AROI ICRO Pre conference Workshop-AROICON 2022

*Land mark Clinical Trials in Oncology - Past, Present and Future*

# Organ Preservation in Carcinoma Larynx and Hypopharynx

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# Initial Staging work-up

1. Careful history with special attention to tobacco abuse

2. Not only DL scopy as well as FOL/ indirect laryngoscopy for cord status

3. Imaging: Locoregional and distant

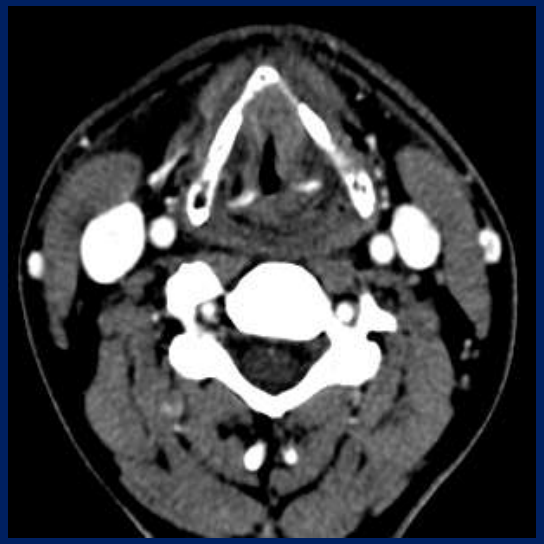
4. Functional evaluation:
    1. FEES
    2. Barium Swallow
    3. Modified Water swallow test
    4. Video fluoroscopy

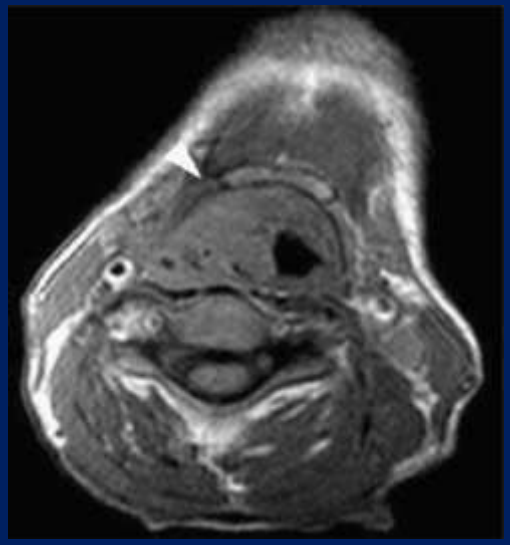
- Dental Evaluation if RT is being considered
- Nutritional assessment

# Imaging

- Used to assess the extent of disease and nodal involvement.

- Multidetector CT is the first line imaging investigation for staging laryngeal carcinoma.
- Sensitivity, specificity and accuracy rates of 92%, 100%, and 93% respectively.#
- CT can upstage upto 21% of early Ca glottis.*





- MRI has a sensitivity of 89-94%, a specificity of 74-88%, and negative predictive value of 94-96% for the detection of neoplastic cartilage invasion.#

# Lell et.al. Multiplanar functional imaging of the larynx and hypopharynx with multislice spiral CT.Eur Radiol 2004;14:2198-2205

* Barbera L, Groome PA, Mackillop WJ, et al. The role of computed tomography in the T classification of laryngeal carcinoma. Cancer 2001;91(2):394–407

# Laryngopharyngeal Cancers

- Single modality treatment for stage I and Stage II disease (either surgery or RT) with focus on voice preservation and long term toxicity (Not being covered)
- Patients with T3 cancers: Organ preserving surgery vs Radical Surgery vs CTRT : ???? Equivalent locoregional control
- Patients with involvement of cartilaginous framework (T4 disease): Total Laryngectomy f/b PORT with voice rehabilitation for optimal disease control
- Organ preservation is not the same as Function preservation
- Long term toxicities of organ preservation need special attention

# Endpoints of Interest

- Local control
- Ultimate Local control
- Cause specific survival
- Overall survival

} Good disease control

- Voice preservation
- Preservation of swallowing
- Respiration preservation
- Reduce chances of aspiration
- Acceptable QOL

} Preservation of organ and function

Head & Neck Cancers (Advanced)

# Organ Preservation Strategies

- **Shift in focus from**

  **survival** ↓

  **organ preservation**

  ↓

  **organ function conservation**

- **No compromise in the cure rates**
- **Surgery reserved for salvage**

# Basis of the Idea

- Favorable responses to NACT prior to surgery
- High rates of CR
- Uncompromised survival
- Favorable responses to NACT predict favorable responses to RT
- Pilot studies – avoidance of surgery and prolonged survival with laryngeal preservation in Laryngo –hypopharyngeal tumors (Karp/Jacobs /Urba *et al*.)
- Patient preferences and Quality of Life (QoL)

# Early attempts

- Harwood/ Croll- T3N0 Glottis , selected T4( without gross cartilage invasion or LN mets ), T3/4N0M0 Supraglottis
  - ✓50% survival at 5 yrs
  - ✓Larynx preserved in 2/3
  - ✓In survivors – upto ¾
  - ✓How to select
  - ✓**NACT emerged as an effective method of triage**

Two approaches were under discussion:

(a) Induction PF followed by RT in good responders (tumor regression of at least 50%) or by surgery in other patients and

(b) upfront surgery and postoperative RT.

# Intact Laryngeal function: Non surgical Conservation

- Organ Conservation Protocols

✓ Induction chemotherapy

✓ Concurrent CTRT

Concurrent RT with Targeted therapy: Bonner
Induction CT +/- Targeted therapy: TREMPLIN, DeLOS II

✓ NACT- CTRT

✓ Altered fractionation

# INDUCTION CHEMOTHERAPY PLUS RADIATION COMPARED WITH SURGERY PLUS RADIATION IN PATIENTS WITH ADVANCED LARYNGEAL CANCER

THE DEPARTMENT OF VETERANS AFFAIRS LARYNGEAL CANCER STUDY GROUP*

322 Patients (Stage III and IV)

R

166
Upfront Surgery + PORT

166
Induction chemotherapy f/b Definitive RT

Cisplatin(P) +5FU(F) on Day 1,22,43

If PR/CR after 2 # 3rd cycle f/b RT

If no response Surgery f/b PORT

| Treatment schedule | | | |
|---|---|---|---|
| Inj Cisplatinum | 100 mg/m2 | Rapid IV infusion | D1, D22, D43 |
| Inj 5-FU | 1000 mg/m2 | Continuous 24-hour IV infusion | For 5 days (following above, D1, D22, D43) |
| Definitive RT | 6600 to 7600 cGy to the primary tumor site | Doses to the nodes:<br>N0: 5000 cGy<br>cN< 2cm: 6600 cGy<br>cN: 2 - 4cm: 7000 cGy<br>cN: >4cm: 7500 cGy<br>All areas presumed to be at risk for microscopic disease received at least 5000 to 5040 cGy. | • Dose to the spinal cord< 4500 cGy.<br>• Conventional fractionation @200cGy/ #<br>• 5#/ week |
| Adjuvant RT | At high risk for a local recurrence: 5000 to 5040 cGy + 1000 cGy.<br>At normal risk: 5000 to 5040 cGy.<br>Any residual disease: 5000 to 5040 cGy plus an additional 1500 to 2380 cGy. | | |
| All surgery was dependant on extent of disease | | | |

- Response assessment: Physical examination, IDL (Days 18-21, after start of C2)

CR: complete disappearance of all clinically evident tumor
PR: 50 percent reduction in the sum of the product of the longest dimension and its perpendicular for each tumor, as compared with the initial tumor dimensions.

- Responses at Primary and Node were graded separately

- Response of the primary tumor determined the patient's eligibility to proceed with radiation.
- Patients with at least a partial response at the primary tumor site and no progression of any neck adenopathy received a third cycle of chemotherapy and definitive radiation.

- Patients without at least a partial response in the larynx and those with any evidence of disease progression (including neck disease) underwent immediate surgical resection and postoperative radiation therapy.

- After the induction chemotherapy was completed, a direct laryngoscopy, a tumor assessment, and a biopsy of the primary tumor were performed to obtain histologic confirmation of the response.

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Table 1. Characteristics of the Patients According to Treatment Assignment.

| Characteristic | Surgery | Chemotherapy | All |
|---|---|---|---|
| No. of patients | 166 | 166 | 332 |
| Stage | | | |
| III | 95 | 93 | 188 |
| IV | 71 | 73 | 144 |
| Tumor class | | | |
| T1,2 | 15 | 16 | 31 |
| T3 | 109 | 107 | 216 |
| T4 | 42 | 43 | 85 |
| Node class | | | |
| N0 | 94 | 86 | 180 |
| | | 34 | 60 |
| | | 16 | 37 |
| | | 30 | 55 |
| | | 61 | 124 |
| | | 105 | 208 |
| | | 17 | 30 |
| | | 90 | 188 |

| | |
|---|---|
| T1/T2 | 9% |
| T3 | 65% |
| T4 | 26% |

| | |
|---|---|
| Supraglottis | 63% |
| Glottis | 37% |

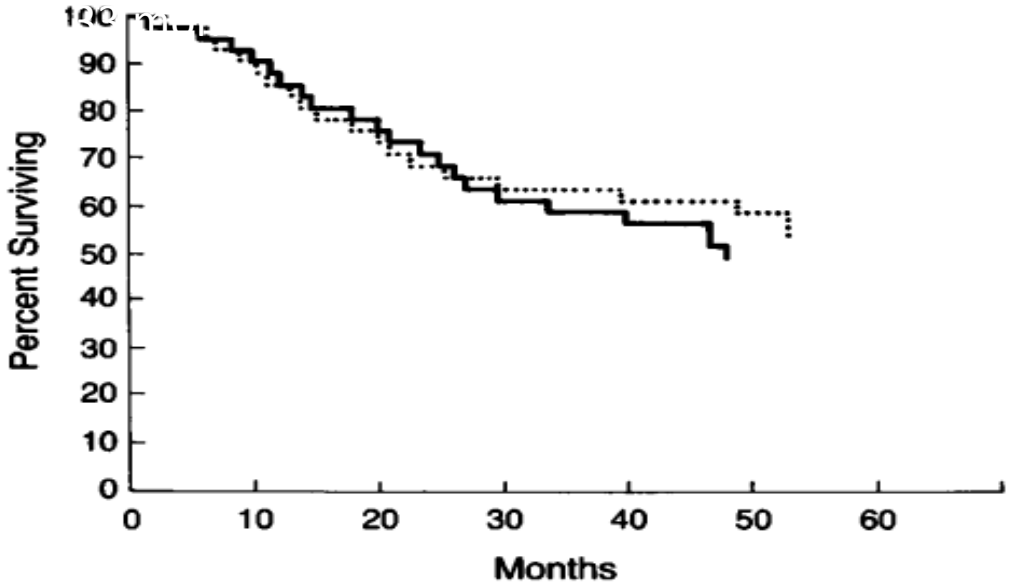



Figure 1. Overall Survival of 332 Patients Randomly Assigned to Induction Chemotherapy and Radiation Therapy (Solid Line) or Conventional Laryngectomy and Postoperative Radiation (Dotted Line).

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

- In the induction chemotherapy plus RT group, at 2 years **64% of all patients retained their larynx**, and 64% were free of disease.

| Stage/T size | Rate of Salvage laryngectomy |
|---|---|
| III/IV | 29%/44% |
| T3 or lesser/T4 | 29%/56% |

## Table 2. Causes of Death, According to Treatment Assignment.

| Cause | Surgery (N = 166) | Chemotherapy (N = 166) |
|---|---|---|
| | *no. of patients (%)* | |
| Cancer | 38 (23) | 42 (25) |
| Complication of therapy | 4 (2) | 4 (2) |
| Other | 14 (8) | 13 (8) |
| Unknown | 2 (1) | 6 (4) |
| All | 58 (35) | 65 (39) |

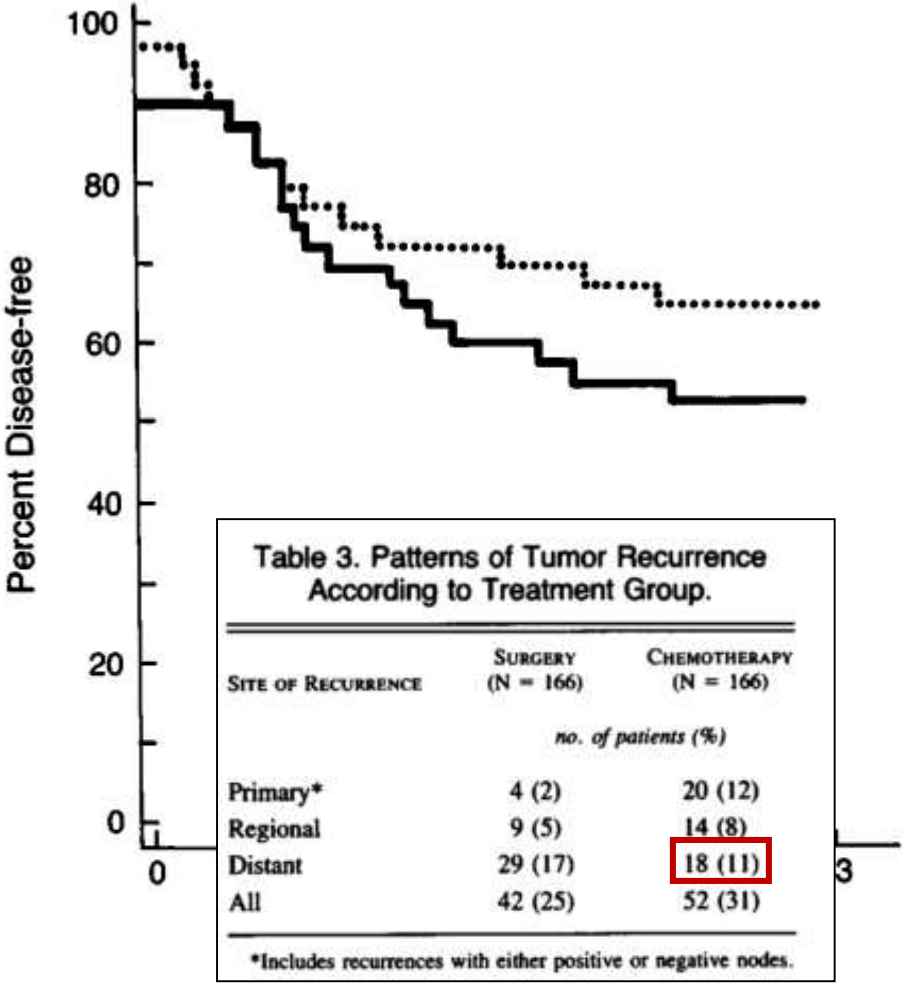
## Table 4. Prognostic Factors for Clinical Complete Tumor Regression After Induction Chemotherapy in Advanced Laryngeal Carcinoma (logistic regression)

| Variable | Single | Multivariable | Stepwise |
|---|---|---|---|
| T-class (T1-3 *v* T4) | .0191 | .1880 | |
| Karnofsky PS (< 80 *v* > 80) | .0967 | .0929 | |
| WBC count (< 5,000, 5,000-10,000 > 10,000/μL) | .0741 | .1175 | |
| Hgb (< mean *v* > mean) | .0741 | .6342 | |
| T size (> 4, 4-9, 10-14, > 15 cm) | .0103 | .0421 | .0075 |
| Growth pattern (1, 2 *v* 3, 4)* | .0205 | .0115 | .0093 |

NOTE. Not significant variables were as follows: nodes, age, site, other histology, tumor grade.

Abbreviations: T, tumor; PS, performance status; Hgb, hemoglobin.

*1, 2 = pushing borders or well-formed infiltrating cords; 3, 4 = thin, irregular infiltrating cords or groups of cells or dissociated cells.




### 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.

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).

**Complete responders had better outcomes**

This study set the stage for further larynx preservation studies and established induction chemotherapy as standard of care.

# Critique

- The control rates for T3 cancers (65% of enrolled patients) were similar to historic published results with radiation alone and were a basis for criticism by radiation oncologists who argued that a comparator radiation-alone arm was needed.

- Anatomical rather than functional larynx preservation

- Non responders→ All total laryngectomy??

# When did it not work?

- Fixed cord
- Cartilage invasion
- T4 vs T3 ( attained statistical significance )
- Stage IV tumors ( attained statistical significance )

*Additionally*

- Local recurrences – 30 to 70 % , 70% within 1 yr

# 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*

**Results:** Patients randomized to the CT + RT group had significantly better ($P<.05$) quality-of-life scores on the SF-36 mental health domain (76.0) than the surgery and RT group (63.0), and also had better HNQOL pain scores (81.3 vs 64.3). Compared with patients who underwent laryngectomy, patients with intact larynges (CT + RT with larynx) had significantly less bodily pain (88.5 vs 56.5), better scores on the SF-36 mental health (79.8 vs 64.7), and better HNQOL emotion (89.7 vs 79.4) scores. More patients in the surgery and RT group (28%) were depressed than in the CT + RT group (15%).

- Pts who had successful **organ preservation tended to have better scores** on all domains of SF-36 compared to laryngectomy
- Pts who had successful organ preservation are associated with **better quality of life related to freedom from pain, better emotional well-being and lower levels of depression**.

