Management of Locally Advanced Head & Neck Cancers

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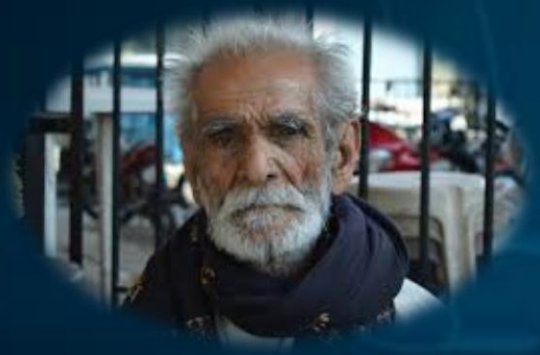
The Indian patient with HN SCC

CHALLENGING & COMPLEX DECISION MAKING PROCESS



Patient factors[1,2]
(e.g. Karnofsky performance status, age, sex, preference)

Disease factors[1,2]
(e.g. TNM status, co-morbidities, symptoms)

Social Factors
(e.g. Financial, family support, distance from the hospital)

Treatment factors[1–3]
(e.g. surgical intervention, acute and late toxicities)

1. Terrell JE, et al. Arch Otolaryngol Head Neck Surg 2004;130:401–408;
2. Meyer F, et al. Int J Radiat Oncol Biol Phys 2012;82:1454–1462;
3. Ronis DL, et al. Arch Otolaryngol Head Neck Surg 2008;134:241–248.

Definition of locally advanced head and neck SCC?

Definition of locally advanced HNSCC

- **Stage III/IV**
- Large primary tumors (>4cm) which may invade adjacent structures and/or spread; encompass internal carotid
- Oral cavity: bone/skin involvement, involves masticator space, pterygoid plates, skull base
- Oropharynx: larynx, extrinsic muscles of tongue, pterygoid msucles, skull base
- Hypopharynx: thyroid/cricoid cartilage, thyroid gland, esophagus, prevertebral fascia
- Larynx: cord fixation, thyroid cartilage, prevertebral space

What are the functional problems that patients with advanced HNSCC face?

The importance of preserving organ function in head and neck cancer

Loss of organ function in patients with head and neck cancer has a detrimental effect on quality of life

Issues related to loss of function in head and neck cancer

- Breathing difficulties
- Eating difficulties
- Speaking difficulties

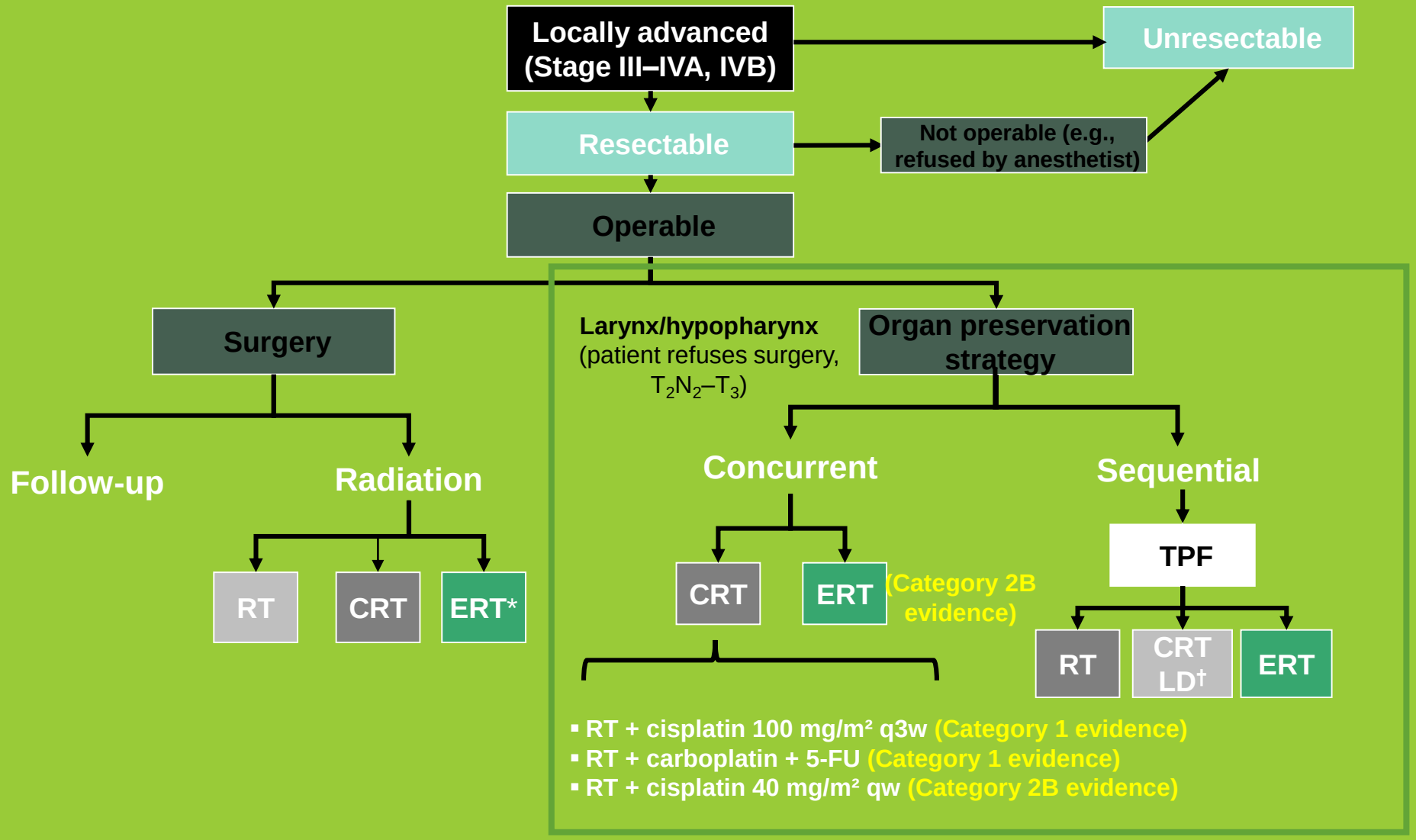
Impact on daily life

- Participating in meals within their usual social setting
- Ability to maintain personal hygiene
- Oral communication
- Professional and social activities
- Psychological impact

The extent of functional problems in head and neck cancer is an independent predictor of patient survival

Tschiesner, U. GMS Curr Top Otorhinolaryngol Head Neck Surg 2012;11:Doc07

Patient journey: SCCHN LA population[1]



1. National Comprehensive Cancer Network Clinical (NCCN) Practice Guidelines in Oncology: Head and Neck Cancers V3. 2021; 2. Erbitux SmPC, 06/2014

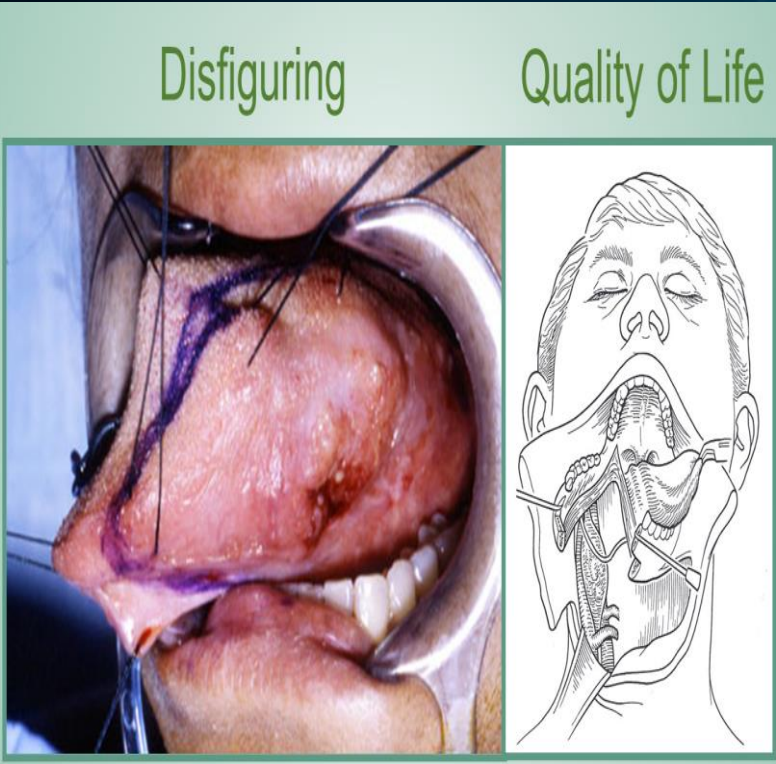
Strategies for functional organ function preservation in HNSCC

Concurrent CTRT

Induction Chemotherapy

Sequential Therapy

Major surgery may have a significant effect on long-term QoL in SCCHN



EORTC study (N=174 patients who underwent total laryngectomy)[1]

Negative impacts of surgery that do not recover to baseline in 1 year[1]

Physical functioning	Dyspnea
Role functioning	Appetite loss
Social functioning	Financial difficulties
Social contact	Senses
Fatigue	Speech

Single-center study (N=570 patients with SCCHN)[2]

Patients undergoing laryngectomy or other primary site surgery, often with postoperative RT*

→ Significant negative association between presence of a feeding tube and QoL, including lower scores on 6 of 8 SF-36 domains ($p<0.01$) and all 4 HNQoL domains ($p<0.01$)

* 58% of patients (320/553) underwent surgery; 63% of patients (348/553) received RT and 20% of patients (113/553) received CT prior to surgery

EORTC, European Organization for Research and Treatment of Cancer; HNQoL, Head and Neck QoL; QoL, quality of life; SF-36, Medical Outcomes Study Short-Form 36-Item Health Survey

1. Singer S, et al. Head Neck 2014;36:359–368;
2. Terrell JE, et al. Arch Otolaryngol Head Neck Surg 2004;130:401–408

CASE A.

48 year old non-smoker c/o swelling in the left neck and hoarseness of voice. On examination he has a large growth involving the left lateral half of the tongue, extending to the right side with ankyloglossia, s/o extrinsic tongue muscle involvement. He also has skin induration in the left submandibular region extending upto the level of the hyoid bone and bilateral cervical lymphadenopathy.

Biopsy is consistent with squamous cell carcinoma.

CT Neck confirms physical examination findings.

What is your radiological modality of choice for detecting moderately advanced disease?

CT WITH CONTRAST

MR WITH CONTRAST

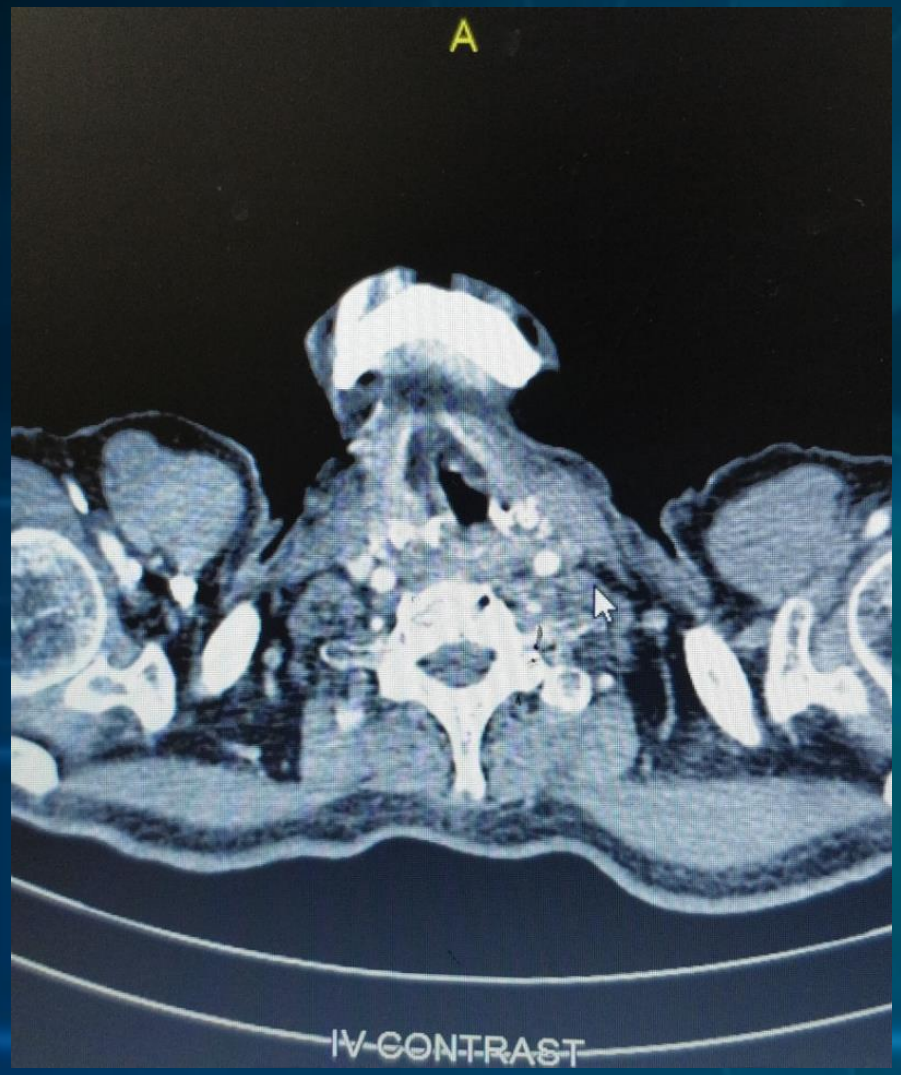
PET-CT

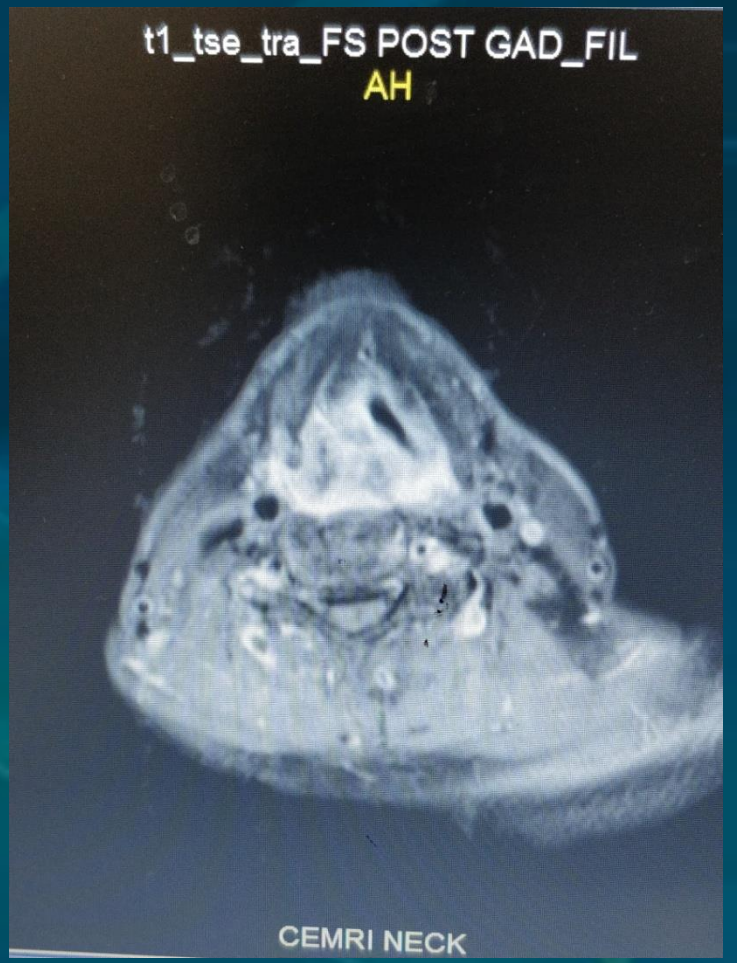
CT features suggestive of cartilage involvement and ELS

