The International Federation of Head and Neck Oncologic Societies

Current Concepts in Head and Neck Surgery and Oncology 2017

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Larynx Cancer and Larynx Preservation: Non Surgical Treatment

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Larynx Cancer: Epidemiology and Risk Factors

- 2016 estimates
  - ~13,430 new laryngeal cancers in US
  - More common in men (4:1)
  - Squamous Cell Cancer (95%)
- Median age at diagnosis is 65 years
- More common in African-Americans
- Smoking
- Industrial Chemicals
- HPV uncommon (5%)

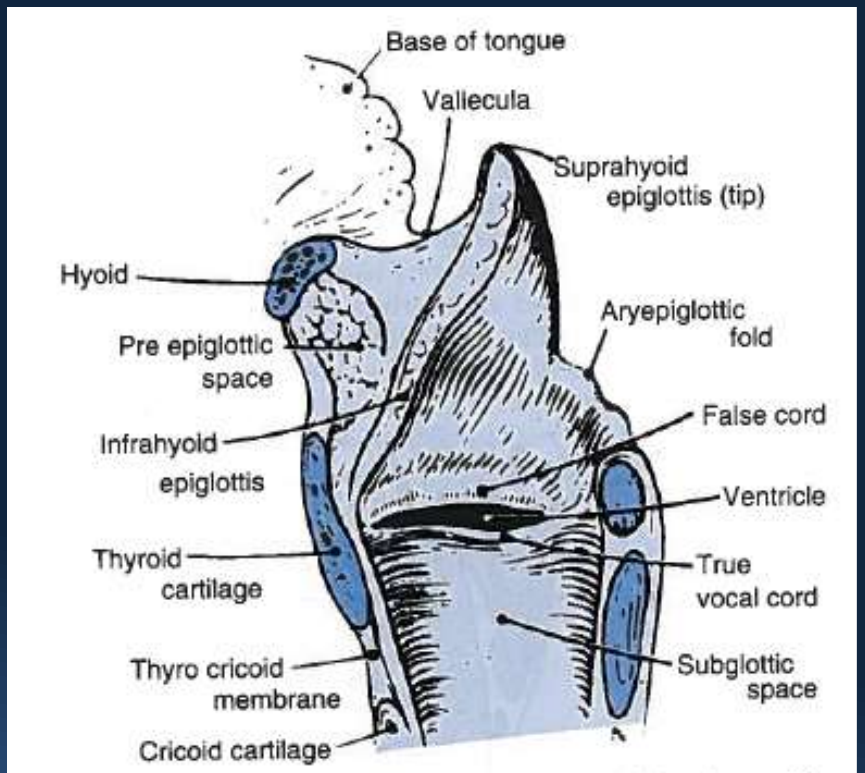

FIGURE 18-1. Diagrammatic sagittal section of the larynx. Note adjacency of the epiglottis to the preepiglottic space, and also note the proximity of the cephalic extent of this space to the base of the tongue. Finally, note intimate relationship of the subglottic mucosa to the cricothyroid membrane anteriorly. This is the point of exit for anterior cancers that are diverted caudally from the glottic level.

Source: Redrawn from Sabotta J. *Atlas der anatomie des menschen in 2 volumes.* 20th ed. Munich, Germany: Urban & Fischer Verlag; 1975 (Fig. 769), with permission.

Mendenhall, et al. "Cancer of the Larynx"; Head and Neck Cancer: A Multidisciplinary Approach, 4th Edition, eds. Harrison LB, Sessions RB, Kies MS. Lippincott Williams & Wilkins, Philadelphia, 2013

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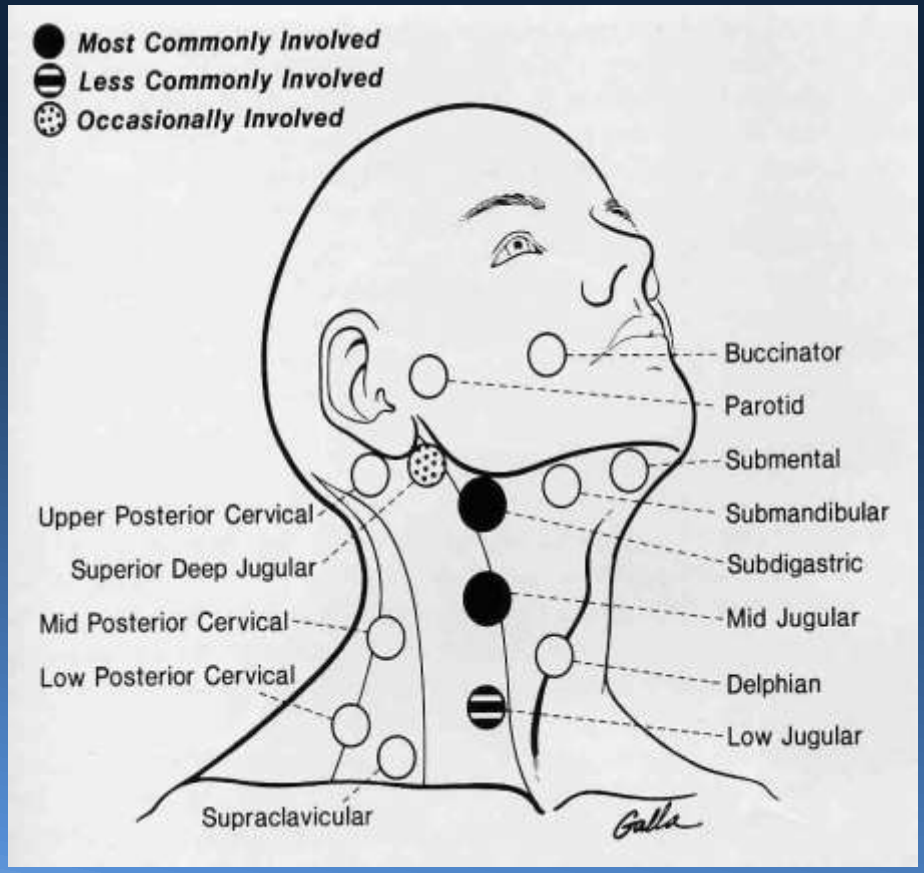
Lymphatic Spread For Glottic Larynx

- Glottis has no lymphatic drainage
- Risk of LN involvement increases with T stage
  - T1: 0-2%
  - T2: 11%
  - T3-4: 33%

Lymphatic Spread for Supraglottic Larynx

- ~55% have clinically involved nodes
- Upper/mid jugular nodes predominantly
- MDACC study of T2/T3 disease who underwent supraglottic laryngectomy + neck dissection showed ~2/3 had involved nodes; ~1/3 had palpable nodes at presentation and ~1/3 had pathologic involvement

