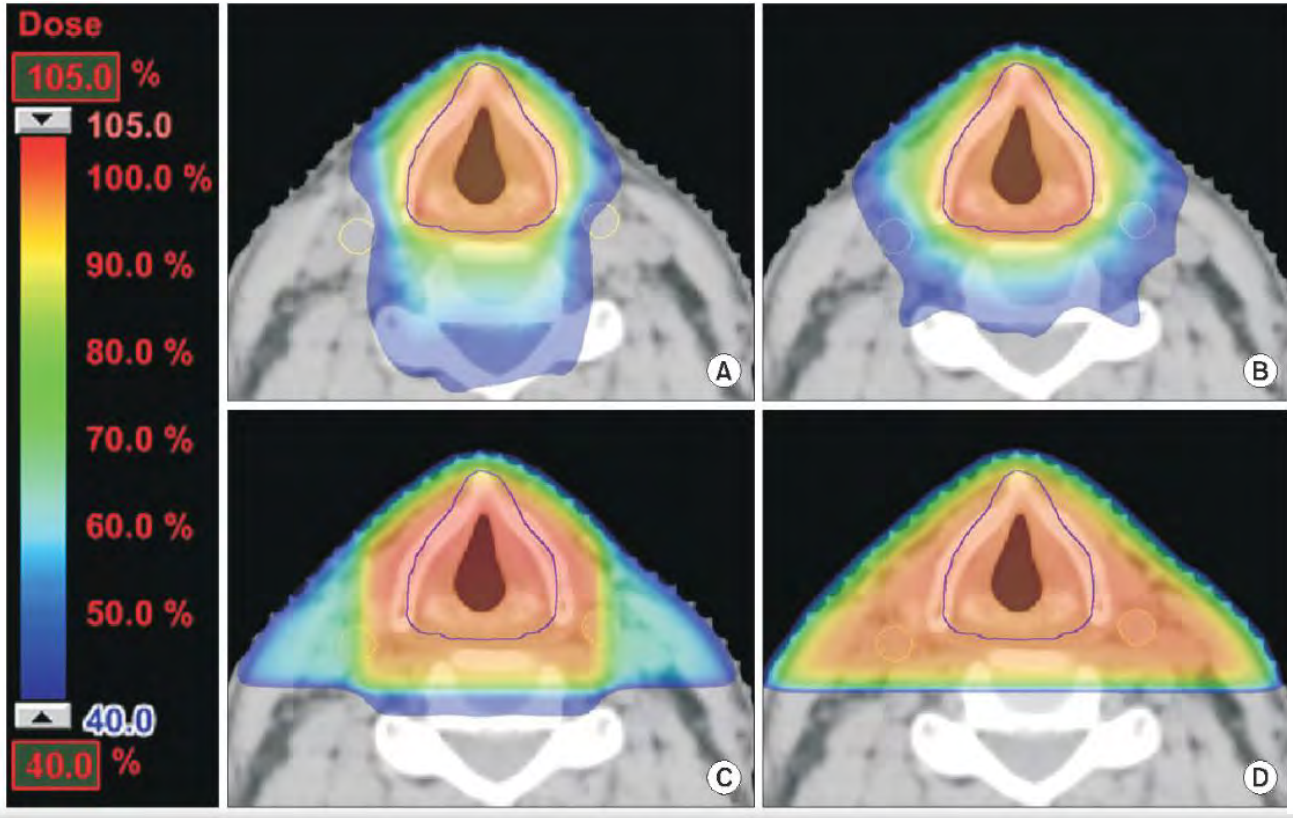
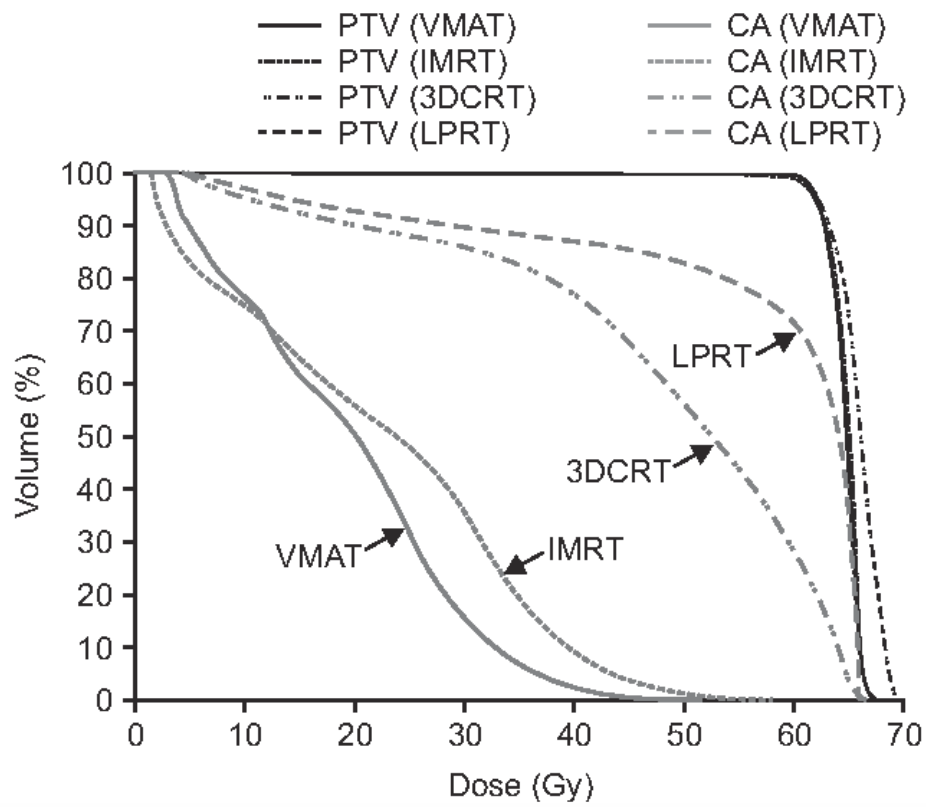


Fig. 2. Isodose curves on an axial slice for a representative case planned with (A) volumetric modulated arc therapy, (B) intensitymodulated radiotherapy, (C) 3-dimensional conformal radiotherapy, and (D) lateral parallel-opposed photon field radiotherapy. The carotid arteries were delineated in yellow line. Collapse



Pushing dose to the spinal cord

Published in Radiation Oncology Journal 2016

Volumetric modulated arc therapy for carotid sparing in the management of early glottic cancer

Young Suk Kim, Jaegi Lee, Jong In Park, W. Sung, S. Lee, G. Kim

Published in final edited form as:
Laryngoscope. 2020 January ; 130(1): 146–153. doi:10.1002/lary.27873.

Outcomes of Carotid-Sparing IMRT for T1 Glottic Cancer: Comparison with Conventional Radiation

Multidisciplinary Larynx Cancer Working Group[‡]

Abstract

Objectives—We aim to report oncologic outcomes after conventional radiotherapy (ConRT) using opposed lateral beams and intensity modulated radiation therapy (IMRT) for T1N0 glottic squamous cell carcinoma.

Study design—Retrospective case-control study.

Methods—We retrospectively reviewed demographic, disease, and treatment characteristics for patients treated at our institution during 2000–2013.

- The CTV encompassed the entire thyroid and cricoid cartilages with the anterior margin covering the thyroid cartilage with up to a 5-mm margin and the posterior margin covering the posterior limit of the thyroid and cricoid cartilages.

- Organs at risk included the spinal cord with maximum dose < 20 Gy, the parotid gland with mean dose < 26 Gy, the submandibular gland with mean dose < 40 Gy, the mandible with maximum dose < 60 Gy, as well as the right and left carotid arteries.

- Pushing the dose to carotids as low as possible but with no specific constraints because of the lack of well-defined dose thresholds associated with carotid toxicity

Patients, disease and treatment characteristics.

Characteristic	ConRT (n=153) (%)	IMRT (n=62) (%)	Significance
Sex			
Female	24 (16)	5 (8)	p = 0.1
Male	129 (84)	57 (92)	
Ethnicity			
Black/African-American	13 (8)	5 (8)	p = 0.3
Hispanic/Latino	27 (18)	7 (11)	
White	108 (71)	45 (73)	
Other/unspecified	5 (3)	5 (8)	
Age			
<60 years	53 (35)	27 (44)	p = 0.2
>60 years	100 (65)	35 (56)	
Pathologic grade			
Well differentiated	37 (24)	12 (19)	p = 0.8
Moderately differentiated	69 (45)	33 (53)	
Poorly differentiated	8 (5)	3 (5)	
Unknown/unspecified	39 (26)	14 (23)	
Smoking history at diagnosis			
None	22 (14)	19 (31)	p = 0.01
Positive	131 (86)	43 (69)	
T stage			
T1a	107 (70)	47 (76)	p= 0.4
T1b	46 (30)	15 (24)	
Radiation beam energy			
6 MV	66 (43)	62 (100)	p < .0001
^{60}Co	87 (57)	0 (0)	
Mean ± SD total radiation dose (Gy)	64.1 ± 3.4	64.3 ± 2.1	p = 0.4
Mean ± SD no. of fractions received	30.2 ± 3.0	29.7 ± 2.4	p = 0.3
Mean ± SD BED (2GyE)	77.9 ± 3.9	78.4 ± 2.1	p = 0.9

The median follow-up for all patients was 68 months (range 3–172). The median follow up for the ConRT cohort was 81.5 months (range 3–172) while median follow up for the IMRT cohort was 39.0 months (range 9–103).