- **Sclerosis**: High sens/ low spec of 40% for thyroid cartilage; 76% cricoid, 79% arytenoid. Low PPVs for thyroid, cricoid and arytenoid (15-35%)
- **Cartilage erosion**: Specificity of 93% for all cartilages. Higher PPVs for bicortical erosion
- **ELS**: Low sensitivity (44%), high specificity (95%) for thyroid cartilage. Specificity lowered (81%) in ELS through routes other than cartilage
- NPV of CT is consistently high (95-100%)

Selective utilization of MR in larynx

When CT is equivocal, an MR might help in terms of demonstration of signal intensity changes

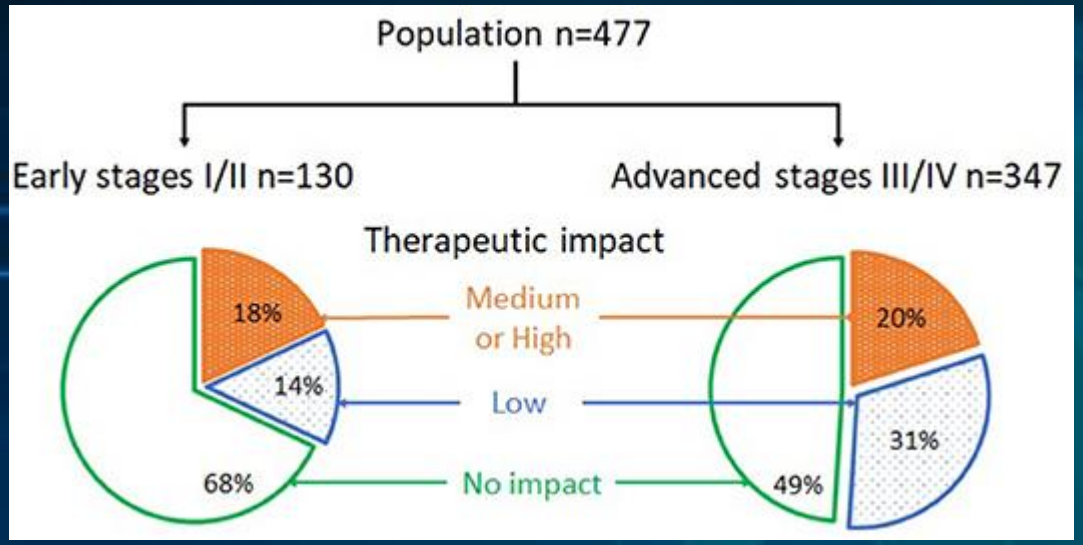




Integration of 18-FDG PET/CT in the Initial Work-Up to Stage Head and Neck Cancer: Prognostic Significance and Impact on Therapeutic Decision Making

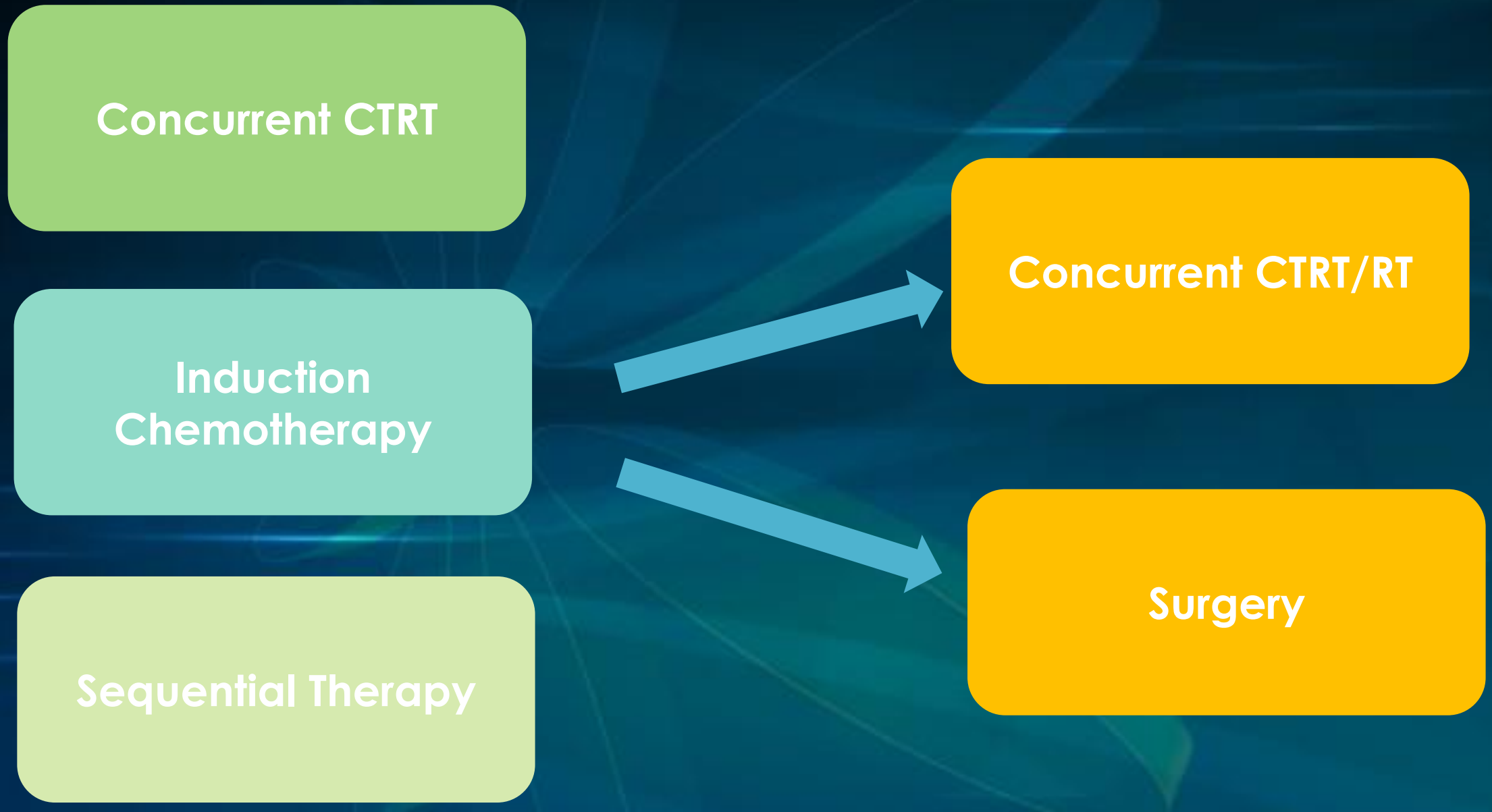
Restage with PET-CT: 221 (46.3%)
Downstaging: 56/477 (11.7%)
Upstaging:165/477 (34.6%)

Change in lymph node status (38.2%)
Occult metastases (4.5%)
Synchronous primary cancer (7.3%)



Characteristics		*n* (%)
Gender		
	Male	414 (86.8)
	Female	63 (13.2)
Age (average in years ± SD)	62.3 ± 9.7	
Primary location		
	Oral Cavity	99 (20.8)
	Oropharynx	187 (39.2)
	Larynx	103 (21.6)
	Hypopharynx	88 (18.4)
CWU staging		
	Early stages I/II	130 (27.3)
	Advanced stages III/IV	347 (73.7)

What will be your treatment approach?


Concurrent CTRT
Induction Chemotherapy
Sequential Therapy
Concurrent CTRT/RT
Surgery

What are the potential advantages of Induction chemotherapy (ICT)?

When goal of treatment is organ preservation, Induction chemotherapy can be useful

- Can achieve similar OS and LRC to standard CRT[1]
- Can reduce the rate of distant failure compared with no induction[1]
- Provides a reliable tumor response[2]
- Does not compromise subsequent response to therapy[3]

1. Pignon J-P, et al. Radiother Oncol 2009;92:4–14;
2. Decker DA, et al. Cancer 1983;51:1353–1355;
3. Ensley JF, et al. Cancer 1984;54:811–814

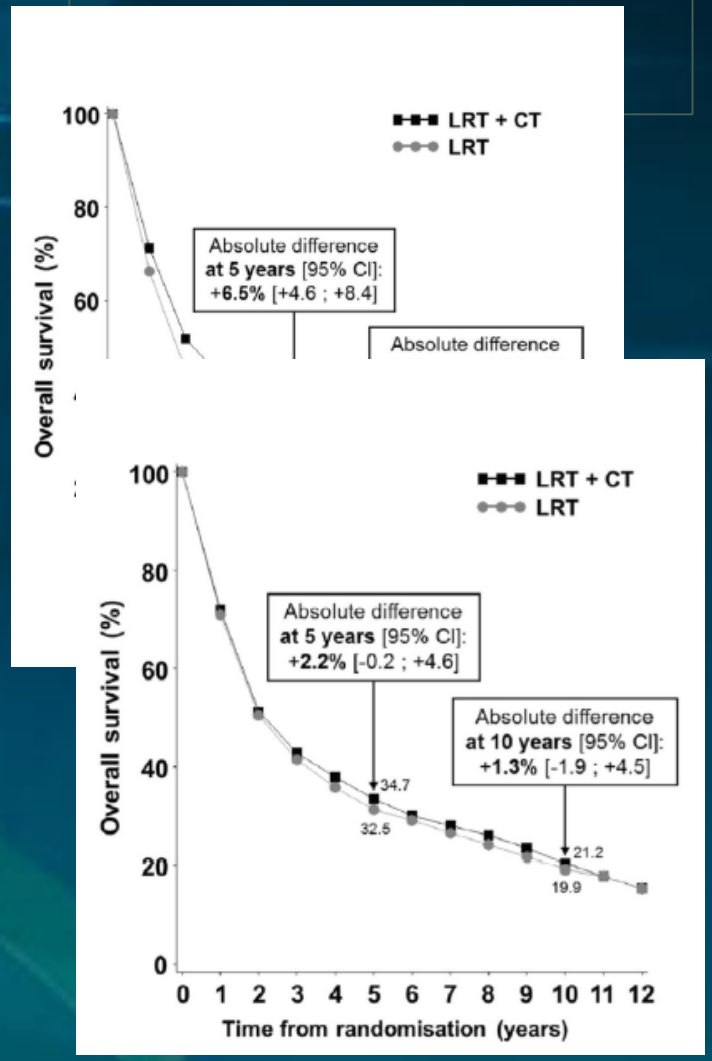
Induction chemotherapy and MACH-NC Analysis

2021 Update: 107 trials Included 19.805 patients

Meta-analysis on individual data of 63 randomized trials:

Locoregional treatment vs the same + Chemotherapy

Chemotherapy	Number of patients	Absolute benefit at 5 years	HR (95% CI)	p
Adjuvant	1,854	1 %	0.98 (0.85-0.94)	.74
Induction	**5,269**	**2 %**	**0.95 (0.88-1.01)**	**.70**
Concomitant	3,727	8 %	0.81 (0.76-0.88)	<.0001
Induction cisplatin based chemo		**5%**		
Total	10,850	4 %	0.90 (0.85-0.94	<.0001



Was induction chemotherapy ineffective?

Pignon JP et al. Lancet 2000;355:949-955

Lacas et al. Radiother Oncol. 2021 March

H&N07 (GSTTC)

Induction TPF followed by concomitant treatment versus concomitant treatment alone in locally advanced Head and Neck Cancer: A phase II-III trial

SCC
Stage III–IV a,b
PS: 0–1
Oropharynx
Hypopharynx
Oral cavity 20%-22%
n=421

R

Induction
TPF Q3 weeks
for 3 cycles

n=129 → Cisplatin + 5-FU

n=79 → Cetuximab + RT (2 Gy/day, 5 days/week)

No induction

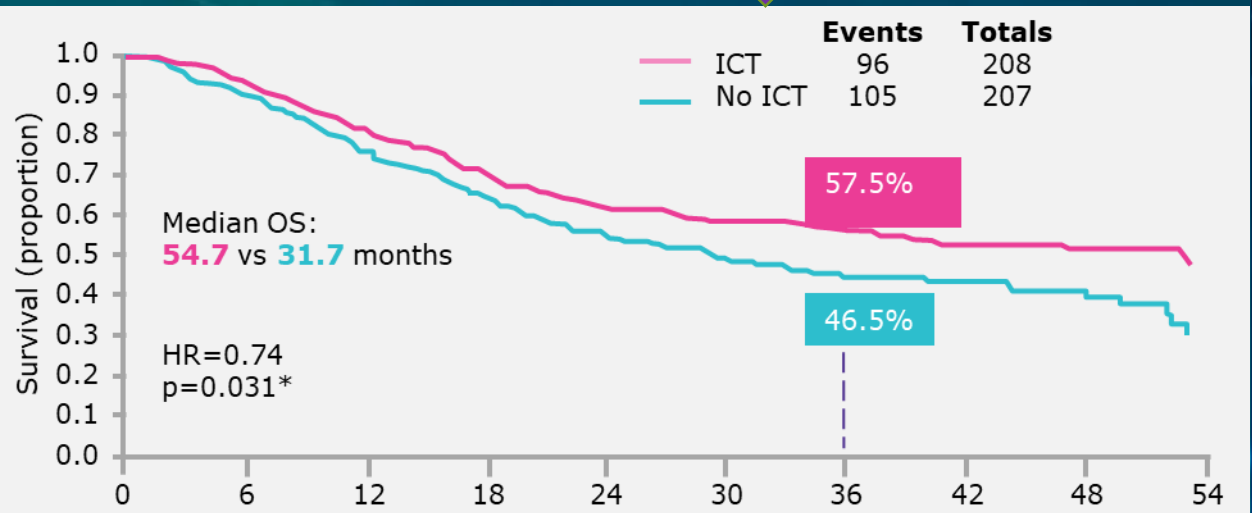
n=128 → Cisplatin + 5-FU

n=78 → Cetuximab + RT

Stratification for:

T stage (T1–2 vs. T3–4)
N stage (N0–1 vs. N2–3)
Primary tumor site (oral cavity/oropharynx vs. hypopharynx)

A statistically significant benefit was observed with ICT vs no-ICT for OS



This is the only Phase III study to report a significant difference in OS with ICT vs no-ICT

2 cycles of cisplatin 20mg/m$_2$ from days 1 to 4 plus 5-fluorouracil 800mg/m$_2$/day, 96 hours continuous infusion, administered during weeks 1 and 6 of the radiation treatment.