Lymphatics: Supraglottis

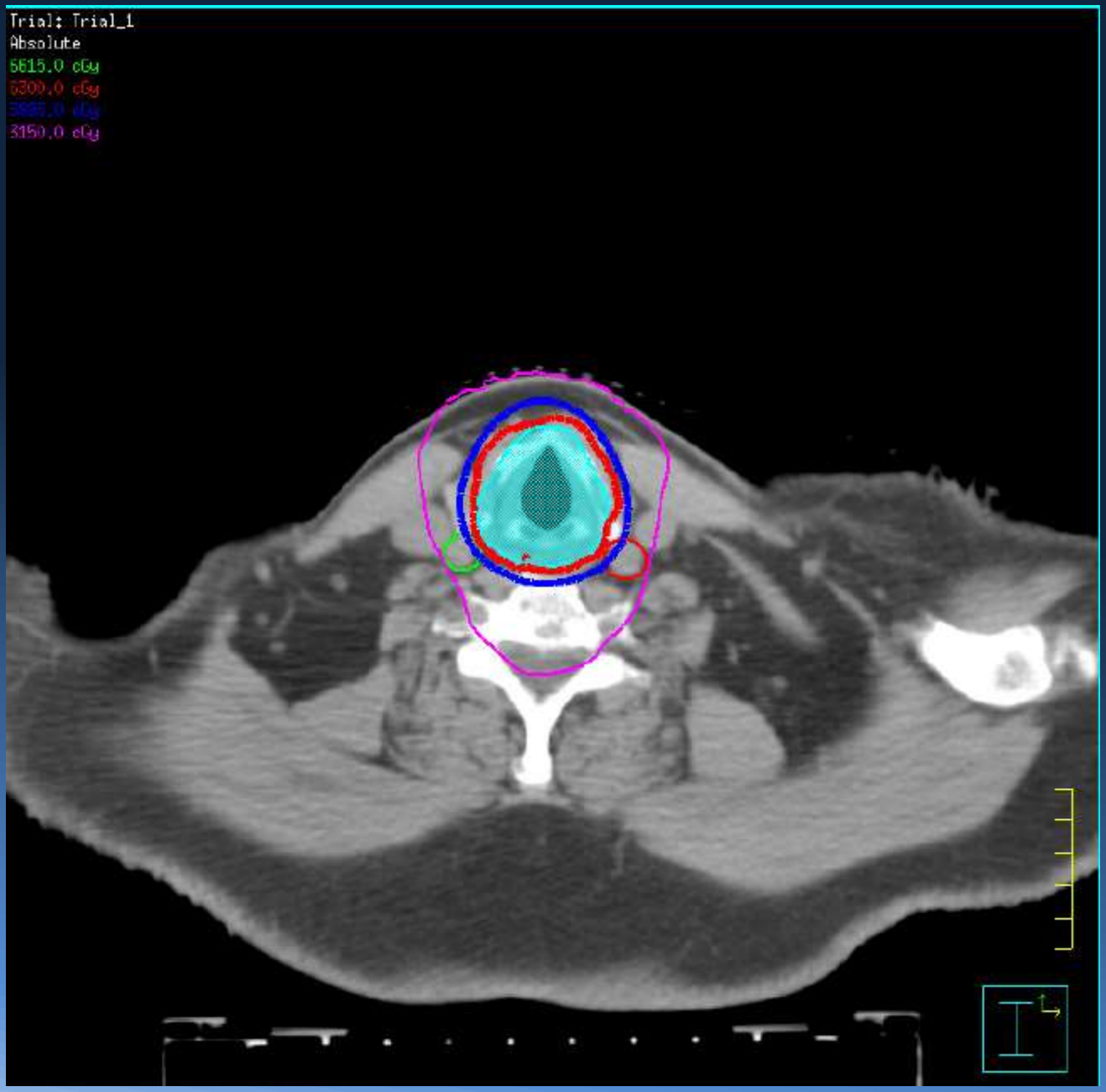


Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to 1 subsite of supraglottis, with normal vocal cord mobility
T2	Tumor invades mucosa of more than 1 adjacent subsite of supraglottis or glottis or region outside the supraglottis, without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space and/or inner cortex of thyroid cartilage
T4a	Moderately advanced local disease: Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx
T4b	Very advanced local disease: Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis	
T1a	Tumor limited to 1 vocal cord (may involve anterior or posterior commissure) with normal mobility
T1b	Tumor involves both vocal cords (may involve anterior or posterior commissure) with normal mobility
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space, an/or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease: Tumor penetrates the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx
T4b	Very advanced local disease: Tumor invades prevertebral space, encases carotid artery, or involves mediastinal structures

Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N3	Metastasis in a lymph node, >6 cm in greatest dimension
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Treatment Options/Considerations for Early Stage Larynx Cancer

- Primary Radiation Therapy
- Primary Surgery
- Voice Quality
- Treatment Efficiency
- Cost



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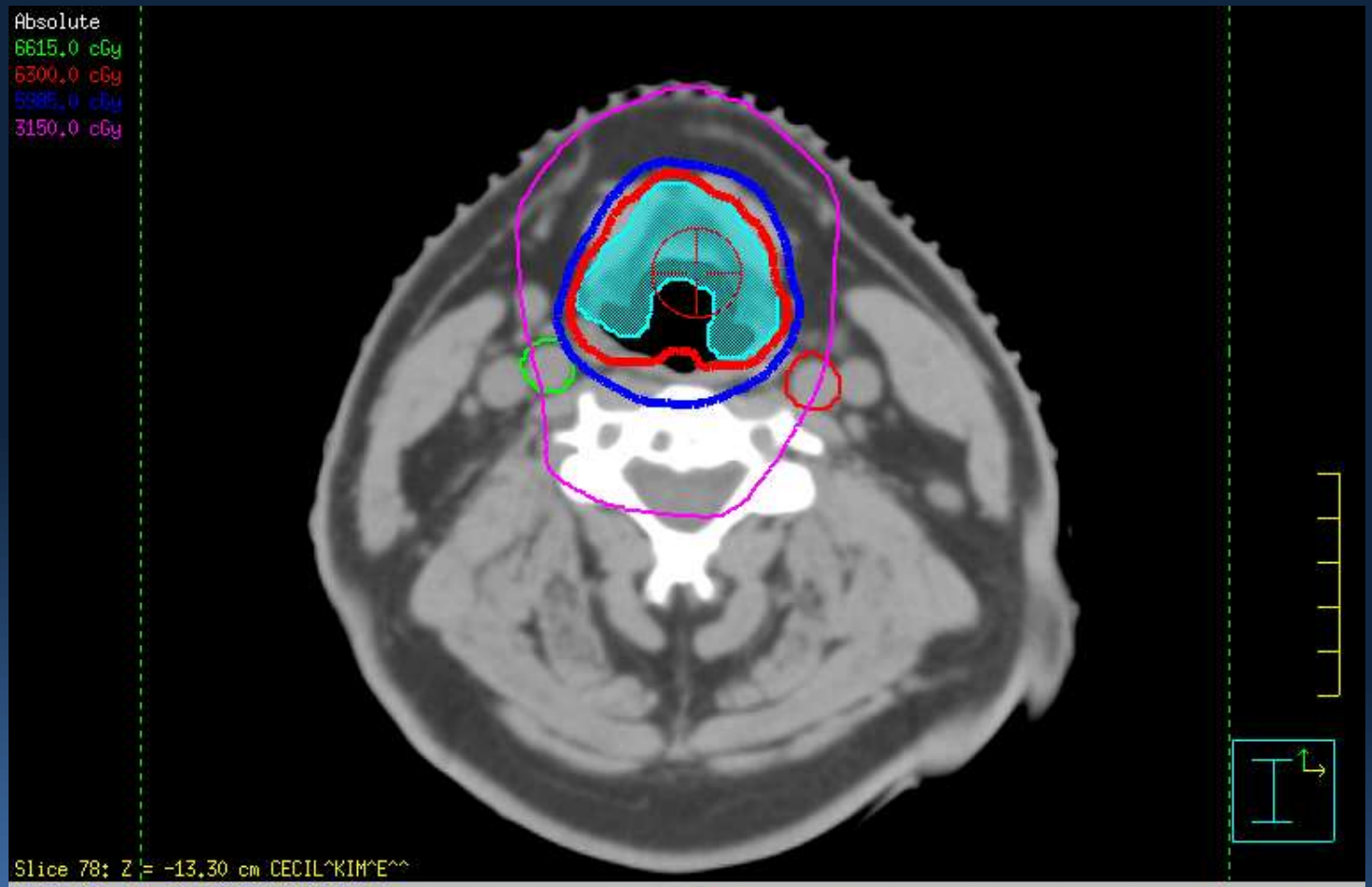