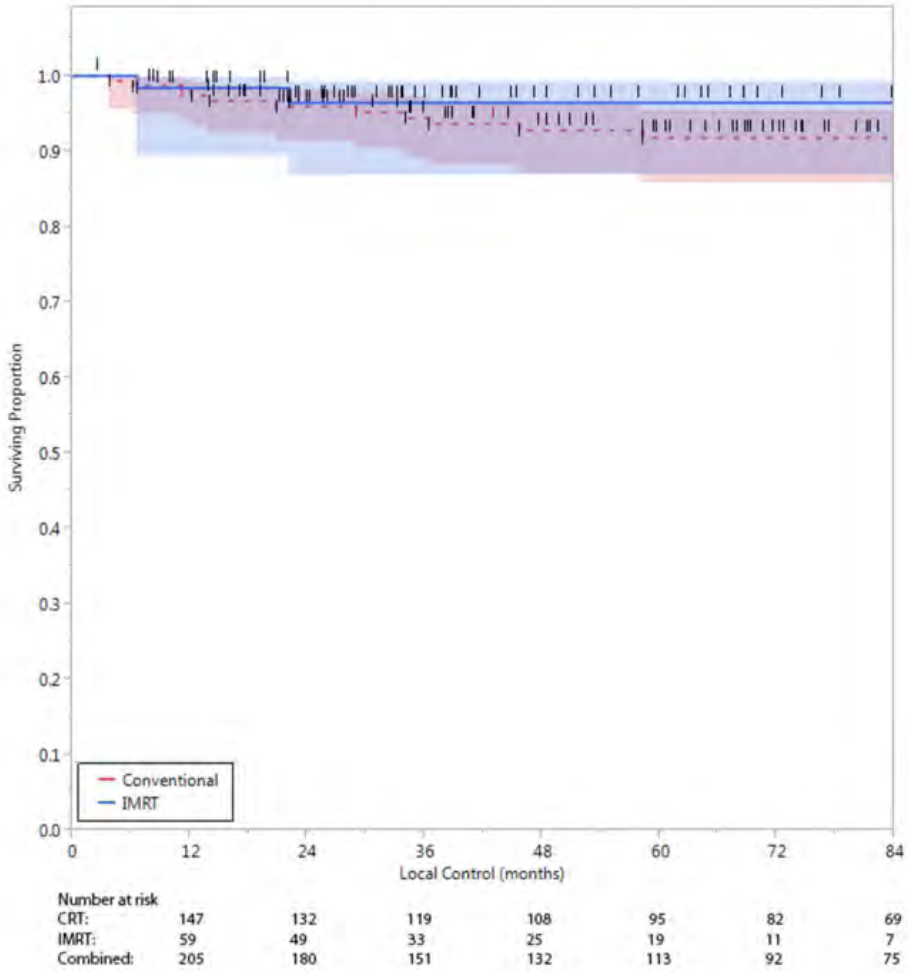
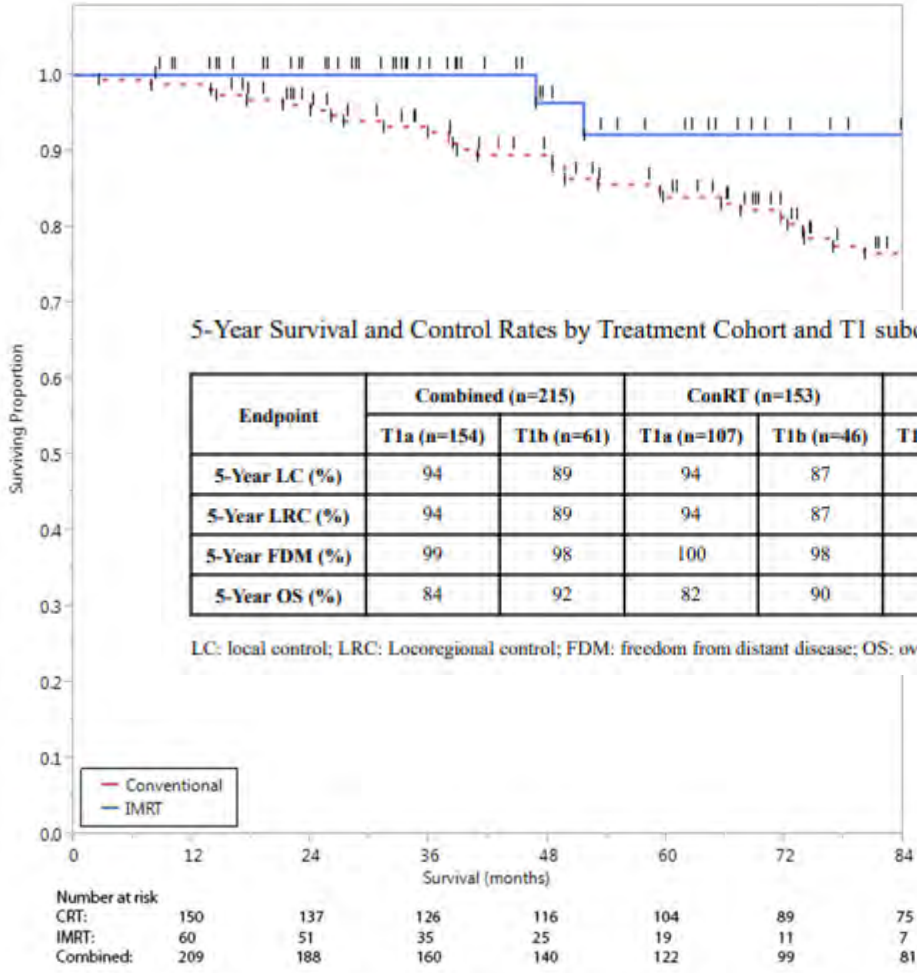


Figure 1:
Kaplan Meier Curves showing the Local Control for Conventional vs. IMRT Cohorts through 84 months. Shaded areas denote 95% confidence intervals.



5-Year Survival and Control Rates by Treatment Cohort and T1 subcategory.

Endpoint	Combined (n=215)		ConRT (n=153)		IMRT (n=62)	
	T1a (n=154)	T1b (n=61)	T1a (n=107)	T1b (n=46)	T1a (n=47)	T1b (n=15)
5-Year LC (%)	94	89	94	87	95	100
5-Year LRC (%)	94	89	94	87	95	100
5-Year FDM (%)	99	98	100	98	96	100
5-Year OS (%)	84	92	82	90	90	100

LC: local control; LRC: Locoregional control; FDM: freedom from distant disease; OS: overall survival.

Figure 2:
Kaplan Meier Curves showing the Overall Survival for Conventional vs. IMRT Cohorts through 84 months.

Post-RT cerebrovascular events occurred in 4 patients in the ConRT cohort (3%) (two within 3-years post-RT and two late after 5-years) while none of the patients in the IMRT cohort suffered any post-RT cerebrovascular events (p=0.7)