Terrell JE et al. Arch Otolaryngol Head Neck Surg. 1998

# 1996: EORTC 24891 trial:
## First randomized trial of Organ Preservation in Hypopharyngeal Cancers

Larynx Preservation in Pyriform Sinus Cancer: Preliminary Results of a European Organization for Research and Treatment of Cancer Phase III Trial

*Jean-Louis Lefebvre, Dominique Chevalier, Bernard Luboinski, Anne Kirkpatrick, Laurence Collette, Tarek Sahmoud**

*For the EORTC Head and Neck Cancer Cooperative Group*

Journal of the National Cancer Institute, Vol. 88, No. 13, July 3, 1996

# Hypopharyngeal Cancers: EORTC:24891

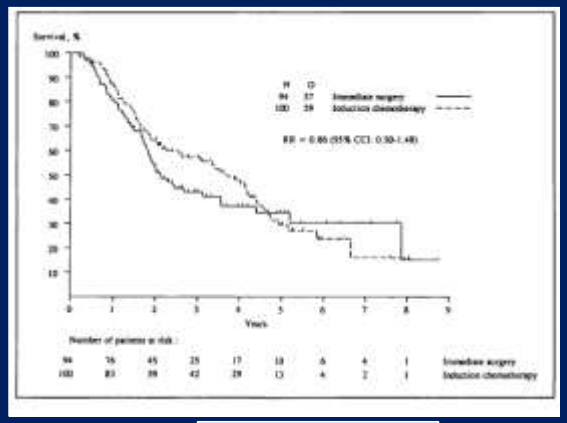
194 (202) Patients Hypophayrnx Squamous Cancer StageII, III,IV

- Surgery → Adjuvant RT → RT 50Gy/25#
- Induction Chemo (IC) x2 Cisplatin/5FU
  - IC x1 → Definitive RT
  - RT 66-76Gy
  - Non responders: Surgery +/-PORT

| | |
|---|---|
| T2 | 20% |
| T3 | 75% |
| T4 | 5% |

| | |
|---|---|
| Pyriform Sinus | 78% |
| Aryepiglottic fold | 22% |

Median survival (immediate surgery): 25 months vs (ICT) 44 months

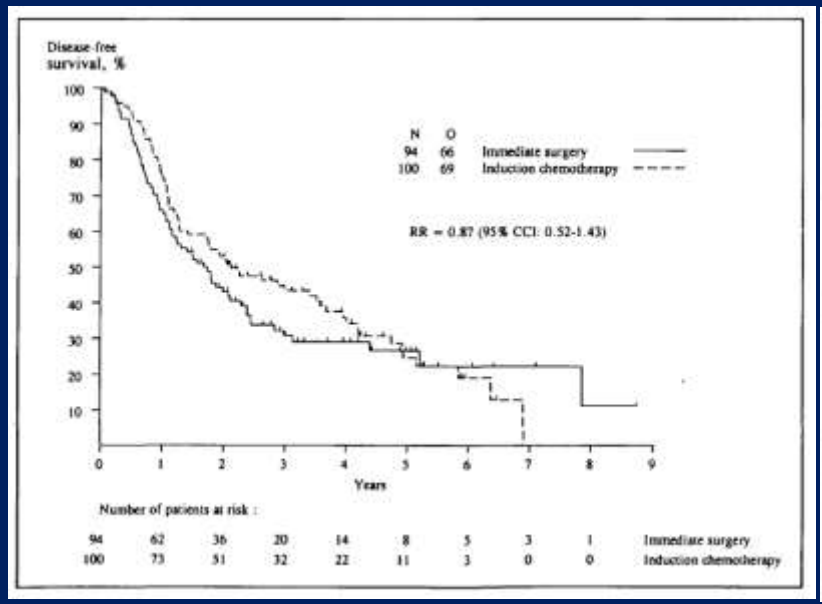


Overall Survival

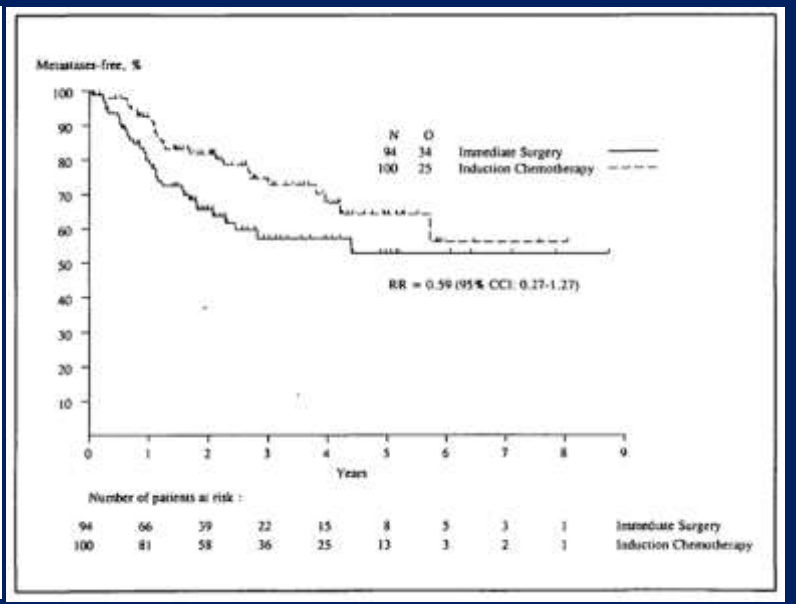
**3 year Functional Larynx Preservation Rate: 42%**

Lefebvre JL et al. JNCI 1996

## Disease free survival

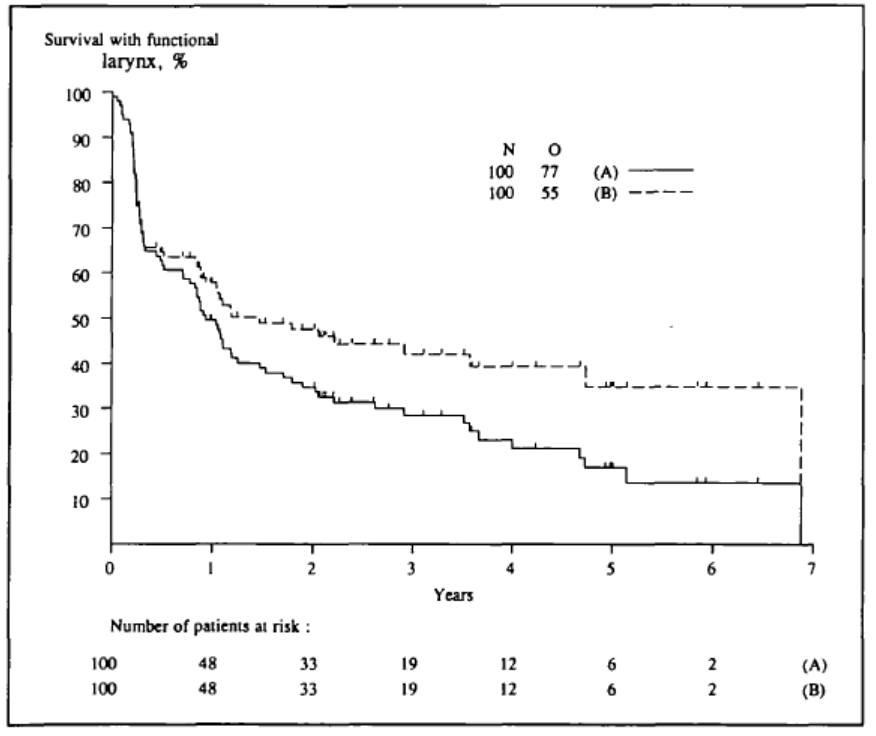



## Metastasis Free Survival




- Treatment failures at local, regional and second primary sites occurred at approximately the same frequencies in both arms
- Fewer failures at distant sites in the induction-chemotherapy arm

# Larynx Preservation




3- and 5-year estimates of retaining a functional larynx in patients in the ICT arm 42% and 35%, respectively

# Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891

**Table 2.** Pattern of failure

| Sites of failure[a] last failure (%) | Surgery arm ($n = 94$) | | | Chemotherapy arm ($n = 100$) | | |
|---|---|---|---|---|---|---|
| | Initial number of failures ($n$) | Number salvaged | Ultimate[b] number of failures, $n$ (%) | Initial number of failures ($n$) | Number salvaged | Ultimate[b] number of failures, $n$ (%) |
| Local | 13 | 2 | 11 (11.7) | 20 | 6 | 14 (14.0) |
| Regional | 20 | 2 | 18 (19.1) | 24 | 5 | 19 (19.0) |
| Distant | 34 | 0 | 34 (36.2) | 28 | 0 | 28 (28.0) |

**Background:** W… immediate surger… **Material and m**… laryngectomy wit… to three… comple… noninfe… survival… **Result**… patients… 13.8% respect… **Concl**… half of t…

…rvation approach to …approach (total …hemotherapy arm up …)wed for …ll survival [OS, …PFS) and …and 49 …ear OS rate was …0.8%, …wed more than

| | 3 years (%) | | 10 years (%) | |
|---|---|---|---|---|
| | Surgery | ICT | Surgery | ICT |
| OS | 43 | 57 | 13.8 | 13.1 |
| DFS | 31 | 43 | - | - |
| PFS | - | - | 8.5 | 10.8 |
| Larynx preservation | - | 42 | - | 8.7 |

Annals of Oncology 23: 2708–2714, 2012, doi:10.1093/annonc/mds065

# EORTC 24891 vs VA trial

| | VA trial (n=332) | EORTC 24891 (n=194) |
|---|---|---|
| Inclusion<br><br>Exclusion | Glottic, Supraglottic or Subglottic<br>T1N1 | PFS or AE fold<br><br>N2c tumors excluded after amendment |
| Treatment Arms | Neck dissection not done in T3N0 and midline T4N0 | All patients underwent neck dissection |
| Survival Endpoints<br>Chemo response | 2 year OS 68% in both arm<br>31% had complete response to 2 cycle of Chemo | 3 year OS 43% Sx arm, 57% IC arm<br>54% had CR to 2-3 cycles of chemo |
| Larynx Preservation | 2 year Larynx Preservation 66% in IC arm | 3 and 5 year functional Larynx survival 42% and 35% in IC arm |
| Pattern of failure | Local and Regional Failure higher in IC arm, Distant metastasis higher in Sx arm | No difference in local or locoregional failure in 2 arms, Higher number of distant metastasis in Surgery arm |
| Other Prognostic Factors | Volume of disease, T4 stage | T4 stage, Nodal status, ECOG PS |

- Induction chemotherapy was validated both for laryngeal and hypopharyngeal cancers
- Larynx could be preserved in about two-thirds of the patients without compromising survival or disease control.

**BUT** the definition of “laryngeal preservation” had to be clearly defined.

- ✓ Consider both the organ and its function
- ✓ No laryngectomy
- ✓ No long-term tracheotomy and
- ✓ No long-term feeding tube

*NACT had minimal impact on overall survival…..*

*There was need for more intensive local therapy.*

# RTOG 91-11

547 Patients Laryngeal Squamous Cancer StageII III,IV

- Induction Chemo (IC) x2 Cisplatin/5FU
  - Response → RT +/- salvage surgery
  - No response → Surgery +/-PORT
- Concurrent CT+RT
- RT alone

| | |
|---|---|
| T2 | 12% |
| T3 | 78% |
| T4 | 10% |

| | |
|---|---|
| Supraglottis | 69% |
| Glottis | 31% |

The primary end point used for sample size calculation was the composite end point, **laryngectomy-free survival**

| 2 yr (Median FU: 3.8 years) | Local Control | DFS | OAS | Intact Larynx | Laryngectomy free survival | Distant Mets |
|---|---|---|---|---|---|---|
| Induction Chemo | 61% | 38% | 55% | 75% | 59%, 43% (5yr) | 15% |
| CT+RT | 78% | 36% | 54% | 88% | 66% 45% (5yr) | 12% |
| RT alone | 56% | 27% | 56% | 70% | 53% 38% (5yr) | 22% |

Forastiere A et al. NEJM 2003

- Higher Larynx preservation  in CTRT arm
- Locoregional control was also significantly better with CTRT
- Both of the chemotherapy-based regimens suppressed distant metastases and resulted in better disease-free survival than radiotherapy alone
- Overall survival rates were similar in all three groups
- High-grade toxic effects was greater with the chemotherapy-based regimens
- The mucosal toxicity of concurrent radiotherapy and cisplatin was nearly twice as frequent as the mucosal toxicity of the other two treatments during radiotherapy

# Long-Term Results of RTOG 91-11: A Comparison of Three Nonsurgical Treatment Strategies to Preserve the Larynx in Patients With Locally Advanced Larynx Cancer

*Arlene A. Forastiere, Qiang Zhang, Randal S. Weber, Moshe H. Maor, Helmuth Goepfert, Thomas F. Pajak, William Morrison, Bonnie Glisson, Andy Trotti, John A. Ridge, Wade Thorstad, Henry Wagner, John F. Ensley,*

- Afte… …nificant diffe…
- Afte… …te favo… …ant (Nor…
- LP(8… …mitant cispl…
- **Lary… …t arm (23%… …oup.**
- Late…

**Table 3.** Cause of Death

| Cause of Death | RT + Induction Chemotherapy | | RT + Concomitant Chemotherapy | | RT Alone | |
|---|---|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % | No. of Patients | % |
| Cancer under study | 45 | 37.5 | 38 | 29.2 | 60 | 48.4 |
| Second malignancy | 15 | 12.5 | 18 | 13.8 | 15 | 12.1 |
| Complications of protocol treatment | 9 | 7.5 | 9 | 6.9 | 5 | 4.0 |
| Complications of other treatment | 3 | 2.5 | 2 | 1.5 | 3 | 2.4 |
| Unrelated to cancer or treatment | 25 | 20.8 | 40 | 30.8 | 21 | 16.9 |
| Unknown/not reported | 23 | 19.2 | 23 | 17.7 | 20 | 16.1 |
| Total deaths | 120 | | 130 | | 124 | |

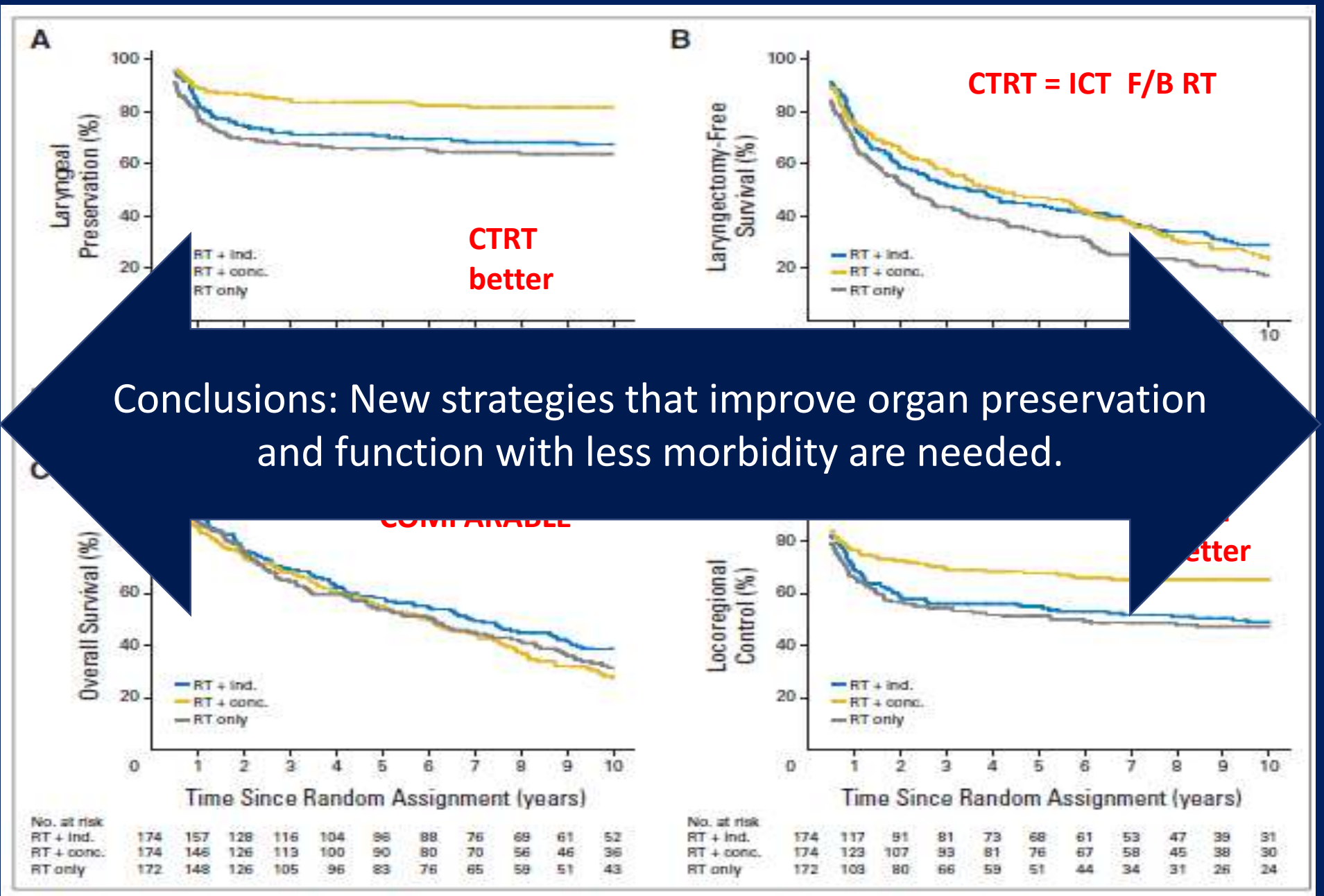
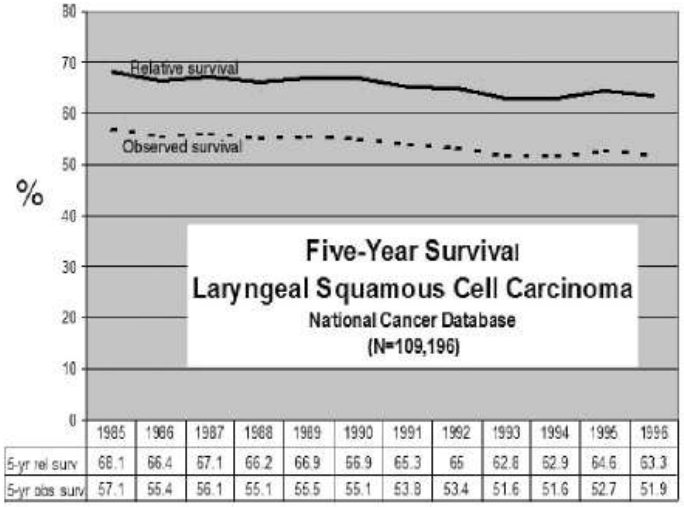



**Fig 2.** (A) Laryngeal preservation, (B) laryngectomy-free survival, (C) overall survival, and (D) locoregional control according to treatment group. conc., concomitant; ind., induction; RT, radiation therapy.

*The Laryngoscope*
Lippincott Williams & Wilkins, Inc.

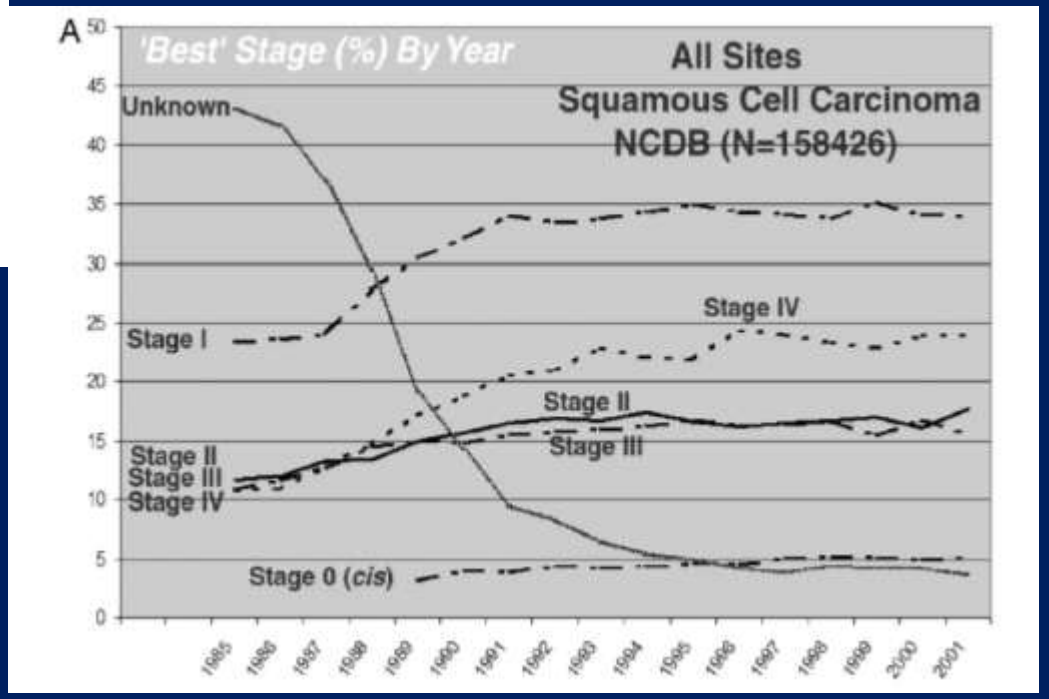

# Laryngeal Cancer in the United States: Changes in Demographics, Patterns of Care, and Survival

Henry T. Hoffman, MD, MS, FACS; Kimberly Porter, MPH; Lucy H. Karnell, PhD; Jay S. Cooper, MD; Randall S. Weber, MD; Corey J. Langer, MD; Kie-Kian Ang, MD, PhD; Greer Gay, PhD; Andrew Stewart, MA; Robert A. Robinson, MD, PhD




| | 1985 | 1986 | 1987 | 1988 | 1989 | 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5-yr rel surv | 68.1 | 66.4 | 67.1 | 66.2 | 66.9 | 66.9 | 65.3 | 65 | 62.8 | 62.9 | 64.6 | 63.3 |
| 5-yr obs surv | 57.1 | 55.4 | 56.1 | 55.1 | 55.5 | 55.1 | 53.8 | 53.4 | 51.6 | 51.6 | 52.7 | 51.9 |

Fig. 2. Survival for patients with laryngeal squamous cell carcinoma within the NCDB decreased progressively from the mid-1980s to the mid-1990s.



# LARYNX PRESERVATION CLINICAL TRIAL DESIGN: KEY ISSUES AND RECOMMENDATIONS—A CONSENSUS PANEL SUMMARY

JEAN-LOUIS LEFEBVRE, M.D.,* AND K. KIAN ANG, M.D.,† ON BEHALF OF THE LARYNX PRESERVATION CONSENSUS PANEL

I. J. Radiation Oncology ● Biology ● Physics Volume 73, Number 5, 2009

**Purpose:** To develop guidelines for the conduct of Phase III clinical trials of larynx preservation in patients with locally advanced laryngeal and hypopharyngeal cancer.