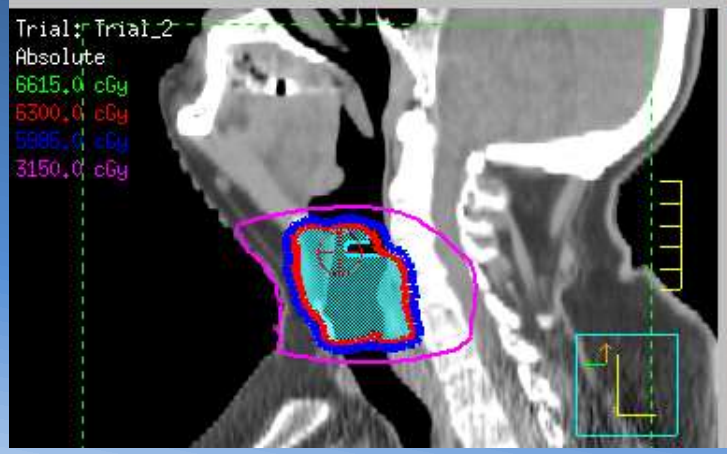

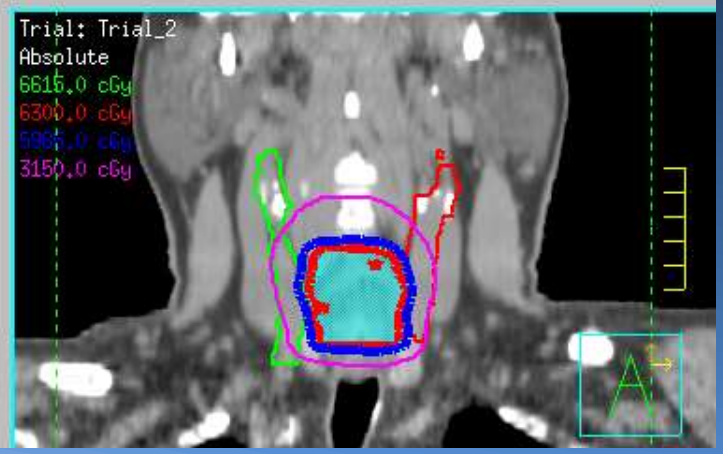

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Definitive Radiotherapy for Squamous Cell Carcinoma of the Glottic Larynx

Table. — Actuarial Local Control Rates by Tumor Stage for Squamous Cell Carcinoma of the Glottic Larynx

Tumor Stage	No. of Patients	5-y Local Control Rate, %	5-y Ultimate Local Control Rate, %
Tis	37	91	91
T1a	253	94	98
T1b	72	93	97
T2a	165	80	96
T2b	95	70	93
T3[a]	87	63	89[b]
T4[a]	22	81	86[b]

[a]Selected low-volume T3 to T4 disease. [b]Crude ultimate local control rates. Data from reference 6.

Mendenhall, et al. “Cancer of the Larynx”; Head and Neck Cancer: A Multidisciplinary Approach, 4th Edition, eds. Harrison LB, Sessions RB, Kies MS. Lippincott Williams & Wilkins, Philadelphia, 2013

TABLE 18.5 Survival Data for T_{is}–T_2 Glottic Carcinoma

Study	Treatment	Follow-up[a]	Number of Patients	Stage	Survival Rate (%)	
					Cause-Specific Survival (Interval)	Absolute Survival (Interval)
Spector et al. (1999)[71]	Laser	Minimum, 3 yr	61	T1	95% (5 yr)	84% (5 yr)
Steiner (1993)[40]	Laser	Median, 6.5 yr	159	pTis–T2	100% (5 yr)	87% (5 yr)
Peretti et al. (2000)[70]	Laser	Mean, 6.3 yr	140	pTis–T2	98% (5 yr)	93% (5 yr)
Spector et al. (1999)[71]	OPL	Minimum, 3 yr	404	T1	97% (5 yr)	84% (5 yr)
Thomas et al. (1994)[77]	OPL	Median, 6.6 yr	159	Tis–T1	—	84% (5 yr)
Spector et al. (1999)[79]	OPL	Minimum, 5 yr	71	T2	—	~92% (5 yr)
Mendenhall et al. (2001)[35]	RT	Minimum, 2 yr	230	T1a	98% (5 yr)	82% (5 yr)
		Median, 9.9 yr	61	T1b	98% (5 yr)	79% (5 yr)
			146	T2a	95% (5 yr)	77% (5 yr)
			82	T2b	90% (5 yr)	77% (5 yr)
Le et al. (1997)[81]	RT	Median, 9.7 yr	315	T1	96% (10 yr)	65% (10 yr)
			83	T2	91% (10 yr)	63% (10 yr)
Wang (1997)[80]	RT	NS	665	T1	98% (5 yr)	—
			145	T2a	92% (5 yr)	—
			92	T2b	84% (5 yr)	—
Garden et al. (2003)[83]	RT	Median, 6.8 yr	230	T2	92% (5 yr)	73% (5 yr)

OPL, open partial laryngectomy; RT, radiotherapy; NS, not stated.

[a] Follow-up period for total number of patients.

Source: From Mendenhall WM, Werning JW, Hinerman RW, et al. Management of T1–T2 glottic carcinomas *Cancer.* 2004;100:1786–1792, with permission.

Mendenhall, et al. "Cancer of the Larynx"; Head and Neck Cancer: A Multidisciplinary Approach, 4th Edition, eds. Harrison LB, Sessions RB, Kies MS. Lippincott Williams & Wilkins, Philadelphia, 2013.