Ghi MG, et al. Ann Oncol 2017:28(9):2206-12

Indian Experience: Neo-adjuvant Chemotherapy in borderline resectable patients of Oral Cavity Cancer, TMH, Mumbai

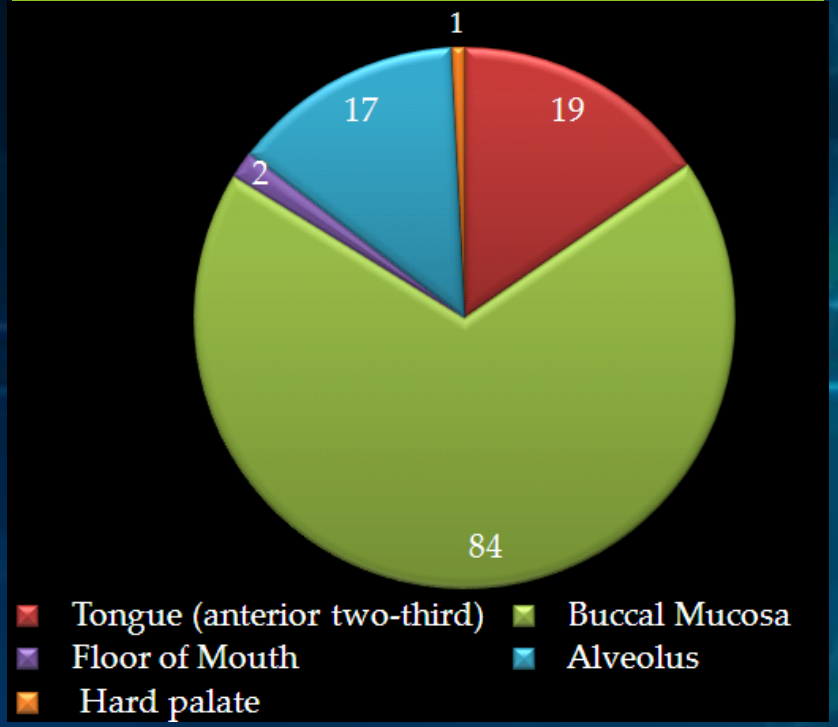
Patil VM et al; Induction chemotherapy in technically unresectable locally advanced oral cavity cancers: Does it make a difference? Indian J Cancer 2013;50:1-8

Patients (N=123)
- M-111, F-12
- Borderline unresectable oral cavity cancer
- Median Age = 42 years (23- 72 yrs)

3 drug regimen (N=26)

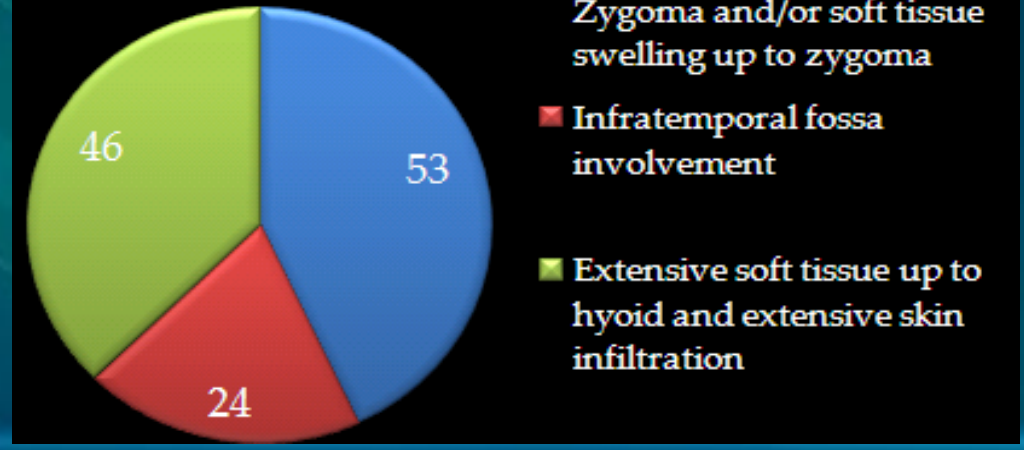
2 drug regimen (N=97)
DC (n=17); PC (n=70); PCa (n=10)

Site of Cancer*



*No: of patients

Reason for neoadjuvant chemotherapy*

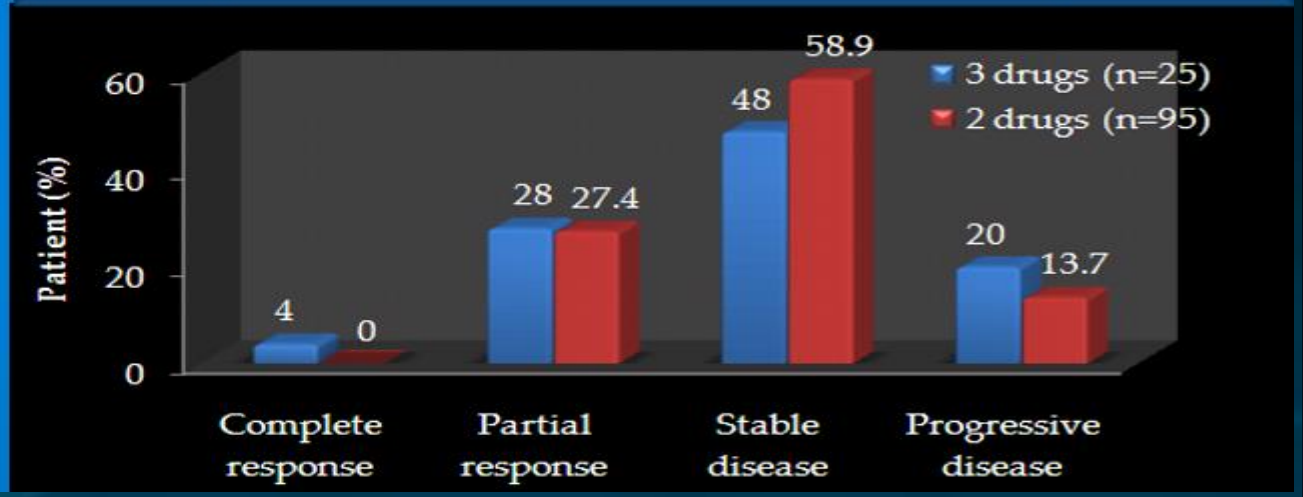


Results

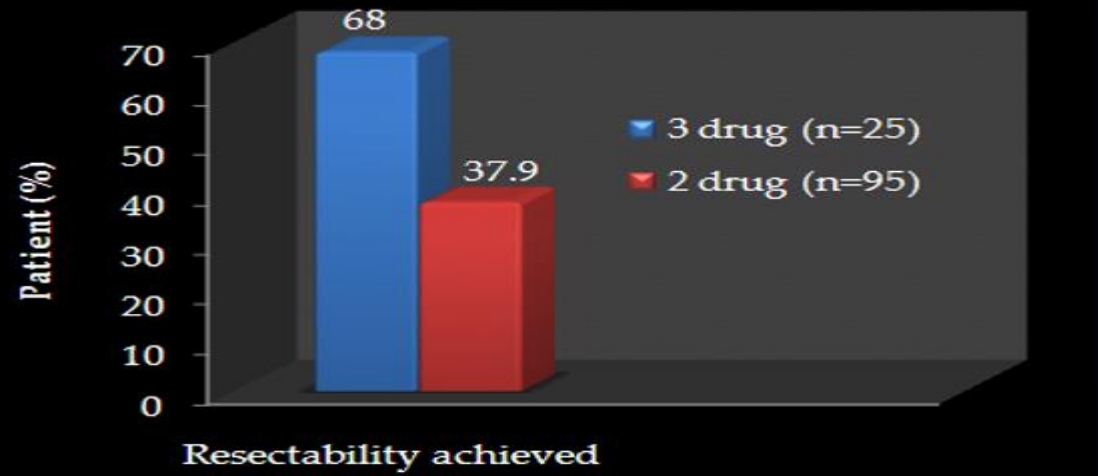
Response rates

- 3 drug regimen – 32%
- 2 drug regimen – 27.37%

Response rates achieved at the end of 2 cycles



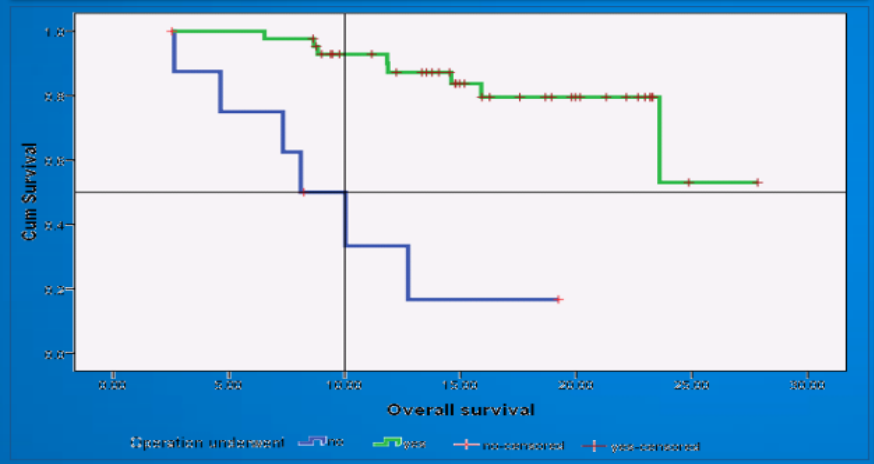
Resectability* achieved at the end of 2 cycles



p= 0.029 (3 drug regime vs. 2 drug regimen)

- The estimated median overall survival for the whole population is 12.7 months.
- The estimated median survival was not reached for patients undergoing resection.

Survival Functions



- It was statistically significantly more than for those who were treated with nonsurgical modalities, in whom it was 8 months (p= 0.0001).
- The only variable that significantly affected survival among the tested variables of age, primary site, lymph node status, duration of treatment and modality of local treatment was the performance of surgery as compared to nonsurgical treatment.

Which patient will you select for Induction chemotherapy (ICT)?

Absolute contra-indications to cisplatin

Oral Oncol. 2016 Feb;53:10-6. Clinical recommendations for defining platinum unsuitable head and neck cancer patient populations on chemoradiotherapy: A literature review. Ahn MJ, D'Cruz A, Vermorken JB

	Clinical condition	Parameter for selection	Rationale
1	Performance status	ECOG>/=3	Poor compliance
2	Renal dysfunction	CCR <50ml/min	Worsening toxicity; fluid overload or dehydration
3	Otologic disorders	Pre-existing hearing loss or tinnitus >/=gr 3; Abnormal audiometry	Permanent hearing loss affection QOL
4	Neurologic disorders	Neuropathy >/=Grade 2	Worsening neuropathy
5	Known hypersensitivity to platinum therapy	h/o Allergy to platinum or mannitol	Unforseen reaction
6	Pregnancy & Lactation	Avoid pregnancy; no breast feeding	Fetal toxicity
7	HIV/AIDS	CD4 count <200/microl	Weakened immune system

High risk cases for cisplatin

Oral Oncol. 2016 Feb;53:10-6. Clinical recommendations for defining platinum unsuitable head and neck cancer patient populations on chemoradiotherapy: A literature review. Ahn MJ, D'Cruz A, Vermorken JB

	Clinical condition	Parameters for selection
1.	Performance status	ECOG score 2
2.	Biologic age	>70 years; geriatric assessment
3.	Renal dysfunction	CCR 50-60ml/min
4.	Borderline function (Otologic & Neurologic)	History
5.	Other organ dysfunction (anemia/ hepatic impairment)	Marrow, hepatic, respiratory dysfunction >/=grade 2
6.	Co-morbidities	CAD, HTN, DM, recurrent pulmonary infections
7.	HIV/AIDS or Immunocompromised	CD4 count<350/microl
8.	Previous platinum therapy/induction chemo	>200mg/m2; >3 cycles TPF
9.	Weight loss/ Nutritional status	>/= 20%
10.	Concomitant nephrotoxic drugs	History
11.	Socio-economic status, social and home support	History

Available at www.sciencedirect.com

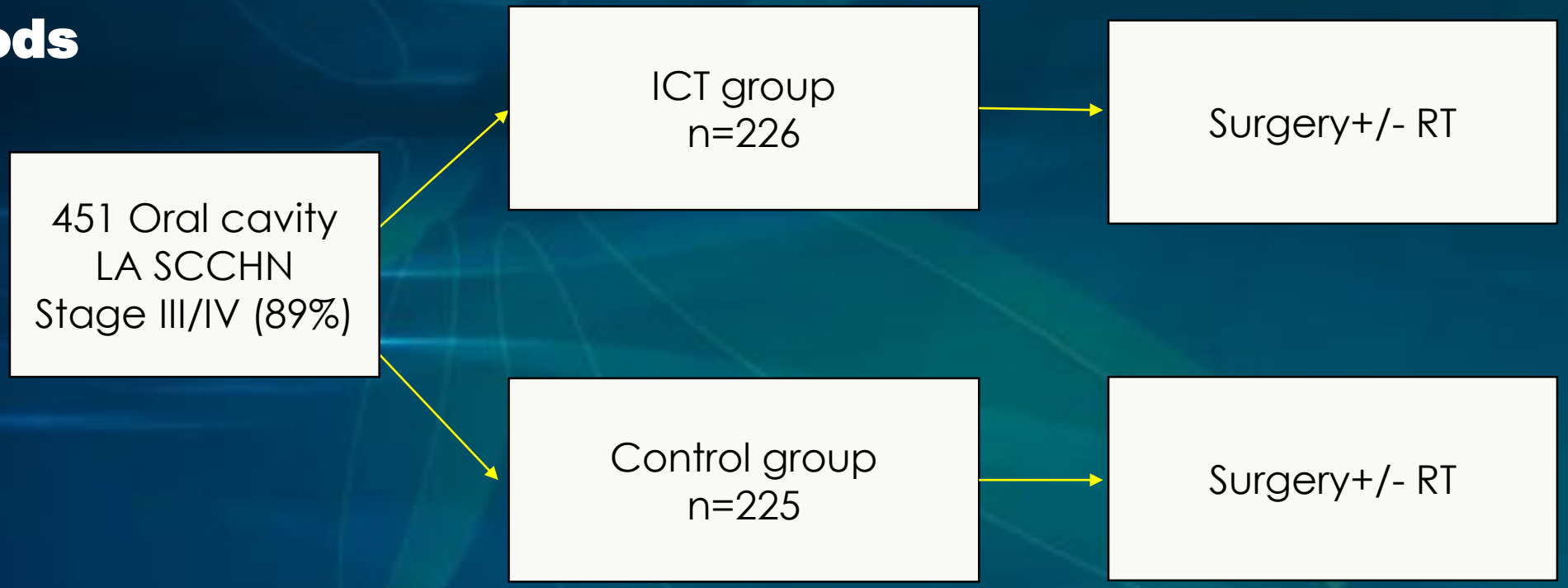
ScienceDirect

journal homepage: www.ejcancer.com

Induction chemotherapy prior to surgery with or without postoperative radiotherapy for oral cavity cancer patients: Systematic review and meta-analysis