**Methods and Materials:** A multidisciplinary international consensus panel developed recommendations after reviewing results from completed Phase III randomized trials, meta-analyses, and published clinical reports with updates available through November, 2007. The guidelines were reviewed and approved by the panel.

**Results:** According to the recommendations, the trial population should include patients with T2 or T3 laryngeal or hypopharyngeal squamous cell carcinoma 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. The panel created a new endpoint: laryngo-esophageal dysfunction–free survival. Events are death, local relapse, total or partial laryngectomy, tracheotomy at 2 years or later, or feeding tube at 2 years or later. Recommended secondary endpoints are overall survival, progression-free survival, locoregional control, time to tracheotomy, time to laryngectomy, time to discontinuation of feeding tube, and quality of life/patient-reported outcomes. Correlative biomarker studies for near-term trials should include estimated glomerular filtration rate, excision repair cross-complementary-1 gene, E-cadherin and $\beta$-catenin, epiregulin and amphiregulin, and TP53 mutation.

**Conclusions:** Revised trial designs in several key areas are needed to advance the study of larynx preservation. With consistent methodologies, clinical trials can more effectively evaluate and quantify the therapeutic benefit of novel treatment options for patients with locally advanced laryngeal and hypopharyngeal cancer. 

# What do the Meta-Analyses suggest? (Pre-taxanes)

# Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data

- **3 Trials , N-602,** Median follow-up of **5·7 years**
- **Larynx Preserved in 23% of pts alive at 5 yrs**
- There was significant heterogeneity between the three trials (p=0·05).

| @ 5yrs | ICT f/b RT | Sx | P value |
|---|---|---|---|
| OS | 39% | 45% | 0.1 |
| DFS | 34% | 40% | 0.05 |

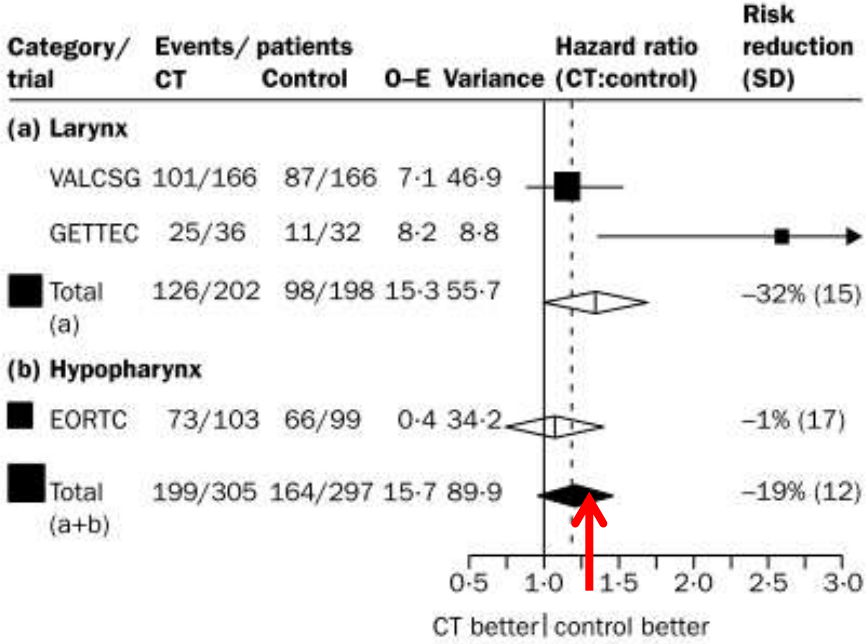



Figure 6: **Hazard ratio of death of neoadjuvant cisplatin-fluorouracil followed by radiotherapy in responders or by radical surgery plus radiotherapy in non-responders compared with radical surgery plus radiotherapy**

Overall hazard ratio 1·19 (95% CI 0·97–1·46), p=0·10. Test for heterogeneity, p=0·05.

Pignon et al Lancet, 2000

# MACH NC 2000

Meta-analysis of locoregional treatment with and without chemotherapy: effect on survival

| Trial category | Hazard ratio (95% CI) | Chemo-therapy effect (p) | Heterogeneity (p) | Absolute benefit | |
|---|---|---|---|---|---|
| | | | | At 2 years* | At 5 years* |
| Adjuvant | 0·98 (0·85–1·19) | 0·74 | 0·35 | 1% | 1% |
| Neoadjuvant | 0·95 (0·88–1·01) | 0·10 | 0·38 | 2% | 2% |
| Concomitant | 0·81 (0·76–0·88) | <0·0001 | <0·0001 | 7% | 8% |
| Total | 0·90 (0·85–0·94) | <0·0001 | <0·0001 | 4% | 4% |

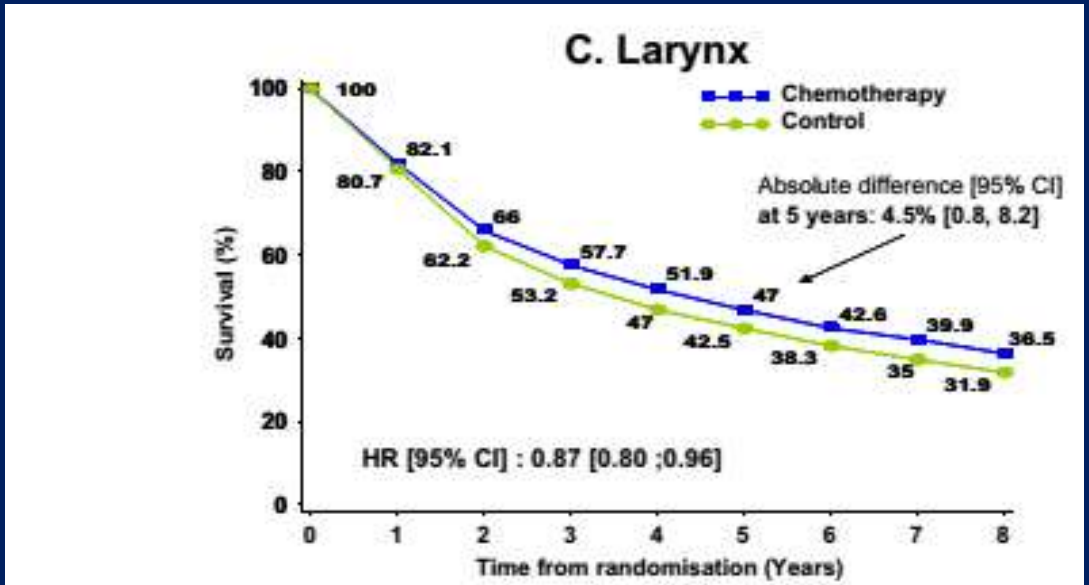
*Assuming survival rates of 50% at 2 years and 32% at 5 years in control groups.

Level one evidence of significant benefit of addition of CT in terms of OS

Pignon et al, Lancet,2000

# MACH-NC - Laryngeal cancer

- 3216 patients with laryngeal cancer and 61 comparisons are included.
- The HR of death associated with chemotherapy is 0.87
- Absolute 5-year overall survival benefit of 4.5% increasing from 42.5% to 47.0%.



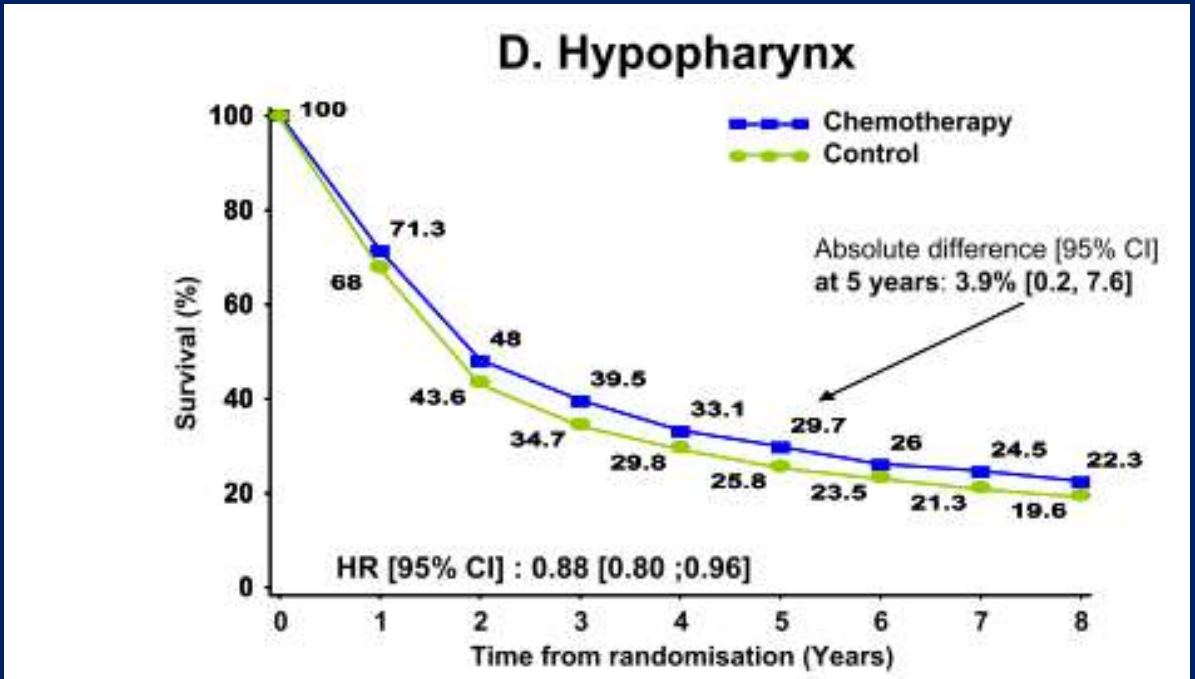

Number of deaths/person-years:

| | Years 0-2 | Years 2-5 | Years >= 6 |
|---|---|---|---|
| LRT+CT | 550/2628 | 253/2126 | 122/1387 |
| LRT | 591/2558 | 250/1923 | 108/1146 |

Blanchard et.al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): A comprehensive analysis by tumour site; Radiotherapy and Oncology 100 (2011) 33–40

# MACH-NC - Hypopharyngeal cancer

- The HR of death associated with chemotherapy is 0.88
- Absolute 5-year overall survival benefit of 3.9%




Blanchard et.al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): A comprehensive analysis by tumour site; Radiotherapy and Oncology 100 (2011) 33–40

# MACH NC 2011-Site wise anlaysis

Hazard ratios of death and 5-year absolute benefit (overall survival) associated with the use of chemotherapy according to tumour site and chemotherapy timing.

| | | Timing of chemotherapy | | | Test of interaction* |
|---|---|---|---|---|---|
| | | Adjuvant | Neoadjuvant | Concomitant | |
| Oral cavity | HR [95% CI] | 0.94 [0.76; 1.17] | 0.93 [0.82; 1.05] | 0.80 [0.72; 0.89] | $p = 0.15$ |
| | 5-year abs benefit [CI] | +0.4% [−7.6; 8.4] | +2.2% [−2.9; 7.3] | +8.9% [4.4; 13.4] | |
| Oropharynx | HR [95% CI] | 1.15 [0.92; 1.44] | 1.00 [0.90; 1.11] | 0.78 [0.72; 0.85] | $p < 0.0001$ |
| | 5-year abs benefit [CI] | −0.4% [−9.6; 8.8] | +1.4% [−2.9; 5.7] | +8.1% [4.8; 11.4] | |
| Larynx | HR [95% CI] | 1.05 [0.83; 1.33] | 1.00 [0.81; 1.23] | 0.80 [0.71; 0.90] | $p = 0.05$ |
| | 5-year abs benefit [CI] | +0.1 [−8.5; 8.7] | +3.8% [−4.6; 12.2] | +5.4% [0.5; 10.3] | |
| Hypopharynx | HR [95% CI] | 1.06 [0.82; 1.38] | 0.88 [0.75; 1.02] | 0.85 [0.75; 0.96] | $p = 0.31$ |
| | 5-year abs benefit [CI] | −2.3% [−13.7; ; 9.1] | +5.3% [−0.8; 11.4] | +4% [−1.1; 9.1] | |

OS is better in all sites with CCRT only

**Table 2.** Late Effects and Function Assessments

| Study | Site | Treatment Groups | Toxicity Scale | Late Effects | Function Assessment |
|---|---|---|---|---|---|
| VALCSG[12,16,17] | Larynx | a) TL → RT<br>b) PF → RT | Not specified in report | Not reported | Voice quality and communication*<br>Swallowing and eating related† |
| RTOG 91-11[13,14] | Larynx | a) PF → RT<br>b) RT + P<br>c) RT | NCI-CTC and RTOG late toxicity scoring system | NSD in 10-year cumulative grade 3-5 late toxicity: 30.6% *v* 33.3% *v* 38% | Voice quality,† swallowing,† and QOL |
| EORTC 24954-22950[10] | Larynx<br>Hypopharynx | a) PF → RT (70 Gy)<br>b) PF alternating/RT (60 Gy) | Not specified in report | NSD in grade 3-4 mucosal: 35% *v* 34%; connective tissue: 41% *v* 35% | Measures not specified; % of patients with intelligible voice and normal intake reported |
| GORTEC 2000-01[11] | Larynx<br>Hypopharynx | a) PF → RT<br>b) TPF → RT | NCI-CTC and RTOG late toxicity scoring system | Grade 3 to 4 subcutaneous tissue: 7% *v* 4% | Not reported |
| EORTC 24891[8,9] | Hypopharynx | a) TLP → RT<br>b) PF → RT | Not specified in report | Not reported | Not reported |

1. Although CRT improves LRC and OS, and allows for organ preservation, toxicities are increased compared with RT alone. **The most common acute grade 3 to 4 complications (leukopenia, anemia,mucositis, and dysphagia) are increased from14% to 43% over RT.**
2. **CRT patients were more likely to have a diet limited to soft foods or liquids,or require gastrostomy tube use at 1 year** (26% compared with 18%with RT), but at 2 years there were no differences between the treatment groups (16% with CRT, 14% with induction followed by RT and 15% with RT)

However, not all patients are suitable for CT based organ preservation

## Role of altered fractionation…

# A RADIATION THERAPY ONCOLOGY GROUP (RTOG) PHASE III RANDOMIZED STUDY TO COMPARE HYPERFRACTIONATION AND TWO VARIANTS OF ACCELERATED FRACTIONATION TO STANDARD FRACTIONATION RADIOTHERAPY FOR HEAD AND NECK SQUAMOUS CELL CARCINOMAS: FIRST REPORT OF RTOG 9003

First Report of RTOG 9003. Int J Radiat Oncol Biol Phys. 2000; 48:7–16.

- Eligibility criteria
- Age > 18 years.
- KPS > 50
- No previous RT
- Stage III-IV SCC Oral cavity, Oropharynx, Supraglottic larynx OR Stage II–IV carcinoma of BOT or Hypopharynx.

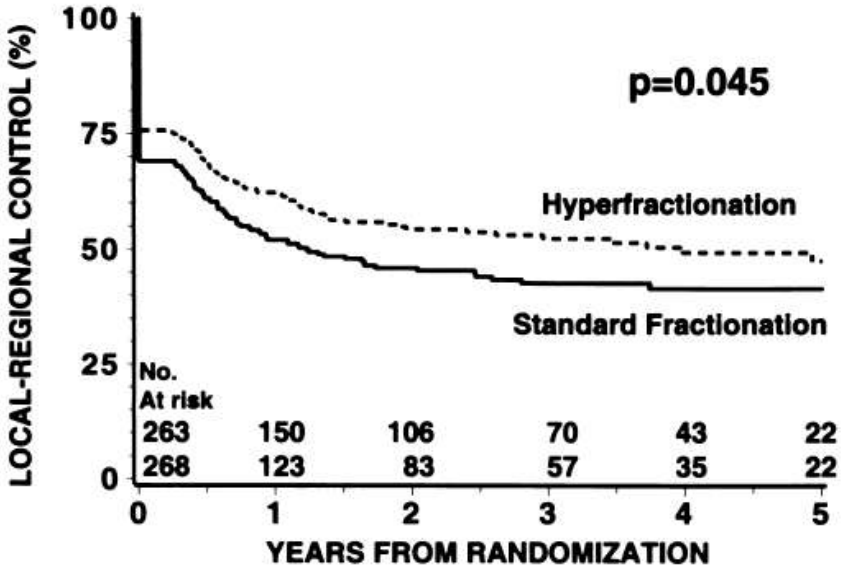
- Demographic profile
- Total no of patients: 1073
- M:F=80:20 (percentage)
- Median age 61 years
- MC site oropharynx (60%)
- Stage II (3.4%), III (28.3%) and IV (68.3%)

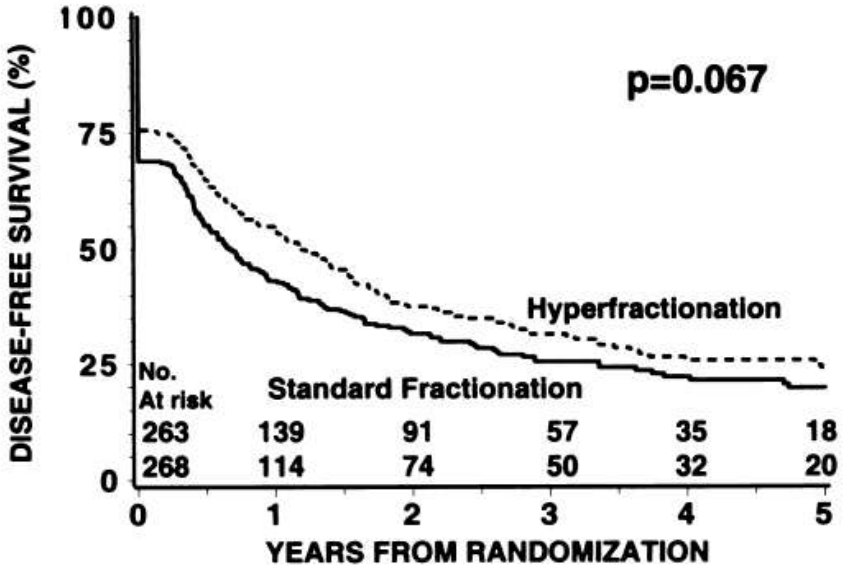
**Median follow-up: 23 months for all analyzable & 41.2 months for surviving patients.**