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

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- Randomized trial of CO2 laser vs RT to 66 Gy
- 60 pts with T1a glottic SCCA in Helsinki
- At 6 and 24 months, compared:
  - Voice quality, breathiness, strain, video-laryngo-stroboscopic findings, self-rated voice quality and impact on daily life
- RT pts showed improvement in breathiness over time, glottal closure, less inconvenience in daily life
- Conclusion: "XRT may be treatment of choice when requirements for voice quality are demanding"

RT Results for T1 Glottis: Fraction Size vs Outcome

Author	Control	p Value
Schwaibold	1.8 Gy: 75% 2 Gy: 100%	<0.01
Mendenhall	2-2.2 Gy: 88% 2.25-2.3 Gy: 96%	None
Kim	1.8 Gy: 79% 2 Gy: 96%	0.05
Burke	<2 Gy: 44% >2 Gy: 92%	<0.01
Yamazaki	2 Gy: 77% 2.25 Gy: 92%	0.004

Table 4. Multivariate analysis of prognostic factors for local control

Variable	Strata	Odds ratio	95% CI	*p*
Arm	A vs. B	3.38	1.31–8.66	0.003
Age (y)	≤64 vs. ≥65	0.62	0.26–1.47	0.61
Gender	Male vs. female	0.65	0.06–6.92	0.72
Hemoglobin (g/dL)	≤14 vs. ≥14.1	0.97	0.41–2.36	0.97
Type of tumor	Superficial vs. exophytic + ulcerative	0.77	0.34–1.79	0.77
Tobacco smoking	Yes vs. no	2.25	0.55–8.87	0.26
Anterior commissure involvement	Yes vs. no	0.25	0.04–1.29	0.25
T stage	T1a vs. T1b	5.02	0.84–30.1	0.07

Abbreviation: CI = confidence interval.

Yamazaki et al., 2006
Intl J. Rad Onc Biol Phys 2006 Jan 1;64(1):77-82.

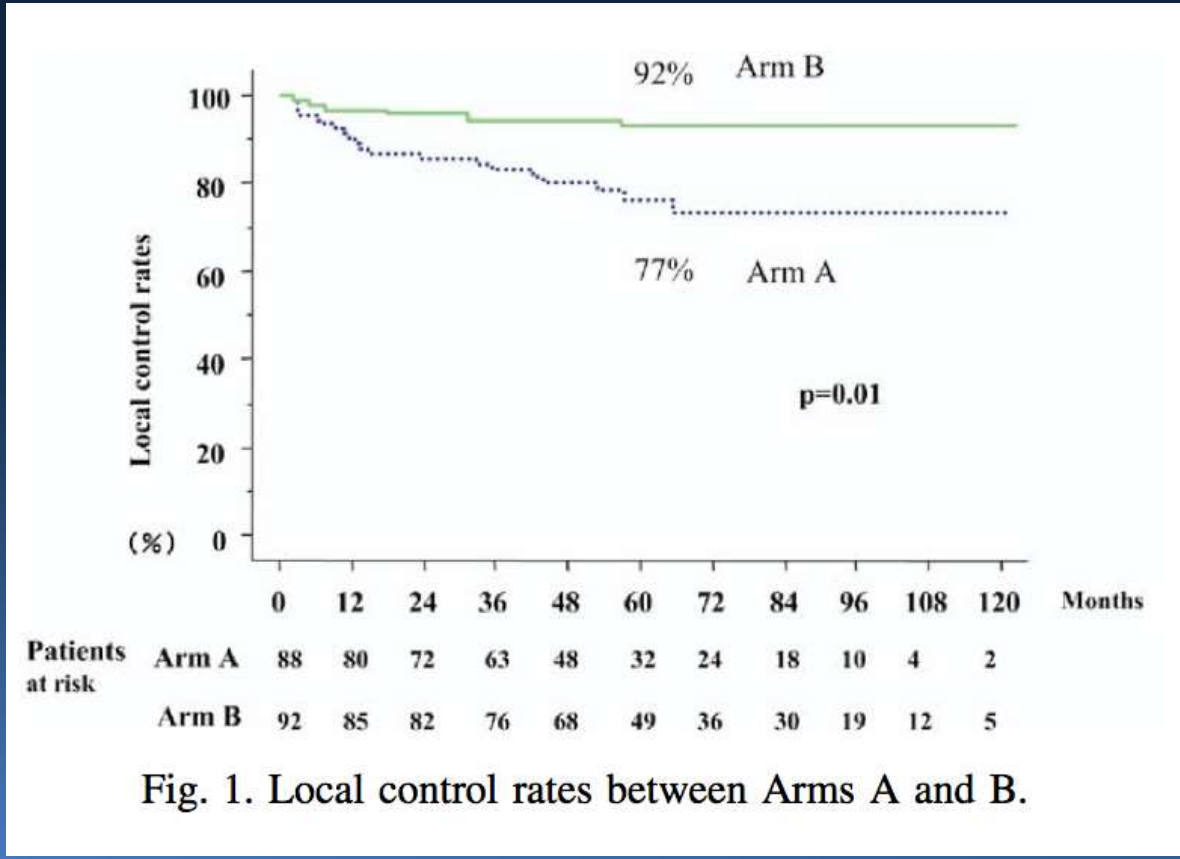

Fig. 1. Local control rates between Arms A and B.

A= 2 Gy
B=2.25 Gy

Yamazaki et al., 2006
Intl J. Rad Onc Biol Phys 2006 Jan 1;64(1):77-82.

Long Term Follow Up and Pattern of Failure for T1-T2 glottic cancer after definitive radiation therapy

# Patients	253
M/F	87%, 13%
Follow Up	83 months median
Dose	63 Gy
Fractionation	2.25 Gy/fraction
LRC T_1	99.5%
LRC T_2	91%
5 yr CSS	100%

Mourad, W., Hu, K., Shourbaji, R., Woode, R., and Harrison, LB. AM.J.Clin.Onc. Vol.36(6), 580-583 (2013)

IMRT

- Increasing use since early 2000's
- Majority of data for nasopharynx and oropharynx, very few larynx or hypopharynx included
- Offers better sparing of normal tissues, notably parotids and carotid artery for larynx cancer patients

Risk-adapted partial larynx and carotid artery sparing modulated radiation therapy of glottic cancer