Gustavo N. Marta [a,*], Rachel Riera [b], Paolo Bossi [c], Lai-ping Zhong [d], Lisa Licitra [c], Cristiane R. Macedo [e], Gilberto de Castro Junior [f], André L. Carvalho [g], William N. William Jr. [h], Luis Paulo Kowalski [i]

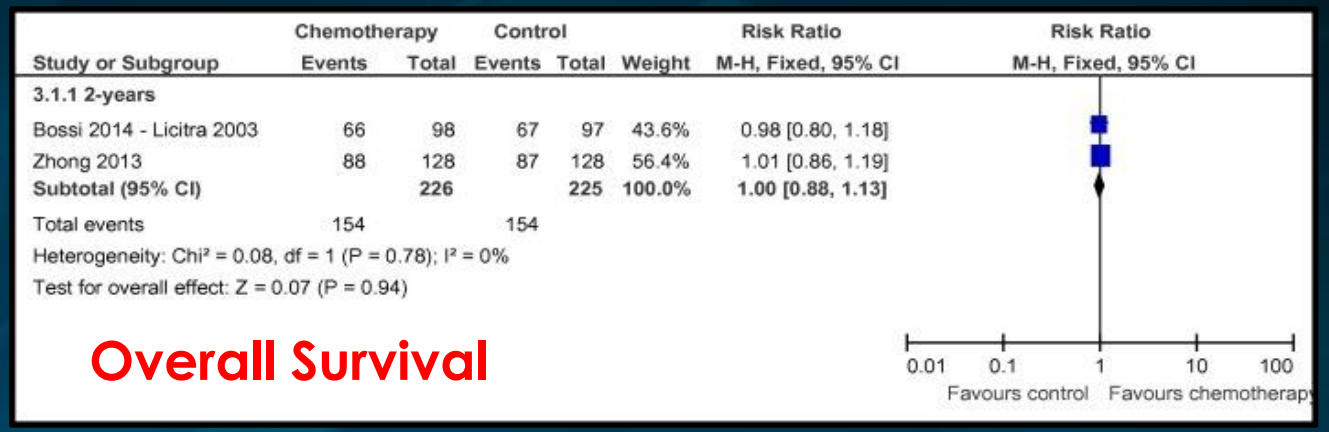
Methods



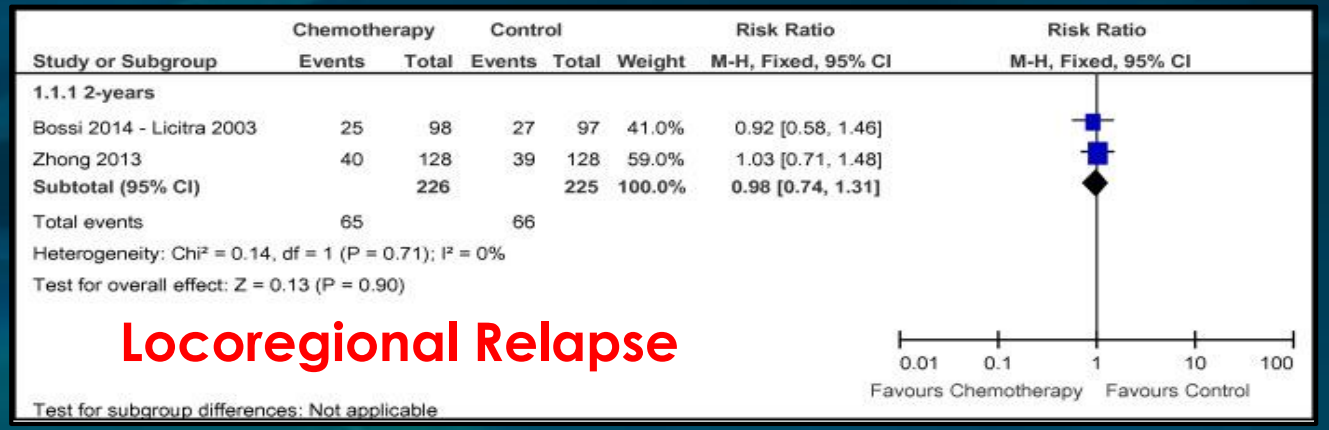
Meta-analysis included trials in patients with oral SCC only where surgery represented the main treatment strategy

No significant overall benefit in favour of induction chemotherapy was found regarding loco-regional recurrence, disease-free survival and overall survival.

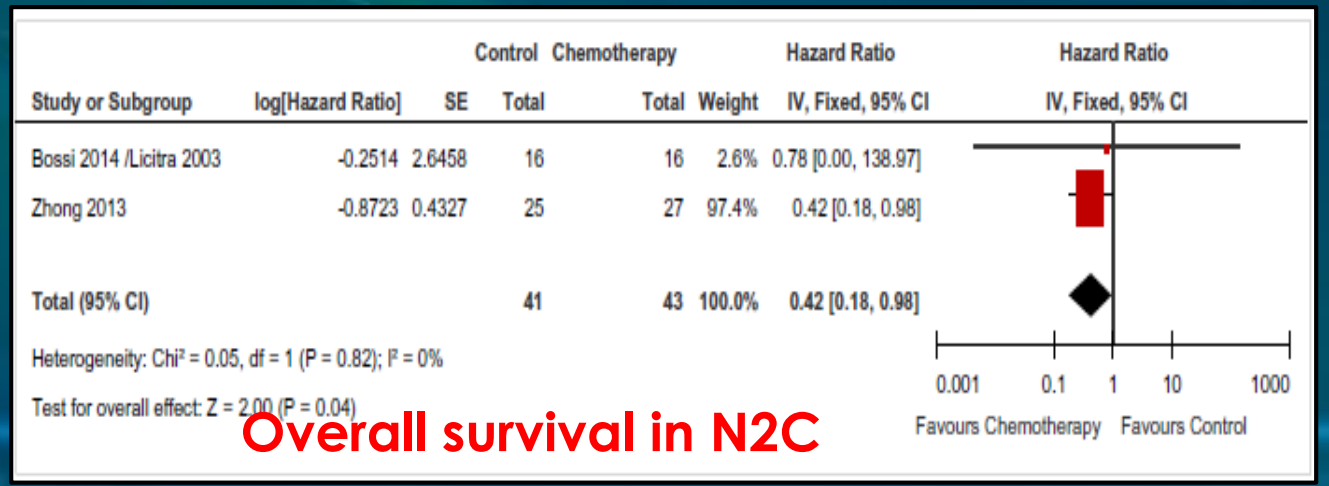
However, subgroup analysis of cN2 patients showed statistically significant benefit in overall survival in favour of ICT



Overall Survival



Locoregional Relapse

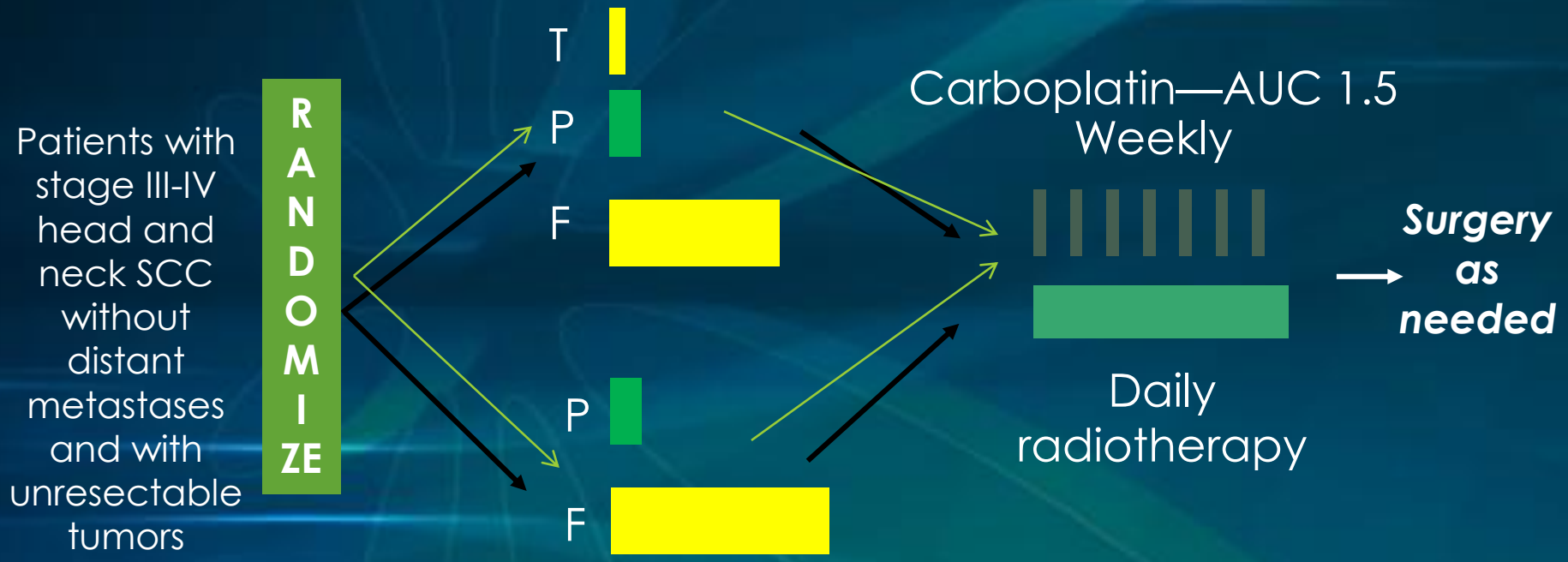


Overall survival in N2C

Bossi et al Eur J of Cancer 2015;51:2596–2603

What is your go to regimen for ICT?

