

Head and Neck Cancer **(Neo) Adjuvant therapy**

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Tata Medical Center: Kolkata

ICRO JIPMER Aug 2017

Oral Cavity



Oral Cavity Cancers treated with Surgery first: higher chance of cure...



Clinical Oncology (1998) 10:155–160
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**Clinical
Oncology**

Early Closure of a Randomized Trial: Surgery and Postoperative Radiotherapy Versus Radiotherapy in the Management of Intra-oral Tumours

result, but, after 35 patients had been entered, the trial was closed prematurely with a marked difference in overall survival in favour of the combination arm ($P = 0.0006$).

At this analysis, carried out 23 months after trial closure, the survival difference between the two arms remains statistically significant for all causes of mortality ($P = 0.001$; relative death rate = 0.24; 95% CI 0.10–0.59).

Are Oral Cavity Cancers clinico-pathologically similar to other HNSCA?



- Anatomical Barriers
- Patterns of Nodal Spread
- Most reports/trials included patients with non nasopharyngeal head and neck sites together...

Why need adjuvant therapy after major surgery?



- Stage III/IV a/b cancers have a 30-40% 5 year survival
- A more than 15% risk of recurrence has traditionally been used to recommend adjuvant therapy

Selecting patients?

Risk factors for recurrence

Primary

- positive or close (<5mm) resection margin
- pT3/T4 tumours
- oral cavity site
- perineural invasion
- lymphovascular space invasion
- Depth of invasion
- subglottic extension

Nodal

- Extra capsular extension
- 2 or more nodes or 2 or more nodal stations involved
- Node more than 3cm in size

Olsen KD et al Arch Otolaryngol Head Neck Surg 1994;120:1370-1374

Huang et al Int J Radiat Oncol Biol Phys 1992;23:737-742

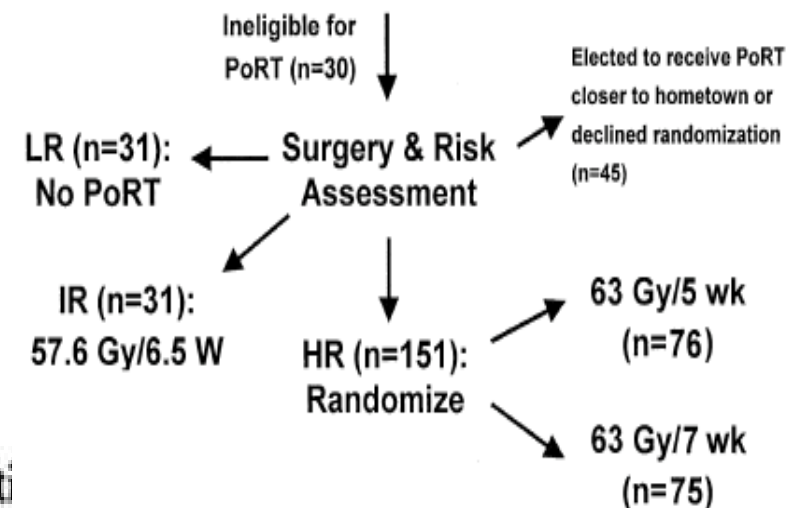
Risk stratification of patients

HIGH RISK PATIENTS:

- ◆ Extracapsular extension of nodal disease
- ◆ ≥ 2 of the following risk factors
 - ◆ oral cavity site
 - ◆ microscopically positive mucosal margins
 - ◆ nerve invasion
 - ◆ ≥ 2 involved neck nodes
 - ◆ > 1 positive nodal group
 - ◆ node size > 3 cm
 - ◆ > 6 week interval between surgery and radiation

Study Design and Population

Registered (8/91 - 8/97): 288 Patients



MODERATE RISK PATIENTS: One risk factor (excluding extracapsular extension)

