The International Federation of Head and Neck Oncologic Societies

Current Concepts in Head and Neck Surgery and Oncology 2018

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The Nonsurgical Approach to Larynx Preservation: RT ± Chemotherapy

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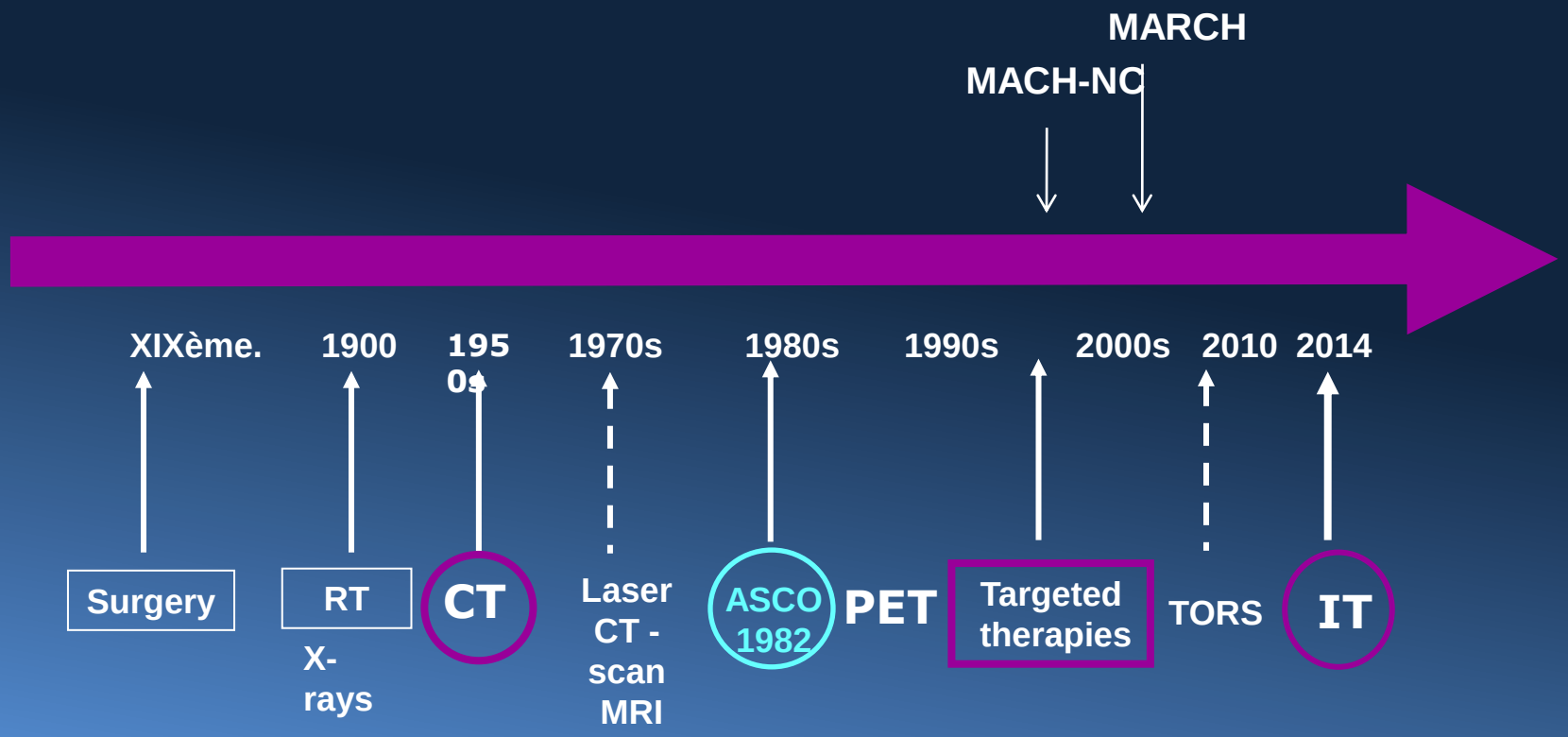
IFHNOS 2018 World Tour

Outline

- Milestones in HNSCC management
- Role of induction chemotherapy
- First generation larynx preservation trials
- The importance of timing chemotherapy
- Second generation larynx preservation trials
- The design of future trials
- Conclusions

Milestones in Head and Neck Cancer Management



MARCH, meta-analysis of radiotherapy in squamous cell carcinomas of head and neck; MACH-NC, meta-analysis of chemotherapy in head and neck cancer; RT, radiotherapy; CT, chemotherapy; PET, positron emission tomography; TORS, Trans-oral robotic surgery; IT, immunotherapy

Modified from Jean-Louis Lefebvre (with permission)

Radical (Mutilating?) Surgery in LC and HPC

Total laryngectomy (± partial pharyngectomy),
Centre Oscar Lambret (1974 - 1983): 5-yr results

site:	#	control > clavicles	survival
larynx *	254	88 %	48 %
hypopharynx **	244	84 %	35 %

NB: postop RT * 40 %. ** 100%

Courtesy of J.L. lefebvre

Milestones in Systemic Therapies (± RT) in Head and Neck Squamous Cell Cancer

1960s		Single agent chemotherapy Methotrexate
1970s		Combination chemotherapy regimens Platinum compounds
1980s		Induction chemotherapy larynx preservation
1990s		Concurrent CRT standard Taxanes
2000s		Induction chemotherapy revisited Targeted therapy Immunotherapy

Rationale for 1st Generation LP Trials

- High response rates with induction chemotherapy (PF)
  - Response > 90%, complete response > 60% (Decker et al, Cancer 1983)
- Chemotherapy may predict radiosensitivity
  - 42/60 CR/PR → after RT, CRR 97%
  - 18/60 NC/PD → after RT, CRR 6% (Ensley et al, Cancer 1984)

The Concept of Larynx Preservation (LP)