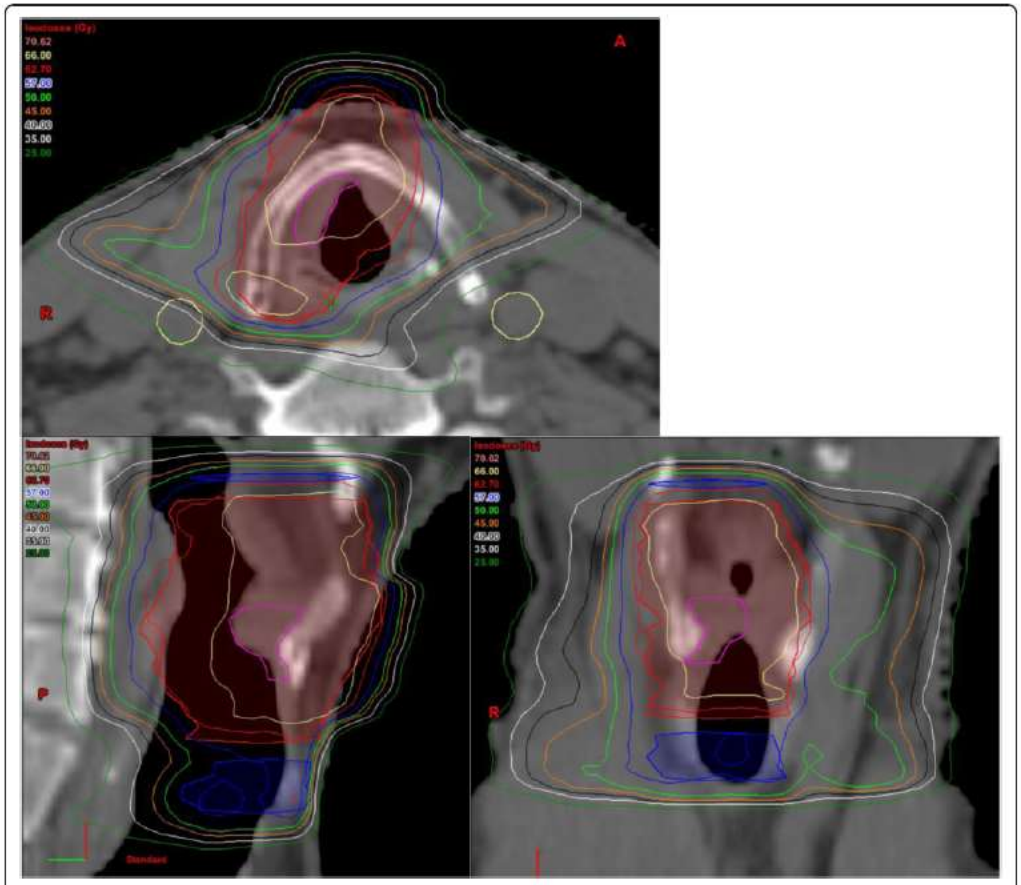

Figure 2 Treatment plan of a patient with a T1N0 glottic carcinoma with high dose coverage of involved side only, red: larynx sparing PTV1: 66 Gy, blue: PTV2 (60 Gy), yellow: carotid arteries.

Janssen et al. Radiation Oncology 2014, 9:136
http://www.ro-journal.com/content/9/1/136

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Risk-adapted partial larynx and carotid artery sparing modulated radiation therapy of glottic cancer

Figure 3 Example of treatment plan of a patient with a T3N0 glottic carcinoma, red: larynx sparing PTV1 (70 Gy), blue: PTV2 (60 Gy), green: PTV3 (54 Gy), pink: GTV.

Janssen et al. Radiation Oncology 2014, 9:136
http://www.ro-journal.com/content/9/1/136

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Risk-adapted partial larynx and carotid artery sparing modulated radiation therapy of glottic cancer

# patients	77
T_{1-2}	17, 24
T_{3-4}	15, 13
Recurrent	8
Chemo	39
Follow Up (median)	28 months

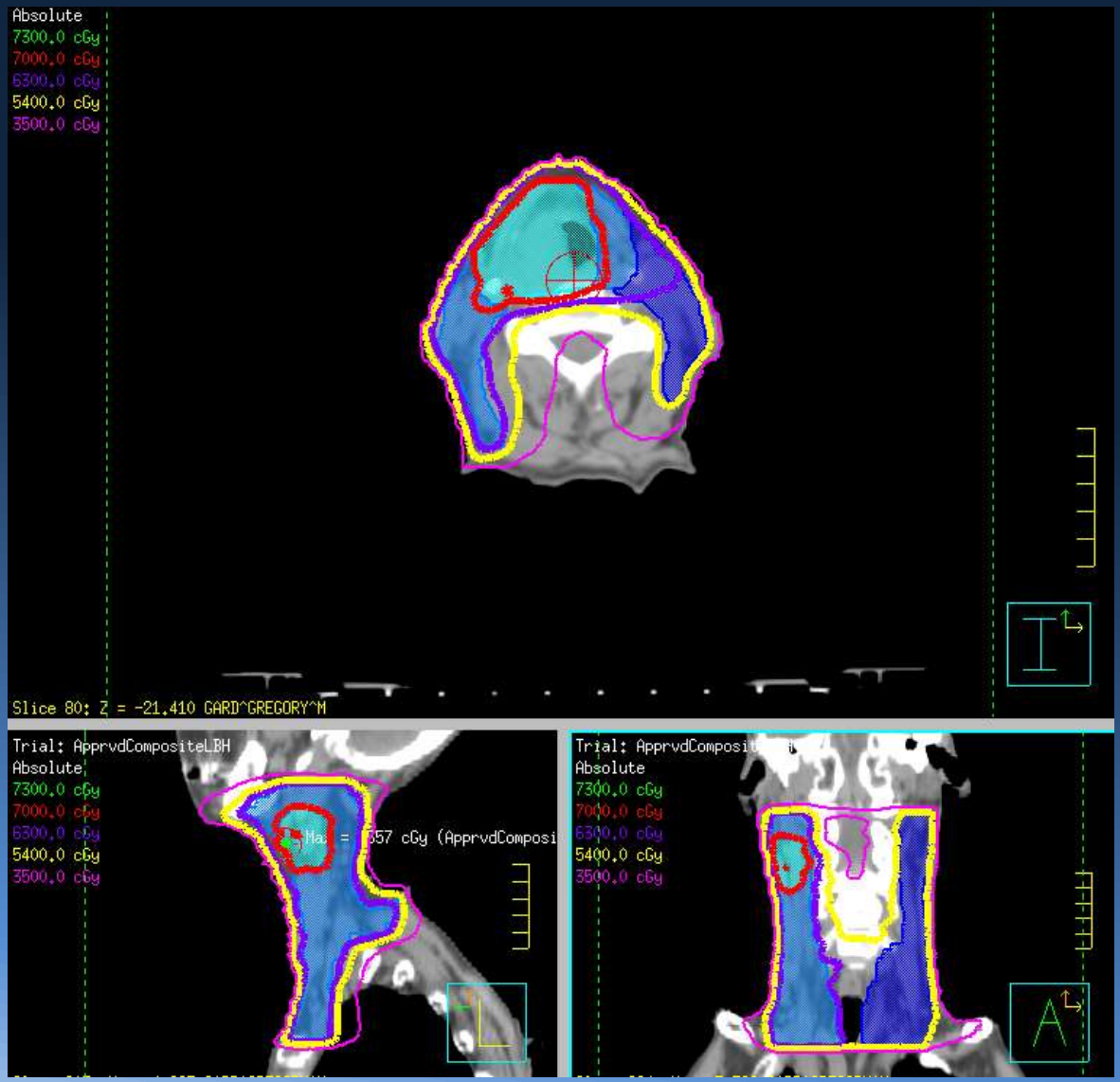
Janssen et al. Radiation Oncology 2014, 9:136
http://www.ro-journal.com/content/9/1/136

Risk-adapted partial larynx and carotid artery sparing modulated radiation therapy of glottic cancer