Peters LJ et al. Int J Radiat Oncol Biol Phys 1993;26(1):3-11

Ang KK et al Int J Radiat Oncol Biol Phys 2001;51(3):571-8

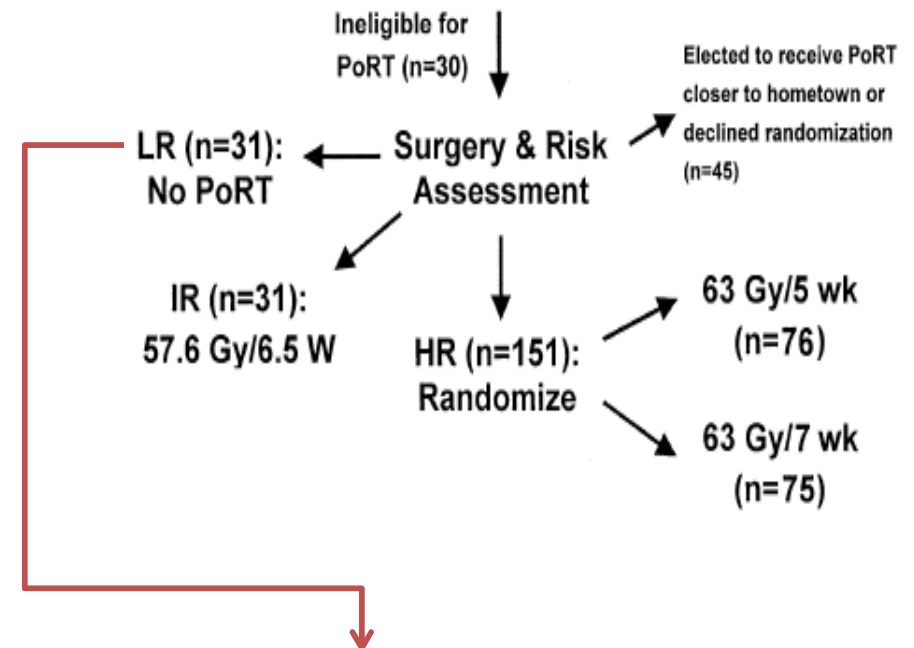
Selecting patients for intervention

MD Anderson Studies

- oral cavity, oropharynx, hypopharynx. p T3 to T4 in 61%
- 58% had N2 to N3 neck disease.
- 86% III/IV disease

Study Design and Population

Registered (8/91 - 8/97): 288 Patients



Peters LJ et al. Int J Radiat Oncol Biol Phys 1993;26(1):3-11

Ang KK et al Int J Radiat Oncol Biol Phys 2001;51(3):571-8

- local–regional control rate of 83%. = **LOW RISK, not for RT**

Does RT help in the adjuvant setting?

Huang et al

Int J Radiat Oncol Biol Phys 1992

1982-88, 441 cases

125 ECS or positive margins 71 Surgery, 54 PORT.

LC@ 3 years S vs PORT:

- ECS: 31% vs 6% ($P=0.03$)
- positive margins, 41% vs 49% ($P=0.04$), respectively; and
- ECS and positive margins: 0% and 68% ($P=0.001$), respectively.
- multivariate analysis of local control
- use of PORT ($P=0.0001$)
- macroscopic
- extracapsular extension ($P=0.0001$)
- margin status ($P=0.09$) significantly impacted local control. DFS@ 3 years was 25vs 45%

Lundahl et al / Kao et al

Int J Radiat Oncol Biol Phys 1998/2008

95 patients with

node-positive squamous cell carcinoma who were treated with S +/- PORT

- 56 matched pairs of patients were identified
- recurrence in the dissected neck ($RR=5.82$; $P=0.0002$)
- death from any cause higher for Surgery only group ($RR=1.67$; $P=0.0182$)

Which patients may NOT benefit from RT?

RT proven to reduce risk:

- **Extra capsular extension**
- **Node positivity**
- **positive or close (<5mm) resection margin**
- **Advanced T stage**

What about other risk factors?

- pT1-T2 N0 tumours?
- perineural invasion
- lymphovascular space invasion
- Depth of invasion
- subglottic extension
- Oral Cavity site

CLINICAL INVESTIGATION

Head and Neck

TREATMENT RESULTS OF POSTOPERATIVE RADIOTHERAPY ON SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY: COEXISTENCE OF MULTIPLE MINOR RISK FACTORS RESULTS IN HIGHER RECURRENCE RATES

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 LI-YU LEE, M.D.,^{¶||**} SHIANG-FU HUANG, M.D.,^{§||**} CHIEN-YU LIN, M.D.,^{*,||**} ERIC YEN-CHAO
 CHEN, M.D.,^{*,||} I-HOW CHEN, M.D.,^{§||} CHUN-TA LIAO, M.D.,^{§||} AND
 JOSEPH TUNG-CHIEH CHANG, M.D., M.H.A.^{*,||††}