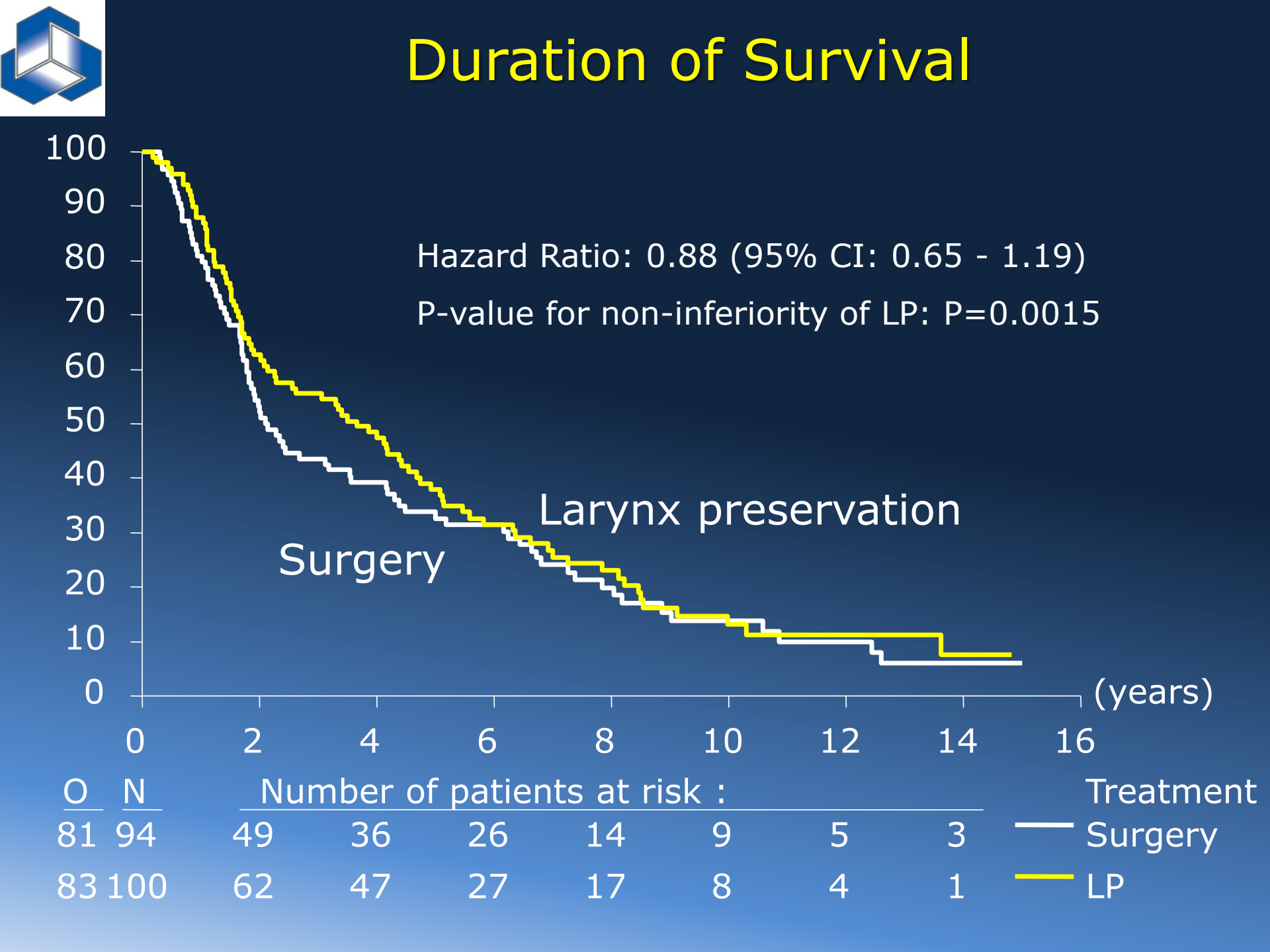
- As good responders to induction PF seem to be good responders to subsequent radiotherapy (RT), it was an intriguing question whether patients who were candidates for total laryngectomy (TL) could be selected to undergo a non-surgical procedure and keep their larynx in place
- As TL (with postop RT) provided good local control and survival, was this approach risky
- Primary endpoint of these 1st generation LP trials was overall survival (OS)

Induction Chemotherapy in Resectable SCCHN
Larynx preservation: 1st generation trials

Study Group	Tumor Size and stage	Treatment arms	No. of pts	Survival (at 5 &10 yrs)	LP
VA	Larynx	TL + RND + RT	332	45% & 30%	
	T1-T4, N2-3	**PFx3 → RT***		42% & 25%	64%[+]
EORTC	Hypopharynx	TL + RND + RT	202	33% & 14%	
	T2-T4, N0-3[+]	**PFx3 → RT***		38% & 13%	62%

** non-responders → S + RT ; [+]N2c was excluded (VA trial reported in 1992; EORTC 24891 trial in 1996 and 2012)*
[+]64% is reported in the initial report, not reported in the updated results. ***PF= cisplatin 100 mg/m² d1, 5-FU 1000 mg/m²,d1-5***

Duration of Survival



Conclusions from VA Study and EORTC 24891

- There was no significant difference in survival
- Around 60% of larynges could be preserved in the chemotherapy arm without a negative effect on survival:
- Concept is validated for both larynx and hypopharynx cancer
- Patients with T4 disease are not good candidates for this approach
- Next trials should focus larynx preservation and the function of the larynx

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Rationale for the 2nd Generation LP trials

MACH-NC Meta-analysis

Regimens	Absolute benefit at 5 years	Risk reduction	p
Adjuvant	1 %	2 %	NS
Neoadjuvant	2 %	5 %	NS
- NACT with PF	5 %	12%	0.01
Concurrent	8 %	19%	< 0.0001

Pignon et al, Lancet 335:949, 2000 (Pooled data from trials performed between 1965 and 1993)

Monnerat et al, Ann Oncol 2002; 13: 995-1006

Sequential vs Concurrent (or Alternating) CRT
Larynx preservation: 2nd generation trials

Study Group	Tumor size and stage	Treatment arms	No. of pts	Survival 5 & 10 yr	LP/SFL at 10 yr
RTOG 91-11[A]	Glottic & supragl.	**PFx3 → RT**	173	58% & 39%	68%
	N0-1, N2, N3	**CCRT (CDDP)**	172	55% & 28%	**82%**
	T2, T3^{+}, T3^{-}, T4	RT	173	54% & 32%	64%
EORTC 24954[B]	Larynx & Hypophar	**PF x 2-4 → RT**	224	49% & 34%	56%*
	T2-T4, N0-N2	PF alt. RT	286	52% & 32%	56%*