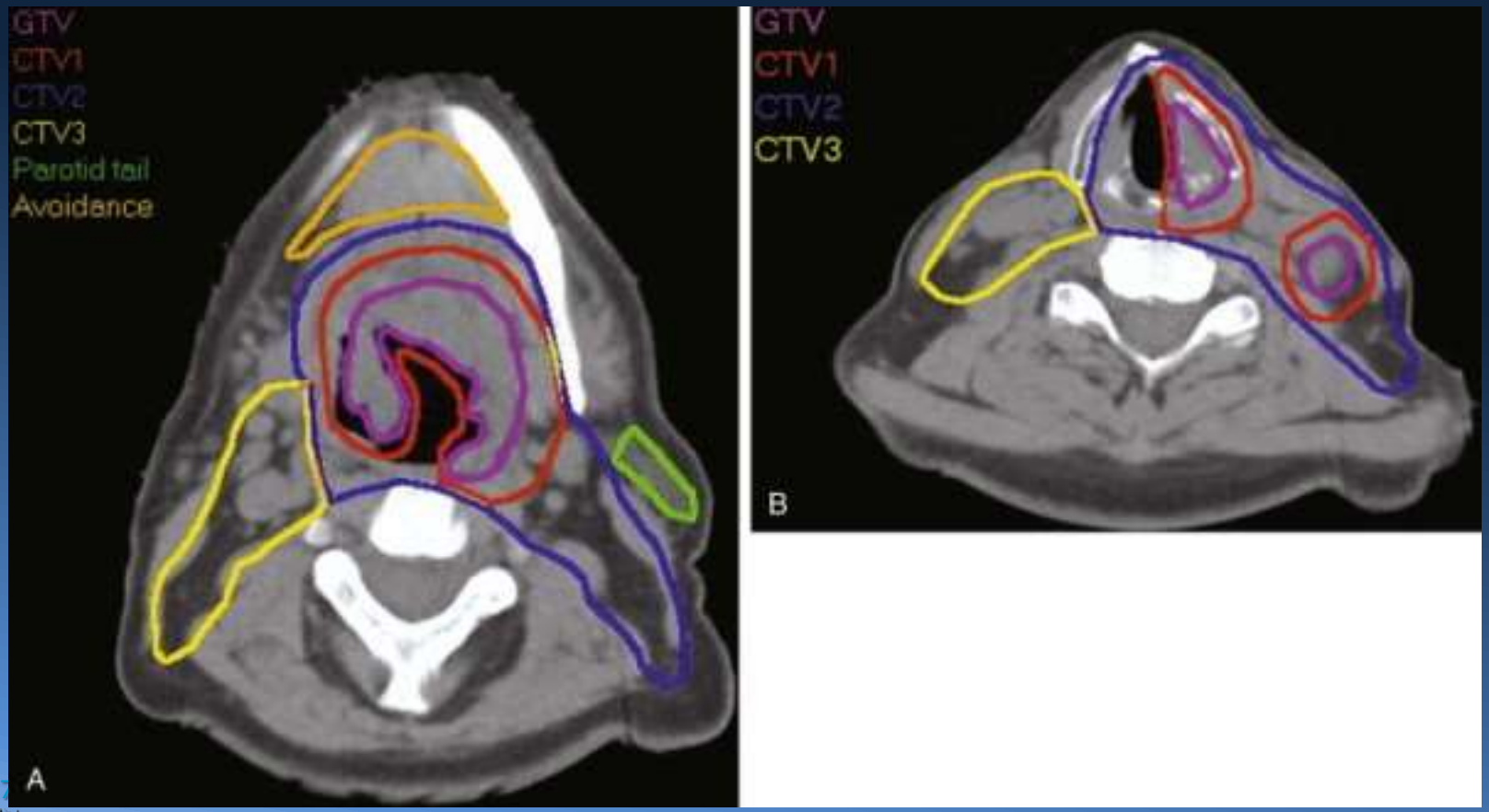
3 Yr. LC	
T_{1-2}	95%
T_{3-4}	65%
Recurrent	38%

Janssen et al. Radiation Oncology 2014, 9:136
http://www.ro-journal.com/content/9/1/136

Supraglottic Cancer



IMRT


GTV
CTV1
CTV2
CTV3
Parotid tail
Avoidance
A
GTV
CTV1
CTV2
CTV3
B

Supraglottic Cancer

TABLE 18.12 Supraglottic Larynx: Local Control after Radiotherapy

Series	Institution	Number of Patients	T1	T2	T3	T4
Fletcher and Hamberger (1974)[107]	M.D. Anderson Hospital	173	88%	79%	62%	47%
Ghossein et al. (1974)[105]	Fondation Curie	203	94%	73%	46%[a]	52%
Wang and Montgomery (1991)[108]	Massachusetts General Hospital	229 q.d.	73%	60%	54%	26%
		209 b.i.d.	89%	89%	71%	91%
Nakfoor et al. (1998)[109]	Massachusetts General Hospital	164	96%	86%	76%	43%
Sykes et al. (2000)[110]	Christie Hospital	331[b]	92%[c]	81%[c]	67%[c]	73%[c]
Hinerman et al. (2002)[51]	University of Florida[d]	274	100%	86%	62%	62%

Note: Some figures were estimated as closely as possible to fit table format if the information was not specifically stated in the cited reference.

[a]All had cord fixation.

[b]All N0.

[c]After 17 were salvaged by total laryngectomies.

[d]1998 AJCC staging; q.d., once a day; b.i.d., twice a day.

Source: Hinerman RW, Mendenhall WM, Amdur RJ, et al. Carcinoma of the supraglottic larynx: treatment results with radiotherapy alone or with planned neck dissection. *Head Neck*. 2002;24:456–467, with permission.

Mendenhall, et al. "Cancer of the Larynx"; Head and Neck Cancer: A Multidisciplinary Approach, 4th Edition, eds. Harrison LB, Sessions RB, Kies MS. Lippincott Williams & Wilkins, Philadelphia, 2013

Locally Advanced Larynx Cancer: Larynx Preservation Goals

- Cure
- Voice preservation
- Optimize swallowing functionality
- Minimize xerostomia

Larynx Preservation: Selection Factors

- Stage and extent of disease
- Patient motivation
- Social support
- Is the patient reliable to return for routine follow-up?
- Multidisciplinary team

Risk Stratification Outcome T3 glottic Cancer

Risk	Volume	Cartilage Sclerosis	Local Control
Low	<3.5cm^3	0,1	90%
Moderate	>3.5cm^3 >3.5cm^3	≥2 0	43%
High	>3.5cm^3	≥2	14%

Pameijer et al; Int. J Rad Onc.Biol Physics 1997;37(5):1011-1021

VA Larynx Trial

- 332 patients with stage III/IV larynx cancer
- Median followup 33 months
- Randomization
  - 3 cycles induction cis/5FU → RT
  - Laryngectomy + PORT

Wolf, et al. N Engl J Med 1991; 324:1685-1690 June 13, 1991DOI: 10.1056/NEJM199106133242402