Locally Advanced Laryngeal Cancer

Laryngeal Cancer Treatment Approaches

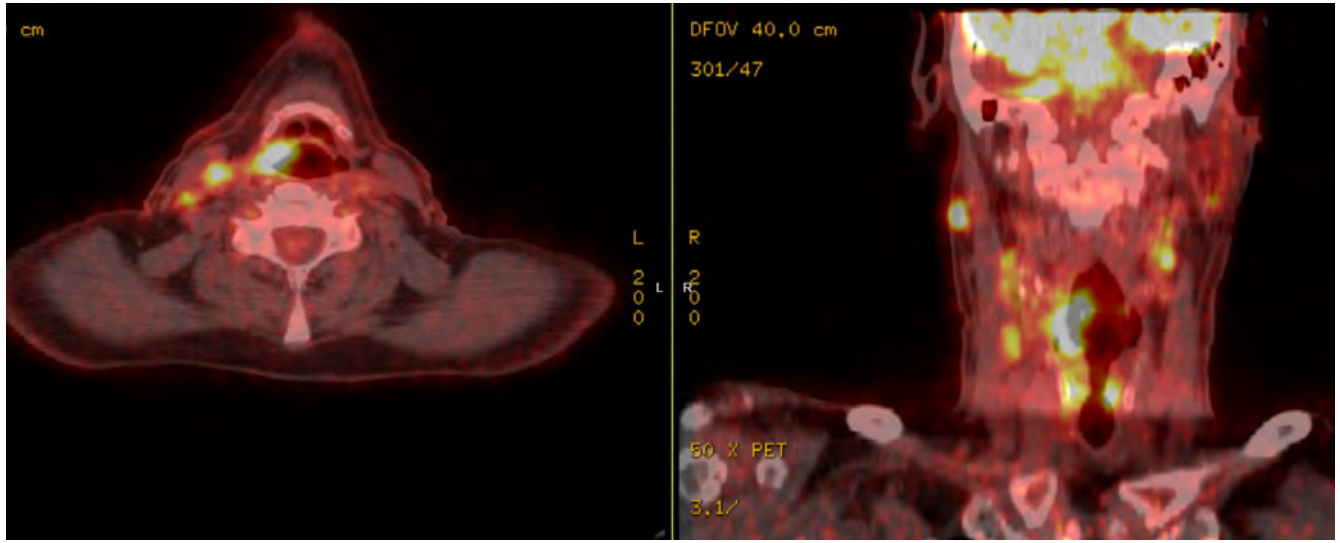
Stage	Treatment options
T1/T2 and N0/N1	Surgery Definitive radiotherapy
T3/T4 or N2/N3	Combined Modality Surgery, RT, CT
Recurrent or M1	Combined modality Or palliative therapy CT, CT/IO, IO

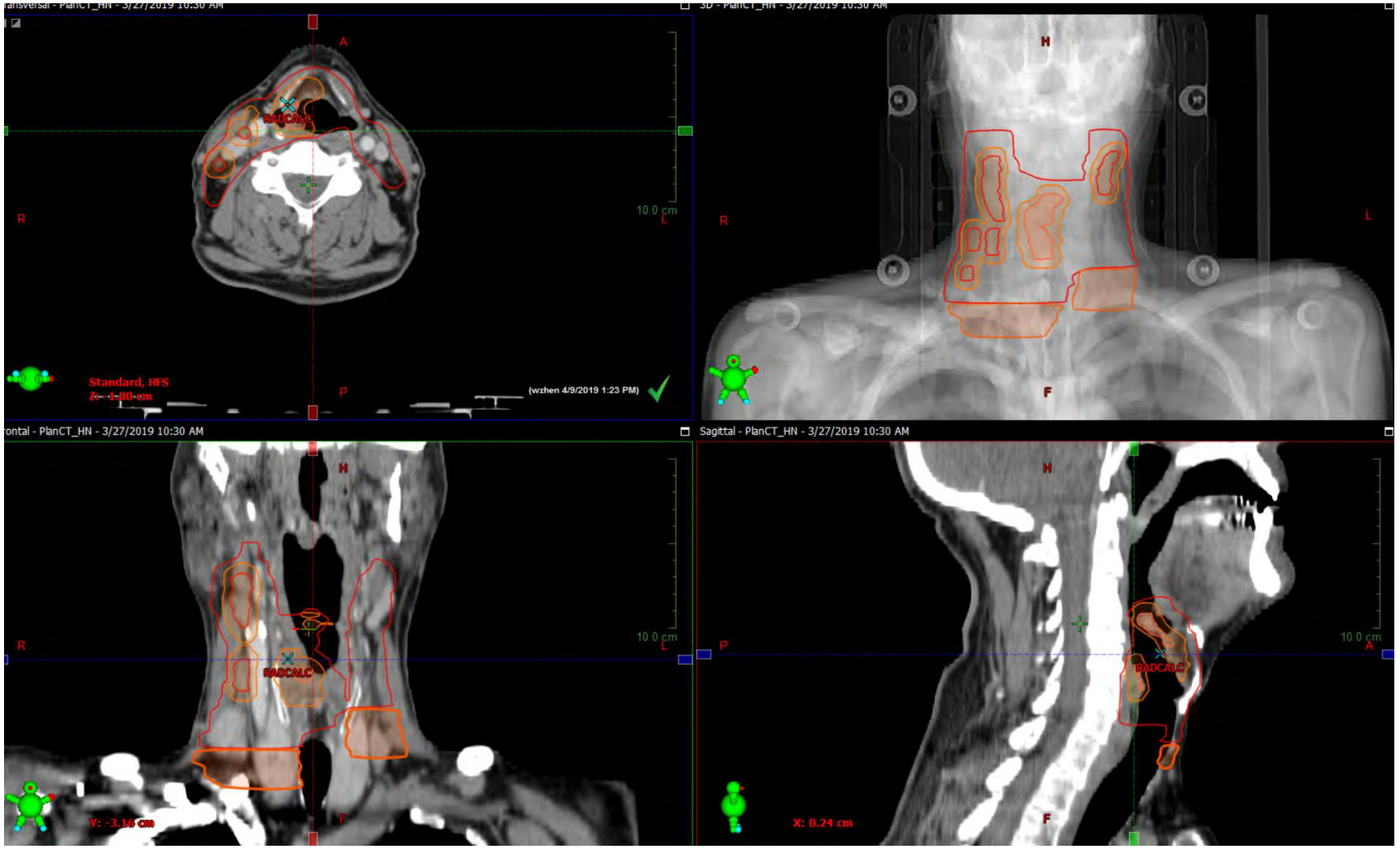
A 64 y.o. 60-pack-year smoker presents with progressive dysphonia and bilateral neck nodes