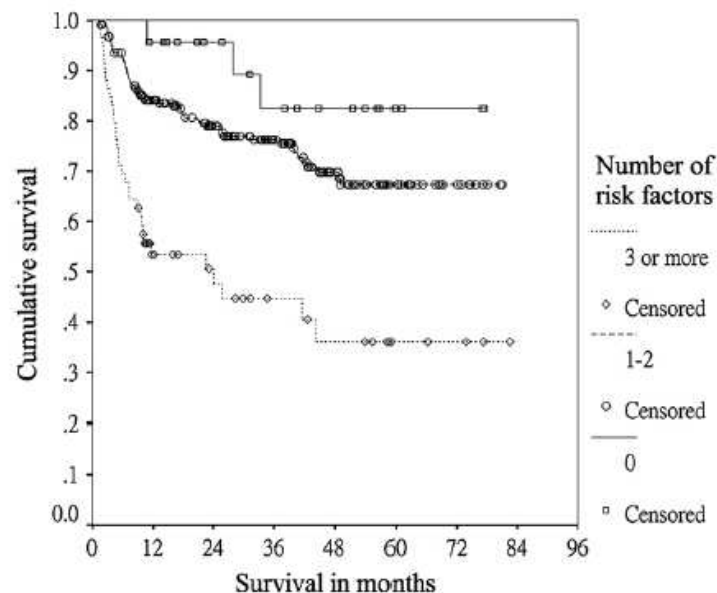


Fig. 1. Recurrence-free survival of patients with intermediate squamous cell carcinoma of the oral cavity with different numbers of significant variables in univariate analysis ($p < 0.01$ in multivariate analysis).

Current TMC clinical protocol: early oral cavity cancers

- Any margin close or positive: Adjuvant chemoradiation
- The remaining patients undergo risk stratification based on the following risk factors:

The DFS figures are based on a revised analysis on 110 patients who had clear margins and all other risk factors known

1. Oral Tongue Primary
2. pT2
3. LVI+
4. PNI+
5. Tumor thickness $\geq 5\text{mm}$
6. Poorly differentiated tumor

0-2 risk factors positive: No adjuvant treatment

Actuarial 3 year Disease-free survival 95%

3-6 risk factors positive: Adjuvant Radiotherapy

Actuarial 3 year disease free survival 64%

TMC Audit: T1/2 N0 (n=120)



- Median FU 23 months
- 38% received RT, as per MDT
- Thirteen patients had recurrence (local 8; nodal 4, distant 3, including overlapping failures).
- **All locoregional failures were within the radiotherapy volumes.**
- The 2 year and 3 year disease-free-survival (DFS) was 89% and 82% respectively.

ESTRO 2016

FACTOR	N (%)	3 Year DFS	P
Tongue Primary (vs others)	66 (55%)	76.0 (vs 91.7%)	0.1
pT2 (vs pT1)	67 (56.3%)	72.5 (vs 95.6%)	0.039
LVI (VS Absent)	10 (8.3%)	58.3 (vs 83.6%)	0.024
PNI (v absent)	38 (31.7 %)	75.0 (vs 85.6%)	0.013
Depth of invasion >= 5 mm(vs < 5 mm)	72 (61%)	73.8 (vs 97.5%)	0.017
Poorly diff cancer (vs Mod or well diff)	10 (8.3%)	88.9 (vs 81.2%)	0.956
Close or +ve margins (vs clear margins)	7 (5.8%)	83.3 (vs 80.9%)	0.854



DOES ADJUVANT RADIATION THERAPY IMPROVE OUTCOMES IN pT1-3N0 ORAL CAVITY CANCER WITH TUMOR-FREE MARGINS AND PERINEURAL INVASION?

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 SHU-HANG NG, M.D., §§§ CHUEN HSUEH, M.D., ¶§§ LI-YU LEE, M.D., ¶§§ CHIH-HUNG LIN, M.D., ||§§
 I-HOW CHEN, M.D., *§§ SHIANG-FU HUANG, M.D., *§§ ANN-JOY CHENG, PH.D., **§§
 LAI-CHU SEE, PH.D., ††§§ AND TZU-CHEN YEN, M.D., PH.D., ††§§