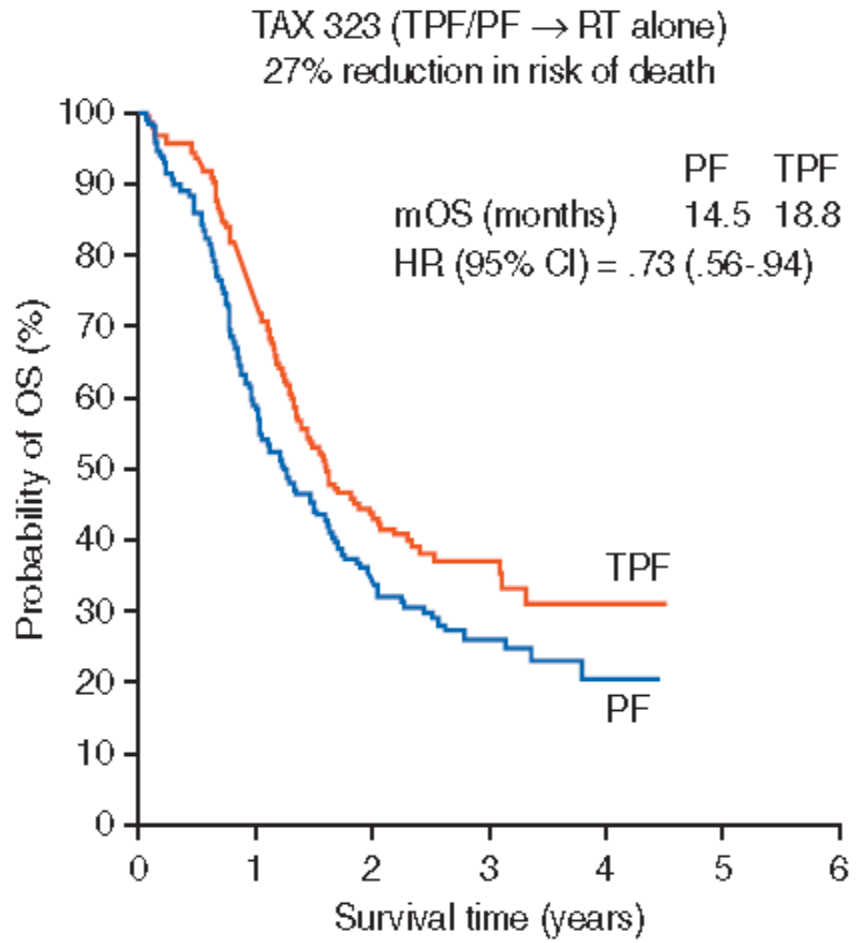
Phase III TAX 324 Trial: TPF vs PF



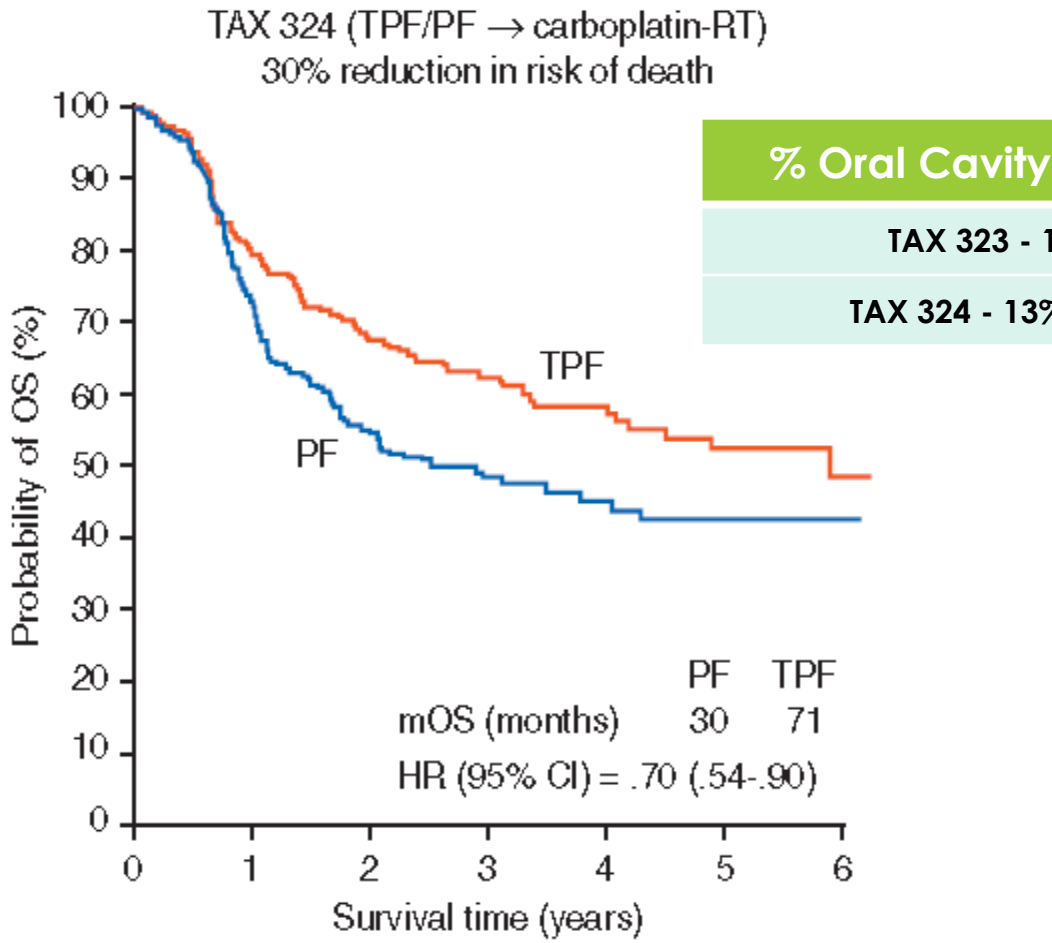
TPF: docetaxel 75 mg/m^2 on Day 1 + cisplatin 100 mg/m^2 on Day 1 + 5-FU 1000 mg/m^2/day by continuous infusion on Days 1-4; q 3 wks x 3 cycles.
PF: cisplatin 100 mg/m^2 on Day 1 + 5-FU 1000 mg/m^2/day as continuous infusion on Days 1-5; q 3 wks x 3 cycles.

Posner MR, et al. N Engl J Med. 2007;357:1705-1715.

Neoadjuvant Chemotherapy – TPF vs PF



Vermoken et al, NEJM 2007
Unresectable disease



Posner et al, NEJM 2007
Resectable/unresectable disease

% Oral Cavity Patients
TAX 323 - 17%
TAX 324 - 13%-15%

Haddad R.I, et al. Annals of Oncology 2018; 29: 1130-1140

Oral Oncology 50 (2014) 1000–1004

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

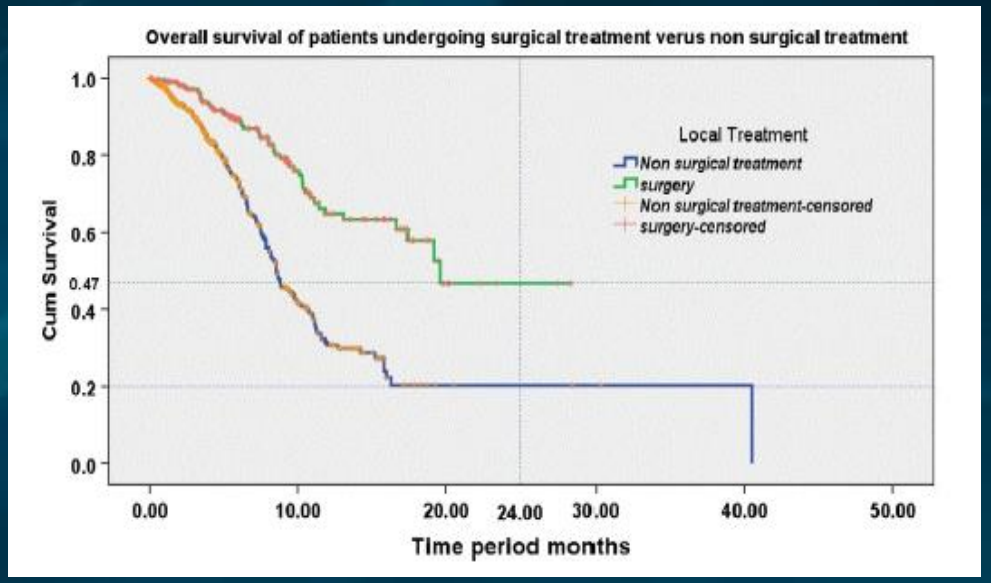
Neoadjuvant chemotherapy followed by surgery in very locally advanced technically unresectable oral cavity cancers

V.M. Patil[a], K. Prabhash[a,*], V. Noronha[a], A. Joshi[a], V. Muddu[a], S. Dhumal[a], S. Arya[b], S. Juvekar[b], P. Chaturvedi[d], D. Chaukar[d], P. Pai[d], S. Kane[e], A. Patil[e], J.P. Agarwal[c], S. Ghosh-Lashkar[c], A. Dcruz[d]

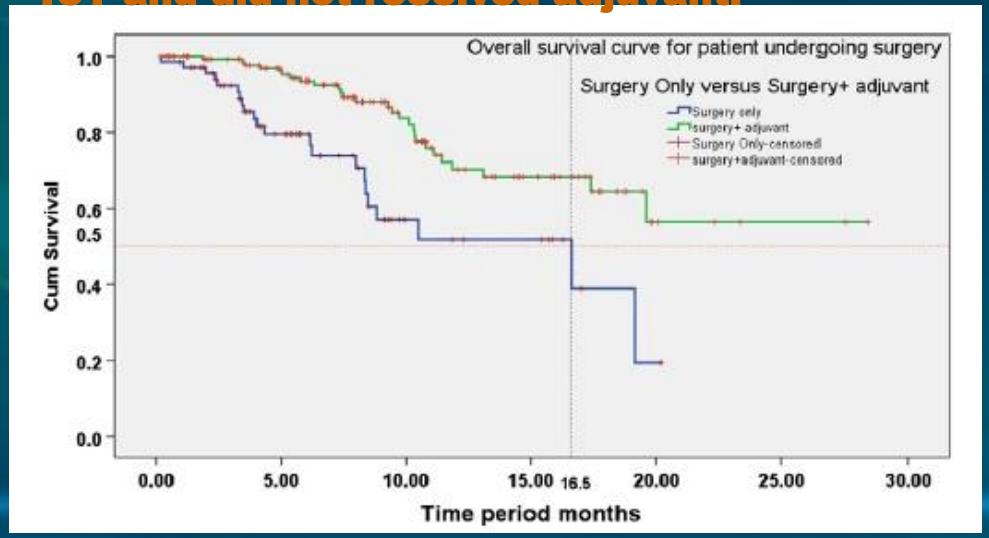
- 721 patients with stage IV oral-cavity cancer received NACT.
- Three-drug regimen in 74 patients (10.2%); 647 (89.8%) received 2 drug regimen (combination of docetaxel with cisplatin).
- The 2-drug regimen selected over 3 drug regimen due to logistics in 485 patients (75%) and co morbidities in 162 patients (25%).
- Results:
  - 310 (43%) underwent subsequent surgery **(LRC 32% vs 15% in non-surgical arm; OS 19.6 VS 8.1months)**
  - 167 CTRT
  - 3 radical RT
  - 241 palliative treatment

Results: NACT may improve survival

OS of surgical resection post ICT Vs non surgical treatment modality



OS of surgical resection ICT and received adjuvant treatment Vs surgical resection post ICT and did not received adjuvant.



Journal of Clinical Oncology > List of Issues > Volume 38, Issue 15_suppl >

HEAD AND NECK CANCER

Neoadjuvant nivolumab (N) plus weekly carboplatin (C) and paclitaxel (P) in resectable locally advanced head and neck cancer.

Ralph Zinner, Jennifer M Johnson, Madalina Tuluc, Joseph M. Curry, Adam Luginbuhl, Christopher C Fundakowski, ...

Background: Despite multimodality standard therapy, patients (pts) with resectable locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) are at high risk for recurrence. Pts with pathologic complete response (pCR) or major pathologic response (MPR) to neoadjuvant chemotherapy have improved overall survival. PD-1 checkpoint inhibitors are approved in combination with platinum-based chemotherapy in the 1st-line treatment of recurrent/metastatic SCCHN. We hypothesize the addition of N to wkly carboplatin C and P will increase the pCR rate at the primary site compared to historical controls. **Methods:** This is an investigator-initiated trial for pts with newly diagnosed (AJCC 8th) stage III-IV HPV- (oral cavity (OC), oropharynx (OP), hypopharynx (HP), and larynx (L) or stage II-III HPV+ OP SCCHN without distant metastasis who are surgical candidates. Neoadjuvant chemo starting d1 is C AUC 2 IV wkly x 6 plus P 100 mg/m2 IV wkly x 6 plus N 240 mg IV q 2 wks x 3 with surgery on wk 8. The primary endpoint is pCR at the primary site. To estimate pathologic response, the resected pathology specimens are cut >1 section/cm. Using the Aperio Digital scanning system, slides are imaged, and then annotated by at least 2 pathologists for viable tumor vs. treatment effect with areas automatically calculated to yield the percentage of viable tumor. Our primary endpoint will be reached if 11/37 planned pts have a pCR at the primary site. **Results:** From 11/17-12/19, 27 pts received the study regimen and had surgery (1/27 had an unknown primary; thus, inevaluable for the primary endpoint). Of 27 pts, median age was 59 (46-83), women 31%, HPV+ 15%, OC 73%, OP 19%, HP 7%, L 4%; stage III 33%, stage IVA 67%. Gd 3 toxicities were in 37% pts; 1 pt febrile neutropenia, 3pts anemia, 1pt diarrhea, 1pt cellulitis and 1pt rash. Four pts had gd 3-4 neutropenia. Dose reductions were in 2 pts, and 4 pts had 1 wkly dose dropped. All 27 pts went to surgery, none with PD by CT; all with negative margins. One pt died with rapid recurrence; no other recurrences (median f/u 13 mos). Our primary endpoint was met; 11/26 (42%) pts (excluding pt with unknown primary) had a pCR at the primary site. 9/23 (39%) HPV- pts, had a pCR. MPR or pCR was 18/26 (69%) and in HPV- pts, 15/23 (65%). 2/11 pts had microscopic residual disease in 1 LN each. **Conclusions:** The combination of N and wkly PC was well tolerated. The primary endpoint of pCR at the primary site in > 11/37 pts was met with the 27th pt. Accrual continues. Exploratory outcomes assessing markers of immune bias in tumor tissue and plasma are in process. Clinical trial information: NCT03342911.

JAMA Oncol. 2020 Oct; 6(10): 1–9.
Published online 2020 Aug 27. doi: 10.1001/jamaoncol.2020.2955
PMCID: PMC7453348
PMID: 32852531

Neoadjuvant Nivolumab or Nivolumab Plus Ipilimumab in Untreated Oral Cavity Squamous Cell Carcinoma

A Phase 2 Open-Label Randomized Clinical Trial

- 29 patients with OC SCC; >T2; either Nivolumab (3mg/kg week 1&3) or Nivolumab+Ipilimumab (1mg/kg week 1 only)
- Surgery 3 to 7 days after last dose
- N and N+I arms
  - pathologic downstaging 53%, 69%
  - RECIST response 13%, 38
  - Four patients had major/complete pathologic response greater than 90% (N, n = 1; N+I, n = 3)
  - With 14.2 months median follow-up, 1-year progression-free survival was 85% and overall survival was 89%.

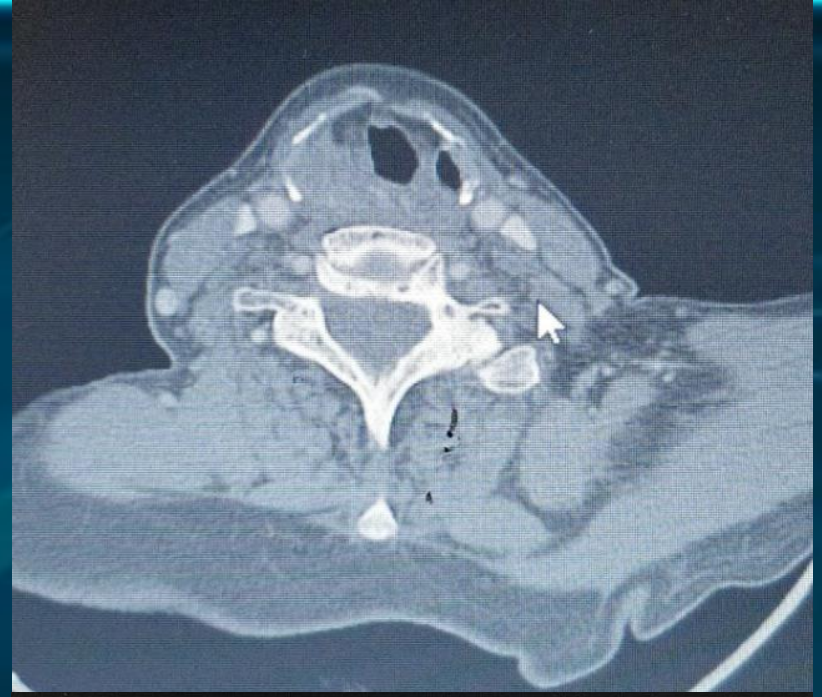
Any downside to ICT?