Biopsy showed squamous cell carcinoma

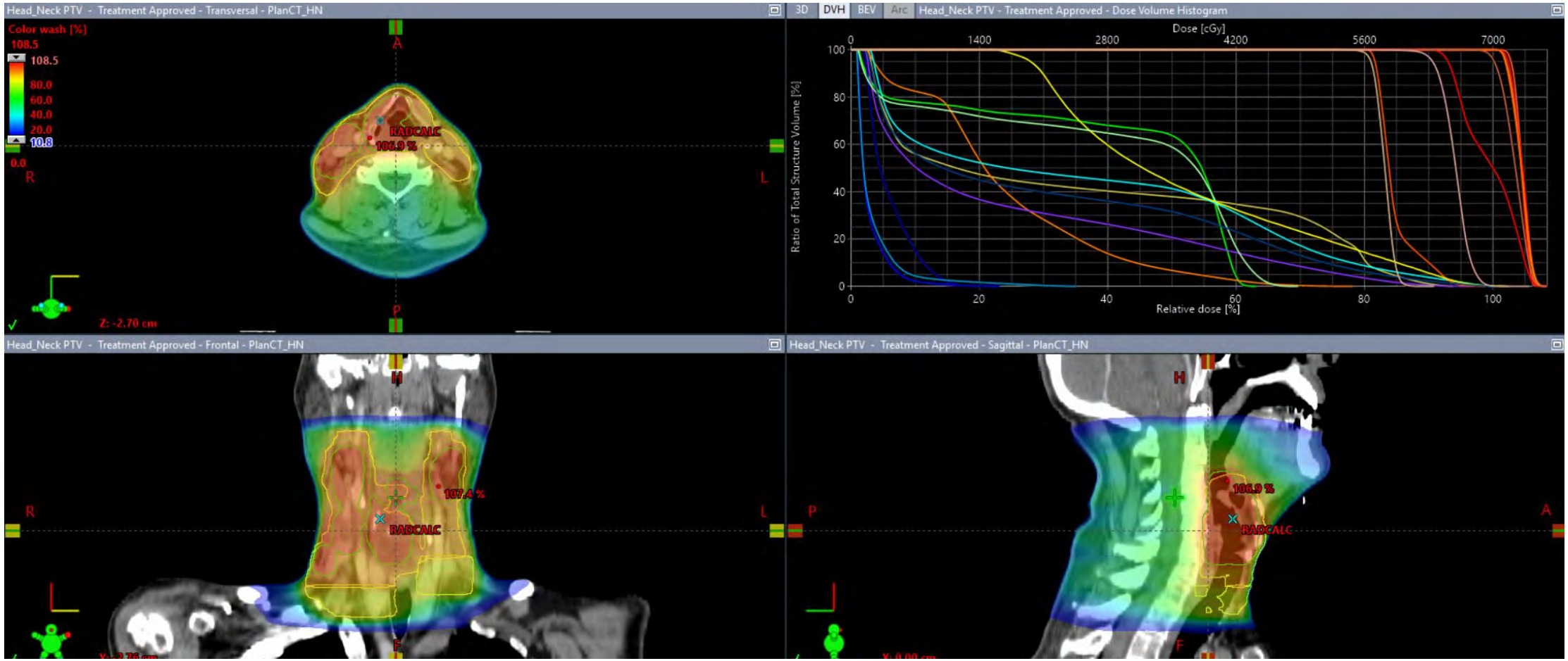
T3N2cM0

Received 70Gy with 3 cycles of cisplatin



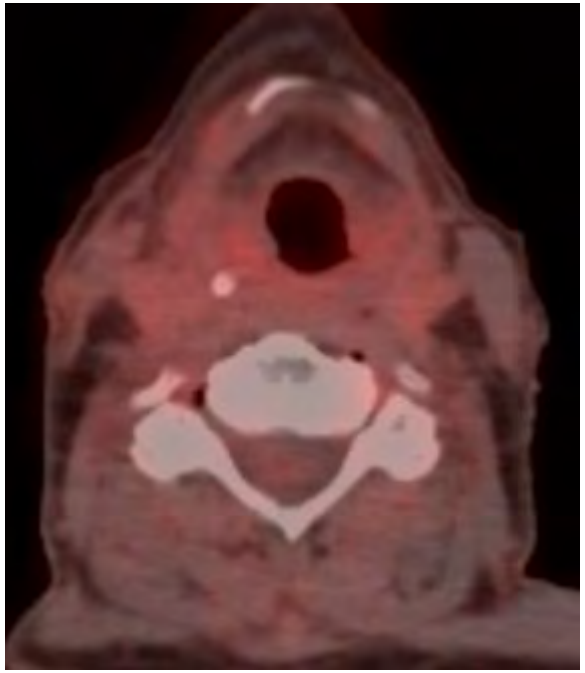


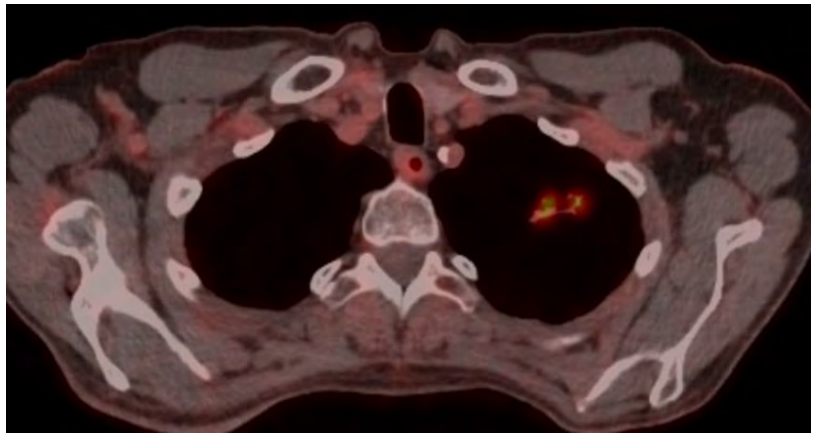
CTV 70, 63 and 56

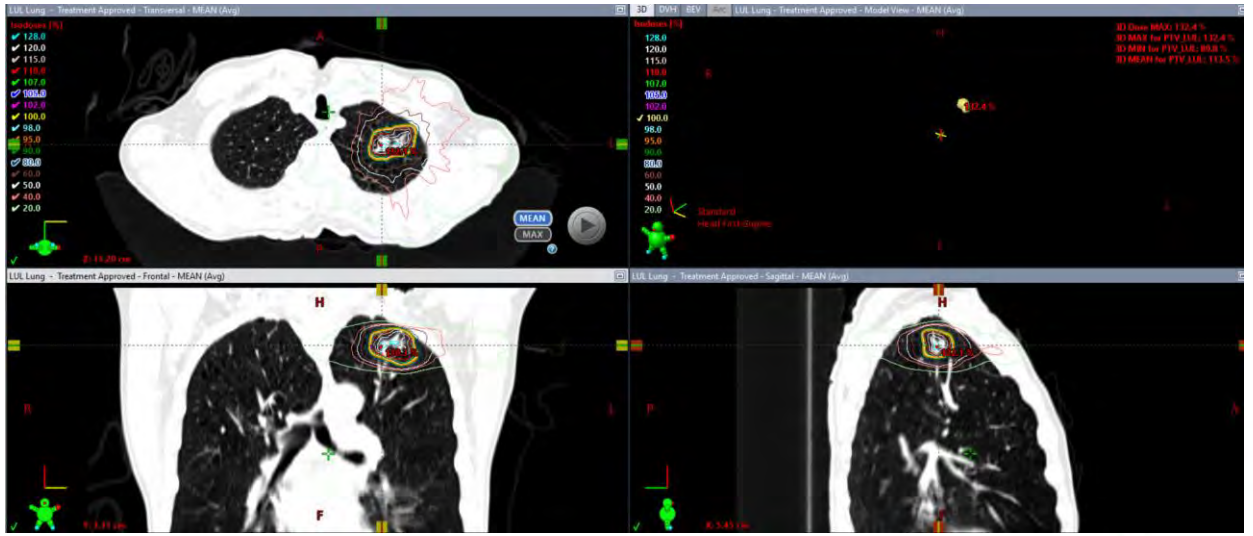

Head_Neck PTV - Treatment Approved - Transversal - PlanCT_HN
Color wash [%]
108.5
108.5
80.0
60.0
40.0
20.0
10.8
0.0
A
P
R
L
RADCALC
106.9 %
Z: -2.70 cm
3D
DVH
BEV
Arc
Head_Neck PTV - Treatment Approved - Dose Volume Histogram
Dose [cGy]
0
1400
2800
4200
5600
7000
Ratio of Total Structure Volume [%]
100
80
60
40
20
0
0
20
40
60
80
100
Relative dose [%]
Head_Neck PTV - Treatment Approved - Frontal - PlanCT_HN
H
F
R
L
107.4 %
RADCALC
Head_Neck PTV - Treatment Approved - Sagittal - PlanCT_HN
H
F
P
A
106.9 %
RADCALC

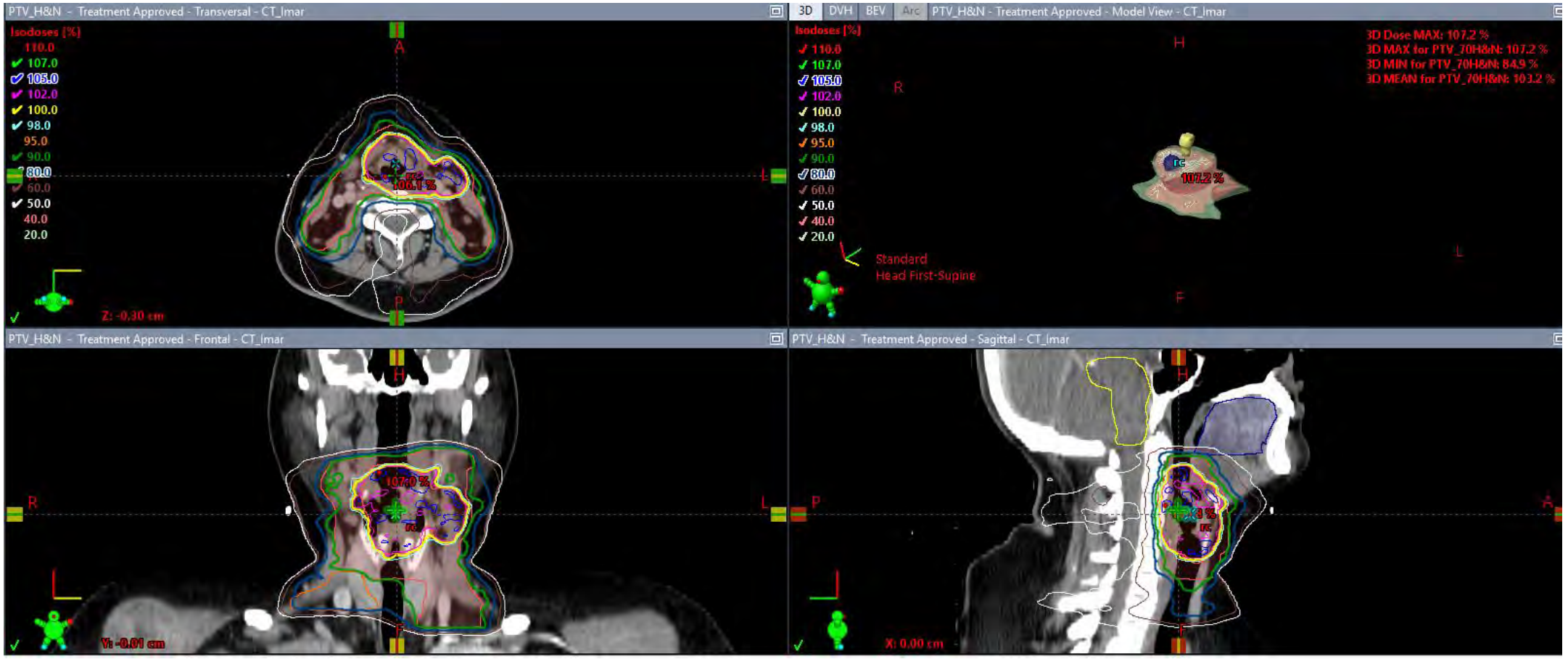
NED in HN 4 years post chemoradiation.
Functionally doing well with mild dysphonia. No dysphagia.