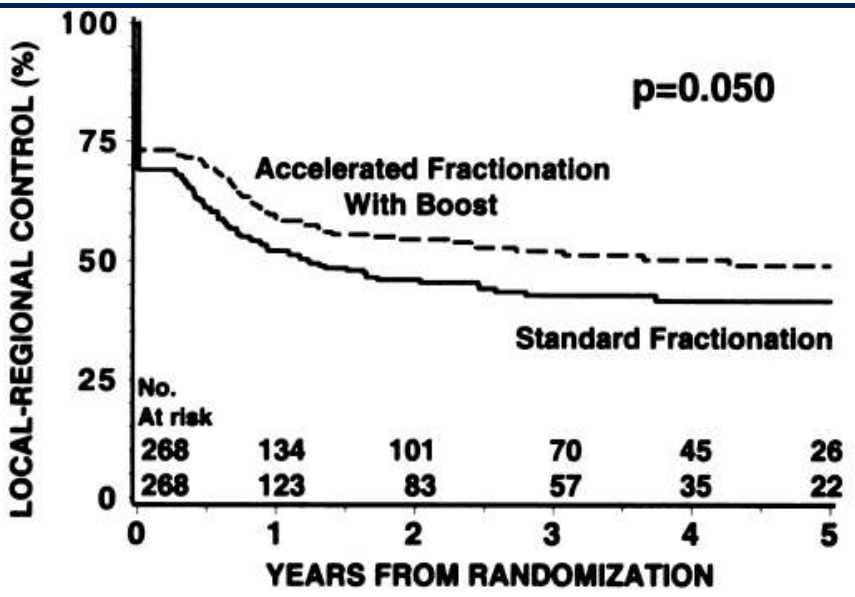
# Randomization
# 1073 patients

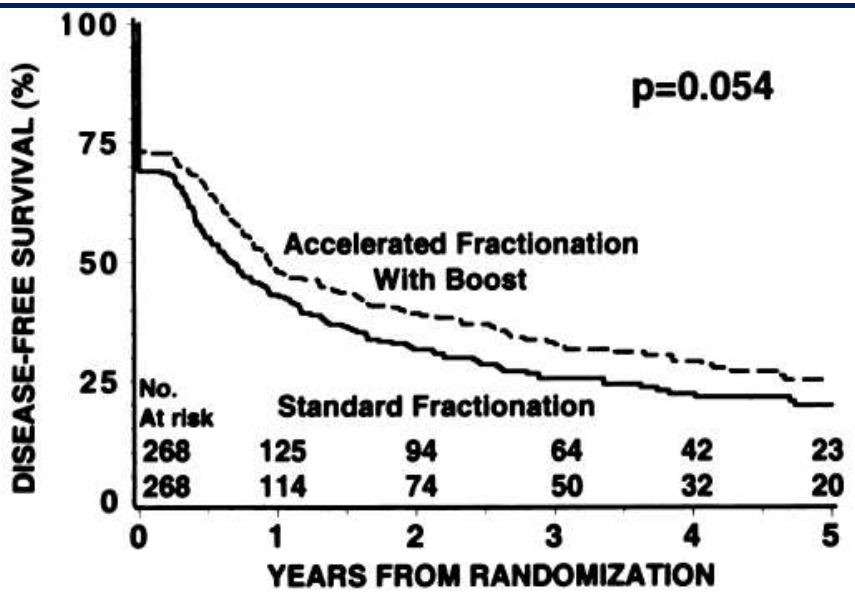
| Arm1 | Arm2 | Arm3 | Arm4 |
|---|---|---|---|
| **SFX** | **HFX** | **AFX-S** | **AFX-C** |
| 2 Gy/fraction<br>OD | 1.2 Gy/fraction<br>BD | 1.6 Gy/fraction | 1.8 Gy/fraction |
| 5 days/week | 5 days/week | 5 days/week | 5 days/week to large field<br>+<br>1.5 Gy/fraction to boost in last 12 # |
| 70 Gy/35 # | 81.6 Gy/ 68 # | 67.2 Gy/42 #<br>2-week rest after 38.4 Gy | 72 Gy/42 # |
| 7 weeks | 7 weeks | 6 weeks | 6 weeks |

# *Results (at 2 years)*



# Tumour Control Outcomes

Table 2. 2-Year local-regional control, disease-free survival, and overall survival by treatment

| 2-Year endpoints | Standard fractionation ($N$ = 268) | Hyper-fractionation ($N$ = 263) | Accelerated fractionation with split ($N$ = 274) | Accelerated fractionation with concomitant boost ($N$ = 268) |
|---|---|---|---|---|
| Local-regional control | 46.0% | 54.4% | 47.5% | 54.5% |
| Disease-free survival | 31.7% | 37.6% | 33.2% | 39.3% |
| Overall survival | 46.1% | 54.5% | 46.2% | 50.9% |

Conclusion:

- HFX and AFX-C had significantly better LRC than SFX / AFX-S
- Trend towards improved DFS with both but no significant difference in OS

# Toxicity Outcomes ≥ Grade III

| | Acute Toxicity | p value (to SFX) | Late Toxicity | p value (to SFX) |
|---|---|---|---|---|
| SFX | 35% | | 26.8% | |
| HFX | 54.5% | <0.0001 | 28% | NS |
| AFX-S | 50.4% | 0.0002 | 27.6% | NS |
| AFX-C | 58.8% | <0.0001 | 37.2% | 0.011 |

Conclusions:

- AF had more acute toxicities.
- AFX-C had more late effects + consequential late effects

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Clinical Investigation: Head and Neck Cancer

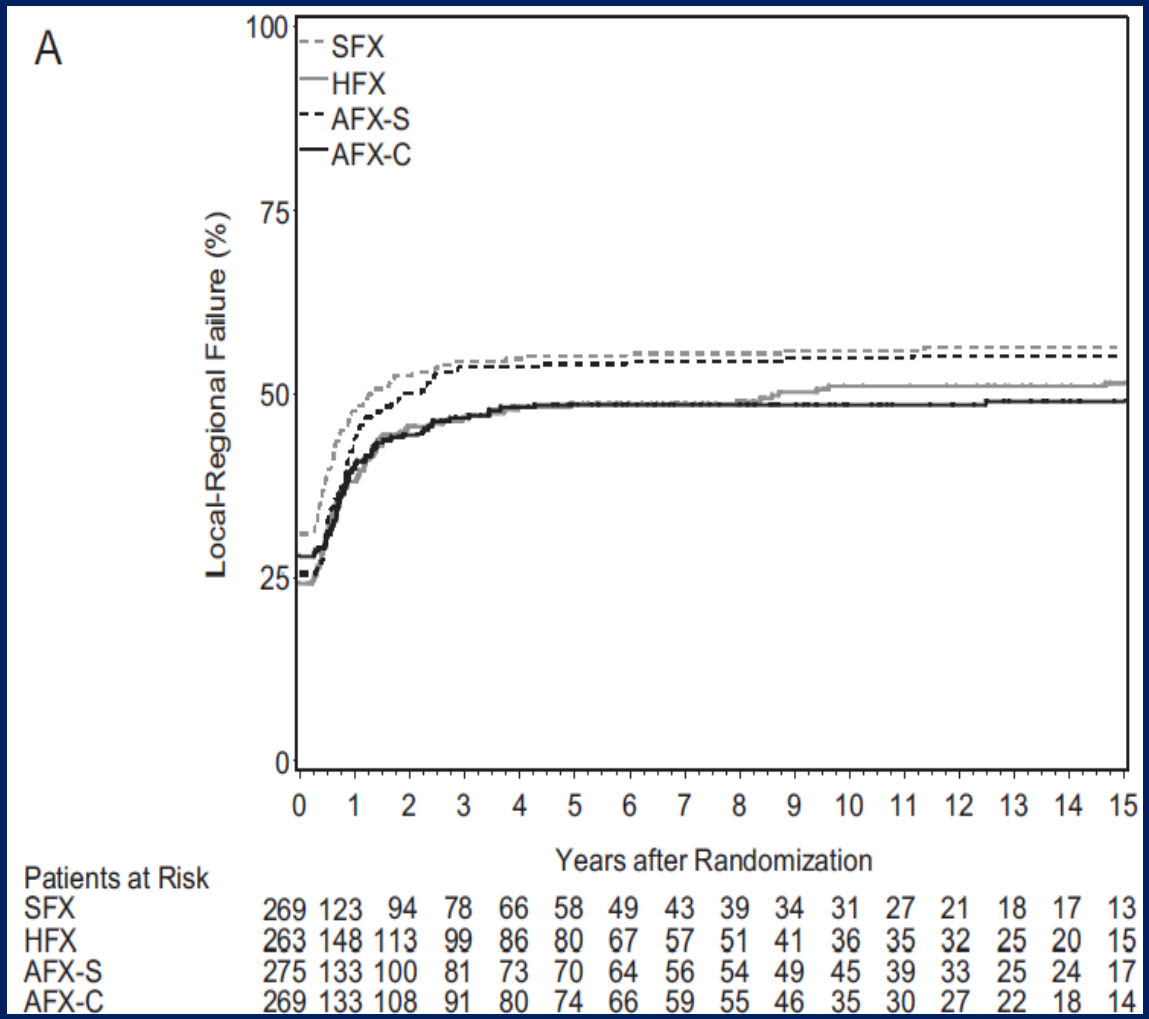
# Final Results of Local-Regional Control and Late Toxicity of RTOG 9003: A Randomized Trial of Altered Fractionation Radiation for Locally Advanced Head and Neck Cancer

Jonathan J. Beitler, MD, MBA,* Qiang Zhang, PhD,† Karen K. Fu, MD,‡ Andy Trotti, MD,§ Sharon A. Spencer, MD,‖ Christopher U. Jones, MD,¶ Adam S. Garden, MD,# George Shenouda, MD,** Jonathan Harris, MS,† and Kian K. Ang, MD, PhD (deceased)#

- Censoring of events at 5 years (97% local recurrences in 5 years, ? SMN afterwards)
- Median F/U of 14.1 years.

Int J Radiation Oncol Biol Phys, Vol. 89, No. 1, pp. 13e20, 2014

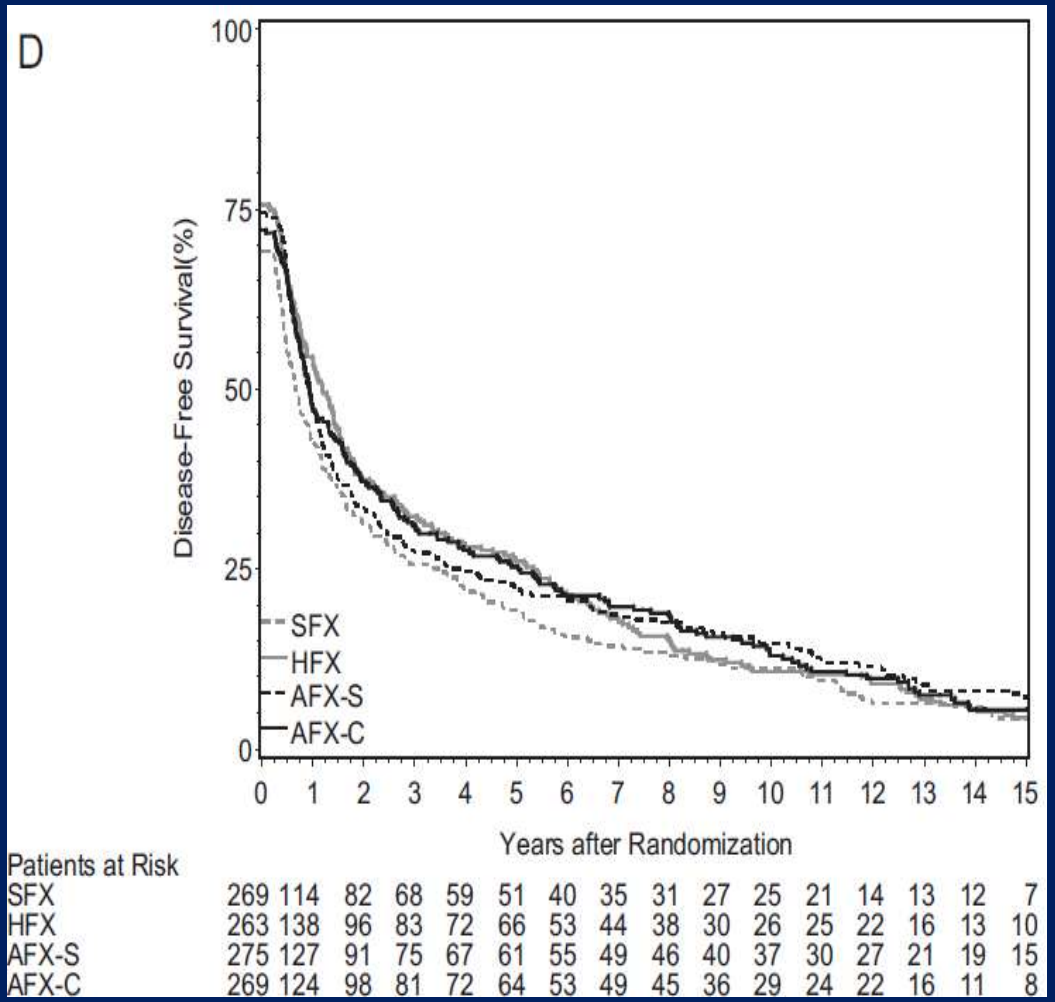
# LRC




- HFX Vs SFX
- p 0.045 & 0.05 (censored)
- AFX-C Vs SFX
- p 0.05 & 0.82 (censored)

- 19% reduction of LR failure with HFX & AFX-C

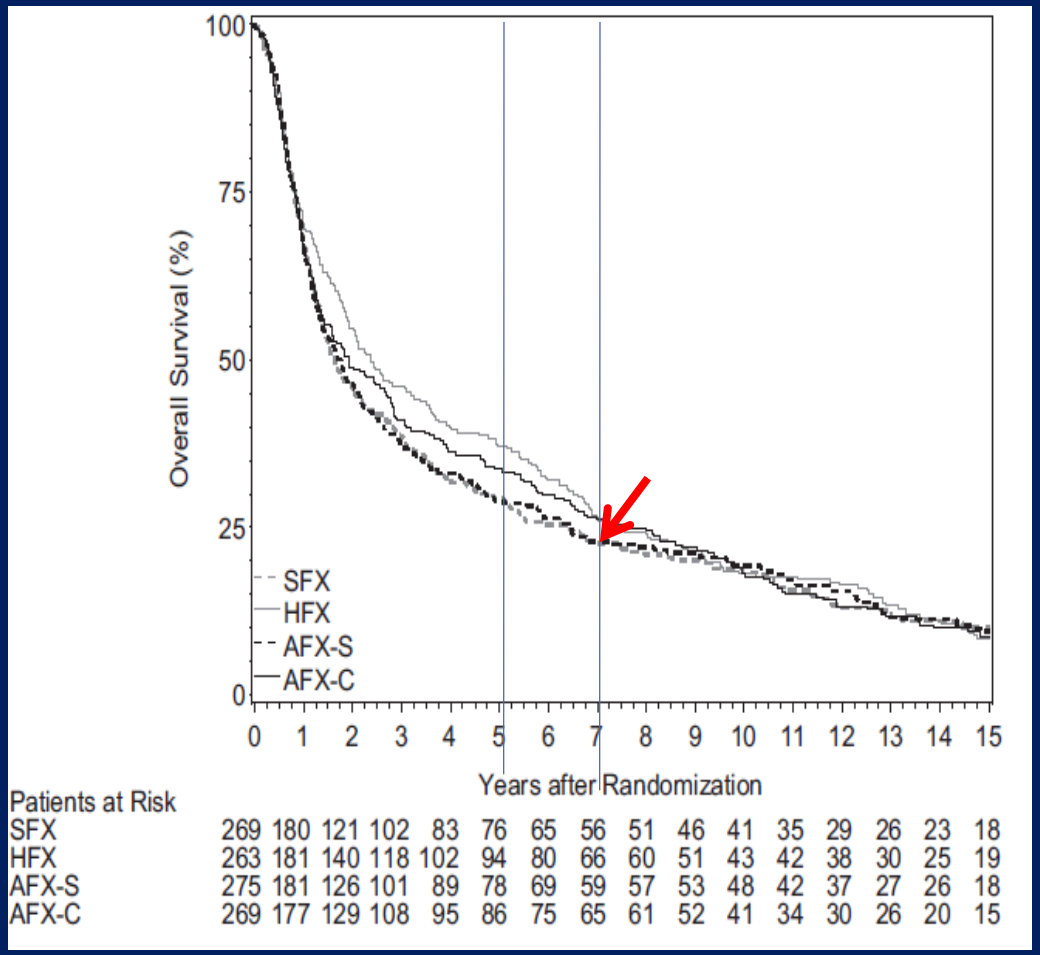
# DFS




- p for HFX 0.04,
- p for AFX-S 0.05
- p for AFX-C 0.05

- Compared to SFX, DFS was improved in all experimental arms

# OS




- When death was censored at 5 years, HFX had significantly better results compared to other arms (p 0.05)
- Survival curves rejoined at 7 years (peak of late toxicity induced deaths).

# Toxicity Outcomes

- No difference in toxicities in experimental arms compared to SFX
- Pooled cohort of accelerated patient: might have increased toxicity (p 0.06)
- On individual patient toxicity assessment, trend towards increased toxicity with AFX-C (p 0.09)

# Conclusions of RTOG 9003

- HFX and AFX-C has significant benefit over SFX or AFX-S in terms of LC.
- HFX has OS benefit if events are censored at 5 years.
- Trend of higher toxicities with AFX-C.
- HFX has the most optimal therapeutic ratio.

- ? HFX in place of CTRT to reduce CTRT late toxicity induced deaths (eg. RTOG 9111)

- IMRT based intensification (HFX / AFX-C with IMRT) has potential improved therapeutic ratio.

# MARCH Meta-analysis

## Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis

*Jean Bourhis, Jens Overgaard, Hélène Audry, Kian K Ang, Michele Saunders, Jacques Bernier, Jean-Claude Horiot, Aurélie Le Maître, Thomas F Pajak, Michael G Poulsen, Brian O'Sullivan, Werner Dobrowsky, Andrzej Hliniak*, Krzysztof Skladowski, John H Hay, Luiz H J Pinto, Carlo Fallai, Karen K Fu, Richard Sylvester, Jean-Pierre Pignon, on behalf of the Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group*

*Lancet* 2006; 368: 843-54

See Comment page 819

Published Online August 17, 2006

DOI:10.1016/S0140-6736(06)69121-6

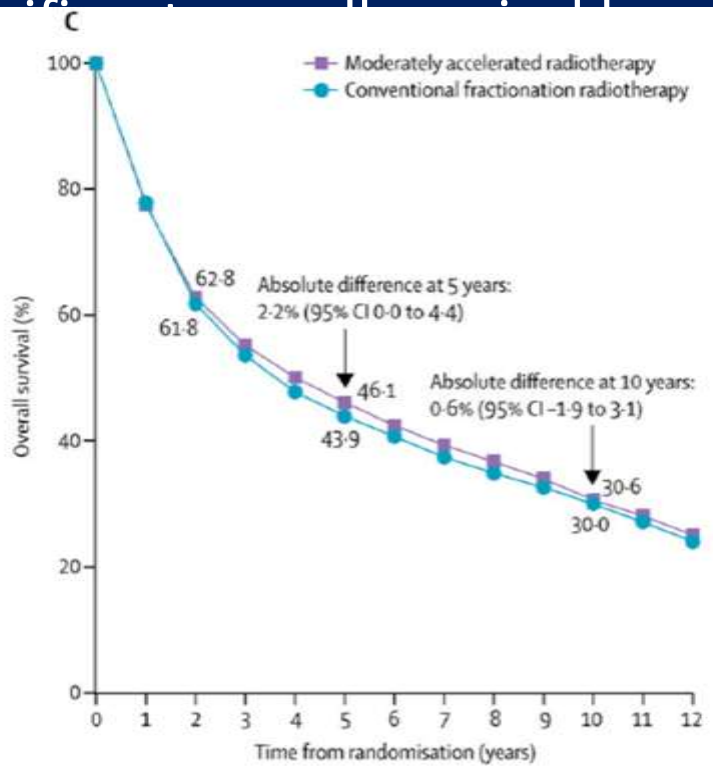
- 15 trials with 6515 patients were evaluated.
- Median follow-up - 6 yrs.
- Tumours sites - **mostly oropharynx and larynx (44 and 34% respectively)**
- 74% had stage III–IV tumours

# Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis

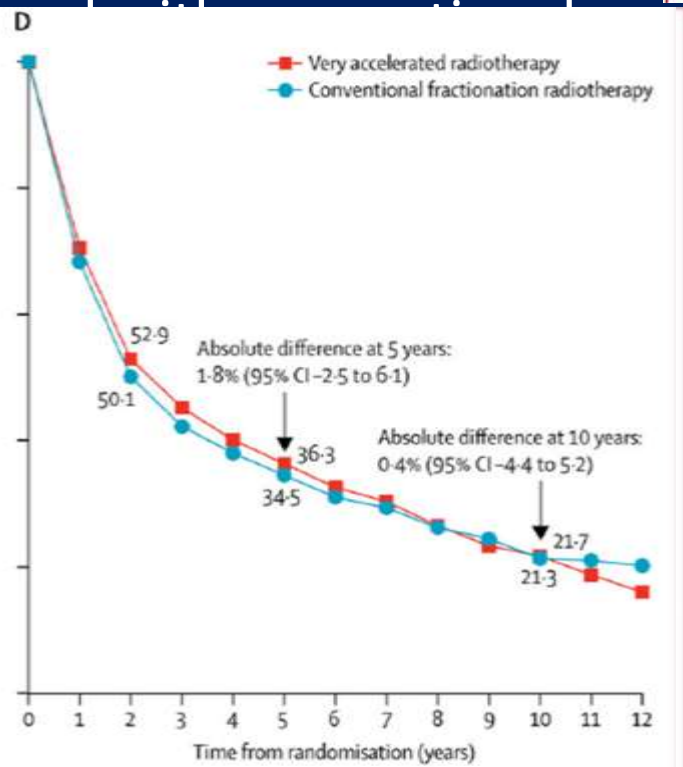
33 Trials

Benjamin Lacas, Jean Bourhis, Jens Overgaard, Qiang Zhang, Vincent Grégoire, Matthew Nankivell, Björn Zackrisson, Zbigniew Szutkowski, Rafał Suwiński, Michael Poulsen, Brian O'Sullivan, Renzo Corvò, Sarbani Ghosh Laskar, Carlo Fallai, Hideya Yamazaki, Werner Dobrowsky, Ku… Co… p†