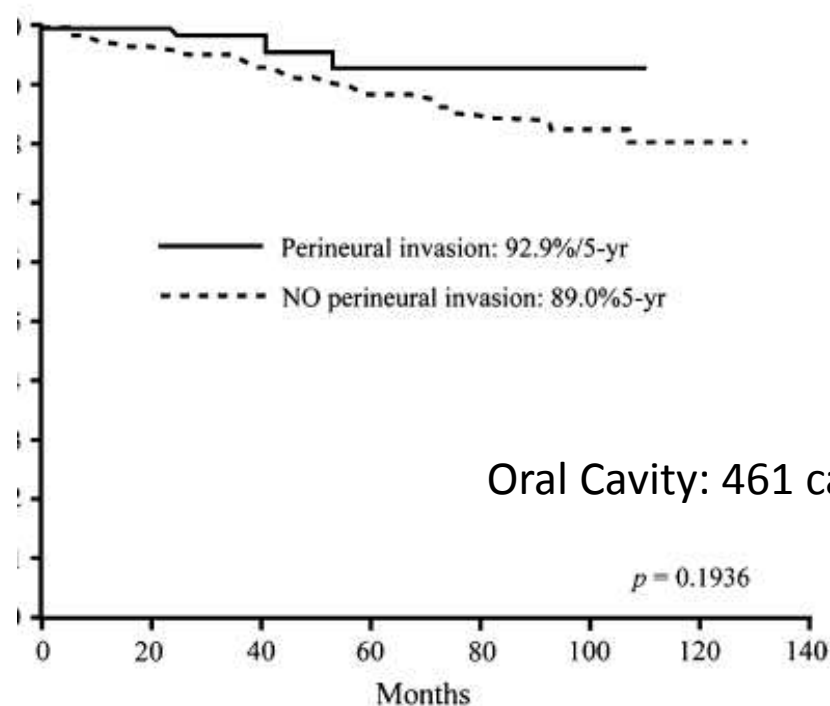


Fig. 1. Kaplan-Meier analysis of the 5-year local control rate in patients with perineural invasion compared with those without.

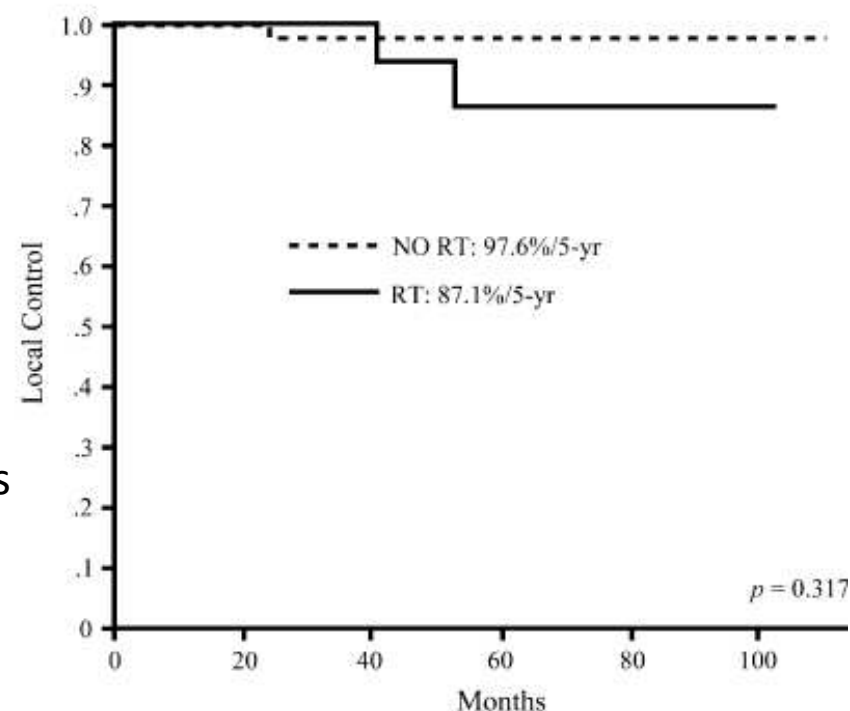


Fig. 3. Kaplan-Meier analysis of the 5-year local control rate in patients with perineural invasion with and without postoperative adjuvant radiotherapy (RT).