Developed stage I SCC of left upper lobe lung









IMRT for T3N1M0 SCC of supraglottic larynx

Challenges for Laryngeal Preservation

All about disease control, functions and overall survival.

+/-

Cost

Goals of laryngeal Cancer Treatment:

- Cure
- Preservation of safe and effective swallowing
- Preservation of usual voice
- Avoidance of permanent feeding tube and tracheostomy

Organ Preservation
≠
Function Preservation

Treatment decision-making for patients with laryngeal cancer consists of a complex trade-off between survival and quality of life

Speech and Survival

- T3 glottic cancer
- Surgery vs. Radiotherapy
- N=37 (firemen, businessmen)
- 19% favored RT despite 20-30% reduction in 3-year survival

Patients' attitudes toward morbidity are important, and survival is not their only consideration. Such attitudes vary enormously from patient to patient.

McNeil at el. N Engl J Med 305:982, 1981

Trade-off between Survival and Laryngeal Preservation in Advanced Laryngeal Cancer: The Otorhinolaryngology Patient's Perspective

Ollivier Laccourreye, MD, David Malinvaud, MD, PhD, [...], and Pierre Bonfils, MD, PhD +3 View all authors and affiliations

Volume 121, Issue 9 https://doi.org/10.1177/000348941212100902

Annals of Otology, Rhinology & Laryngology

- 24.6% of 309 patients (volunteers) made survival their main consideration and would not consider any trade-off.
- Among the 62.5% who considered the trade-off, the percentage of cure that patients were ready to lose in order to preserve their larynx varied from 5% to 100% (mean, 33%; SD, 23%).

Ann Otol Rhinol Laryngol. 2012 Sep;121(9):570-5. doi: 10.1177/000348941212100902.

Adverse prognostic factors for laryngeal preservation

- Male gender
- Anemia (at start of treatment)
- Smoking
- Advanced T stage
- Clinically detectable impaired cord mobility
- Subglottic extension
- Involvement of anterior commissure
- Large tumor volume

Factors that influence selection of initial treatment:

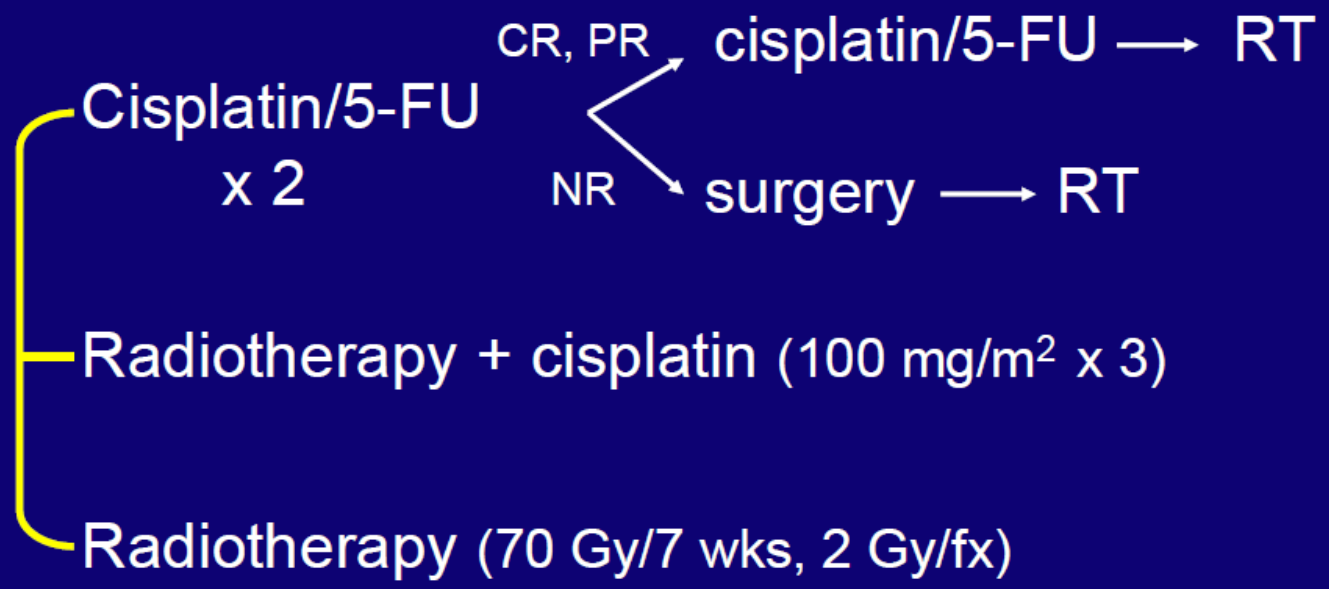
- Tumor size, extent, and location (bulky T3>12cc, extending to post-cricoid area, through outer cortex of TC, etc.)
- Laryngeal function (airway, swallowing)
- Patient age and comorbidities
- Pulmonary
- Available rehabilitation resources
- Clinician expertise and experience
- Patient logistic issues (e.g., professional voice user), comorbidities, and treatment preferences

Landmark Studies for Larynx Preservation

- The Department of Veterans Affairs Laryngeal Cancer Study Group (1991)
- The European Organization for Research and Treatment of Cancer (1996)
- Radiation Therapy Oncology Group Trial 91-11 (2003)

Both the VA and EORTC trials confirmed that LPT did not compromise overall survival comparing TLG+RT, whereas RTOG 9111 confirmed the concurrent CRT to be superior in local control and LP comparing induction chemotherapy followed by RT or RT alone

Intergroup R91-11
Phase III Trial to Preserve the Larynx



Eligibility: Stage III, IV resectable (excluded T1, high volume T4 , cartilage invasion or > 1cm into BOT)

Forastiere A. *NEJM* 2003

RTOG 91-11 selection criteria

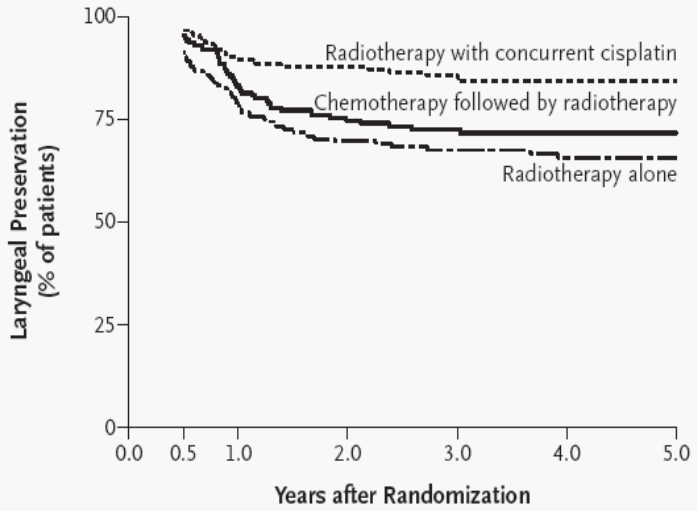
- Patient selection
  - T3
  - Limited T4
- Patient exclusions
  - Large volume T4a
    - Extending through thyroid cartilage
    - Greater than 1 cm extension into base of tongue

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 27, 2003 VOL. 349 NO. 22

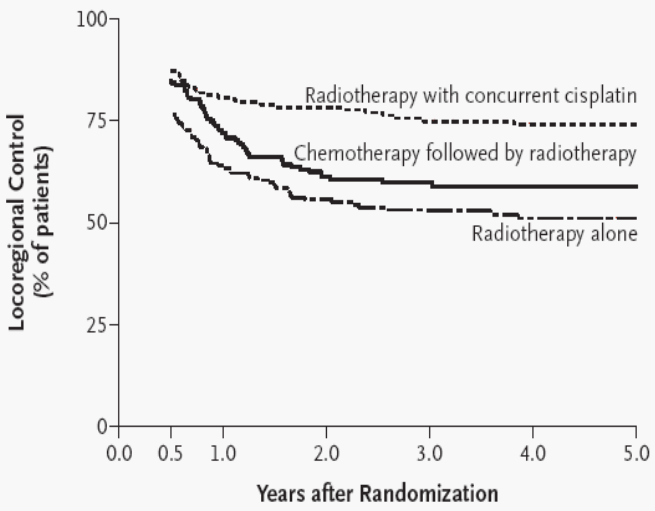
Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer

Arlene A. Forastiere, M.D., Helmuth Goepfert, M.D., Moshe Maor, M.D., Thomas F. Pajak, Ph.D., Randal Weber, M.D., William Morrison, M.D., Bonnie Glisson, M.D., Andy Trotti, M.D., John A. Ridge, M.D., Ph.D., Clifford Chao, M.D., Glen Peters, M.D., Ding-Jen Lee, M.D., Ph.D., Andrea Leaf, M.D., John Ensley, M.D., and Jay Cooper, M.D.