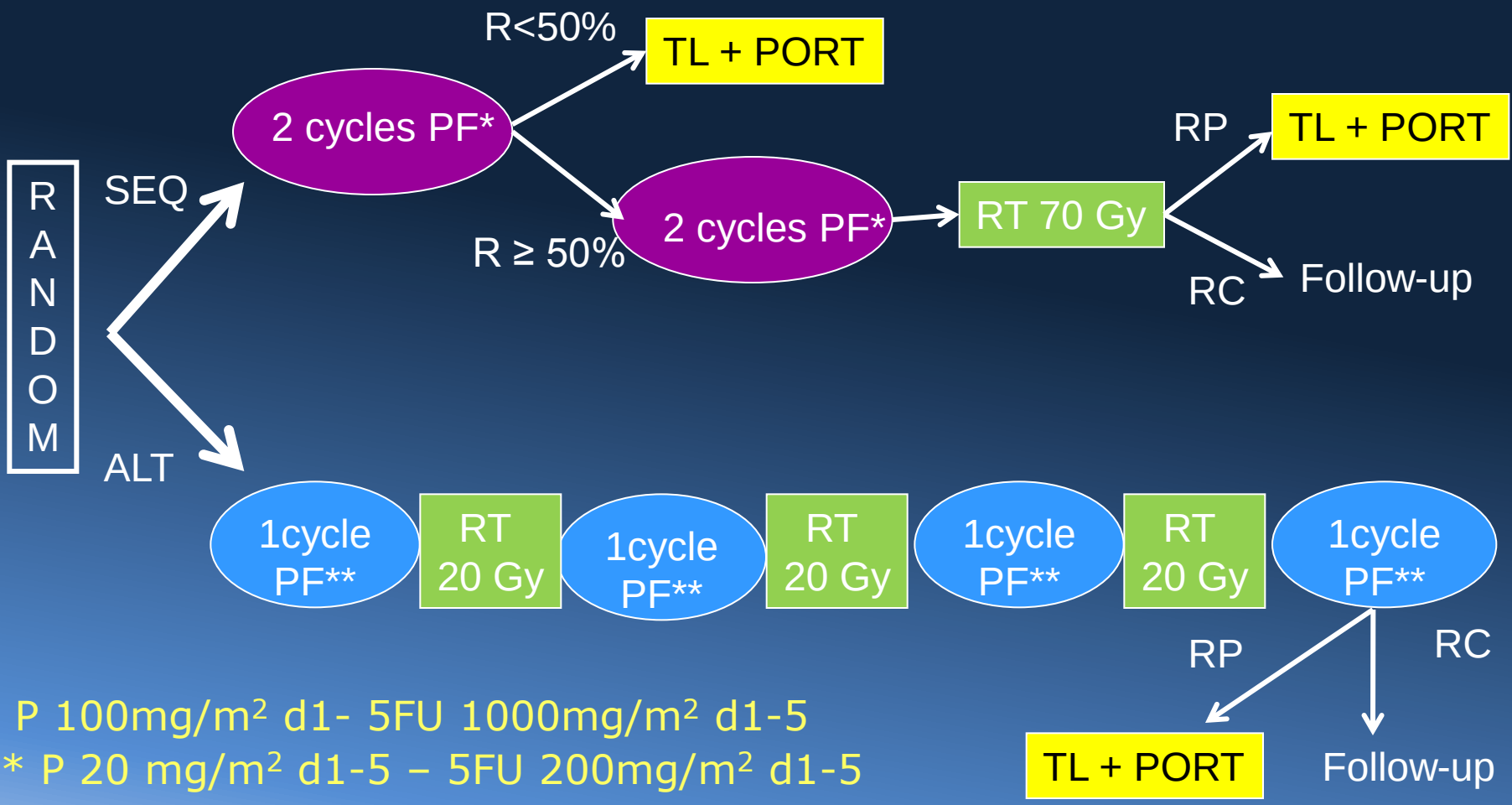
$^{+}$with fixed cord involvement; $^{-}$without cord fixation ; LP= larync preservation; SFL= survival with functional larynx

[A]Forastiere A et al, NEJM2003, ASCO 2006, JCO 2012 (LP= larynx in place; function: voice quality, swallowing & Qol questionnaire)

[B]Lefebvre JL et al, JNCI 2009, De Figueiredo et al EJC, 2016 (LP= larynx in place, no tumor, no tracheotomy, no feeding tube; function assessment : % of patients with intelligible voice, normal intake and normal breathing)

EORTC 24954

Eligible pts. (previously untreated larynx /hypopharynx) amenable to TL



* P 100mg/m² d1- 5FU 1000mg/m² d1-5

** P 20 mg/m² d1-5 – 5FU 200mg/m² d1-5

Lefebvre JL et al. J Natl Cancer Inst. 2009

EORTC 24954: Global Results at 5 Yrs

	Sequential (N=224)		Alternating (N=226)		
	Events	% without event	Events	% without event	p-value
Survival with functional larynx	160	30.5	154	36.2	0.15
Larynx preservation	107	53.2	94	59.8	0.10
Progression-free survival	140	41.0	139	41.8	0.75
Overall survival	125	48.5	122	51.9	0.45

Acute toxicity: SEQ > ALT
Late toxicity: SEQ = ALT

Lefebvre JL et al. J Natl Cancer Inst. 2009

Organ Preservation in Advanced Laryngeal Cancer
RTOG 91-11

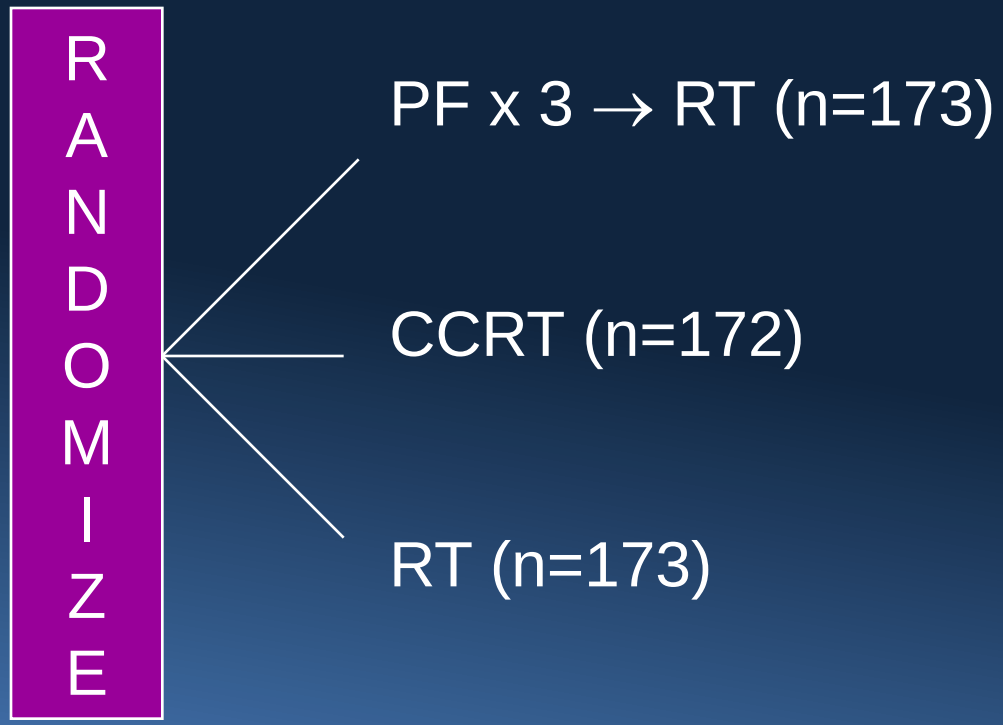
<u>Patients</u>

Stage III or IV

Glottic/supraglottic

SCC (excl. T1 and

Large volume T4)