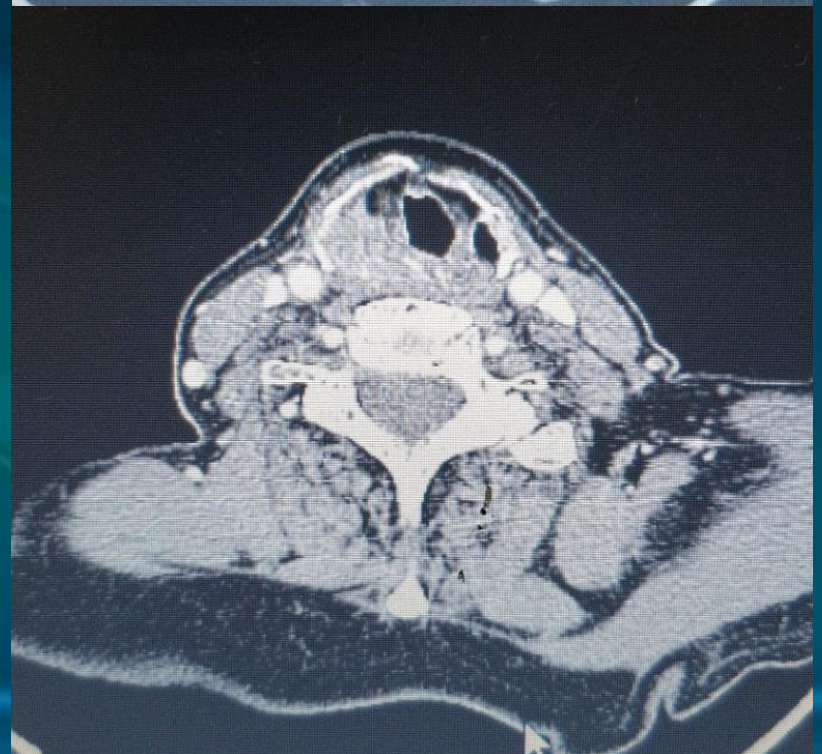
Case B.

- 68 year old diabetic and ex-smoker, with h/o HTN presents c/o odynophagia of two months' duration. He also has noted a right neck mass and dysphagia for one month - 'Drinking water makes me cough slightly'
- Baseline nephropathy (S.Cr 1.6mg/dL), generalized cachexia.
- Office exam: Lesion involving right arytenoid, AE fold, medial wall of R PFS (occluded) with pooling of saliva, overhanging vestibular fold.
- Right Level IIA adenopathy present 2*1.5 cm, mobile, skin uninvolved
- FNAC- metastatic squamous cell carcinoma

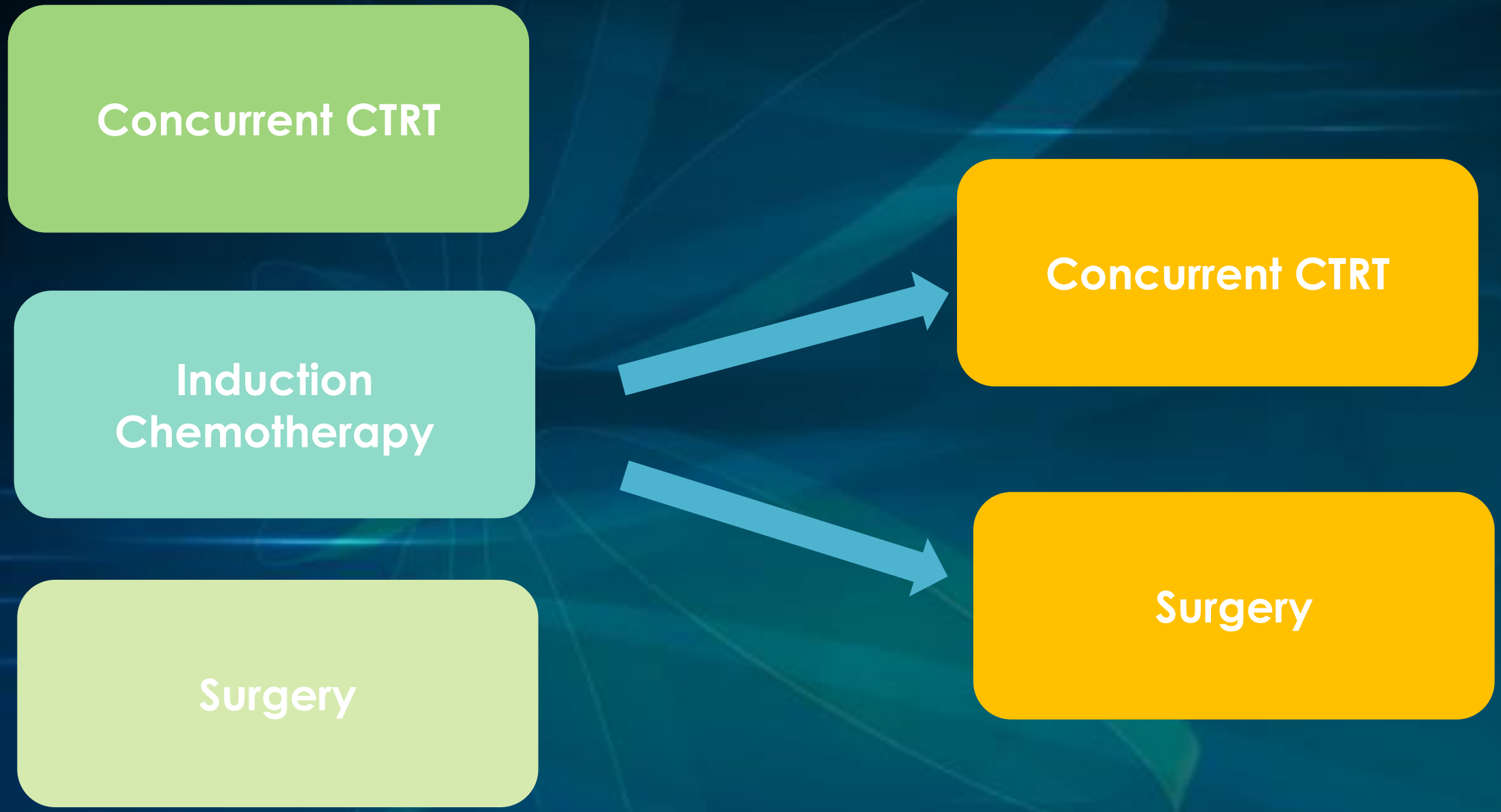
CECT neck and thorax

- Enhancing heterogenous soft tissue mass involving right vestibular fold, arytenoid, AE fold, PFS, pre-epiglottic and paraglottic spaces, not crossing midline
- **Erosion of inner cortex of thyroid cartilage, with possibility of minor extralaryngeal spread through the thyrohyoid membrane**
- Solitary 1.5*1.7 cm lymph node involving right Level IIA, no infiltration of surrounding structures
- CECT thorax negative for distant metastases





What will be your treatment approach?


Concurrent CTRT
Induction Chemotherapy
Surgery
Concurrent CTRT
Surgery

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

THE DEPARTMENT OF VETERANS AFFAIRS LARYNGEAL CANCER STUDY GROUP*

Wolf et al
1991 NEM

- ICT (3 cycles) f/b RT vs Surgery and RT
- No difference in OS
- 64% larynx preservation rate
- 36% required laryngectomy

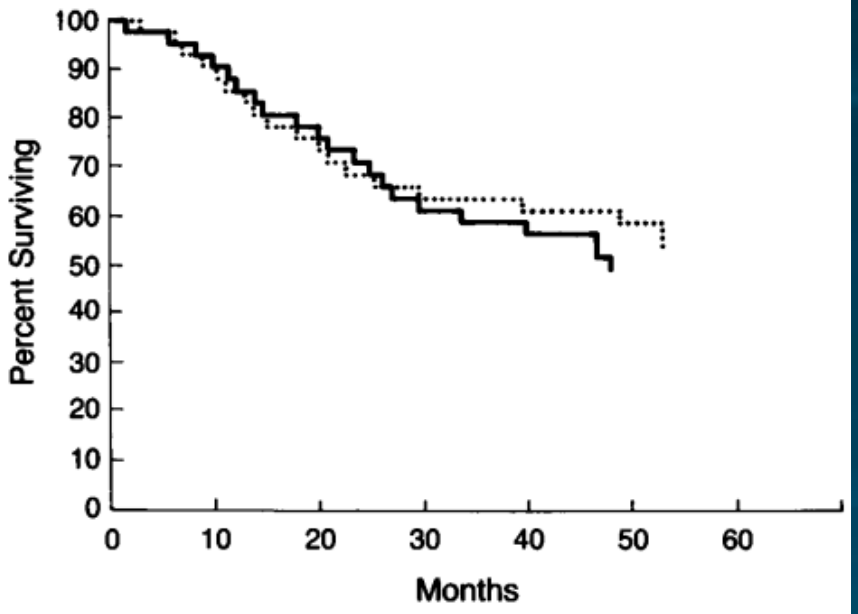


Figure 1. Overall Survival of 332 Patients Randomly Assigned to Induction Chemotherapy and Radiation Therapy (Solid Line) or Conventional Laryngectomy and Postoperative Radiation (Dotted Line).

•. 2000 Feb 15;88(4):876-83

Mature Results of a Phase III Randomized Trial Comparing Concurrent Chemoradiotherapy with Radiation Therapy Alone in Patients with Stage III and IV Squamous Cell Carcinoma of the Head and Neck

Adelstein et al

•. 2000 Feb 15;88(4):876-83

- CTRT (Cis+5FU x2 cycles) vs RT alone
- **5-year OS with RT alone worse as compared to CTRT with primary site preservation with laryngeal primary tumors (16% vs 29%; *p*=0.03) and hypopharyngeal primary tumors (0% vs 14%; *p*=0.008)**, but not for those patients with oropharyngeal primary tumors (63% vs. 64%; p= 0.86).
- **OS not impacted by the addition of concurrent chemotherapy to definitive radiation therapy. Disease clearance, recurrence free interval, and primary site preservation were improved significantly by the chemotherapy.**
- **Large primary site tumor treated with aggressive CT and RT may result in significant functional impairment, and negate the value of any organ preservation achieved.**

The NEW ENGLAND JOURNAL of MEDICINE

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

Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer

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

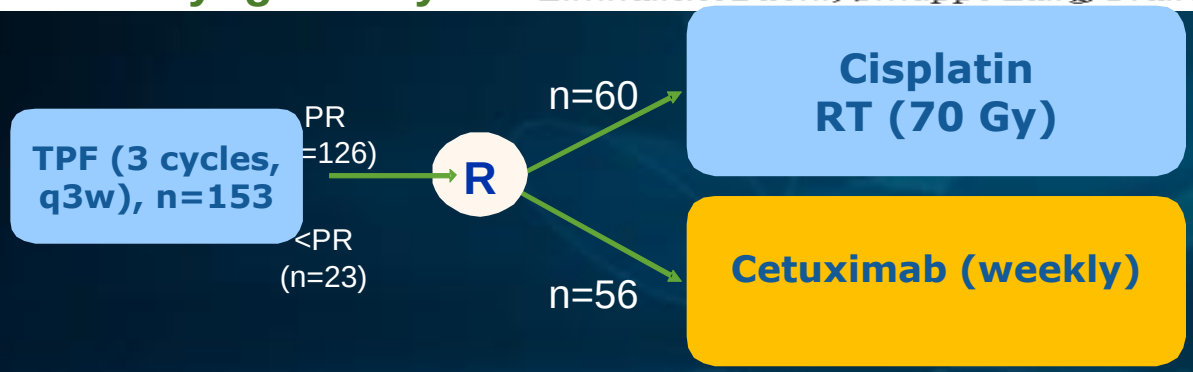
- At 2 years, the proportion of patients with intact larynx after **CTRT (88 %)** differed significantly from the proportions in the groups given **ICT f/b RT (75 %**, P=0.005) or **RT alone (70 %**, P<0.001).
- Locoregional contraol rate significantly better with **CTRT 78% vs 61% with ICT (Cis+5FU) f/b RT vs 56% with RT** alone.
- Both of the chemotherapy-based regimens suppressed distant metastases and resulted in better disease-free survival than radiotherapy alone.
- ***Results have remained consistent on long-term follow up.***

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Patients with Stage III–IV larynx/hypopharynx cancer (T2–T3, N0–resectable N3) suitable for total laryngectomy

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



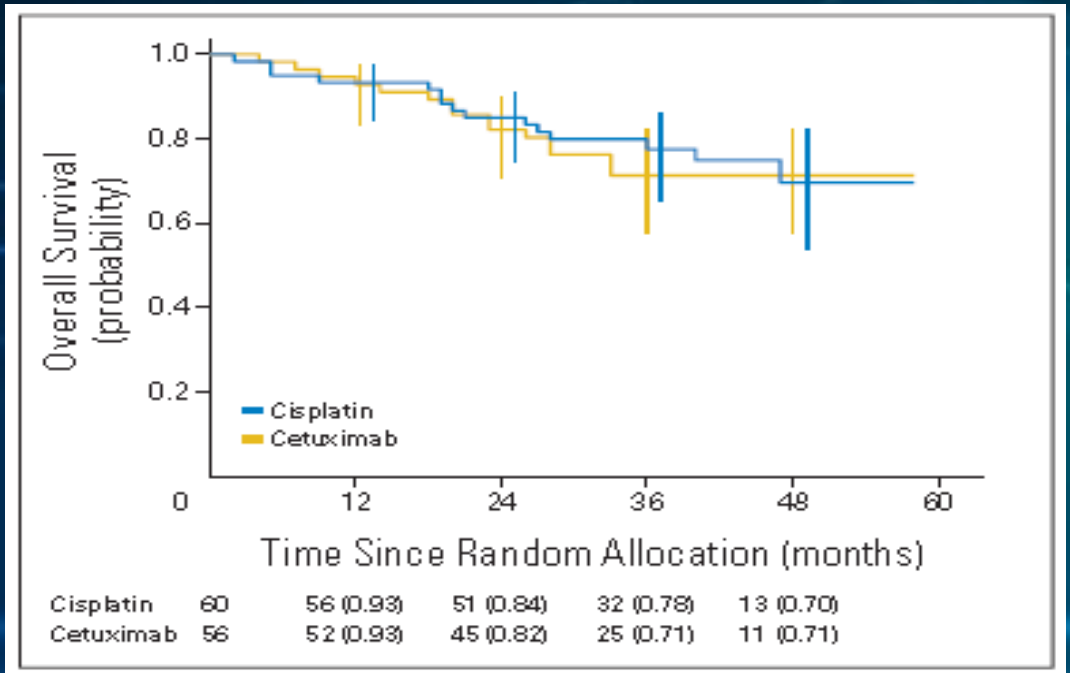


Table 3. Acute Toxicity

Variable	Cisplatin No.	Cisplatin %	Cetuximab No.	Cetuximab %
No. of patients	58*		56	
Mucositis grade				
3	25	43	24	43
4	2	3	1	2
In-field skin toxicity grade				
3	14	24	29	52
4	1	2	3	5
Other toxicity, any grade, justifying protocol modification				
Renal	9	15.5	0	
Hematologic	8	14	0	
Poor performance	7	12	1	1.7
Infusion-related reaction	0		3	5
Protocol modification due to acute toxicity	33	57	19	34

*Two patients did not start treatment.