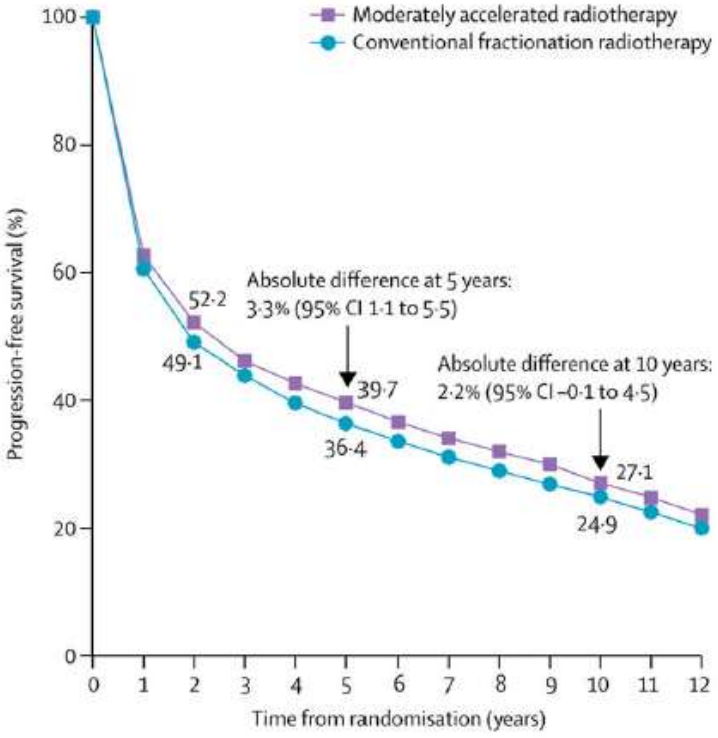
- Altered fractionation radiotherapy was associated with a



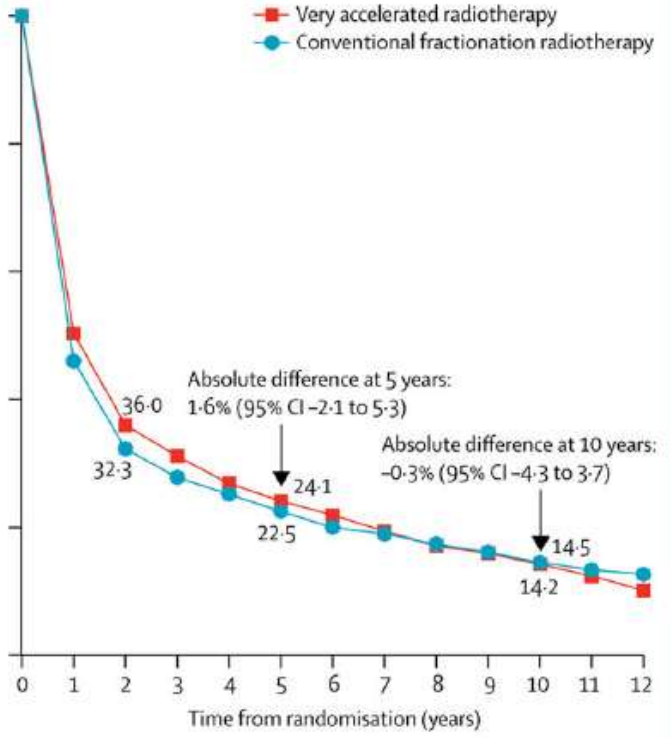

| | Years 0–2 | Years 2–5 | Years 5–10 | Years 10+ |
|---|---|---|---|---|
| Moderately accelerated radiotherapy (deaths/person-years) | 1497/6347 | 610/5816 | 343/4291 | 152/1412 |
| Conventional fractionation radiotherapy (deaths/person-years) | 1525/6292 | 650/5528 | 309/4005 | 153/1334 |




| | Years 0–2 | Years 2–5 | Years 5–10 | Years 10+ |
|---|---|---|---|---|
| Very accelerated radiotherapy (deaths/person-years) | 523/1644 | 174/1348 | 85/825 | 11/78 |
| Conventional fractionation radiotherapy (deaths/person-years) | 481/1325 | 131/1016 | 56/618 | 1/58 |




| | Years 0–2 | Years 2–5 | Years 5–10 | Years 10+ |
|---|---|---|---|---|
| Moderately accelerated radiotherapy (deaths/person-years) | 1902/5503 | 477/5058 | 286/3838 | 141/1305 |
| Conventional fractionation radiotherapy (deaths/person-years) | 2029/5252 | 472/4657 | 260/3399 | 132/1140 |




| | Years 0–2 | Years 2–5 | Years 5–10 | Years 10+ |
|---|---|---|---|---|
| Very accelerated radiotherapy (deaths/person-years) | 693/1283 | 132/959 | 57/541 | 10/56 |
| Conventional fractionation radiotherapy (deaths/person-years) | 630/978 | 85/715 | 37/430 | 2/44 |

- Altered fractionation radiotherapy was associated with significantly reduced cancer mortality, local failure, and regional failure.

- No significant differences were reported between conventional radiotherapy and altered fractionation radiotherapy in terms of non-cancer mortality or distant failure.

- Although no interaction was reported between altered fractionation regimens and the effect on local or regional control, hyperfractionation was associated with a reduction in local and regional failures.

- Moderately fractionated-Reduction in local failure

- Very Accelerated – No effect in reduction of local + regional failure

- When the analysis was restricted to node-positive patients, the interaction between altered fractionated regimens and regional control was not significant, but the effect of altered fractionated radiotherapy was significantly for hyperfractionated radiotherapy.

- The survival benefit decreased when age increased.

- Pure acceleration should therefore be considered only for patient with low nodal burden.

*Although altered fractionation served as a good option in patients in whom chemotherapy could not be given, better options were needed …*

2 options:

A. Intensification of Induction chemotherapy

B. More intensive local therapy→ Induction f/b concomitant chemotherapy .

The demonstration in locally advanced HNSCC mixed-site trials of a higher response rate to TPF compared with PF led investigators to postulate that induction TPF would improve the rates of LP and local control.

# Role of Taxane based ICT

GORTEC 2000-01

TAX 323/324

Meta-analysis

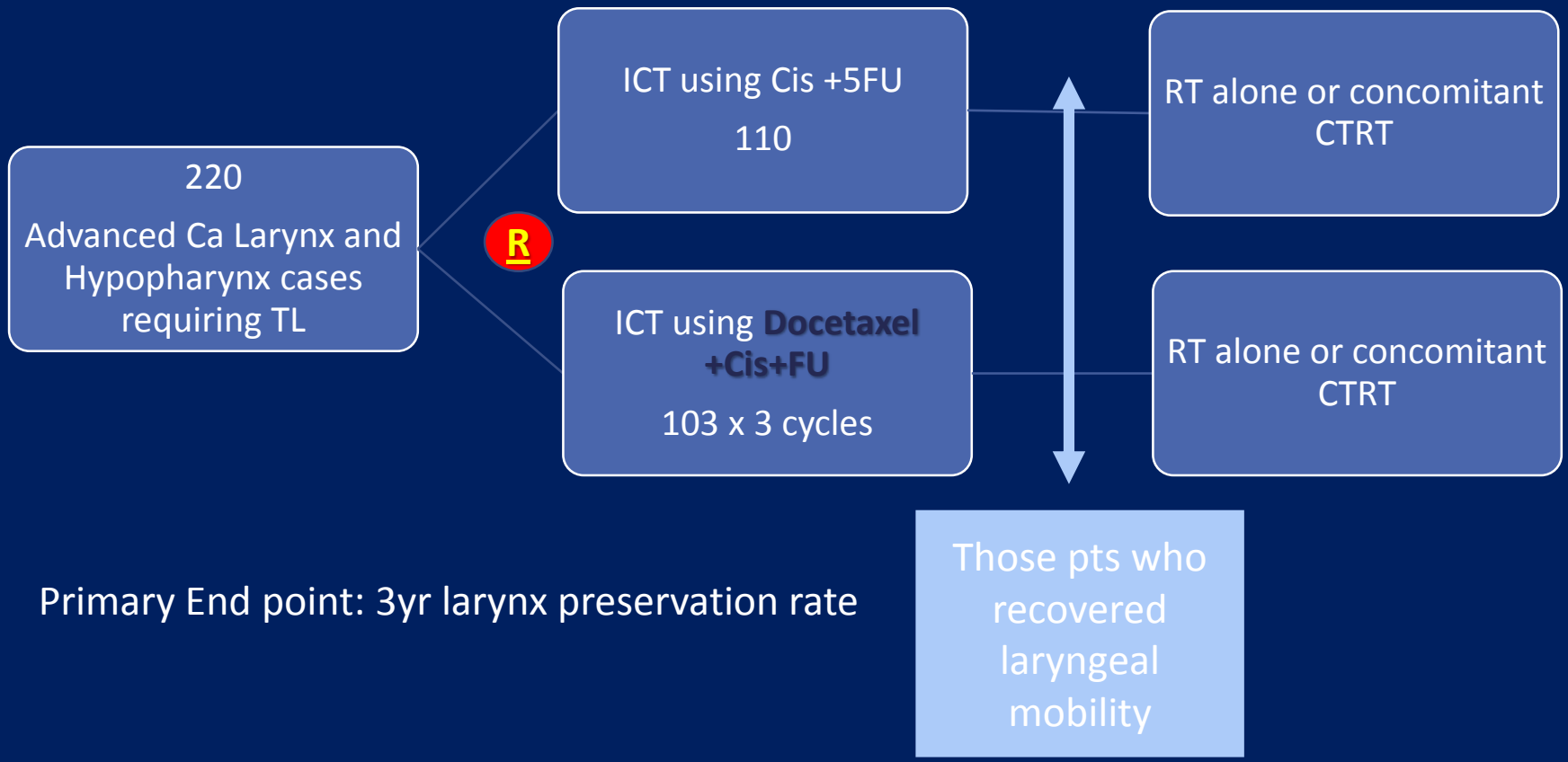
# EORTC 24971/TAX 323 Study Group* 2007 Vs TAX 324

| | TAX 323 | TAX 324 |
|---|---|---|
| Dose of CDDP / 5FU | 75 mg/m$^2$ / 750 mg/m$^2$ | 100 mg/m$^2$ / 1000 mg/m$^2$ |
| Patients | 350 | 250 |
| Primary End Poin | PFS (HR 0.67) | OS (HR 0.65) |
| Control Gro | | |
| Inclusi | | |
| Local RT | | latin |
| Neck Dissection | Considered for all patients | Selected |
| Hypopharyngeal cance | 29.3% | 14% |
| T4 | 73% | 42% |
| N2-3 | 71.8% | 64% |

Addition of docetaxel to PF induction chemotherapy in patients with unresectable squamous-cell carcinoma of the head and neck improved survival and was better tolerated than the classic PF regimen.

# Randomized Trial of Induction Chemotherapy With Cisplatin and 5-Fluorouracil With or Without Docetaxel for Larynx Preservation

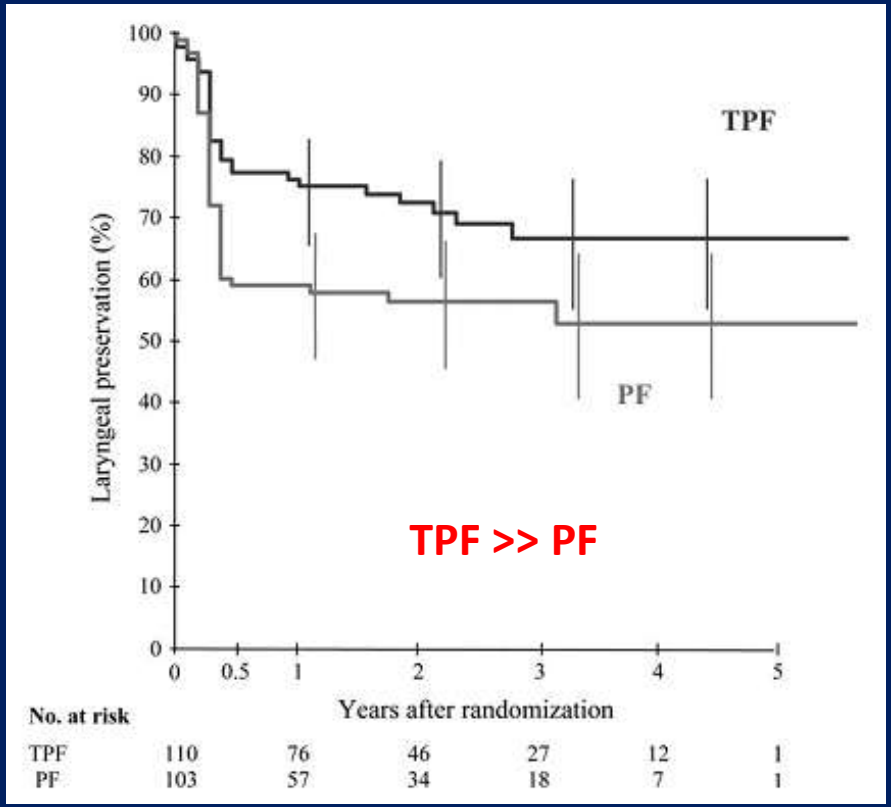
Yoann Pointreau, Pascal Garaud, Sophie Chapet, Christian Sire, Claude Tuchais, Jacques Tortochaux, Sandrine Faivre, Stephane Guerrif, Marc Alfonsi, Gilles Calais




Primary End point: 3yr larynx preservation rate

GORTEC 2000-01,J Natl Cancer Inst 2009;101: 498 – 506

| Characteristic | TPF (N = 110) | PF (N = 103) | P |
|---|---|---|---|
| Age, y | | | .82 |
| Mean | 57 | 56 | |
| Range | 33–72 | 37–75 | |
| Sex, No. (%) | | | .59 |
| Male | 101 (91.8) | 97 (94.2) | |
| Female | 9 (8.2) | 6 (5.8) | |
| Karnofsky performance status, No. (%) | | | .21 |
| 100 | 51 (46.4) | 51 (49.5) | |
| 90 | 41 (37.2) | 28 (27.2) | |
| 80 | 18 (16.4) | 24 (23.3) | |
| Site of primary tumor, No. (%) | | | .68 |
| Hypopharynx | 61 (55.5) | 54 (52.4) | |
| Larynx | 49 (44.5) | 49 (47.6) | |
| Stage of primary tumor, No. (%) | | | .14 |
| T2 | 15 (13.6) | 24 (23.3) | |
| T3 | 80 (72.8) | 63 (61.2) | |
| T4 | 15 (13.6) | 16 (15.5) | |
| Node stage, No. (%) | | | .16 |
| N0 | 36 (32.7) | 48 (46.6) | |
| N1 | 28 (25.5) | 22 (21.4) | |
| N2a | 12 (10.9) | 9 (8.7) | |
| N2b | 13 (11.8) | 15 (14.6) | |
| N2c | 14 (12.7) | 7 (6.8) | |
| N3 | 7 (6.4) | 2 (1.9) | |




| Outcomes | TPF | PF | P value |
|---|---|---|---|
| Larynx preservation @ 3 years | 70.3% | 57.5% | 0.03 |
| Overall response to ICT | 80% | 59% | 0.002 |

# GORTEC 2000-01: Conclusions

**Long Term results @ 105 months**

Laryngeal dysfunction free survival was significantly better in TPF arm.

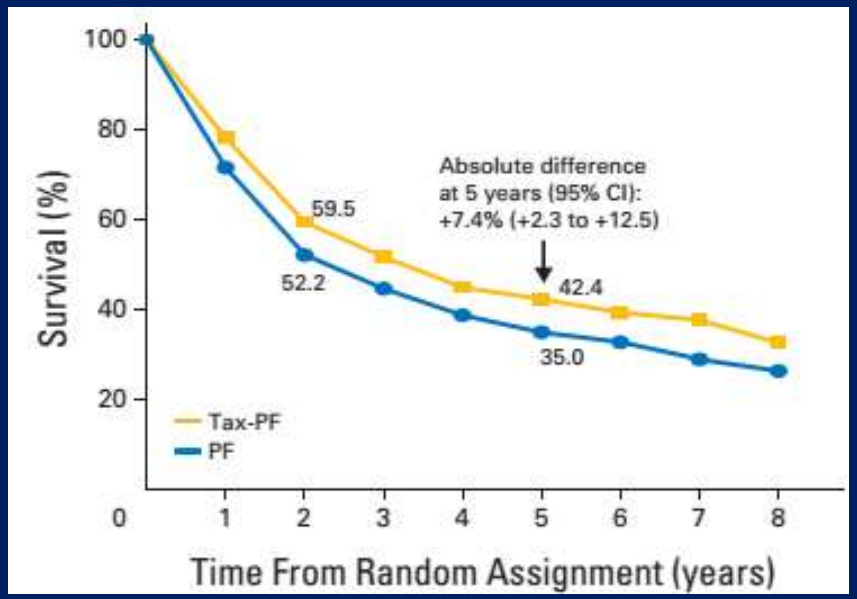
Statistically fewer grade 3–4 late toxicities of the larynx occurred with the TPF

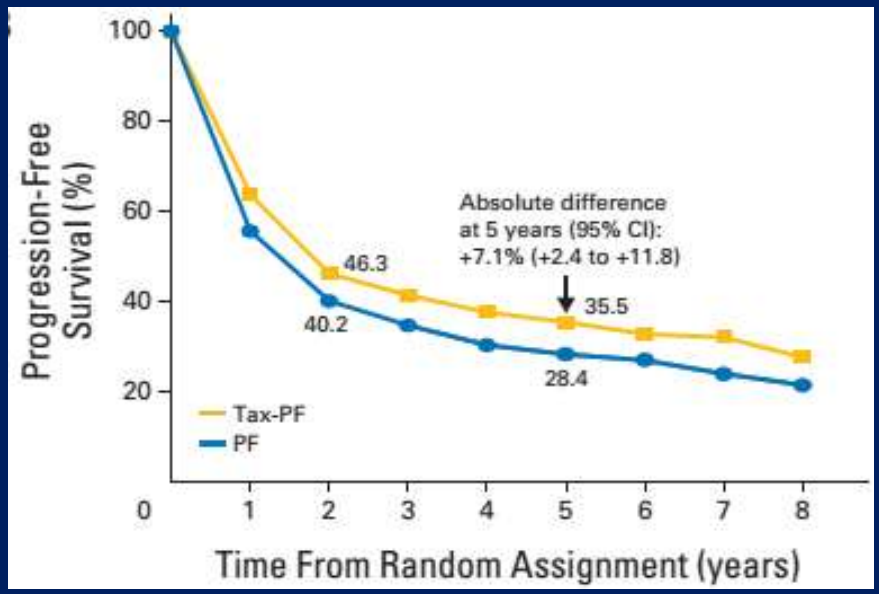
In patients with **advanced larynx and hypopharynx carcinomas**, TPF induction chemotherapy was superior to the PF regimen in terms of overall response rate.