PF = P 100 mg/m² (d1) and F 1000 mg/m d x 5

P during CCRT = 100 mg/m² d1, 22, 43

RT = 70 Gy, given in 35 fractions of 2 Gy over 7 weeks

Forastiere et al, 2003/2006/2012

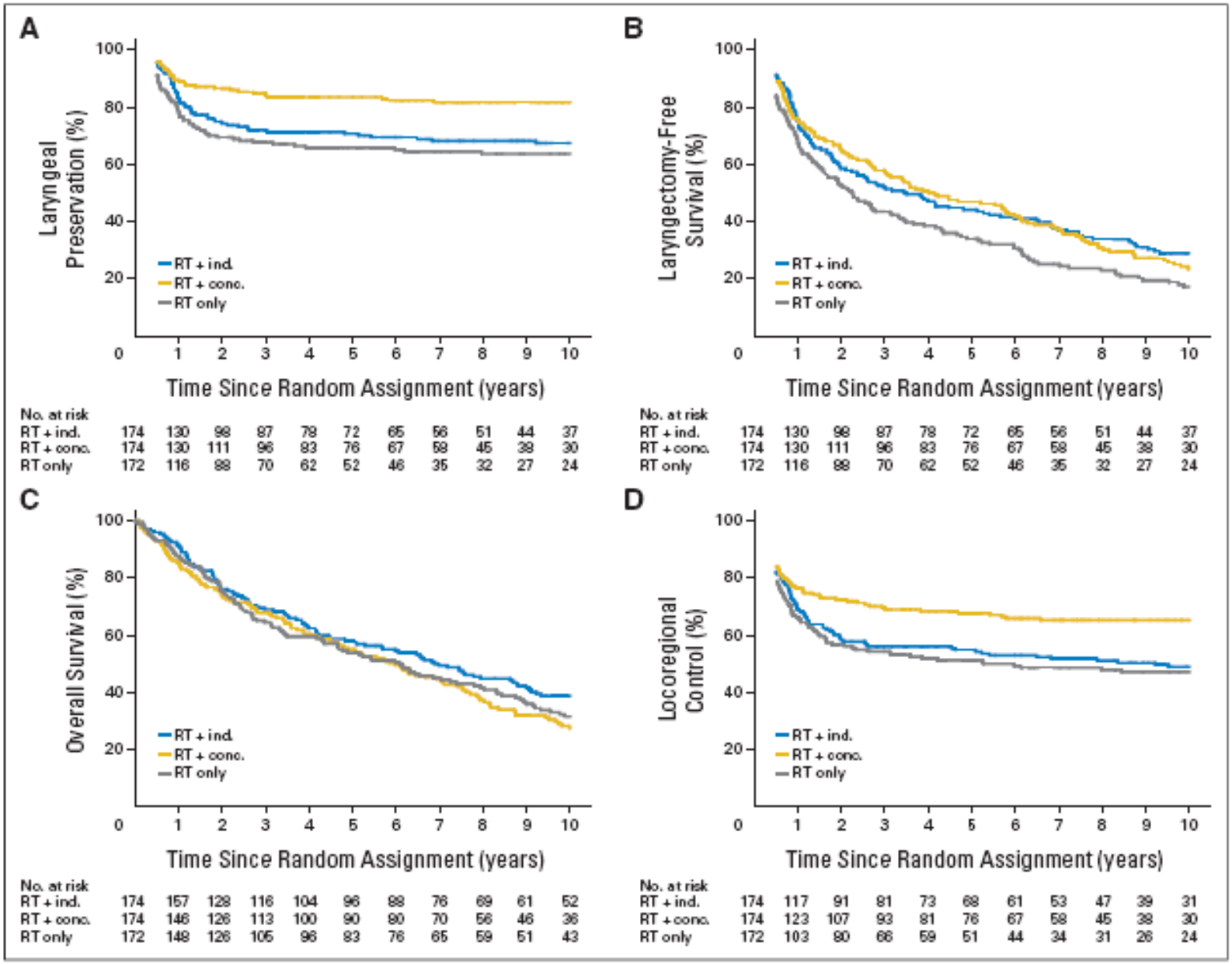


Fig 2. (A) Laryngeal preservation, (B) laryngectomy-free survival, (C) overall survival, and (D) locoregional control according to treatment group. conc., concomitant; ind., induction; RT, radiation therapy.