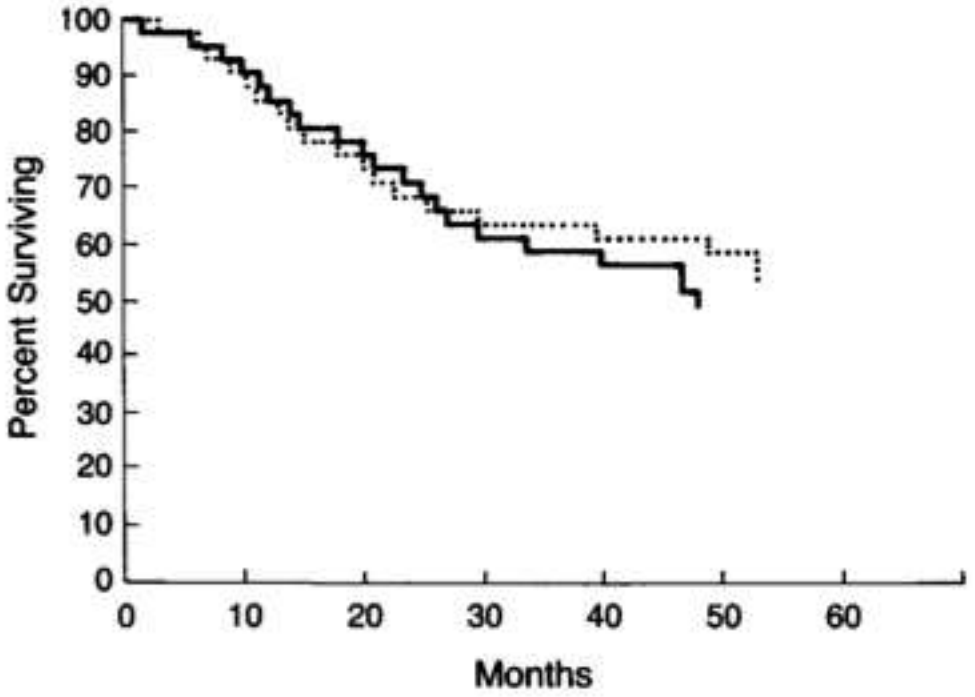


Figure 1. Overall Survival of 332 Patients Randomly Assigned to Induction Chemotherapy and Radiation Therapy (Solid Line) or Conventional Laryngectomy and Postoperative Radiation (Dotted Line).

Survival rates at two years were 68 percent for both groups (P = 0.9846). The median follow-up was 33 months.

Wolf, et al. N Engl J Med 1991; 324:1685-1690 June 13, 1991DOI: 10.1056/NEJM199106133242402

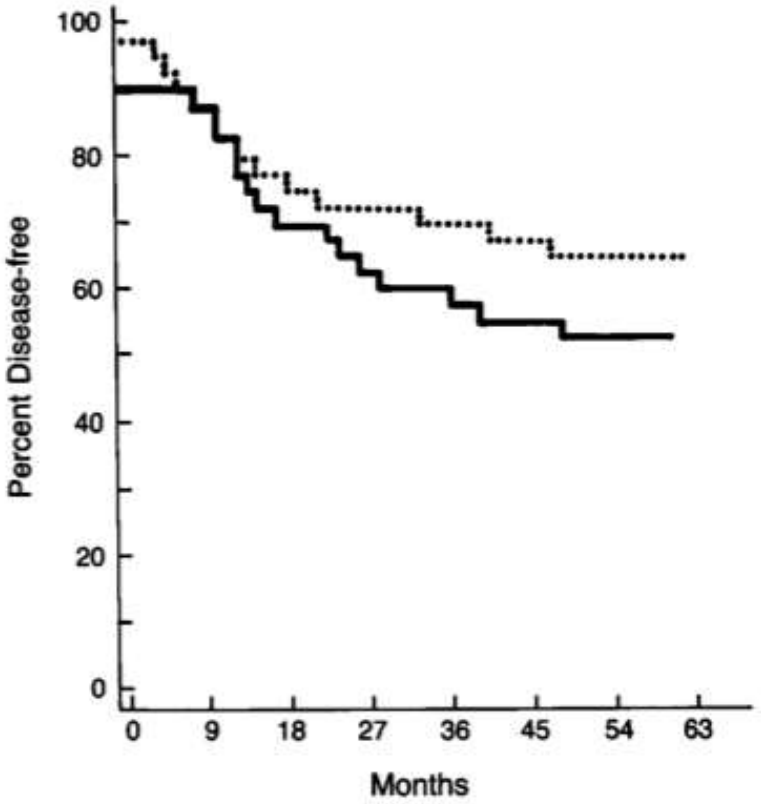


Figure 2. Disease-free Interval for 332 Patients Randomly Assigned to Induction Chemotherapy and Radiation Therapy (Solid Line) or Conventional Laryngectomy and Postoperative Radiation (Dotted Line).

The disease-free interval survival was shorter in the chemotherapy group, but the difference was not statistically significant (P = 0.1195).

Table 3. Patterns of Tumor Recurrence According to Treatment Group.

Site of Recurrence	Surgery (N = 166)	Chemotherapy (N = 166)
	no. of patients (%)	
Primary*	4 (2)	20 (12)
Regional	9 (5)	14 (8)
Distant	29 (17)	18 (11)
All	42 (25)	52 (31)

*Includes recurrences with either positive or negative nodes.

~ 66% **Retained their larynx**

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Wolf, et al. N Engl J Med 1991; 324:1685-1690 June 13, 1991DOI: 10.1056/NEJM199106133242402