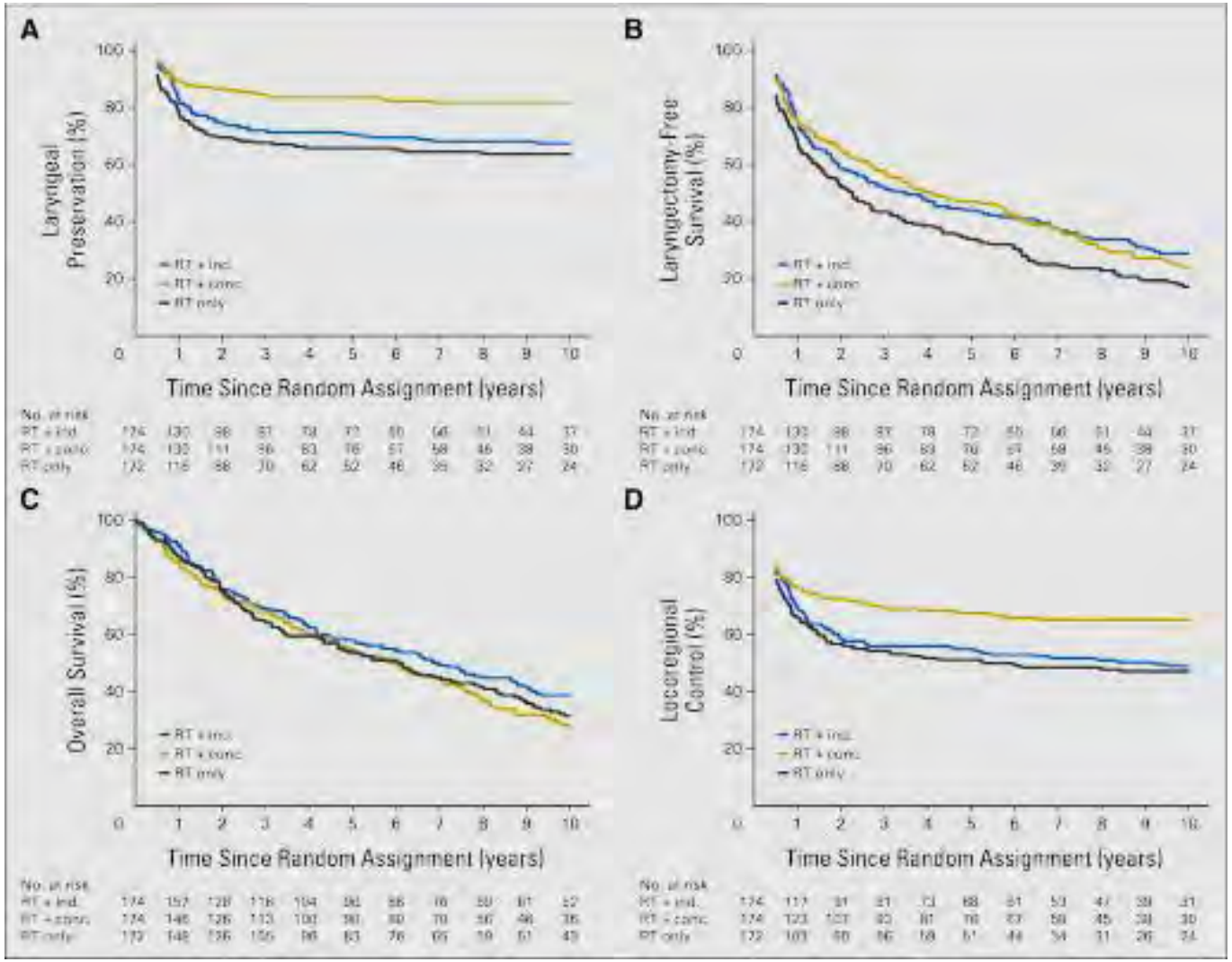
No. at Risk				
Chemotherapy followed by radiotherapy	158	94	75%	20
Radiotherapy with concurrent cisplatin	154	107	88%	28
Radiotherapy alone	146	87	70%	20

Figure 1. Rates of Laryngeal Preservation According to the Treatment Group.



No. at Risk				
Chemotherapy followed by radiotherapy	147	89	61%	19
Radiotherapy with concurrent cisplatin	146	104	78%	28
Radiotherapy alone	127	78	56%	19

Figure 2. Rates of Locoregional Control According to the Treatment Group.



No difference in late effects was detected, but deaths not attributed to larynx cancer or treatment were higher with concomitant chemotherapy (30.8% v 20.8% with induction chemotherapy and 16.9% with RT alone).

(A) Laryngeal preservation, (B) laryngectomy-free survival, (C) overall survival, and (D) locoregional control according to treatment group. conc., concomitant; ind., induction; RT, radiation therapy.

J Clin Oncol. 2013 Mar 1;31(7):845-52.

Conclusion:

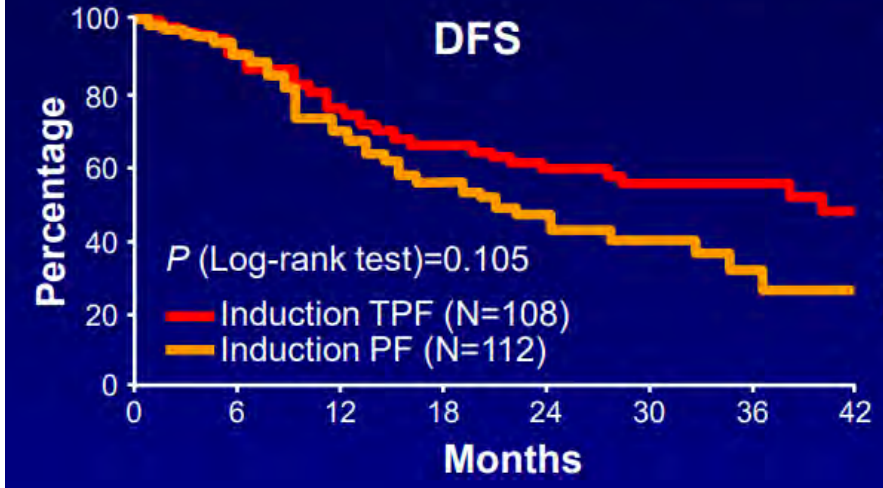
- These 10-year results show that induction PF followed by RT and concomitant CRT had similar efficacy for the composite end point of LFS.
- Locoregional control and larynx preservation were significantly improved with concomitant CRT compared with the induction arm or RT alone.
- New strategies to improve organ preservation and function with less morbidity are needed.

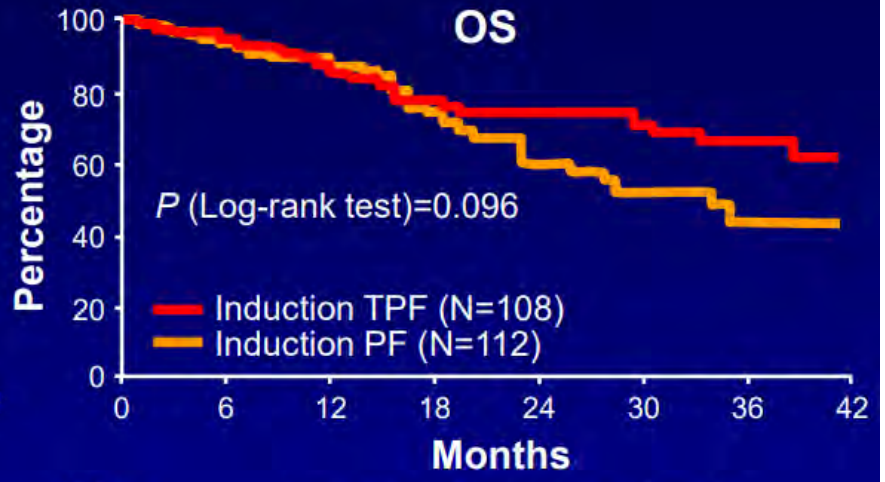
Ongoing clinical trials in laryngeal preservation

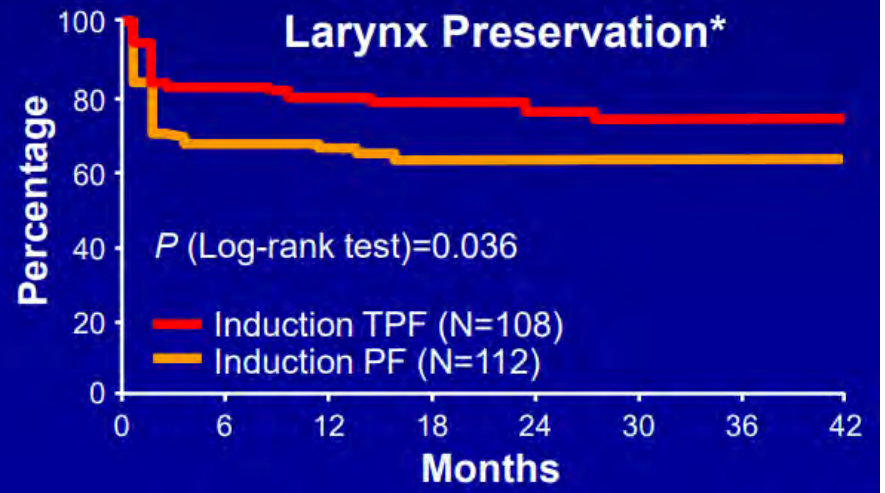
The RTOG 91–11 trial did not contain an arm with TPF induction as this trial was initiated before the TPF induction regimen was proved to be superior to PF in the GORTEC 2000-01, TAX324, etc.