Forastiere et al, November 26, 2012 as 10.1200/JCO.2012.43.6097

RTOG 91-11 (10 years update) Phase III Trial of Larynx Preservation

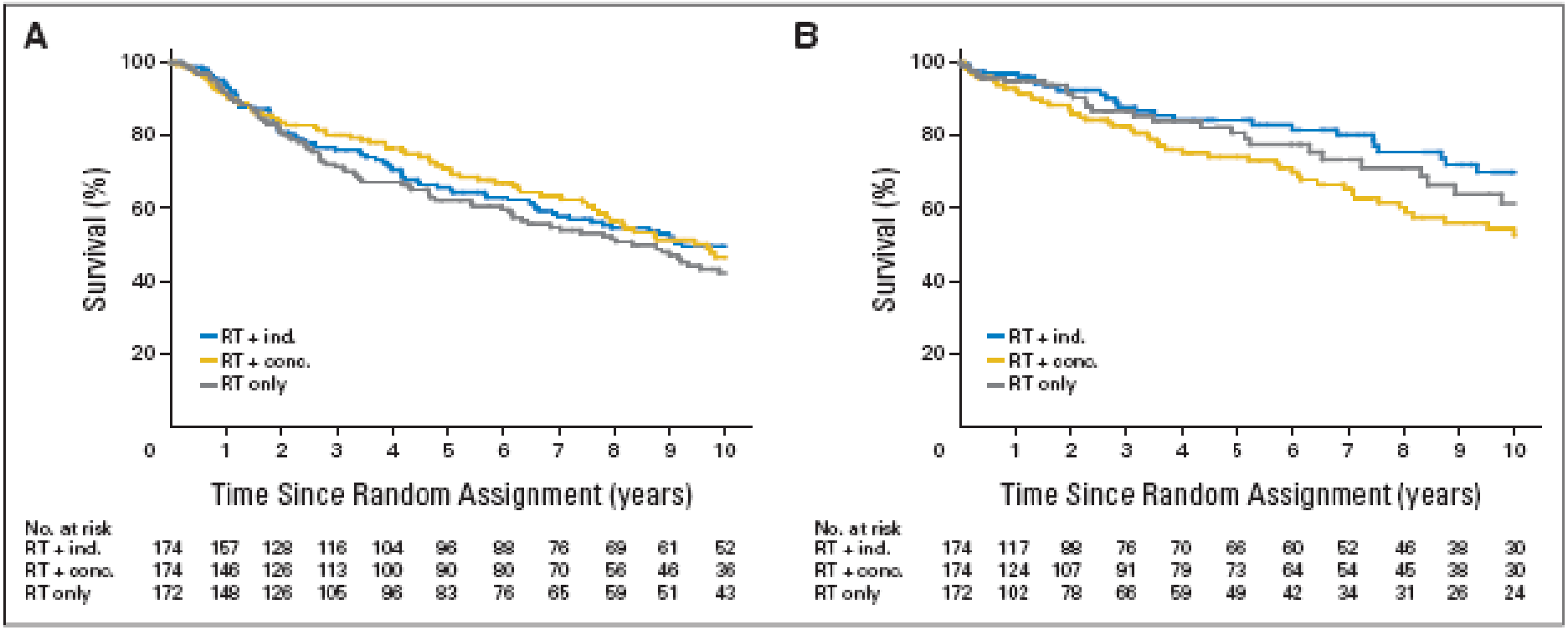
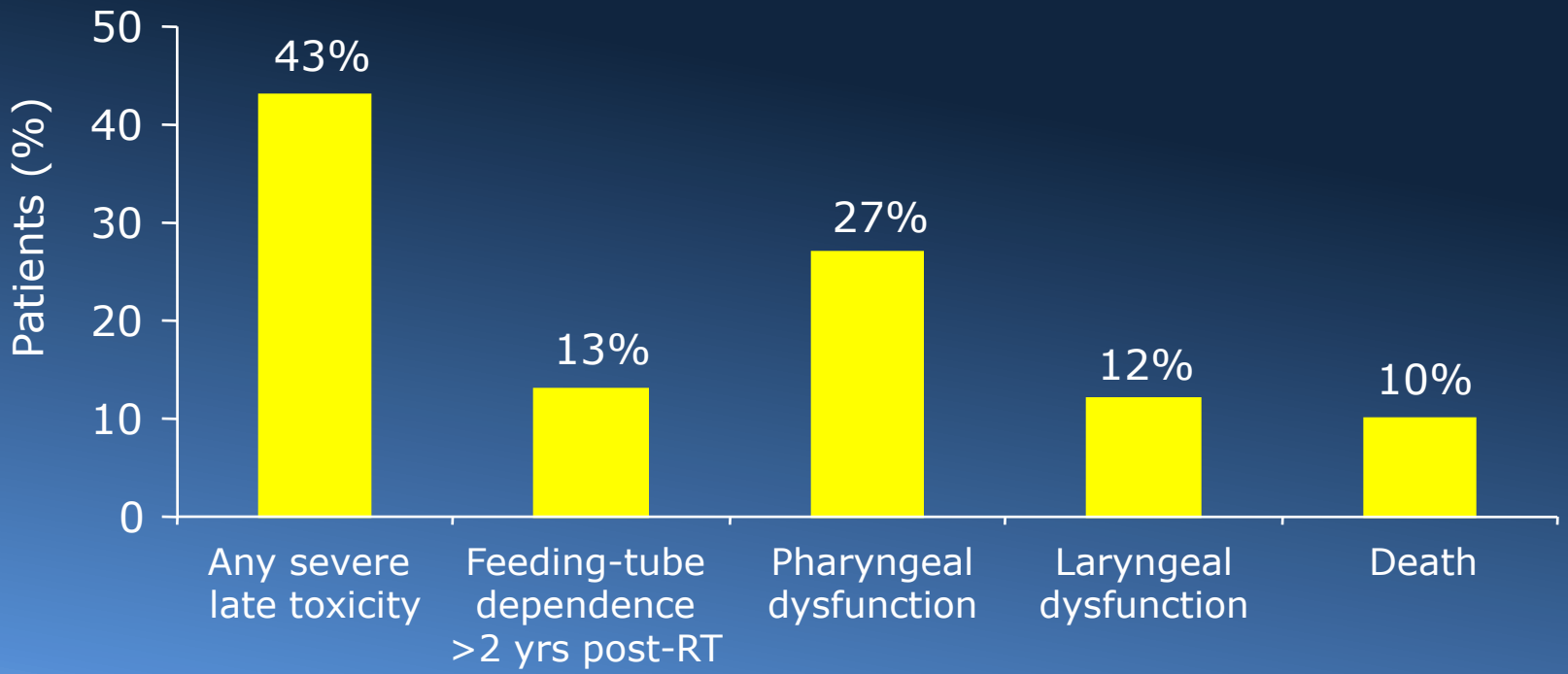


Fig 4. Survival, limited to (A) deaths from study cancer and (B) deaths not caused by study cancer according to treatment group. conc., concomitant; ind., induction; RT, radiation therapy.

Forastiere et al, November 26, 2012 as 10.1200/JCO.2012.43.6097. Exploratory analysis of death not caused by study cancer showed significant disadvantage for CCRT vs ICT→RT (52.8% vs 69.8%, respectively at 10 years; p=.03)

CCRT: Late Toxicity

- Analysis of 230 patients receiving CCRT in 3 studies (RTOG 91-11, 97-03, 99-14)



MVA: significant variables correlating with severe late toxicity were: older age (OR, 1.05 per year; p=.001), advanced T-stage (OR, 3.07; p=.0036), larynx/hypopharynx primary site (OR, 4.17; p=.0041) and neck dissection (OR, 2.39; p=.018)