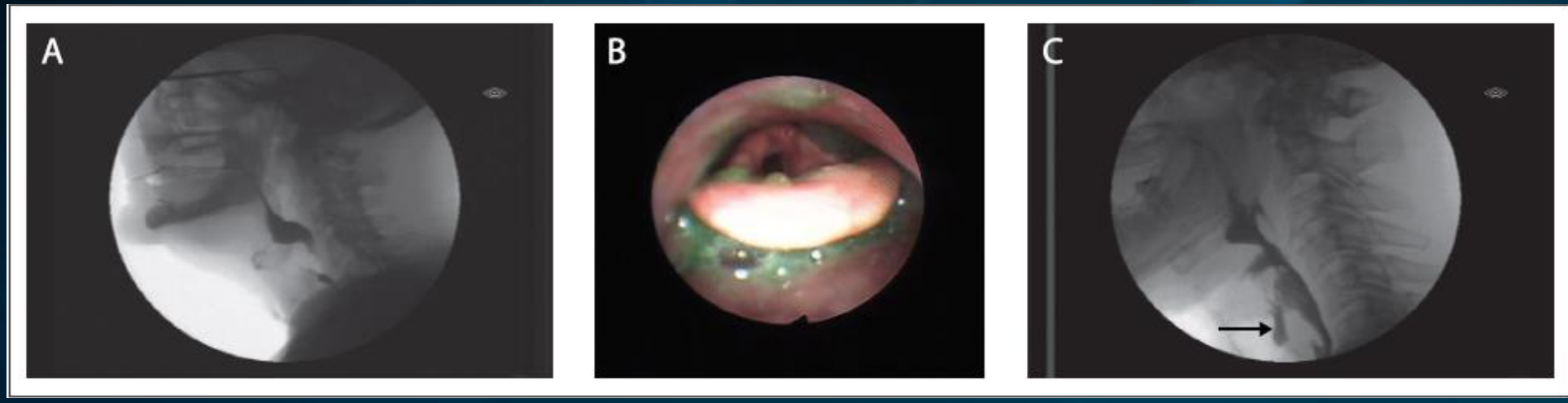
What tools do you use to assess laryngeal function (**dysphagia & aspiration**) and how does this impact your treatment decision?

Assessment of laryngeal function: DYSPHAGIA
Commonly utilized questionnaires

Table1 Overview of selected Functional Health Status questionnaires.

Author(s) in alphabetical order	Questionnaire [1]	Acronym	Scales (Number of items)	Range of score	Target population
Belafsky *et al*[17], 2008	Eating Assessment Tool	EAT-10	- One scale (10 items)	0-40	Adults at risk of dysphagia
Bergamaschi *et al*[18], 2008	DYsphagia in MUltiple Sclerosis Questionnaire	DYMUS	- Dysphagia to solid (7 items) - Dysphagia to liquid (3 items)	0-10	Adults with Multiple Sclerosis
Calis *et al*[19], 2008	Parent questionnaire on subjective feeding experience	N/A	- One scale (3 items)	N/A	Children with severe generalized cerebral palsy and intellectual disability
Chen *et al*[20], 2001	M.D. Anderson Dysphagia Inventory	MDADI	- Global (1 item) - Physical (8 items) - Functional (5 items) - Emotional (7 items)	20-100	Adults with Head and Neck Cancer
Cohen and Manor[21], 2011	Swallowing Disturbance Questionnaire	SDQ	- Related to oral phase (5 items) - Related to pharyngeal phase (10 items)	0.5-44.5	Adults with Parkinson Disease
Dwivedi *et al*[22], 2010	Sydney Swallowing Questionnaire	SSQ	- One scale (17 items)	0-1700	Adults with oral cavity and oropharyngeal cancer
Govender *et al*[23], 2012	Swallowing Outcome after Laryngectomy	SOAL	- One scale (17 items)	0-34	Adults with total laryngectomy
Grudell *et al*[24], 2007	Mayo Dysphagia Questionnaire	MDQ	Total number of items (stem-and-leaf format): 27 - Dysphagia - Heartburn - Acid regurgitation - Dysphagia related to particular foodstuffs or consistencies - Other	N/A	Adults with reflux esophagitis and/or reflux peptic stricture [2]
Sheppard and Hochman[25], 1988	Dysphagia Disorders Survey	DDS	- Related factors to dysphagia (7 items) - Dysphagic symptoms (6 items)	0-36	Children and adults with intellectual and developmental disabilities
Silbergleit *et al*[26], 2012	Dysphagia Handicap Index	DHI	- Physical (9 items) - Functional (7 items) - Emotional (9 items)	0-100	Adults with dysphagia
Skeppholm *et al*[27], 2012	Dysphagia Short Questionnaire	DSQ	- One scale (5 items)	0-18	Adults after anterior cervical spine surgery
Woisard *et al*[28], 2006	Deglutition Handicap Index	DHI	- Physical (10 items) - Functional (10 items) - Emotional (10 items)	0-120	Adults with dysphagia

Assessment of laryngeal function: ASPIRATION

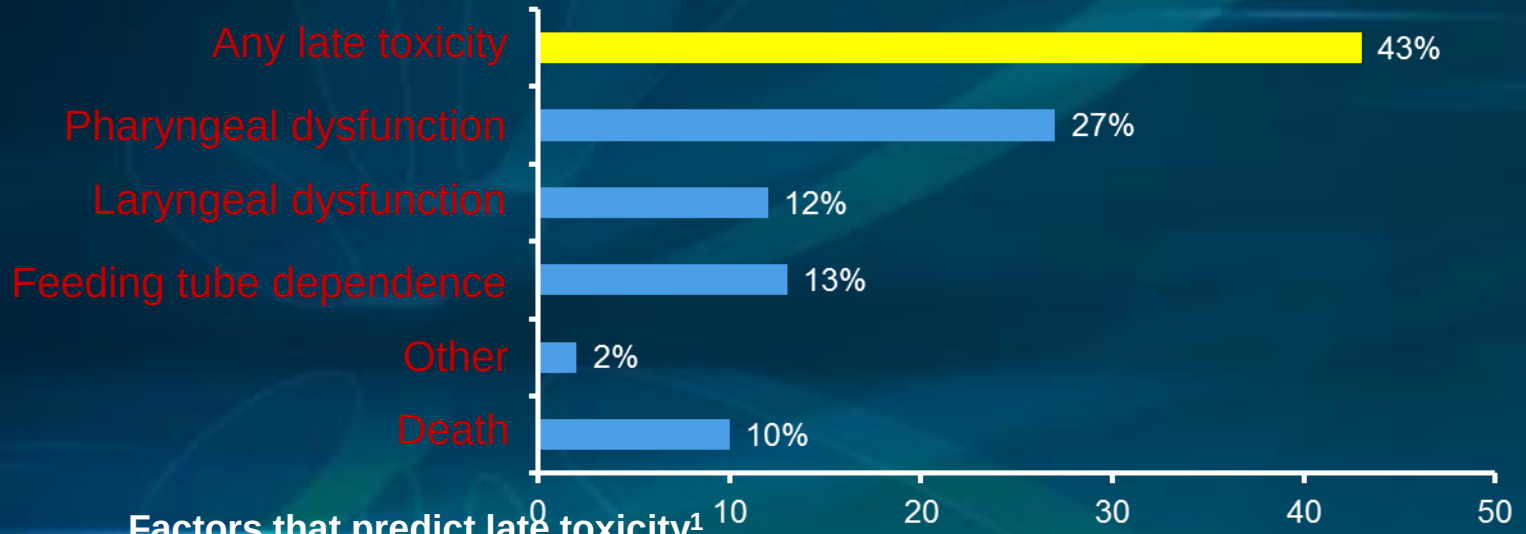


Fiberoptic Endoscopic Evaluation of Swallowing

- Coloured boluses
- Three positions of transnasal fiberoptic scope
- Limitations- can not assess Oral Phase and UES
- Also limited by swallowing white-out and lack of quantification of aspirated bolus

Late toxicity after CRT: Incidence and risk factors

RTOG analysis of three prospective studies of CRT in LA SCCHN (N=230)[1]



Factors that predict late toxicity[1]

Variable	OR (95% CI), p-value
Age (increase per year)	1.05 (1.02–1.09), 0.001
T stage (T3/T4 vs T1/T2)	3.07 (1.44–6.54), 0.0036
Tumor site (larynx/hypopharynx vs oral cavity/oropharynx)	4.17 (1.57–11.03), 0.0041
Neck dissection after RT (yes vs no)	2.39 (1.16–4.92), 0.018

OR, odds ratio

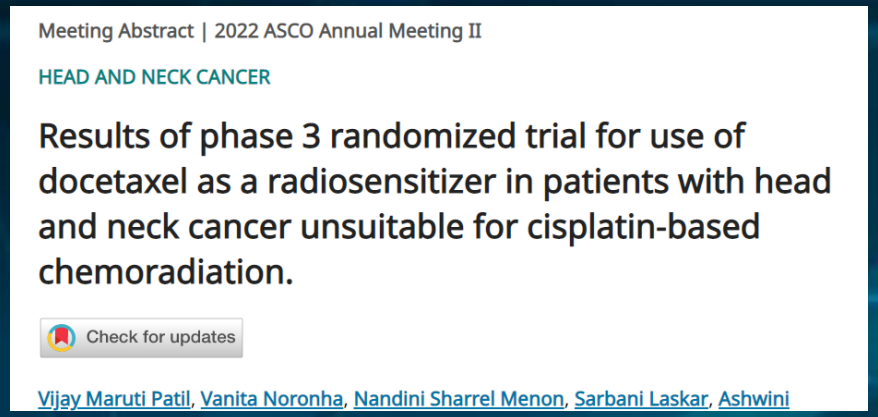
Machtay M, et al. J Clin Oncol 2008;26:3582–3589

Use of Larynx-Preservation Strategies in the Treatment of Laryngeal Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Arlene A. Forastiere, Nofisat Ismaila, Jan S. Lewin, Cherie Ann Nathan, David J. Adelstein, Avraham Eisbruch,

- ***What are the larynx-preservation treatment options for advanced-stage (T3, T4) primary site disease that do not compromise survival?*** *a. What are the considerations in selecting among them?*
- Organ-preservation surgery, combined chemotherapy and RT, and RT alone, all with further surgery reserved for salvage, offer the potential for larynx preservation without compromising overall survival.
- 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.
- 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 rather than with organ-preservation approaches and may be the preferred approach
- All patients should have a multidisciplinary evaluation regarding their suitably for a larynx-preservation approach, and they should be apprised of these treatment options.
- Induction chemotherapy before organ-preservation surgery is not recommended outside a clinical trial.
- Concurrent chemoradiotherapy (CRT) offers a significantly higher chance of larynx preservation than RT alone or induction chemotherapy followed by RT, albeit at the cost of higher acute in-field toxicities and without improvement in overall survival.

What chemotherapy regimen would you use for CTRT with compromised renal function?



Meeting Abstract | 2022 ASCO Annual Meeting II

HEAD AND NECK CANCER

Results of phase 3 randomized trial for use of docetaxel as a radiosensitizer in patients with head and neck cancer unsuitable for cisplatin-based chemoradiation.

Check for updates

Vijay Maruti Patil, Vanita Noronha, Nandini Sharrel Menon, Sarbani Laskar, Ashwini

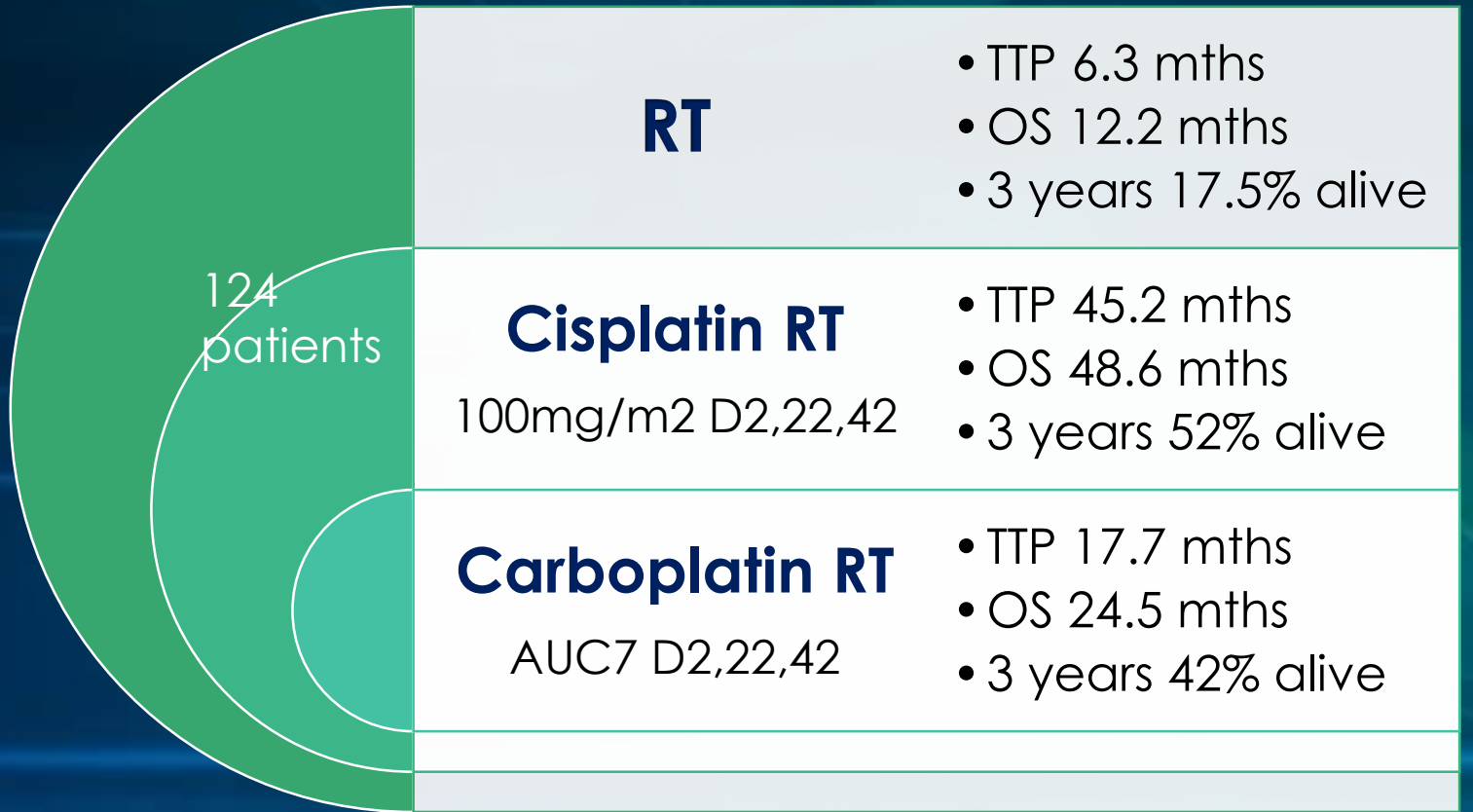
- 356 cisplatin-ineligible LAHNSCC (Ahn criteria) RT vs concurrent docetaxel 15 mg/m2 weekly with RT
- RT vs Docetaxel-RT
  - 2-year DFS was 30.3% versus 42% P-value=0.002
  - OS 15.3 months vs 25.5 months P-value =.0.035
  - Any grade 3 toxicity 58% vs 81.6% P-value=0.000; mucositis odynophagia and dysphagia
  - The addition of docetaxel did not lead to a worsening of TOI scores and FACT-G scores at 6 months.