J Natl Cancer Inst 2009;101: 498 – 506

# Taxane-Cisplatin-Fluorouracil As Induction Chemotherapy in Locally Advanced Head and Neck Cancers: An Individual Patient Data Meta-Analysis of the Meta-Analysis of Chemotherapy in Head and Neck Cancer Group

*Pierre Blanchard, Jean Bourhis, Benjamin Lacas, Marshall R. Posner, Jan B. Vermorken, Juan J. Cruz Hernandez, Abderrahmane Bourredjem, Gilles Calais, Adriano Paccagnella, Ricardo Hitt, and Jean-Pierre Pignon on behalf of the Meta-Analysis of Chemotherapy in Head and Neck Cancer, Induction Project, Collaborative Group*




- TPF significantly improves OS, PFS, loco-regional and distant failure compared with PF.
- TPF is associated with a better compliance.
- **More patients in the TPF group proceeded to conc CTRT, likely reflecting the higher response rates.**

Blanchard et.al. J Clin Oncol 31. © July, 2013

Would induction chemotherapy (IC) be more likely to demonstrate an improvement in survival if two other conditions were met??

- Use of a CRT regimen achieving high rates of locoregional control and
- Treatment of patients at greatest risk for distant metastatsis

# 2013 - PARADIGM

Lancet Oncol 2013; 14: 257–64

## Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial

Robert Haddad, Anne O'Neill, Guilherme Rabinowits, Roy Tishler, Fadlo Khuri, Douglas Adkins, Joseph Clark, Nicholas Sarlis, Jochen Lorch, Jonathan J Beitler, Sewanti Limaye, Sarah Riley, Marshall Posner

**Methods** Adult patients with previously untreated, non-metastatic, newly diagnosed head and neck cancer were eligible. Patients were eligible if their tumour was either unresectable or of low surgical curability on the basis of advanced tumour stage (3 or 4) or regional-node stage (2 or 3, except T1N2), or if they were a candidate for organ preservation. Patients were randomly assigned (in a 1:1 ratio) to receive either induction chemotherapy with three cycles of TPF followed by concurrent chemoradiotherapy with either docetaxel or carboplatin or concurrent chemoradiotherapy alone with two cycles of bolus cisplatin. A computer-generated randomisation schedule using minimisation was prepared and the treatment assignment was done centrally at one of the study sites. Patients, study staff, and investigators were not masked to group assignment. Stratification factors were WHO performance status, primary disease site, and stage. The primary endpoint was overall survival. Analysis was by intention to treat. Patient accrual was terminated in December, 2008, because of slow enrolment. The trial is registered with ClinicalTrials.gov, number NCT00095875.

**Findings** Between Aug 24, 2004, and Dec 29, 2008, we enrolled 145 patients across 16 sites. After a median follow-up of 49 months (IQR 39–63), 41 patients had died—20 in the induction chemotherapy followed by chemoradiotherapy group and 21 in the chemoradiotherapy alone group. 3-year overall survival was 73% (95% CI 60–82) in the induction therapy followed by chemoradiotherapy group and 78% (66–86) in the chemoradiotherapy alone group (hazard ratio 1·09, 95% CI 0·59–2·03; p=0·77). More patients had febrile neutropenia in the induction chemotherapy followed by chemoradiotherapy group (16 patients) than in the chemoradiotherapy alone group (one patient).

**Interpretation** Although survival results were good in both groups there was no difference noted between those patients treated with induction chemotherapy followed by chemoradiotherapy and those who received chemoradiotherapy alone. We cannot rule out the possibility of a difference in survival going undetected due to early termination of the trial. Clinicians should still use their best judgment, based on the available data, in the decision of how to best treat patients. The addition of induction chemotherapy remains an appropriate approach for advanced disease with high risk for local or distant failure.

# Phase III Randomized Trial of Induction Chemotherapy in Patients With N2 or N3 Locally Advanced Head and Neck Cancer

*Ezra E.W. Cohen, Theodore G. Karrison, Masha Kocherginsky, Jeffrey Mueller, Robyn Egan, Chao H. Huang, Bruce E. Brockstein, Mark B. Agulnik, Bharat B. Mittal, Furhan Yunus, Sandeep Samant, Luis E. Raez, Ranee Mehra, Priya Kumar, Frank Ondrey, Patrice Marchand, Bettina Braegas, Tanguy Y. Seiwert, Victoria M. Villaflor, Daniel J. Haraf, and Everett E. Vokes*

285

Non-metastatic N2,N3 SCCHN

R

CRT

ICT ( 2 TPF) F/B CRT

Concurrent chemo RT regimen in both arms included Docetaxel, 5FU, Hydroxyurea

Majority of pts were oropharyngeal cancers , Stage IV A

2014 – DeCide[Docetaxel- Based Chemotherapy Plus or Minus IC to Decrease Events in Head and Neck Cancer], JCO

## 3-year Outcomes

| Endpoint | IC arm (%) | CRT arm (%) | HR | 95% CI | P value |
|---|---|---|---|---|---|
| **Overall Survival** | 75 | 73 | 0.92 | 0.59-4.42 | 0.70 |
| **Distant-Failure Free Survival** | 69 | 64 | 0.84 | 0.56-1.26 | 0.39 |
| **Recurrence Free Survival** | 67 | 58 | 0.76 | 0.52-1.13 | 0.18 |
| **Cumulative incidence of distant failure** | 10 | 19 | 0.46 | 0.23-0.92 | 0.025 |
| **Cumulative incidence of locoregional failure** | 9 | 12 | 0.79 | 0.37-1.68 | 0.55 |

- Only grade 3-4 leukopenia and neutropenia rates were significantly higher in induction chemotherapy.
- Although there was a statistically significant improvement in cumulative incidence of distant metastases in the induction chemotherapy arm, there was no improvement in overall survival.

# Why the negative results?

- Only 79% of patients received the intended two doses of NACT.

- Unrealistic expectation of 15% absolute increment in 3-year overall survival with NACT. (The absolute survival benefit of cisplatin and fluorouracil induction chemotherapy in accordance with meta-analysis of chemotherapy in head and neck cancer was 2.4%.)

- Believing that adding taxane to this regimen would lead to an absolute improvement of more than 10% in overall survival was therefore unrealistic.

# Meta-analysis of Sequential vs Concomitant Chemotherapy in LA-HNSCC

Five prospective randomized controlled trials (RCTs) with **922 patients** were included in meta-analysis-

**No significant differences in OS,PFS, LRR**

IC→CCRT could increase risks of grade 3–4 febrile neutropenia (P = 0.0009) and leukopenia (P = 0.04).

Distant metastasis rate (DMR) decreased (P = 0.006) and complete response rate (CR) improved (P = 0.010) for IC with CCRT.

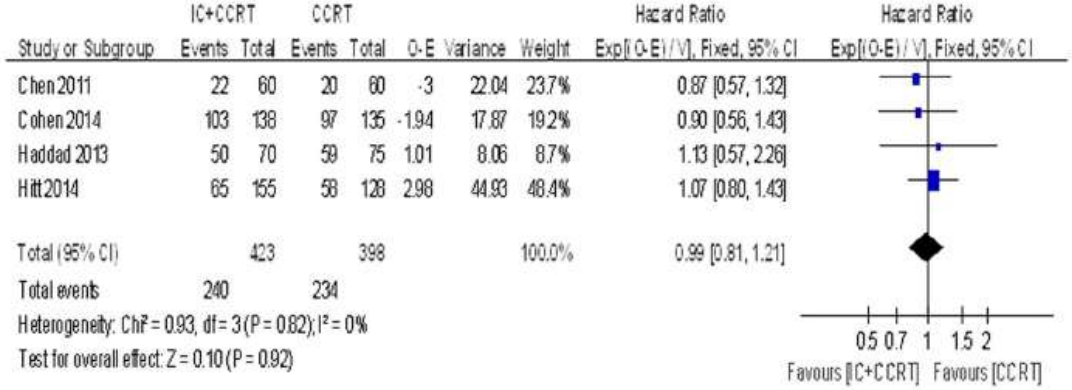



Figure 3. Forest plots of hazard ratios (HRs) for 3-year overall survival (OS) in a fixed-effects model.

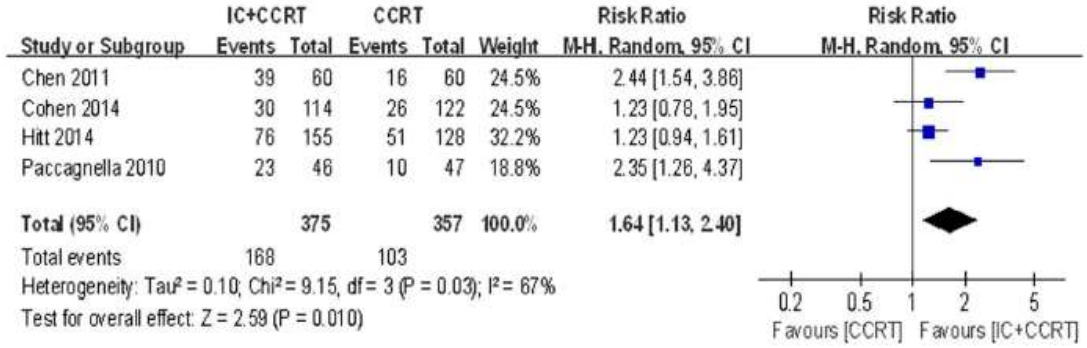



Figure 5. Forest plots of relative risk ratio (RR) for post concurrent chemoradiotherapy of complete response rate (Post-CCRT of CR) in a random-effects model.

Meta-analysis Induction chemotherapy with concurrent chemoradiotherapy versus concurrent chemoradiotherapy for locally advanced squamous cell carcinoma of head and neck, scientific reports, Nature,2013

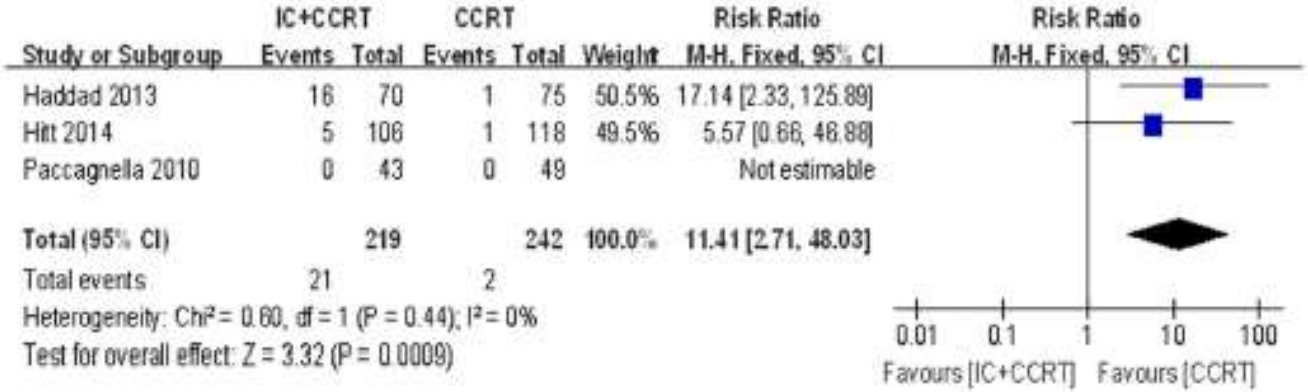



**Figure 7. Forest plots of relative risk ratio (RR) for grade 3–4 febrile neutropenia during CCRT period in a fixed-effects model.**

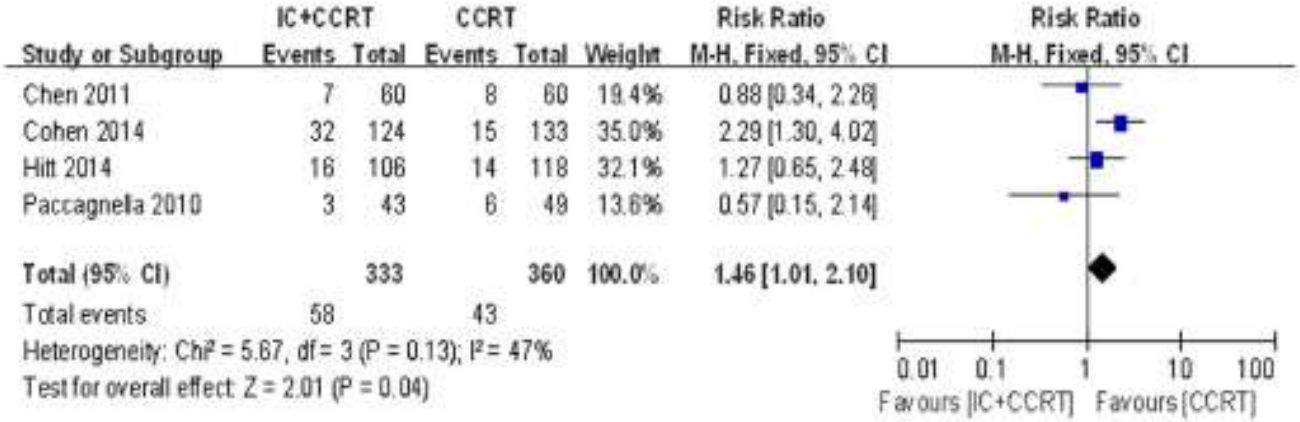



**Figure 8. Forest plots of relative risk ratio (RR) for grade 3–4 leukopenia during CCRT period in a fixed-effects model.**

Meta-analysis Induction chemotherapy with concurrent chemoradiotherapy versus concurrent chemoradiotherapy for locally advanced squamous cell carcinoma of head and neck, scientific reports, Nature,2013

ESMO

ORIGINAL ARTICLE

# Induction TPF followed by concomitant treatment versus concomitant treatment alone in locally advanced head and neck cancer. A phase II–III trial

M. G. Ghi[*], A. Paccagnella[1], D. Ferrari[2], P. Foa[3], D. Alterio[3], C. Codecà[3], F. Nolè[4], E. Veen[4], R. Orecchia[3]

421 patients were finally analyzed: 206 in the IC and 208 in the no-IC arm.

With a median follow-up of 44.8 months, OS significantly higher in the IC arm (HR 0.74; 95% CI 0.56–0.97; P¼0.031).

Complete Responses (0.0028), PFS (0.013) and LRC (0.036) also significantly higher in the IC arm.

Compliance to concomitant treatments was not affected by induction TPF.



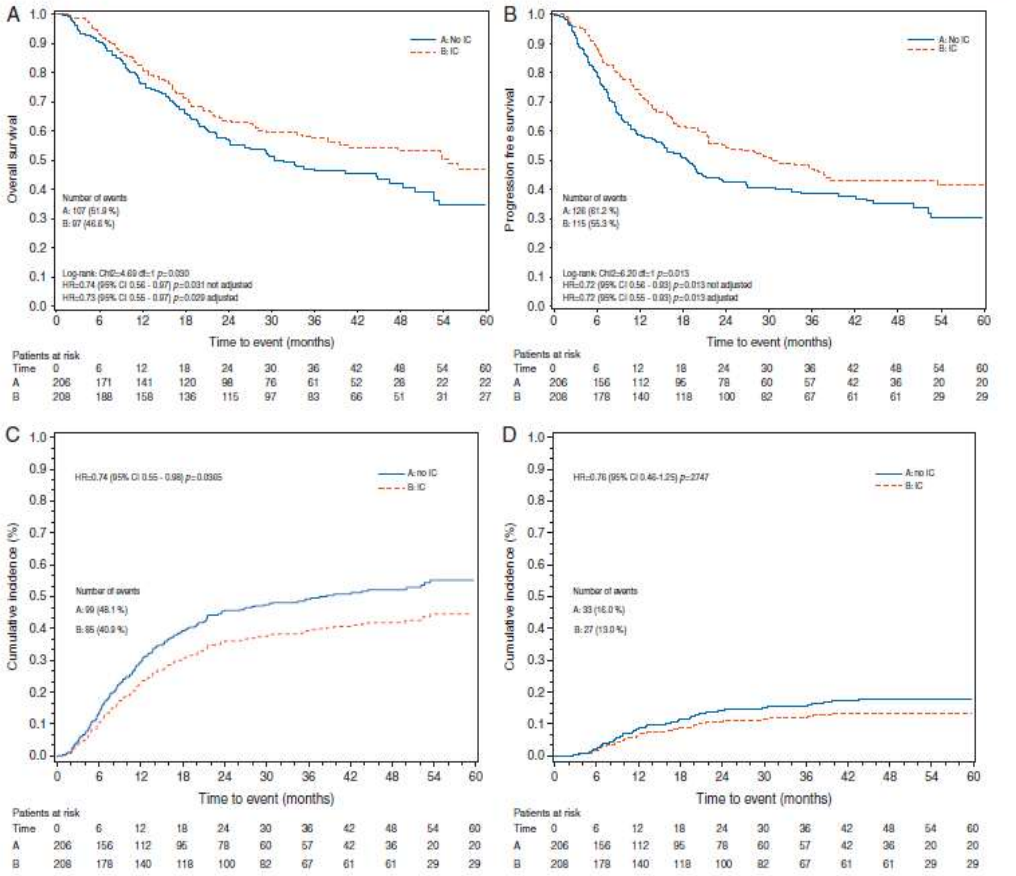



**Figure 2.** Kaplan–Meier curves for OS (A) and PFS (B) of IC versus no-IC and cumulative incidence (competing risk analysis) for loco-regional* (C) and distant events (D). *Loco-regional progression, death from cancer without documented progression or death from unknown causes were considered loco-regional failure.

# Role of biological modifiers??

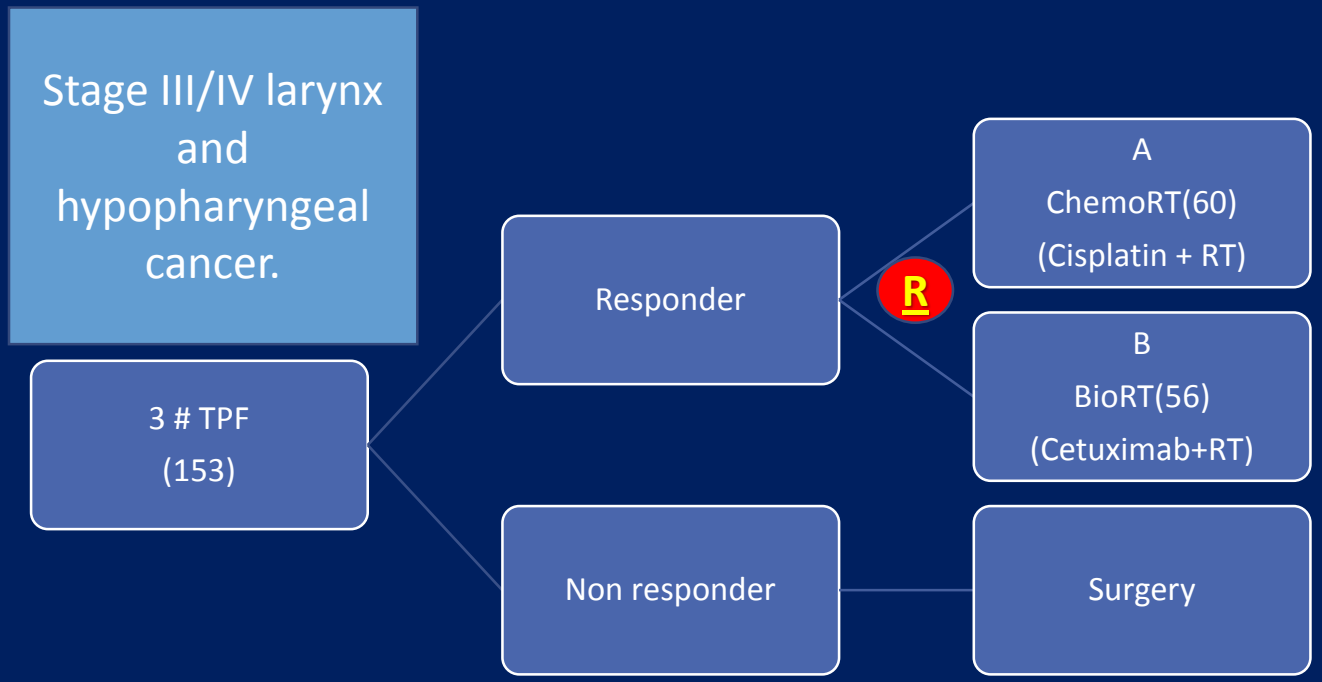
In view of increased toxicities with concurrent chemoradiation thereby affecting OS and QOL

Role of Biological modifiers with RT was explored in Organ preservation.