Machtay M, et al. J Clin Oncol 2008; 26: 3582–3589

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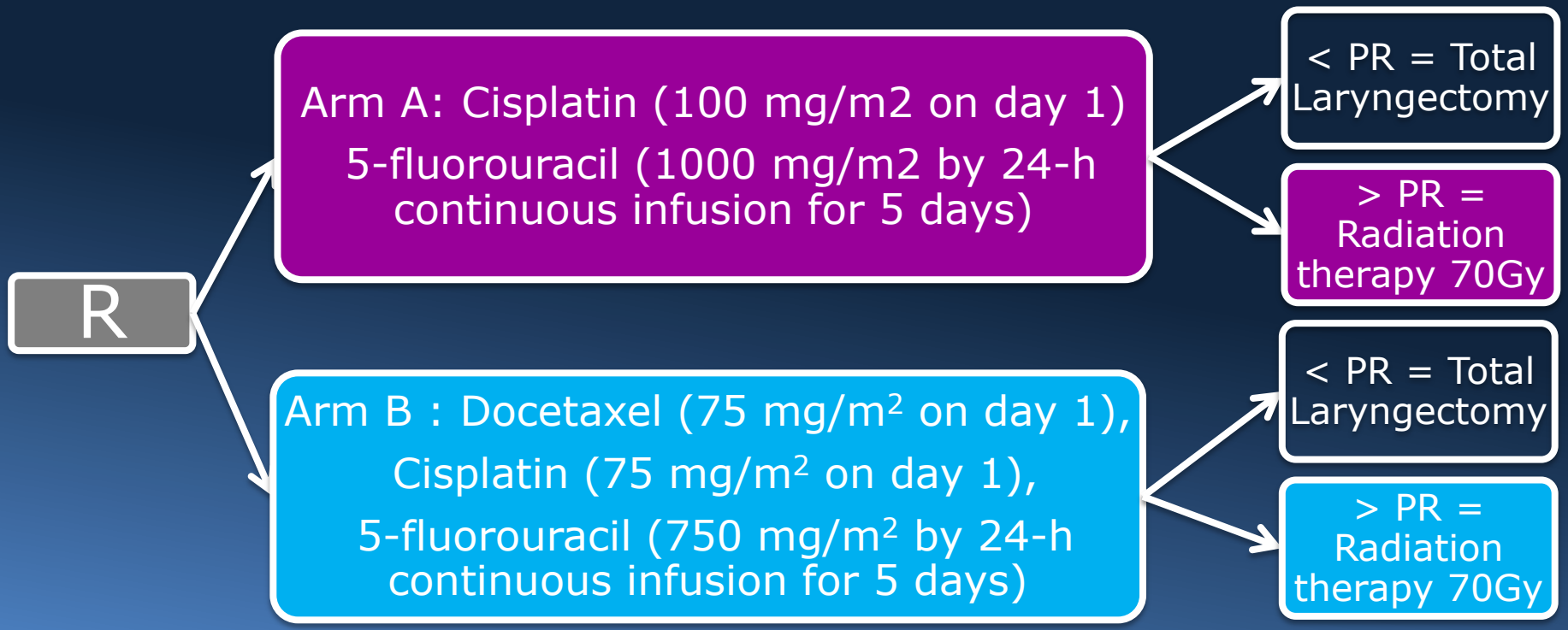
TPF: A Breakthrough in Induction Chemotherapy

- More efficacious (PFS, OS, larynx preservation)
  - *Posner MR et al. with TAX 324 (NEJM 2007)*
  - *Vermorken JB et al with TAX 323 (NEJM 2007)*
  - *Pointreau Y, Janoray et al. with TAX 323 regimen (JNCI 2009, JNCI 2016)*
- Less toxic (less G3-4 PLT↓, nausea/vomiting, stomatitis, hearing loss and toxic death): *European version*
- Better quality of life
  - *Van Herpen et al, BJC 2010; 103: 1173-1181*
- Cost-effective
  - *Liberato NL et al, Ann Oncol 2011 [ahead of print] doi: 10.1093/annonc/mdr545*

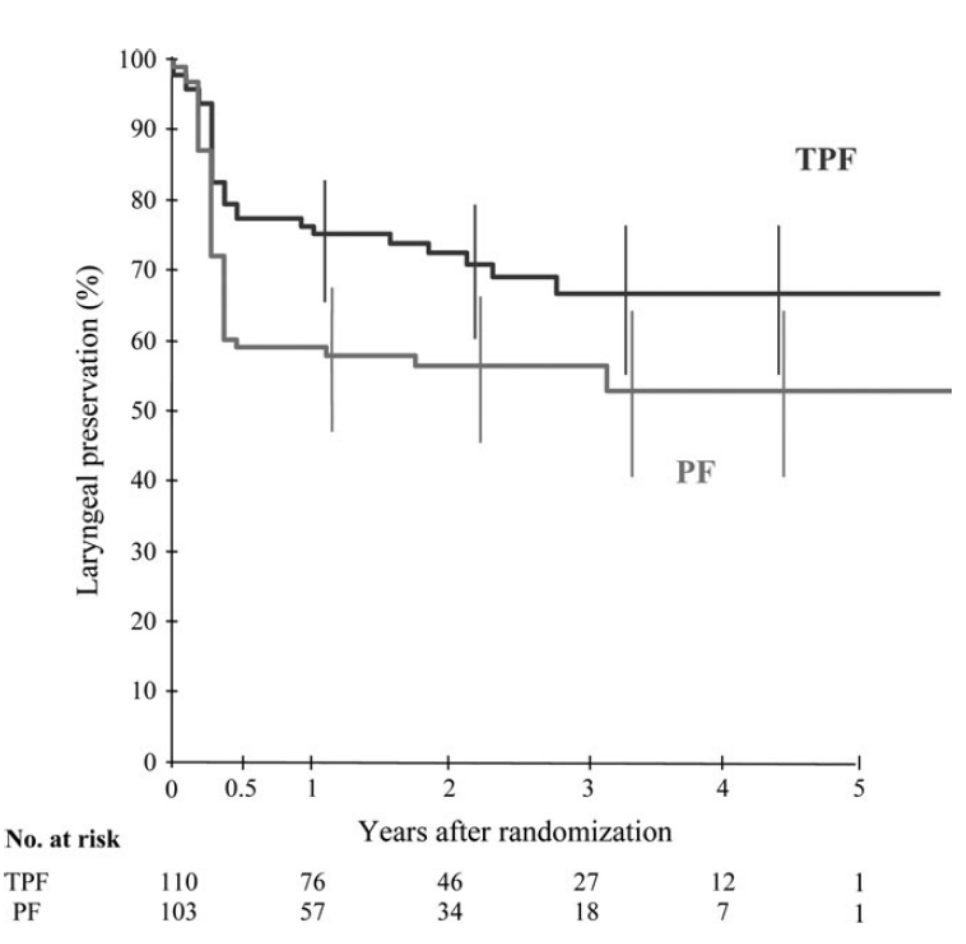
TPF vs PF for Larynx Preservation: GORTEC 2000-01



Eligible: Operable patients with untreated stage III or IV larynx or hypopharynx SCC, requiring total laryngectomy. Primary Endpoint : l3-year larynx-preservation rate. 213 patients included (103 in arm A, 110 in arm B)

Pointreau Y, et al. JNCI 2009; 101: 498-506; Janoray et al. JNCI 2016; 108: djv368

GORTEC 2000-01: PF w/wo Docetaxel for Larynx Preservation



At 3 years: LP 70.3% with TPF, 57.5% with PF (p=0.03)

Pointreau Y, et al. J Natl Cancer Inst 2009; 101: 498-506

Larynx Preservation Clinical Trial Design: Key Issues and Recommendations

A consensus panel summary

Recommendations were developed after reviewing results from completed phase III trials, meta-analyses, and published clinical reports available through November 2007

Recommendations: *the trial population should include patients with T2 or T3 laryngeal or hypopharyngeal SCCHN not considered for partial laryngectomy and exclude those with laryngeal dysfunction or age greater than 70 years. Functional assessments should include speech and swallowing. Voice should be routinely assessed with a simple, validated instrument. The primary endpoint should capture survival and function.*