RTOG 91-11 Schema

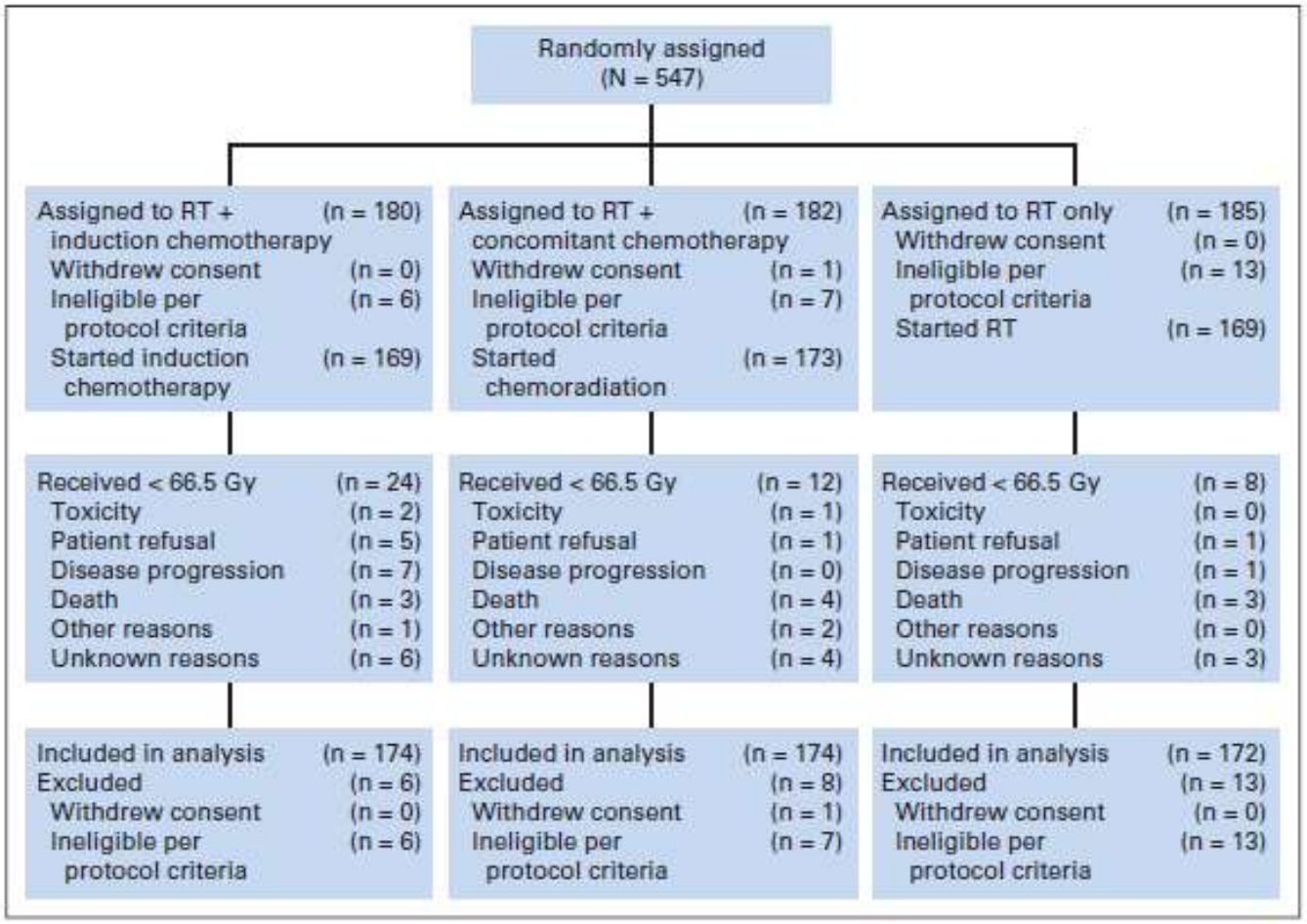

Fig 1. CONSORT diagram. RT, radiation therapy.

J Clin Oncol. 2013 Mar 1; 31(7): 845–852.

RTOG 91-11

Concurrent CRT
RT 70 Gy
Cisplatin 100 mg/m^2
Day 1, 22, 43
(n = 171)

Induction PF
Cisplatin 100 mg/m^2 Day 1
5-FU 1000 mg/m2 CI Day 1-5
3 cycles every 3 wks
(n = 173)

RT alone
70 Gy (2.0 Gy/wk x 5 days/wk)
Neck received at least 50 Gy
(n =171)

RTOG 91-11

- High-volume T4 primaries were excluded
  - Extending >1 cm to BOT
  - Penetrating thyroid cartilage

RTOG 91-11 Outcomes

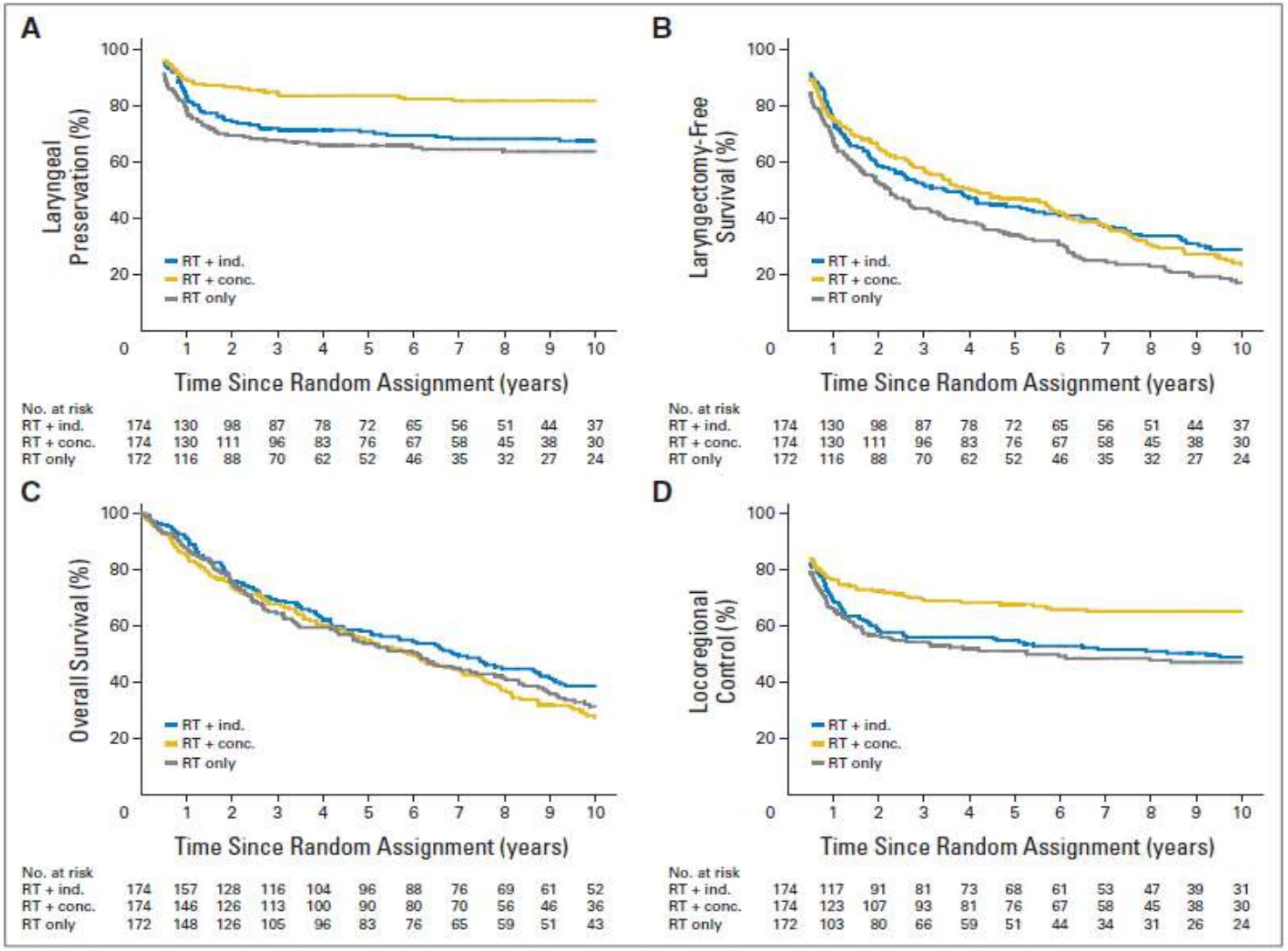

Fig 2 (A) Laryngeal preservation, (B) laryngectomy-free survival, (C) overall survival, and (D) locoregional control according to treatment group. conc., concomitant; ind., induction; RT, radiation therapy.

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Weber, RS: Outcome of salvage total laryngectomy following organ preservation therapy. The RTOG 91-11 trial. Arch Otol 129:2003

	Induction	Concomitant	RT
L-R control	90%	74%	74%
2 yr Survival	76%	71%	69%

Survival following TL not influenced by initial organ preservation treatment.

RTOG 91-11 Update & Conclusions

- Concurrent CRT offers best results
  - CRT and induction C -> RT with improved LRC over RT alone
  - CRT with improved DFS over RT alone
  - No OS difference between the 3 groups
- Induction didn't improve laryngeal preservation or survival over RT alone, so if patients cannot tolerate concurrent chemo offer RT alone
- Goal of CRT in these patients is organ preservation

Conclusions

- Early Stage Larynx cancer highly curable with RT and larynx preservation
- Larynx Preservation appropriate for selected patients with more advanced disease requiring total laryngectomy
- Strong multidisciplinary team required for best outcomes

Thank You

H. Lee Moffitt Cancer Center and Research Institute; Tampa, Florida