# Induction Chemotherapy Followed by Either Chemoradiotherapy or Bioradiotherapy for Larynx Preservation: The TREMPLIN Randomized Phase II Study

*Jean Louis Lefebvre, Yoann Pointreau, Frederic Rolland, Marc Alfonsi, Alain Baudoux, Christian Sire, Dominique de Raucourt, Olivier Malard, Marian Degardin, Claude Tuchais, Emmanuel Blot, Michel Rives, Emile Reyt, Jean Marc Tourani, Lionel Geoffrois, Frederic Peyrade, Francois Guichard, Dominique Chevalier, Emmanuel Babin, Philippe Lang, Francois Janot, Gilles Calais, Pascal Garaud, and Etienne Bardet*

See accompanying editorial doi: 10.1200/JCO.2012.45.8976




**Primary end point**- larynx preservation at 3 months

**Secondary end point**- Larynx dysfunction free survival at 18month
-OS at 18 months

--Despite a higher number of local failures in the B arm, after salvage surgery, the ultimate local failure rate seemed comparable.
-Comparable grade 3-4 toxicities in both arms. (more in field skin toxicity in BioRT arm)

| | Cisplatin | Cetuximab | P value |
|---|---|---|---|

**Table 5.** Treatment Failures and Salvage Surgery

| Variable | Patients 18 Months Post-Treatment | | | | Patients at Last Evaluation* | | | |
|---|---|---|---|---|---|---|---|---|
| | Cisplatin | | Cetuximab | | Cisplatin | | Cetuximab | |
| | No. | % | No. | % | No. | % | No. | % |
| Local (with or without regional) failure | 5† | 8.3 | 8 | 14.3 | 8 | 13.3 | 12 | 21.4 |
| Surgery feasible | 0 | 5 | 7 | 8 | 1 | 8 | 9‡ | 12 |
| Surgery successful | | | | | 0 | 1 | 6 | 8 |
| Ultimate local failure | | | | | 8 | 13.3 | 6 | 10.7 |
| Regional failure only | 5 | 8.3 | 5 | 8.9 | 4 | 6.7 | 5 | 8.9 |
| Surgery feasible | | | | | 1 | 4 | 4 | 5 |
| Surgery successful | | | | | 0 | 1 | 1 | 4 |
| Ultimate regional failure | | | | | 4 | | 4 | |
| Distant metastases | | | | | 5 | 8.3 | 3 | 5.4 |
| Second primary cancer | | | | | 7 | 11.7 | 8 | 14.3 |

*Median follow-up, 36 months; maximum follow-up, 58 months in each arm.
†One patient with uncontrolled disease lost to follow-up.
‡One patient refused all further treatment, including salvage surgery.

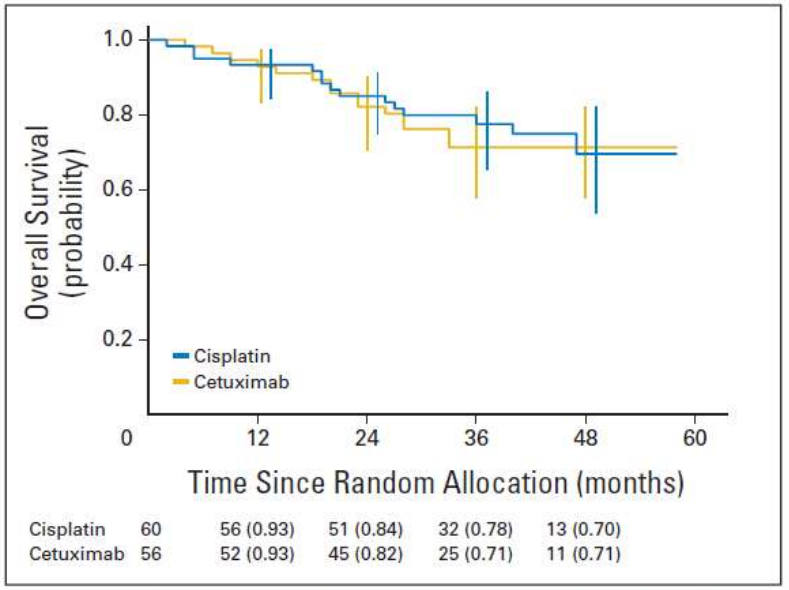



**Fig 2.** Overall survival (intent to treat) for the subgroup of patients who were responding to induction chemotherapy.

**Table 1.** EMPLIN trial: Compliance and larynx preservation [6]

| | Post-TPF induction treatme |
|---|---|
| Laryn… rvation rate 3 months after treatment, *n* (%)[a] | 55 (92) 54 (96) |

Raised the possibility that for larynx cancer, EGFR inhibition/RT may be inferior to cisplatin/RT for achieving local control, both cetuximab/RT and cisplatin/RT were difficult to administer after induction TPF.

**However BioRT is better tolerated than CTRT**

# Induction chemotherapy followed by cisplatin or cetuximab concomitant to radiotherapy for laryngeal/ hypopharyngeal cancer: Long-term results of the TREMPLIN randomised GORTEC trial

radiotherapy (70 Gy) with concurrent cisplatin (100 mg/m$^2$/day on days 1, 22 and 43 of radio-

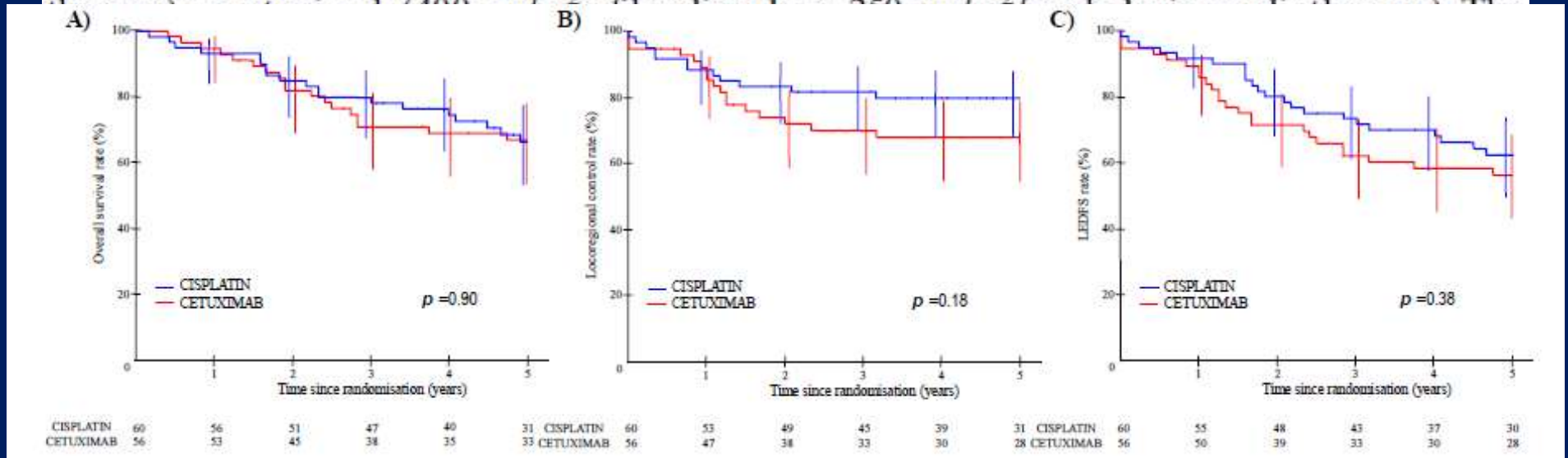



Fig. 2. Efficacy results at 5 years. (A) Overall survival (OS) rates were not statistically different ($p = 0.9$, two-sided log-rank test). (B) Locoregional control rates (LCRs) were not statistically different ($p = 0.18$, two-sided log-rank test). (C) Laryngo-oesophageal dysfunction-free survival (LEDFS) rates were not statistically different ($p = 0.38$, two-sided log-rank test).

toxicity was not statistically different between the two arms. LEDFS appears as a relevant end-point.

European Journal of Cancer 133 (2020) 86–93

# MACH NC 2017 update

| Treatment comparison | Rank | Network meta-analysis | | Number of trials per comparison |
|---|---|---|---|---|
| | | HR | CI 95% | |
| **Compared to platinum-based CRT** | | | | |
| HFCRT | 1 | 0.80 | [0.65-0.99] | 2 |
| IC (TaxPF) followed by LRT | 2 | 0.90 | [0.73-1.12] | 0 |
| ACRT | 3 | 0.97 | [0.86-1.10] | 4 |
| IC (TaxPF) followed by CRT | 4 | 0.98 | [0.80-1.21] | 3 |
| **Compared to LRT** | | | | |
| HFCRT | 1 | 0.62 | [0.51-0.76] | 2 |
| IC (TaxPF) followed by LRT | 2 | 0.70 | [0.57-0.86] | 1 |
| ACRT | 3 | 0.75 | [0.67-0.85] | 1 |
| IC (TaxPF) followed by CRT | 4 | 0.76 | [0.62-0.94] | 0 |
| Platinum-based CRT | 5 | 0.77 | [0.72-0.83] | 23 |

Tax-PF= Taxane, Platin and 5-Fluorouracil.

Supported by INCa (PHRC, PAIR-VADS) and LNCC

Radiotherapy and Oncology 156 (2021) 281–293

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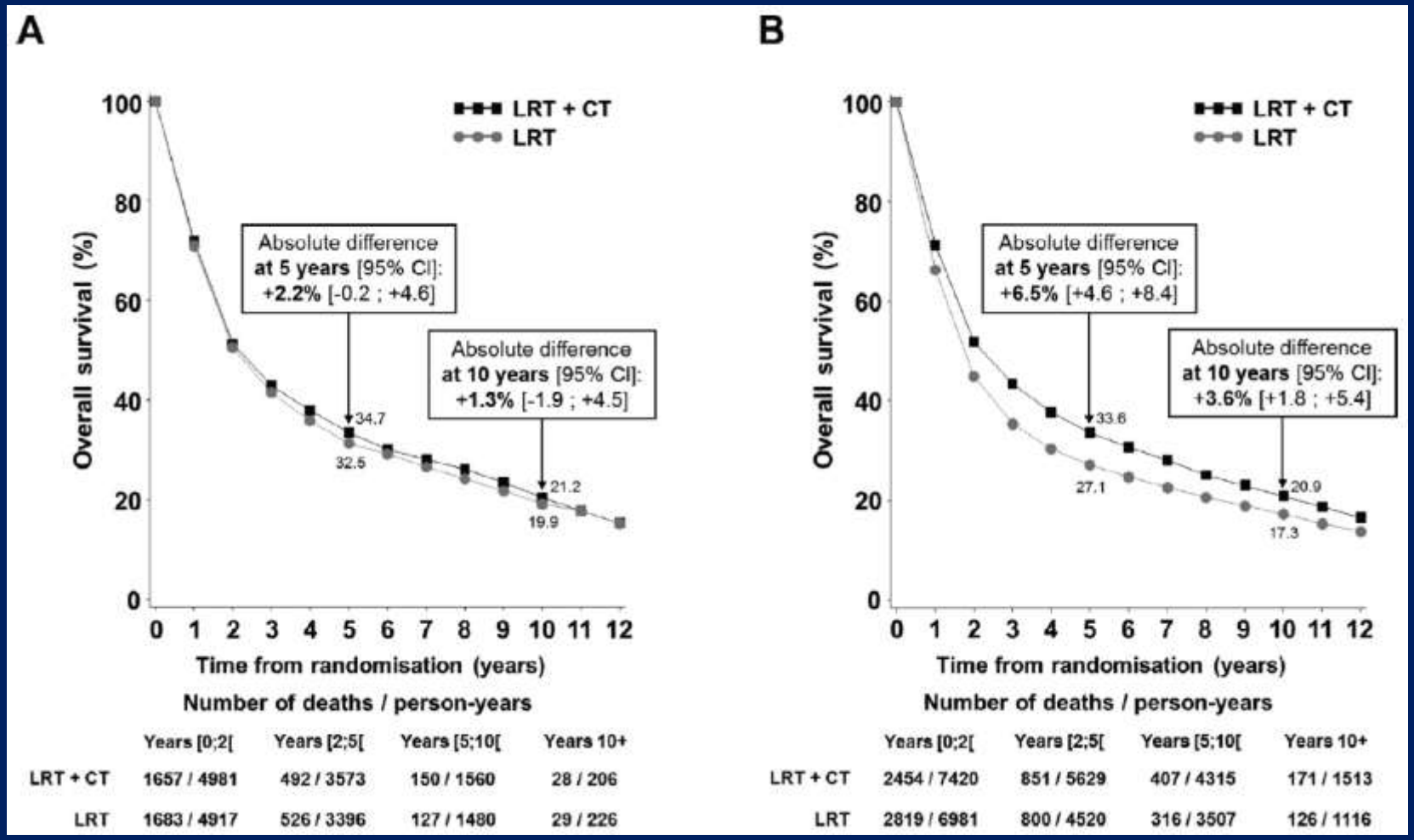
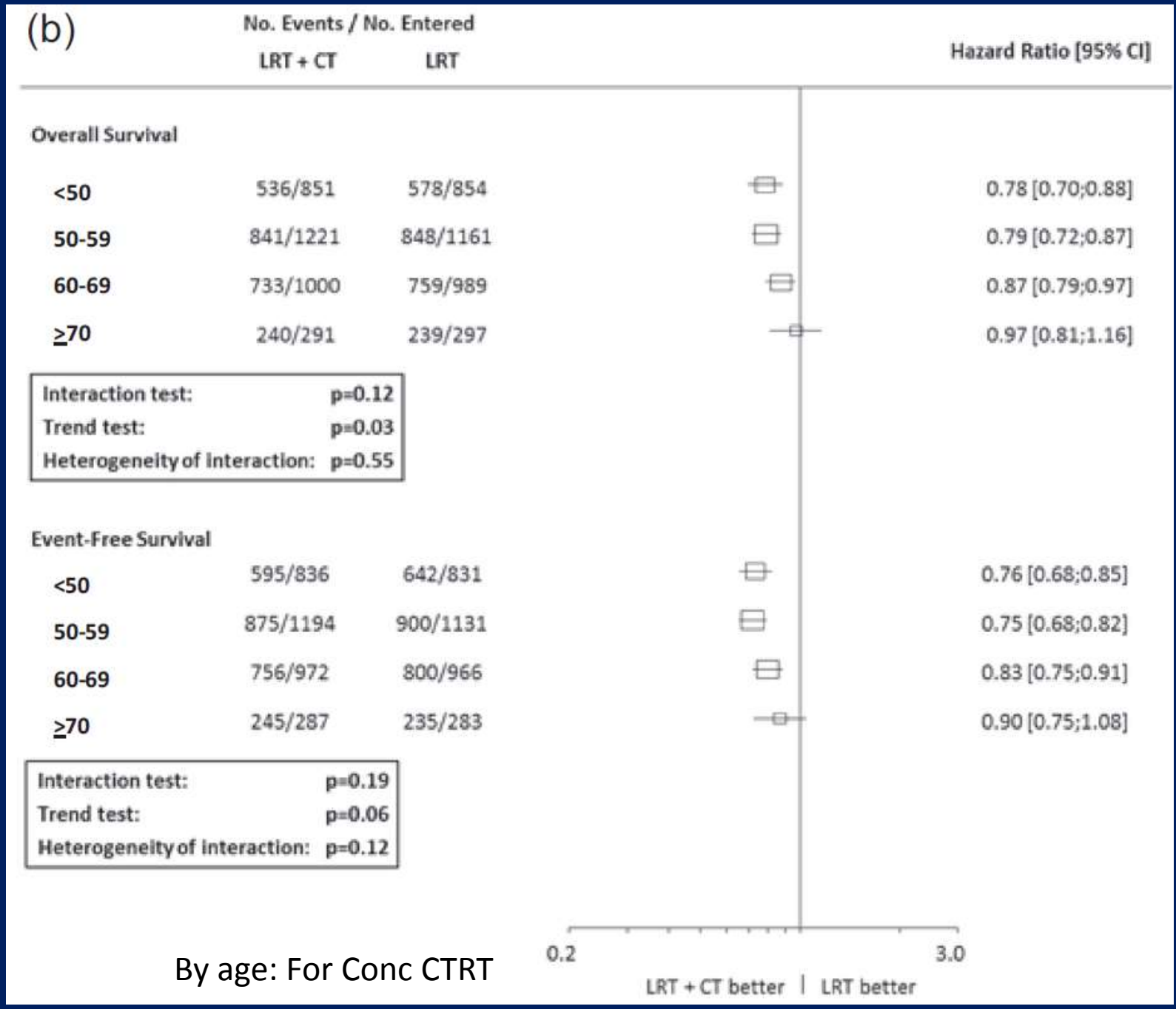
journal homepage: www.thegreenjournal.com

Original Article

# Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group

Benjamin Lacas [a,b], Alexandra Carmel [a], Cécile Landais [a], Stuart J. Wong [c], Lisa Licitra [d], Jeffrey S. Tobias [e], Barbara Burtness [f], Maria Grazia Ghi [g], Ezra E.W. Cohen [h], Cai Grau [i], Gregory Wolf [j], Ricardo Hitt [k], Renzo Corvò [l], Volker Budach [m], Shaleen Kumar [n], Sarbani Ghosh Laskar [o], Jean-Jacques Mazeron [p], Lai-Ping Zhong [q], Werner Dobrowsky [r], Pirus Ghadjar [s], Carlo Fallai [t], Branko Zakotnik [u], Atul Sharma [v], René-Jean Bensadoun [w], Maria Grazia Ruo Redda [x], Séverine Racadot [y], George Fountzilas [z], David Brizel [aa], Paolo Rovea [ab], Athanassios Argiris [ac], Zoltán Takácsi-Nagy [ad], Ju-Whei Lee [ae], Catherine Fortpied [af], Jonathan Harris [ag], Jean Bourhis [b,ah], Anne Aupérin [a,b], Pierre Blanchard [a,b,ai,*], Jean-Pierre Pignon [a,b], on behalf of the MACH-NC Collaborative Group


A
LRT + CT
LRT
Overall survival (%)
Absolute difference at 5 years [95% CI]: +2.2% [-0.2 ; +4.6]
Absolute difference at 10 years [95% CI]: +1.3% [-1.9 ; +4.5]
34.7
32.5
21.2
19.9
Time from randomisation (years)
Number of deaths / person-years
Years [0;2[ Years [2;5[ Years [5;10[ Years 10+
LRT + CT 1657 / 4981 492 / 3573 150 / 1560 28 / 206
LRT 1683 / 4917 526 / 3396 127 / 1480 29 / 226
B
LRT + CT
LRT
Overall survival (%)
Absolute difference at 5 years [95% CI]: +6.5% [+4.6 ; +8.4]
Absolute difference at 10 years [95% CI]: +3.6% [+1.8 ; +5.4]
33.6
27.1
20.9
17.3
Time from randomisation (years)
Number of deaths / person-years
Years [0;2[ Years [2;5[ Years [5;10[ Years 10+
LRT + CT 2454 / 7420 851 / 5629 407 / 4315 171 / 1513
LRT 2819 / 6981 800 / 4520 316 / 3507 126 / 1116