Lefebvre JL and Ang KK. Int J Radiat Oncol Biol Phys 2009

New Endpoints in Larynx Preservation Trials

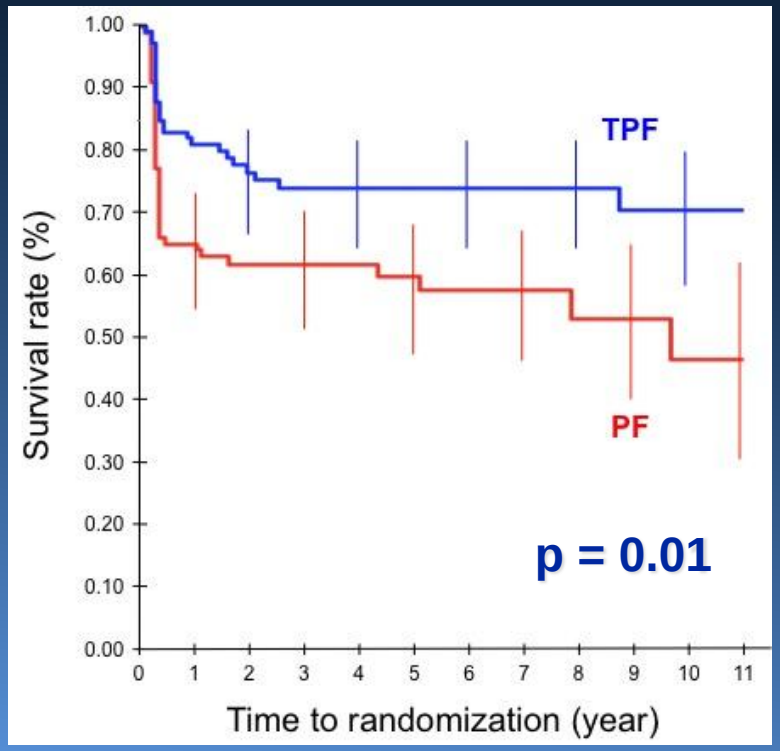
- Primary endpoint:
  - laryngo-esophageal dysfunction-free survival
  - events are
    - death
    - local failure
    - laryngectomy
    - trach for ≥ 2years
    - feeding tube ≥ 2 years

- Secondary endpoints:
    - overall survival
    - progression-free survival
    - locoregional control
    - time to tracheotomy
    - time to laryngectomy

Lefebvre JL and Ang KK. Int J Radiat Oncol Biol Phys 2009

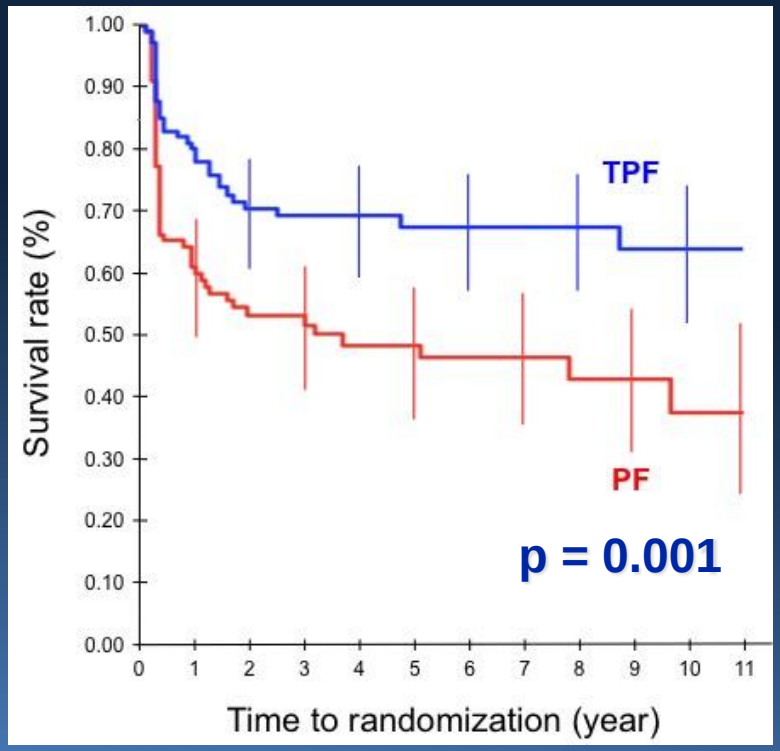
GORTEC 2000-01:Updated Results

Larynx Preservation*



10-yr LP rate 70.3% (TPF) vs 57.5% (PF)

Larynx DysFunction Free Survival

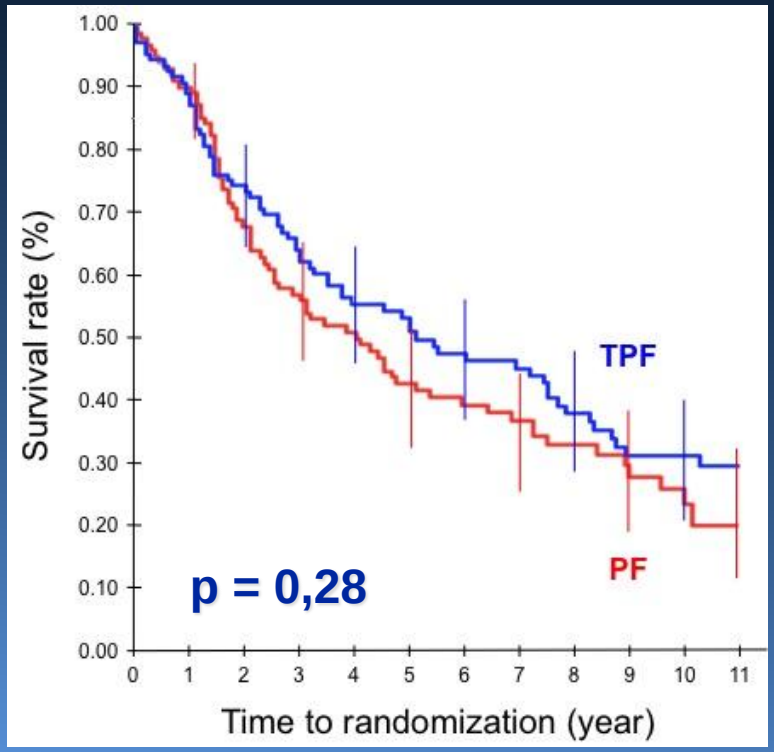


10-yr LDFFS rate 63.7% (TPF) vs 37.2% (PF)