The ongoing French phase III trial (GORTEC 2014-03-SALTORL, clinicaltrials.gov NCT03340896) is comparing induction TPF followed by RT in responders vs. concurrent cisplatin-based CRT with the composite end-point of laryngoesophageal dysfunction-free survival as primary end-point.

GORTEC: Docetaxel/Cisplatin/5-FU vs Cisplatin/ 5-FU ICT for Organ Preservation in Hypopharynx and Larynx Cancer: Results





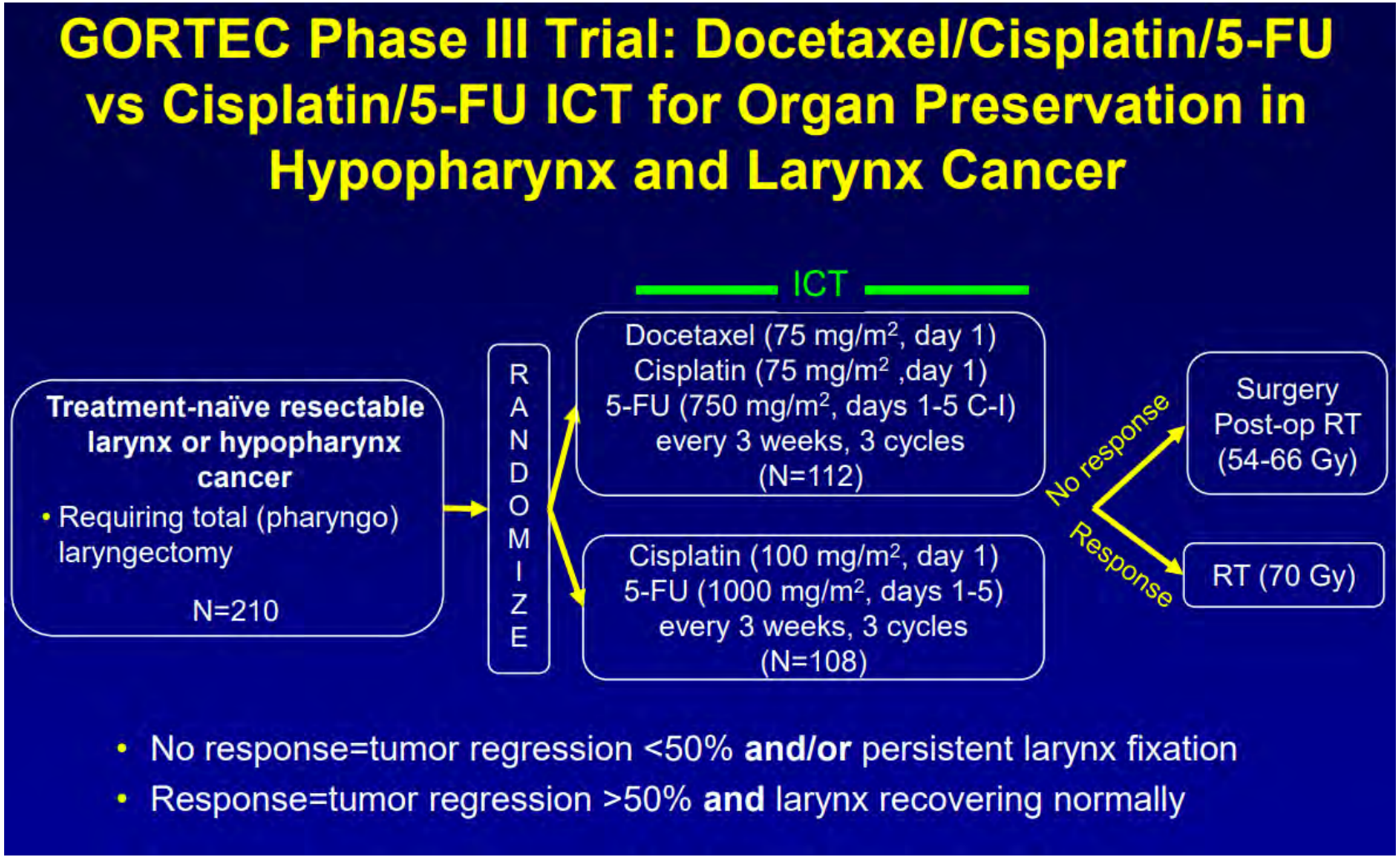


- DFS and OS trends favor TPF but are not statistically significant

*European definition.

Pointreau, JNCI 2009

GORTEC 2014-03-SALTORL, clinicaltrials.gov NCT03340896



The composite end-point of laryngoesophageal dysfunction-free survival as primary end-point!

ORIGINAL ARTICLE

Long-term Quality of Life After Treatment of Laryngeal Cancer

Jeffrey E. Terrell, MD; Susan G. Fisher, PhD; Gregory T. Wolf, MD; for The Veterans Affairs Laryngeal Cancer Study Group

Arch Otolaryngol Head Neck Surg. 1998;124:964-971

VA Study Revisited: Quality of Life

A 1998 follow-up to the VA study identified 25 surviving patients from the surgery + PORT group and 21 patients from the induction chemo + XRT group.

Patients were administered the University of Michigan Head and Neck Quality of Life (HNQOL) instrument, the Medical Outcomes Short-Form 36 (SF-36), and the Beck Depression Inventory (BDI)

Table 1. Domains of the Short-Form 36 General Health Measure*

Domain	Meaning of Score
Physical functioning (PF)	Limitations in performing various physical activities
Role physical (RP)	Problems with work or other daily activities as a result of physical health
Bodily pain (BP)	Extent of pain or limitations due to pain
General health (GH)	Perception of personal health
Vitality (VT)	Level of energy
Social functioning (SF)	Extent and frequency of interference with social activities due to physical and emotional problems
Role emotional (RE)	Problems with work or other activities due to emotional problems
Mental health (MH)	Feelings of nervousness and depression

**Scores standardized with 0 indicating worst and 100, best score.*

VA larynx, long term QOL: significant differences in mental health and pain

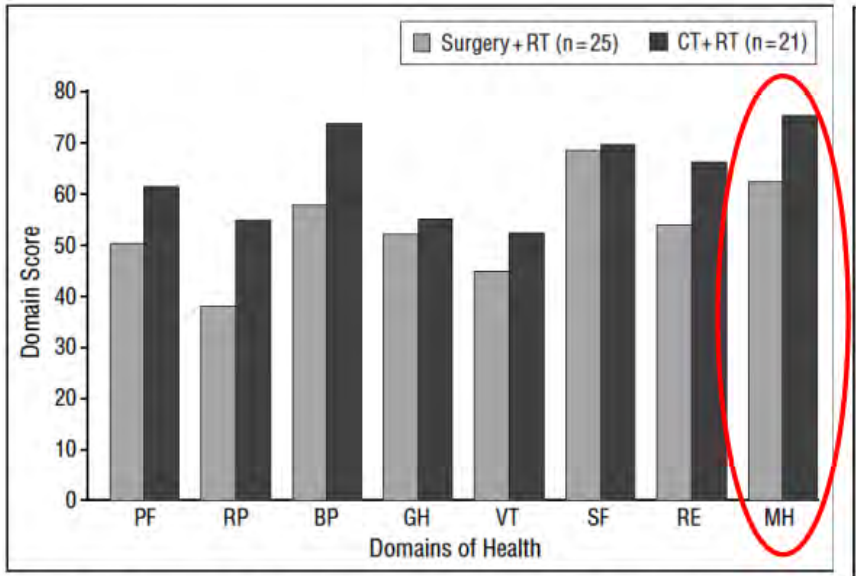


Figure 2. *Comparison of health status for surgery and radiation therapy (RT) vs chemotherapy (CT) + RT patients for domains of the Medical Outcomes Studies Short-Form 36 instrument (see legend to Figure 1 for domains and expansion of abbreviations).* P<.05 *for mental health.*