By age: For Conc CTRT

**Table 1**
Results of the addition of chemotherapy to loco-regional treatment.

| | Overall survival | 120-day mortality | Event-free survival | Cancer mortality[§] | Non-cancer mortality[§] | Loco-regional failure* | Distant failure* |
|---|---|---|---|---|---|---|---|
| *Induction* | | | | | | | |
| No. events/No. patients | 4692/7054 | 470/7054 | 4556/6374 | 979/2031 | 320/2031 | 2574/6342 | 761/5582 |
| HR of chemotherapy effect [95% CI]; *p*-value | 0.96 [0.90; 1.01]<br>*p* = 0.14 | 1.07 [0.89;1.28]<br>*p* = 0.47 | 0.96 [0.90;1.02]<br>*p* = 0.14 | 0.97 [0.86;1.10]<br>*p* = 0.67 | 0.84 [0.67;1.05]<br>*p* = 0.12 | 1.07 [0.99;1.15]<br>*p* = 0.09 | 0.76 [0.66;0.88]<br>*p* = 0.0002 |
| Heterogeneity: *p*-value ($I^2$) | *p* = 0.63 (0%) | *p* = 0.46 (1%) | *p* = 0.25 (12%) | *p* = 0.24 (19%) | *p* = 0.28 (16%) | *P* < 0.0001 (63%) | *P* < 0.0001 (97%) |
| Absolute difference at 5 years [95% CI] | +2.2%<br>[−0.2;+4.6] | NA | +1.4%<br>[−0.9;+3.7] | −0.7%<br>[−5.5;+4.1] | −4.8%<br>[−0.4;−9.2] | +3.2%<br>[+0.8;+5.7] | −4.1%<br>[−6.0;−2.2] |
| Absolute difference at 10 years [95% CI] | +1.3%<br>[−1.9;+4.5] | NA | −0.6%<br>[−3.6;+2.4] | NA | NA | +4.6%<br>[+1.7;+7.5] | −3.5%<br>[−5.7;−1.3] |
| *Concomitant* | | | | | | | |
| No. events/No. patients | 7944/10,680 | 716/10,680 | 8345/10,457 | 3730/6483 | 955/6483 | 4766/10,076 | 1034/9022 |
| HR of chemotherapy effect [95% CI]; *p*-value | 0.83 [0.79;0.86]<br>*p* < 0.0001 | 1.07 [0.92;1.24]<br>*p* = 0.37 | 0.80 [0.77;0.84]<br>*p* < 0.0001 | 0.79 [0.74;0.84]<br>*p* < 0.0001 | 1.01 [0.89;1.16]<br>*p* = 0.83 | 0.71 [0.67;0.75]<br>*p* < 0.0001 | 1.04 [0.92;1.18]<br>*p* = 0.48 |
| Heterogeneity: *p*-value ($I^2$) | *p* = 0.0002 (42%) | *p* = 0.01 (30%) | *p* = 0.04 (24%) | *p* = 0.18 (18%) | *p* = 0.80 (0%) | *P* < 0.0001 (85%) | *P* < 0.0001 (96%) |
| Absolute difference at 5 years [95% CI] | +6.5%<br>[+4.6;+8.4] | NA | +5.8%<br>[+4.1;+7.5] | −9.8%<br>[−12.4;−7.2] | +2.9%<br>[+0.1;+5.7] | −9.3%<br>[−11.3;−7.3] | +0.2%<br>[−1.0;+1.6] |
| Absolute difference at 10 years [95% CI] | +3.6%<br>[+1.8;+5.4] | NA | +3.1%<br>[+1.5;+4.7] | NA | NA | −9.6%<br>[−11.6;−7.5] | +0.2%<br>[−1.2;+1.6] |
| *Adjuvant* | | | | | | | |
| No. events/No. patients | 1605/2915 | 127/2915 | 1461/2416 | NA | NA | 571/2416 | 324/2224 |
| HR of chemotherapy effect [95% CI]; *p*-value | 1.02 [0.92;1.13]<br>*p* = 0.69 | 1.89 [1.33;2.68]<br>*p* = 0.0003 | 0.98 [0.88;1.09]<br>*p* = 0.72 | NA | NA | 0.84 [0.72;1.00]<br>*p* = 0.04 | 0.77 [0.62;0.96]<br>*p* = 0.02 |
| Heterogeneity: *p*-value ($I^2$) | *p* = 0.21 (23%) | *p* = 0.10 (34%) | *p* = 0.03 (47%) | NA | NA | *p* = 0.16 (29%) | *P* < 0.0001 (98%) |
| Absolute difference at 5 years [95% CI] | −0.3%<br>[−4.3;+3.7] | NA | −0.6%<br>[−5.0;+3.8] | NA | NA | −3.7%<br>[−7.2;−0.2] | −3.0%<br>[−6.0;0.0] |
| Absolute difference at 10 years [95% CI] | +1.2%<br>[−4.1;+6.5] | NA | +3.6%<br>[−2.7;+9.9] | NA | NA | −3.6%<br>[−7.2;0.0] | −3.2%<br>[−6.5;+0.2] |
| **Interaction test** (timing × treatment effect) | *p* < 0.0001 | 0.01 | *p* < 0.0001 | *P* = 0.003 | *P* = 0.15 | *p* < 0.0001 | *P* = 0.001 |

$IC_{TaxPF}$-LRT

| | Overall survival | Event-free survival | Locoregional control | Distant control |
|---|---|---|---|---|
| Randomised controlled trials | 115 | 112 | 110 | 100 |
| Comparisons | 154 | 151 | 150 | 137 |
| Patients | 28 978 | 28 315 | 27 309 | 25 042 |
| Events | 19 253 | 20 579 | 10 882 | 3065 |
| Gobal p value | 0·074 | 0·11 | <0·0001 | <0·0001 |
| p value for heterogeneity | 0·013 | 0·054 | <0·0001 | <0·0001 |
| p value for inconsistency | 0·91 | 0·52 | 0·0008 | <0·0001 |
| Hazard ratio (95% CI); P score (%) | | | | |
| Locoregional therapy | 1 (ref); 21% | 1 (ref); 12% | 1 (ref); 15% | 1 (ref); 33% |
| HFCRT | 0·63 (0·51–0·77)*; 97%† | 0·60 (0·49–0·73)*; 97%† | 0·49 (0·30–0·78)*; 88%† | 1·15 (0·15–8·99); 32% |


| | | | | |
|---|---|---|---|---|
| Locoregional therapy | 1 (ref); 21% | 1 (ref); 12% | 1 (ref); 15% | 1 (ref); 33% |
| HFCRT | 0·63 (0·51–0·77)*; 97%† | 0·60 (0·49–0·73)*; 97%† | 0·49 (0·30–0·78)*; 88%† | 1·15 (0·15–8·99); 32% |


**Interpretation** The results of this network meta-analysis suggest that further intensifying chemoradiotherapy, using HFCRT or $IC_{TaxPF}$-CLRT, could improve outcomes over chemoradiotherapy for the treatment of locally advanced head and neck cancer.

| | | | | |
|---|---|---|---|---|
| $CLRT_p$ | 0·77 (0·72–0·83)*; 78% | 0·74 (0·70–0·79)*; 75% | 0·54 (0·46–0·65)*; 84%† | 1·36 (0·61–2·99); 23% |
| HFRT | 0·85 (0·76–0·95)*; 61% | 0·84 (0·76–0·93)*; 55% | 0·81 (0·59–1·11); 42% | 0·32 (0·08–1·27); 71% |
| VART | 0·90 (0·81–1·01); 47% | 0·88 (0·79–0·98); 43% | 0·83 (0·59–1·17); 33% | 0·32 (0·10–1·03); 30% |
| $IC_{cis}$-CLRT | 0·90 (0·72–1·13); 46% | 0·83 (0·66–1·03); 55% | 0·58 (0·31–1·06); 73% | 1·47 (0·10–20·56); 29% |
| MART | 0·94 (0·87–1·01); 37% | 0·89 (0·83–0·96)*; 40% | 0·77 (0·62–0·97)*; 48% | 0·47 (0·16–1·39); 59% |
| LRT-AC | 1·03 (0·90–1·17); 18% | 0·99 (0·86–1·13); 17% | 0·77 (0·53–1·13); 48% | 0·16 (0·03–0·88)*; 84%† |
| $CLRT_{nat}$-AC | 1·07 (0·84–1·36); 16% | 0·95 (0·75–1·20); 28% | 0·77 (0·36–1·65); 47% | 0·19 (0·01–6·83); 71%† |
| $IC_{other}$-CLRT | 1·15 (0·73–1·82); 16% | NA‡ | NA‡ | NA‡ |
| $IC_{other}$-LRT | 1·04 (0·93–1·16); 15% | 1·05 (0·94–1·17); 6% | 1·00 (0·77–1·30); 17% | 2·00 (0·49–8·09); 16% |

ACRT=accelerated radiotherapy with concomitant chemotherapy. $CLRT_{nat}$=locoregional therapy with concomitant chemoradiotherapy without platinum-based chemotherapy. $CLRT_{nat}$-AC=$CLRT_{nat}$ followed by adjuvant chemotherapy. $CLRT_p$=locoregional therapy with concomitant chemoradiotherapy with platinum-based chemotherapy. HFCRT=hyperfractionated radiotherapy with concomitant chemotherapy. HFRT=hyperfractionated radiotherapy. IC-CLRT=induction chemotherapy followed by locoregional therapy with concomitant chemoradiotherapy. IC-LRT=induction therapy followed by locoregional therapy. LRT-AC=locoregional therapy followed by adjuvant chemotherapy. MART=moderately accelerated radiotherapy. NA=not available. Other=other type of induction chemotherapy. PF=cisplatin or carboplatin plus fluorouracil. TaxPF=taxane with cisplatin plus fluorouracil. VART=very accelerated radiotherapy. *Significant. †The three modalities of treatment with the highest P score. ‡No comparison was possible as the trial with this modality of treatment did not have information for event-free survival, locoregional control, and distant control.

chemotherapy†

021; 22: 727–36

# Toxicity in CTRT

- Although CRT improves LRC and OS, and allows for organ preservation, toxicities are increased compared with RT alone.
- The most common acute grade 3/4 complications include:
- Leukopenia
- Anaemia
- Mucositis
- Dysphagia
- Swallowing dysfunction
- Acute CRT toxicities are related to the specific CRT regimen.

Evaluation of Early and Late Toxicities in Chemoradiation Trials JCO September 10, 2007:4096-4103

# Toxicity to Multimodality Treatment

Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review

| Treatment | *n* | Mucositis incidence (% of patients) | Grade 3–4 mucositis (% of patients) |
|---|---|---|---|
| Total[b] | 6181 | 80 | 39 |
| RT-C | 2875 | 97 | 34 |
| RT-AF | 1096 | 100 | 57 |
| RT + CT[c] | 1505 | 89 | 43 |
| CT only | 318 | 22 | 0 |

Oral Pain - 69%

Opioid Use -53%

Overall Incidence of- Hospitalization: 16%

Feeding Tube Insertion: 19%

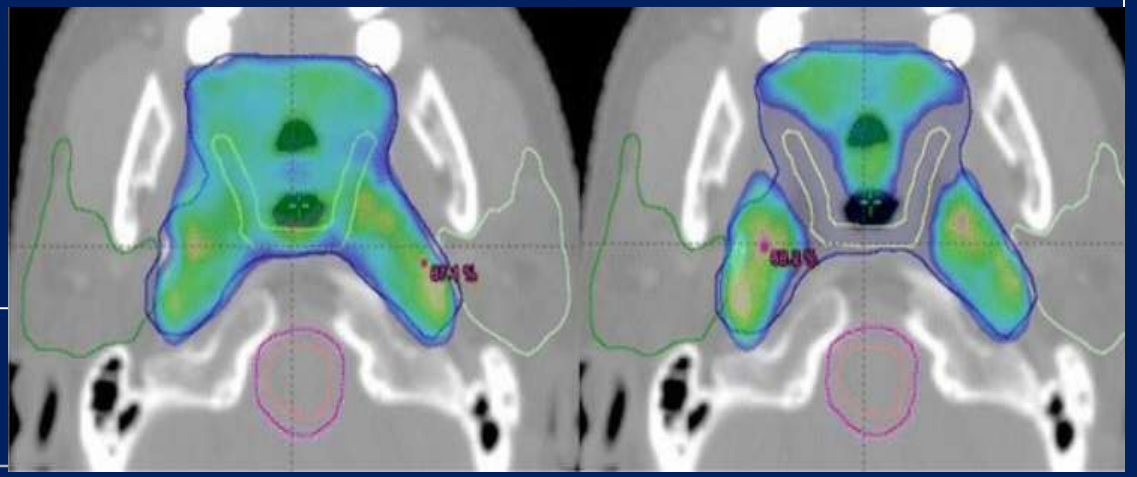
Mean Wt. Loss: 6-12% of BW (34% lost wt)

Dysphagia: 56%

# Late effect of Organ Preservation Protocols

| Author | Regimen | Grade 3-4 xerostomia (fibrosis |
|---|---|---|
| **Wendt (n=270)** | **RT+CH** | |

- All data: Pre-IMRT
- With the advent of better techniques, possible to reduce morbidity
  - DARS optimised
  - Parotid gland sparing
  - Adaptive RT
  - Image-guidanace



Trotti et al.,IJROBP, Vol.47, No.1, pp 1-12, 2000

# Incidence of Morbidity: Pre & Post IMRT

| Toxicity | | 2D/3D-CRT | IMRT | |
|---|---|---|---|---|
| Xerostomia | Acute | 54 – 89 | 24 - 59 | |
| | Late | 46 - 77 | 8 – 38 | |
| Mucositis | Grade 1 | 3 - 7 | OM non-sparing | OM-sparing |
| | | | 0 | 75 |
| | Grade 2 | 78.5 - 87 | 54.2 | 25 |
| | Grade 3-4 | 7 – 28.7 | 45.8 | 0 |
| Dysphagia > Grade 2 | Acute | 35 - 45 | 18 - 21 | |
| | Late | 60 - 63 | 6 - 38 | |
| Fibrosis | | 11.3 - 60 | 2.3 - 15 | |
| Trismus | | 13.9 - 25.4 | 3.3 - 5 | |
| ONJ | | 2 - 22 | 0 - 6 | |
| Hearing Loss | | 39 - 84.5 | 25.8 - 36 | |

# Various Treatment modalities in Locally Advanced Carcinoma Larynx and Hypopharynx

1.Total laryngectomy +/- PORT

2.Organ Preservation startegies:

- ✓ Conservative Surgery
- ✓ Induction chemotherapy (ICT) followed by RT
- ✓ Concurrent chemo-RT
- ✓ ICT followed by CTRT
- ✓ Role of Targeted therapies
- ✓ Altered fractionation

# Factors deciding choice of treatment

## Patient factors

- Age
- Performance Status
- Comorbidity
- Previous Rx
- Reliability for F/U
- Pt.'s choice
- Pt.'s occupation
- Second Primary

## Disease Factors

- Stage
- Site
- Volume
- Cord Mobility

## Treatment factors

- Physician's Expertise
- Cost and Feasibility
- Treatment morbidity

# When not to go ahead with it…

**Table 4**
Hazard ratio of death with locoregional treatment plus chemotherapy versus locoregional treatment alone by patient characteristics for each tumour site.

| Overall survival | | Oral cavity | | Oropharynx | | Larynx | | Hypopharynx | |
|---|---|---|---|---|---|---|---|---|---|
| | | HR [95% CI] | *p*-value | HR [95% CI] | *p*-value | HR [95% CI] | *p*-value | HR [95% CI] | *p*-value |
| Age | ⩽50 | 0.87 [0.75; 1.01] | 0.03* (0.16) | 0.86 [0.76; 0.98] | 0.14 (0.14) | 0.76 [0.58; 0.98] | 0.54 (0.39) | 0.76 [0.61; 0.95] | 0.18 (0.06) |
| | 51–60 | 0.76 [0.67; 0.87] | | 0.83 [0.75; 0.93] | | 0.89 [0.76; 1.04] | | 0.86 [0.73; 1.01] | |
| | 61+ | 0.99 [0.86; 1.13] | | 0.97 [0.87; 1.08] | | 0.89 [0.77; 1.02] | | 0.98 [0.84; 1.14] | |
| Sex | Male | 0.91 [0.84; 0.99] | 0.04** | 0.89 [0.83; 0.96] | 0.50 | 0.86 [0.78; 0.95] | 0.78 | 0.86 [0.78; 0.95] | 0.29 |
| | Female | 0.73 [0.61; 0.88] | | 0.83 [0.69; 1.00] | | 0.90 [0.66; 1.23] | | 1.04 [0.74; 1.46] | |
| Performance status | 0 | 0.92 [0.79; 1.07] | 0.60 | 0.73 [0.64; 0.82] | 0.004*** | 0.87 [0.74; 1.01] | 0.64 | 0.84 [0.70; 1.00] | 0.63 |
| | 1+ | 0.87 [0.77; 0.98] | | 0.91 [0.83; 0.99] | | 0.82 [0.70; 0.97] | | 0.79 [0.68; 0.92] | |
| Stage | I, II | 0.90 [0.66; 1.24] | 0.60 (0.60) | 0.75 [0.56; 1.00] | 0.02**** (0.20) | 0.89 [0.63; 1.24] | 0.98 (0.93) | 1.01 [0.60; 1.70] | 0.52 (0.26) |
| | III | 0.80 [0.68; 0.93] | | 1.01 [0.88; 1.14] | | 0.85 [0.72; 1.01] | | 0.94 [0.77; 1.13] | |
| | IV | 0.87 [0.79; 0.96] | | 0.83 [0.77; 0.90] | | 0.86 [0.76; 0.97] | | 0.84 [0.75; 0.94] | |

- Gross cartilage invasion/ erosion/ lysis
- Dysfunctional larynx
- Patients who prefer avoiding RT
- Poor candidates for CT
- Severe airway compromise requiring a tracheostomy or enteric feeding, are poor candidates for LP

# Options:
# CTRT or ICT f/b CCRT??

## Considerations

- Volume, Site: Larynx vs Hypopharynx
- Functional status: Fixed cord, no aspiration
- Nodal stage → higher risk for distant mets
- Either CTRT or ICT f/b CTRT

# ASCO Clinical Practice Guideline Update: Use of Larynx-Preservation Strategies in the Treatment of Laryngeal Cancer

Arlene A. Forastiere, MD

Gregory T. Wolf, MD

Arlene Forastiere et al. JCO 2018

**Clinical Question 2**

*What are the larynx-preservation treatment options for advanced-stage (T3, T4) primary site disease that do not compromise survival? What are the considerations in selecting among them?*

- Recommendation 2.1—*Reworded*: Organ-preservation surgery, combined chemotherapy and radiotherapy, and radiotherapy alone, all with further surgery reserved for salvage, offer the potential for larynx preservation without compromising overall survival. Anticipated success rates for larynx preservation, associated toxicities, and suitability for a given patient will vary among these approaches. Selection of a treatment option will depend on patient factors, including age, comorbidities, preferences, socioeconomic factors, local expertise, and the availability of appropriate support and rehabilitation services.

# ASCO recommendations cont.....

- Recommendation 2.2—*New*: For selected patients with extensive T3 or large T4a lesions and/or poor pretreatment laryngeal function, better survival rates and quality of life may be achieved with total laryngectomy than with organ-preservation approaches and may be the preferred approach.

Recommendation 2.4—*Updated*: A minority of patients with T3, T4 primary site disease will be suitable for specialized organ-preservation surgical procedures, such as a supracricoid partial laryngectomy. The addition of postoperative radiotherapy will compromise functional outcomes. Induction chemotherapy before organ-preservation surgery is not recommended outside a clinical trial.

Recommendation 2.5—*Updated*: Concurrent chemoradiotherapy offers a significantly higher chance of larynx preservation than radiotherapy alone or induction chemotherapy followed by radiotherapy, albeit at the cost of higher acute in-field toxicities and without improvement in overall survival. The best available evidence supports the use of cisplatin as the drug of choice in this setting.

Recommendation 2.6—*Updated*: There is insufficient evidence to indicate that survival or larynx-preservation outcomes are improved by the addition of induction chemotherapy before concurrent treatment or the use of concurrent treatment with altered fractionation radiotherapy in this setting.

# Conclusion

- Complete staging work-up with optimal imaging and functional evaluation: integration of functional imaging, volumetry

- There is no one standard larynx preservation treatment accepted worldwide.
- CTRT to be preferred with IMRT for optimal DARS sparing and careful assessment of DARS dysfunction
- Role of NACT – Bulky disease, Higher chances of distant mets, Gross exolaryngeal spread without cartilage destruction

- Bio RT may be preferred in case poor tolerability to chemoRT is expected.

- Option of altered fractionation

- **Built-in appropriate follow-up (rehabilitation, imaging) and salvage strategy**

- **Case selection is the cornerstone to successful outcome**

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