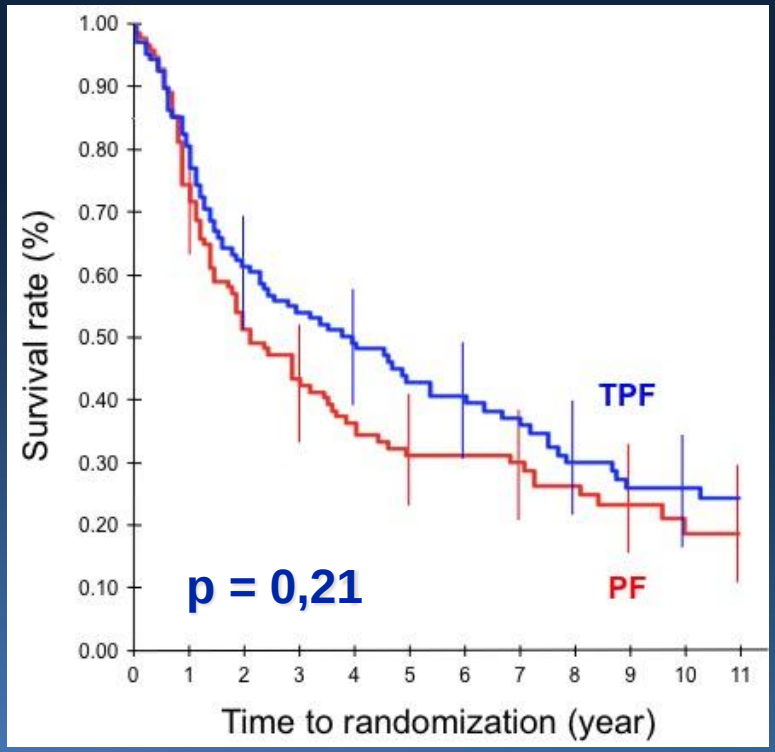
Janoray et al. J Natl Cancer Inst 2016; 108: djv368
** Larynx in place, no tumor, no tracheotomy, no feeding tube*

GORTEC 2000-01:Updated Results

Overall Survival



Disease Free Survival



Janoray et al. J Natl Cancer Inst 2016; 108: djv368

How Aggressive Should We be For Larynx Preservation?

SCRT: ICT followed by CCRT
substancial toxicity
best protocol still unknown
place of biotherapies

CCRT: RT + Px3
substancial toxicity
around 80 % larynx preservation
no impact on survival

triplet ICT: TPF followed by RT
still good tolerance/compliance to Tx
around 70 % larynx preservation
no impact on survival

doublet ICT: PF followed by RT
good tolerance/compliance to Tx
around 60 % larynx preservation
no impact on survival

Courtesy of J-L Lefebvre

Larynx Preservation Protocols: Recent Data

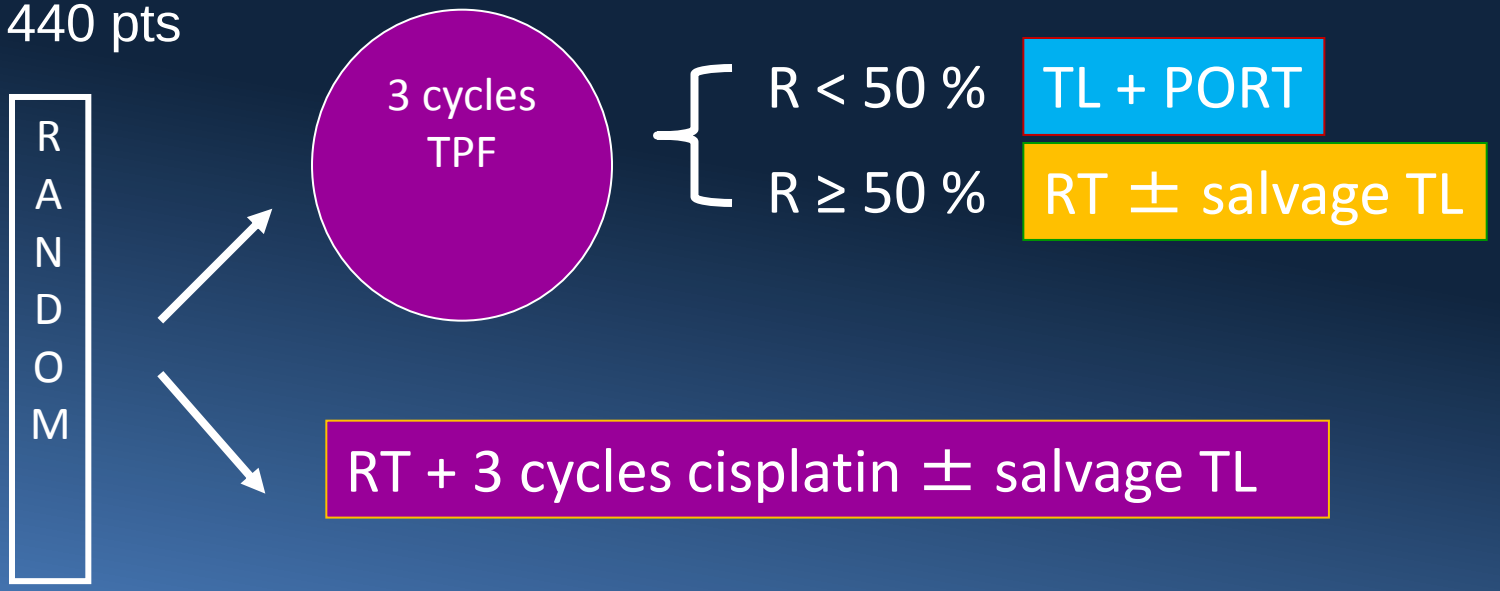
- Sequencial designs with cytotoxic agents only
- Induction chemotherapy followed by CCRT
  - TPF vs PF→RT + weekly carbo: feasible[1]
  - TPF→RT + cisplatin: difficult to tolerate[2] (better than TPF→RT)

- Sequential designs with integration of cetuximab
  - TPF→RT+ cetuximab: feasible[2] (better than TPF→RT?)
  - TPF→RT vs TPFE→RTE: not feasible[3]
  - TP→RT vs TPE→RTE: feasible[3] (better than TPF→RT?)

[1]Posner et al, Ann Oncol 2009; [2]Lefebvre et al, J Clin Oncol 2013, [3]Dietz et al, Ann Oncol (submitted)

SALTORL trial

Previously untreated T2-3, N0-2 larynx or hypopharynx SCC
non eligible for partial surgery
440 pts



Primary endpoint: laryngoesophageal dysfunction free survival

Secondary endpoints: overall survival, disease-free survival
locoregional control, feasibility of salvage surgery
quality of function

General Conclusions on Randomized Trials for Larynx Preservation

- Two validated options for LP as result of large RCTs
  - TPF followed by RT alone for larynx and hypopharynx ca.
  - RT + cisplatin (3 cycles) for larynx cancer

- Data on late toxicity induced by RT result from traditional irradiation techniques. Data of new RT techniques, such IMRT in LP are needed. In SALTORL, IMRT is mandatory

- The role of molecular targeted therapies remains to be determined.