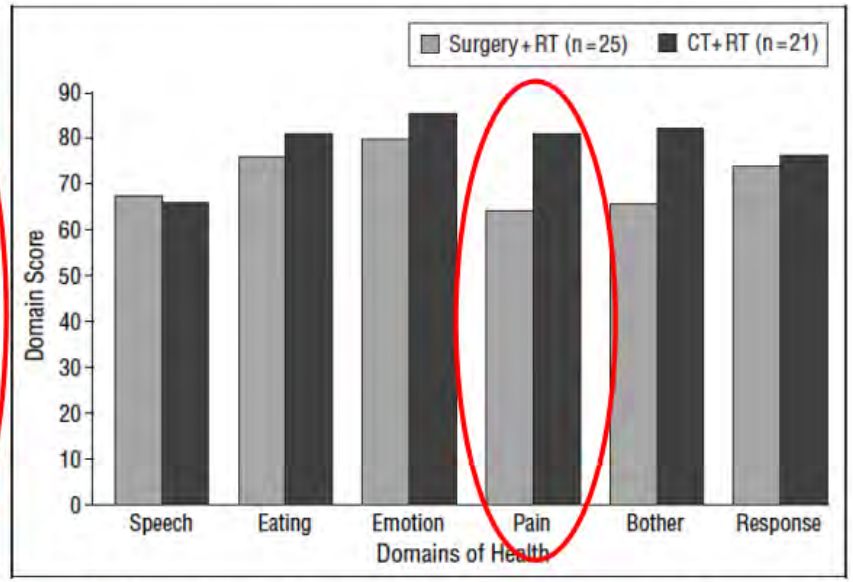


Figure 3. *Comparison of health status for surgery and radiation therapy (RT) vs chemotherapy (CT) + RT patients for 6 domains of the Head and Neck Quality of Life (HNQOL) instrument. Response indicates the treatment item of HNQOL; bother, the overall bother item on the HNQOL.* P<.05 *for pain.*

Arch Otolaryngol Head Neck Surg. 1998;124:964-971

Conclusion:

Better quality-of-life in the CT + RT groups appear to be related to more freedom from pain, better emotional well-being, and lower levels of depression than to preservation of speech function.

Arch Otolaryngol Head Neck Surg. 1998;124:964-971

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A phase I/II trial of concurrent immunotherapy with chemoradiation in locally advanced larynx cancer

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- Cisplatin-based chemoradiation is an established organ-preserving strategy for locally advanced laryngeal cancer, but long-term survival remains suboptimal.
- Immunotherapy has been studied in the metastatic and unresectable recurrent settings.
- However, additional data are needed to assess its role in organ preservation for locally advanced laryngeal cancer.

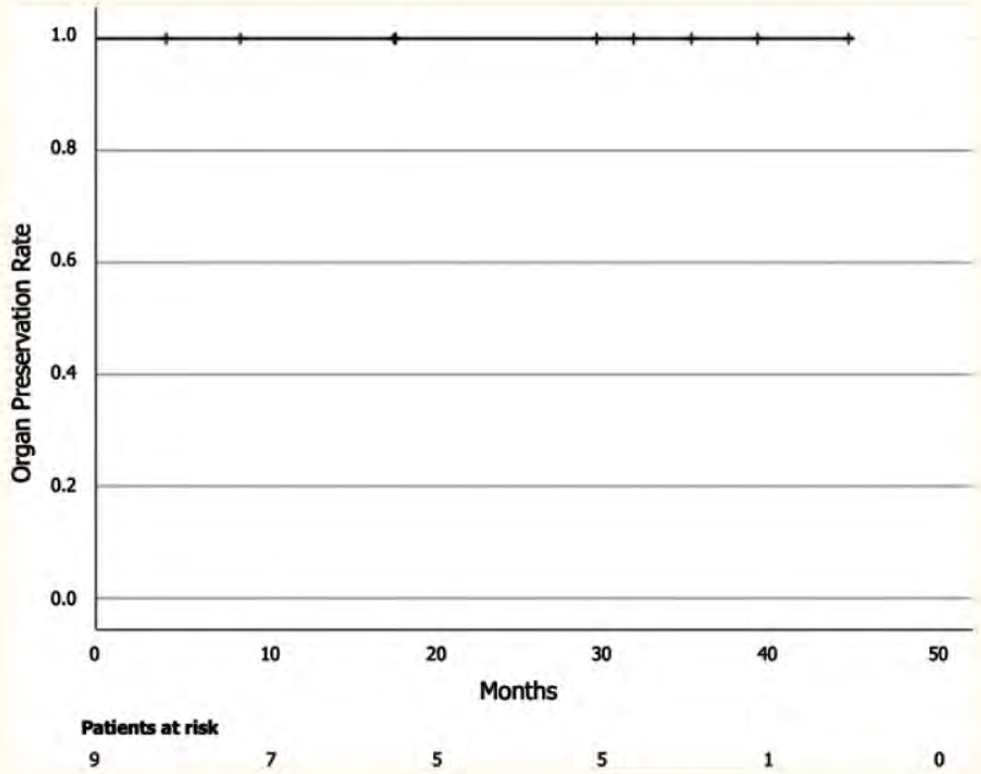

FIGURE 2

Kaplan–Meier curve for OPR. No patient in the trial cohort required laryngectomy, leading to 100% OPR at a median follow-up interval of 30.1 months

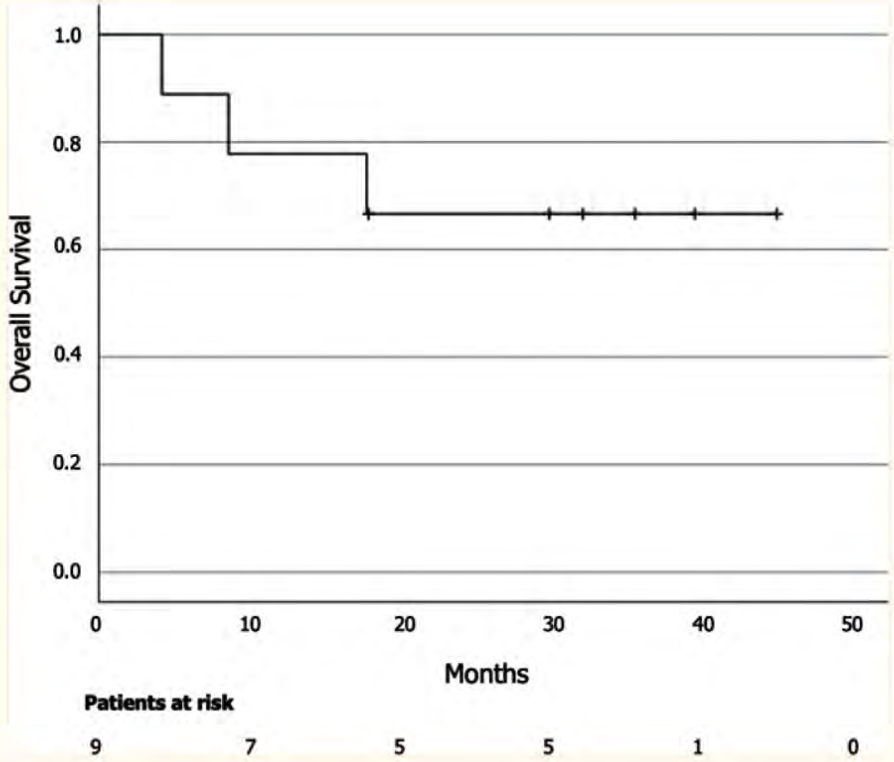

FIGURE 3

Kaplan–Meier curve for OS. The secondary endpoint of 12-month OS was 77.8% and median OS was not reached. Six of the nine patients on the trial were alive at time of last follow-up and two of the patient deaths were due to co-morbid conditions rather than malignancy

TABLE 2

Acute Grade 3+ adverse events observed

		Attribution to treatment (% per Grade)		
Grade	**Total events**	**Cisplatin**	**Radiation**	**Pembrolizumab**
3	23	12 (52%)	7 (30%)	1 (4%)
4	3	2 (67%)	0 (0%)	0 (0%)
5	0	0 (0%)	0 (0%)	0 (0%)

Note: One Grade 3 (colitis) was classified as a late event and was attributed to pembrolizumab. One late Grade 4 event (laryngeal edema) was categorized as possibly related to pembrolizumab.

Summary: Laryngeal preservation

- The decision of enrolling a patient in a laryngeal preservation protocol must be taken by a multidisciplinary tumor board
- Appropriate patient selection is key
- LP does not compromise OS for patients with T3 and limited T4 disease
- Bulky T4 or Tumor with complete TC invasion or involving PC should have primary laryngectomy +/- postoperative RT
- Concurrent CRT offers the highest rate of LP, but potentially with higher non-cancer related late death and late toxifies
- Induction chemo-RT may be superior? (trial with functioning LP is ongoing)
- New clinically trials should focus on functioning LP and less toxicities

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