Carboplatin as a radiation sensitizer?

Medical Oncology
June 2004, Volume 21, Issue 2, pp 95–107 | Cite as

Concomitant radiochemotherapy vs radiotherapy alone in patients with head and neck cancer

A hellenic cooperative oncology group phase III study



TTP p=0.0002
OS p= 0.0003
3 yrs survival

p=<0.001

Indian experience

ORIGINAL ARTICLE
Year : 2017 | **Volume** : 54 | **Issue** : 2 | **Page** : 453-457

Carboplatin-based concurrent chemoradiation therapy in locally advanced head and neck cancer patients who are unfit for cisplatin therapy

V Noronha[1], V Sharma[2], A Joshi[1], VM Patil[1], SG Laskar[3], K Prabhash[1]

63 patients
Carboplatin AUC 2 x7

→

Median OS 28 months
Median PFS 17 months

- Renal dysfunction 41 (65.07%)
- Sensorineural hearing loss in 18 (28.57%)
- Uncontrolled comorbidities in 3 (4.76%)
- Old age in 1 patient (1.6%)

.

- 53 patients (84.1%) completed RT
- Median number of CT cycles was 6
- Grade 3–4 in 32 patients (50.8%)

Carboplatin and 5FU

Phase III trial


VOLUME 22 · NUMBER 1 · JANUARY 1 2004
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Final Results of the 94-01 French Head and Neck Oncology and Radiotherapy Group Randomized Trial Comparing Radiotherapy Alone With Concomitant Radiochemotherapy in Advanced-Stage Oropharynx Carcinoma

Fabrice Denis, Pascal Garaud, Etienne Bardet, Marc Alfonsi, Christian Sire, Thierry Germain, Philippe Bergerot, Beatrix Rhein, Jacques Tortochaux, and Gilles Calais

226 pts
Oropharynx
Stage III-IV

RT

70Gy (2Gy/#)

RT + Chemo

Carbo 70mg/m2 x4 days

5FU 600mg/m2 x4 days CIVI

Week 1,4,7

RT vs CRT
Median OS 13 vs 20mths

At 5.5yrs
OS 16% vs 22%
p=0.05
DFS 15% vs 27%
p=0.01
LCR 25% vs 48%
p=0.002

5 Yr Late Toxic Effects
56% vs 30% p=NS

Carboplatin + 5-FU demonstrates efficacy, but is associated with significant acute toxicities

Prolonged survival

3-year OS	Carboplatin / 5-FU + RT, %	RT, %	p-value
GORTEC 94-01 (LA OPC)[1]	51.0	31.0	0.02
GORTEC 99-02 (LA SCCHN)[2]	42.6	36.5	0.04

Mucositis

Skin problems

Poor nutrition

Hematologic deficits

Death

Toxicity (GORTEC 94-01 [LA OPC])[1]	Carboplatin / 5-FU + RT, n	RT, n	p-value
Mucositis			
Patchy mucositis	57	32	0.005
Confluent fibrinous mucositis	14	7	NR
Skin			
Erythema/pruritus/dry desquamation	44	47	0.02
Moist desquamation	23	12	NR
Nutritional status			
Weight loss >10% of body mass	14	6	0.04
Need for feeding tube	36	15	0.02
Hematology			
Neutrophil count <0.9cells/mm^3	4	0	0.04
Platelet count <50cells/mm^3	6	1	0.04
Hemoglobin level <8g/100mL	0	0	0.05
Toxic death	1	0	NR

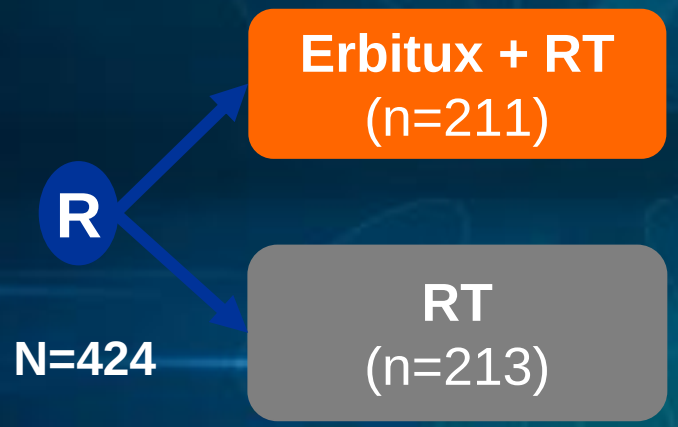
NR, not reported; OPC, oropharyngeal

1. Calais G, et al. J Natl Cancer Inst 1999;91:2081–2086; 2. Bourhis J, et al. Lancet Oncol 2012;13:145–153

Other options: Cetuximab

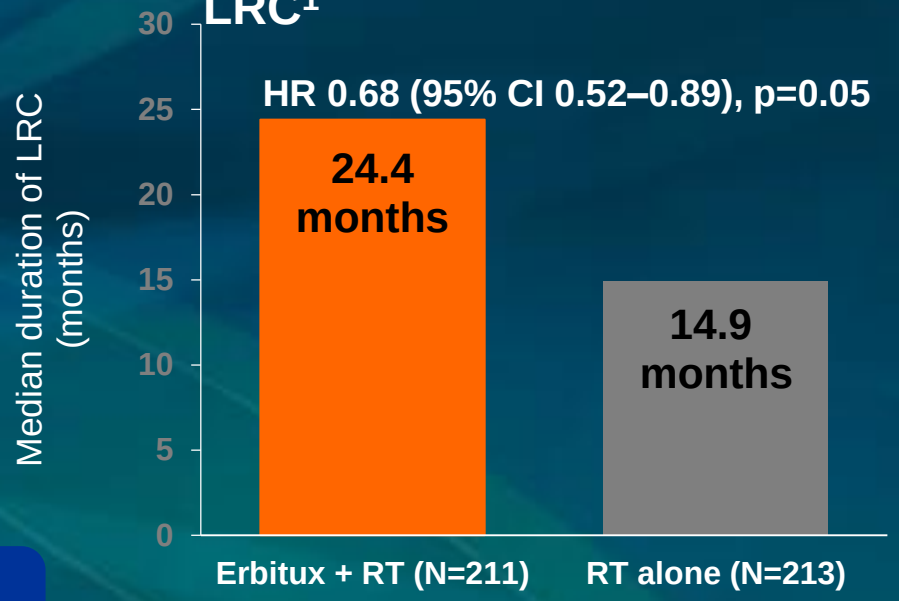
Erbitux + RT is an effective therapy for patients with LA SCCHN,[1,2] up to 59% of whom may not be able to tolerate cisplatin-based regimens[3]

Phase III 'Bonner' study[1]



50% LRC (vs 41%) at 2 years with Erbitux + RT[1]

Primary endpoint: Duration of LRC[1]



Median survival **49 vs 29.3** months p=0.03

1. Bonner JA, et al. N Engl J Med 2006;354:567–578;
2. 2. Bonner JA, et al. Lancet Oncol 2010;11:21–28;
3. 3. Ahn MJ, et al. Oral Oncol 2016;53:10–16.

Almost 50% of patients receiving Erbitux + RT survived ≥5 years, with manageable toxicity[1-3]

Phase III Bonner study: OS (5-year update)[1]

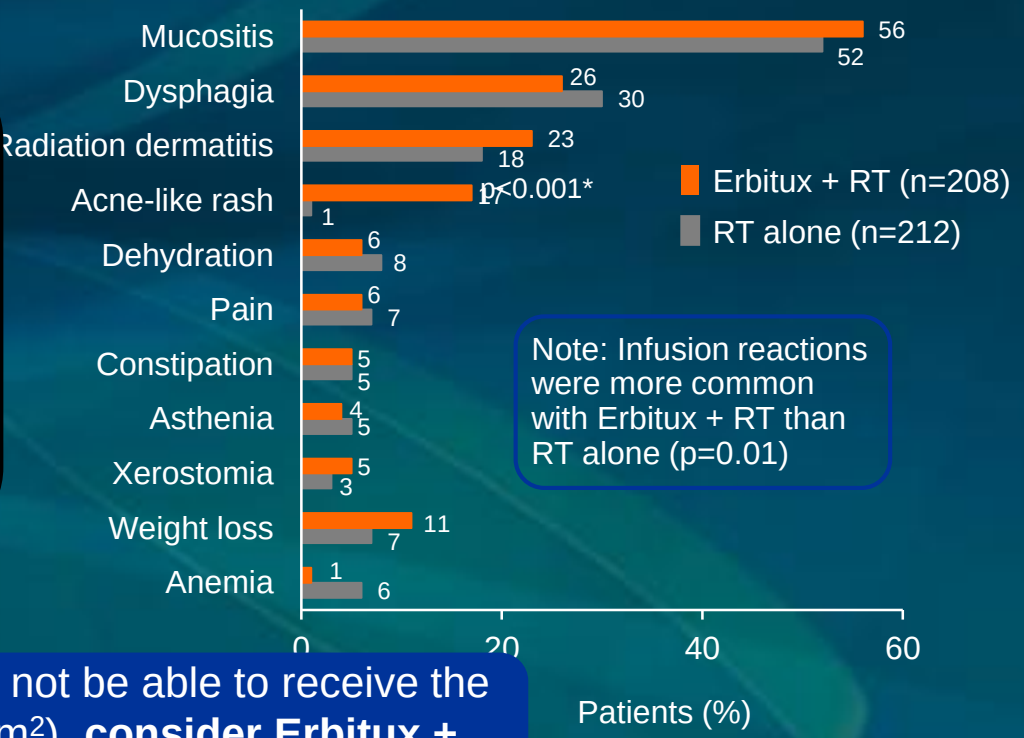
5-year OS

25% higher for Erbitux + RT

vs RT alone

HR 0.73, p=0.018

Phase III Bonner study: Grade 3–5 AEs[2] (≥5% of patients in either arm)



If there is any risk that your patient may not be able to receive the full cumulative cisplatin dose (200mg/m^2), **consider Erbitux + RT[1]**

1. Bonner JA, et al. Lancet Oncol 2010;11:21–28;
2. Bonner JA, et al. N Engl J Med 2006;354:567–578;
3. Erbitux SmPC, June 2014.

Perspective

Cetuximab versus cisplatin in patients with HPV-positive, low risk oropharyngeal cancer, receiving radical radiotherapy

ESMO 2018
Mehanna et al

No differences between groups in the overall number of side effects, or of acute or late severe (grade 3–5) toxic events including dry mouth and difficulty swallowing.

Cetuximab did not cause less toxicity and resulted in worse overall survival and more cancer recurrence than cisplatin.

Bonner trial included both fit and less fit patients (less number)

Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial

Hisham Mehanna, Max Robinson, Andrew Hartley, Anthony Kong, Bernadette Foran, Tessa Fulton-Lieuw, Matthew Dalby, Pankaj Mistry,

- 2 year OS Cisplatin RT 97·5% vs 89·4% Cetuximab RT (p=0·0012).

- Time to any recurrence or distant metastasis
  - At 1 year 3·8% Cisplatin RT vs 12·9% Cetuximab RT
  - At 2 year 6% Cisplatin RT vs 16.1% Cetuximab (p=0·0007)

- Mean global quality-of-life score over time (EORTC QLQ C30). (p=0·27).

Carboplatin vs Cetuximab?

Carboplatin Versus Cetuximab Chemoradiation in Cisplatin Ineligible Patients with Locally Advanced p16 Negative Head and Neck Squamous Cell Carcinoma

C. Barney[1], E. Healy[1], P. Zamora[1], J. Aljabban[1], S.A. Walston Jr.[1], V.M. Diavolitsis[1], D.M. Blakaj[1], J.L. Wobb[1], D.L. Mitchell[1], J.C. Grecula[1], A. Neki[2], R. Rupert[2], P. Savvides[3], A.D. Bhatt[1]

International Journal of Radiation Oncology biology • physics
Official Journal of the American Society for Radiation Oncology ASTRO

1st October 2017

- 90 patients with stage III-IVB, p16(-) HNSCC (oropharynx, larynx, and hypopharynx) ; treated definitively (n=77, 68-70 Gy) or postoperatively (n=13, ≥60 Gy) with IMRT and systemic Rx (n=50; carboplatin alone=26 and carboplatin/paclitaxel=24) or cetuximab (n=40).

	Carboplatin+/- Paclitaxel	Cetuximab	P value
2yr LRC	88.3%	53%	p=0.008
PFS	83.8%	44.5%	p=0.004
Larynx Preservation	82%	54.8%	p=0.228

NRG-RTOG 1016: Phase III Trial Comparing Radiation/Cetuximab to Radiation/Cisplatin in HPV-related Cancer of the Oropharynx

A. Trotti[1], J. Harris[2], M. Gillison[3], A. Eisbruch[4], P. M. Harari[5], D. J. Adelstein[6], E. M. Sturgis[3], J. M. Galvin[7], S.

Conclusions

- Non-inferiority of cetuximab was NOT demonstrated
  - Cisplatin had better OS, PFS, LRC
  - Acute "Toxicity Burden" 40% worse with cisplatin
  - Late "Toxicity Burden" not significantly different

Other options: Nimotuzumab

Cancer

Original Article

A randomized phase 3 trial comparing nimotuzumab plus cisplatin chemoradiotherapy versus cisplatin chemoradiotherapy alone in locally advanced head and neck cancer

Vijay Maruti Patil MD, Vanita Noronha MD, Amit Joshi MD, Jaiprakash Agarwal MD, Sarbani Ghosh-Laskar MD, Ashwini Budrukkar MD, Vedang Murthy MD, Tejpal Gupta MD ... See all authors

The addition of nimotuzumab **significantly** improved PFS, LRC and DFS, and had a trend toward improved OS.

Grade 3 through 5 adverse events were similar between the 2 arms, except for a higher incidence of mucositis in the nimotuzumab CRT arm.

THANK YOU