RT details: Dose



Median dose of at least 60Gy

Even lower risk patients for RT have higher relapse if <57.6Gy

For ECS and positive margins higher dose may benefit

RT cannot compensate for suboptimal margins/surgery

RT : Overall time from Surgery

Egyptian studies: Hypothesis generating (Better LC in higher risk adjuvant patients)

MD Anderson:

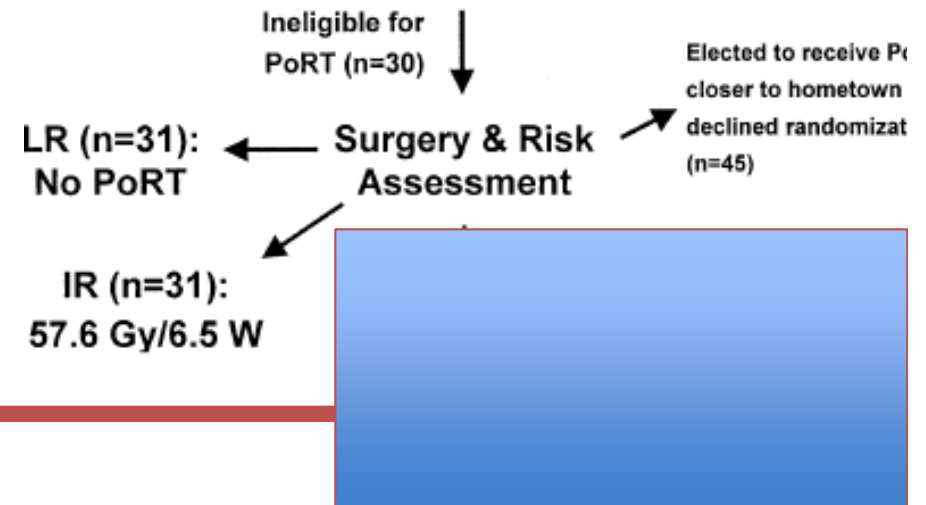
Higher risk arm – Conv RT versus Altered Frac

- Trend to better LC and DFS for Altered Frac
- Delay of starting RT >6weeks = poorer outcome

Overall time from Surgery to Rt completion >100days = poorer outcome

Study Design and Population

Registered (8/91 - 8/97): 288 Patients



Ang KK et al Int J Radiat Oncol Biol Phys 2001;51(3):571-8

Rosenthal et al Head Neck 2002;24:115-126

RT details: Target



Clinical Oncology 29 (2017) 51–59



Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net



Original Article

Postoperative (Chemo)Radiotherapy for Oral Cavity Squamous Cell Carcinomas: Outcomes and Patterns of Failure



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Received 24 June 2016; received in revised form 11 August 2016; accepted 22 August 2016

- Use generous margins to prevent marginal failure
- Address contralateral neck when lymphatics could communicate with contralateral side

Altered fractionation

Adjuvant studies:

- Trend to LC benefit

Increased acute toxicity

Opinion:

- To compensate for overall treatment time, if needed
- Benefit may be in higher risk patients, compared to RT only
- Extra acute toxicity
- Logistically difficult

Sanguineti et al Int J Radiat Oncol Biol Phys 2005;61(3):762–71

Suwinski R et al Radiother Oncol 2008;87 (2):155–63

Chemotherapy Alone prior to RT

Table 1. Actuarial Local Failure, Disease Free Survival and Overall Survival at 4 Years from Intergroup 0034 [17]

	RT	Chemo/RT	
Local failure	29%	26%	n.s.
Disease-free survival	38%	46%	n.s.
Overall survival	44%	46%	n.s.
Distant metastases	30%	20%	p=0.02

ICRO JIPMER Aug 2017

Adjuvant in ALL (mainly non oral) HNSCCA



Concurrent Chemotherapy

- 3 Cisplatin based studies

Table 4. Results for Phase III Randomized Chemoradiation vs. Radiation Alone Trials

	#pt	F/U	LRC	DFS	Survival
RTOG 9501 [26]	459	46 month median	81% vs 70%	33% vs 25%	45% vs 38%
			p = 0.01	p = 0.04	p = 0.19
EORTC 22931 [27]	334	60 month median	82% vs 69%	47% vs 36%	53% vs 40%
			p = 0.007	p = 0.04	p = 0.02
Bachaud (1996) [25]	83	5 year minimum	70% vs 55%	45% vs 23%	36% vs 13%
			p = 0.05	p < 0.02	p < 0.05

Numbers are actuarial at 5 years, and in the case of the RTOG are estimated based on the published actuarial curves. The RTOG trial showed an improvement in locoregional control (the primary endpoint) and DFS, at the expense of increased acute morbidity. The EORTC study and the French study both showed improved local control, DFS, and survival with chemotherapy. None of the studies demonstrated any difference in distant failure or late morbidity [25-27].

- Carboplatin concurrently may not produce similar results as cisplatin

Combined Analyses: Justifying Toxicity to Benefit

Eligibility

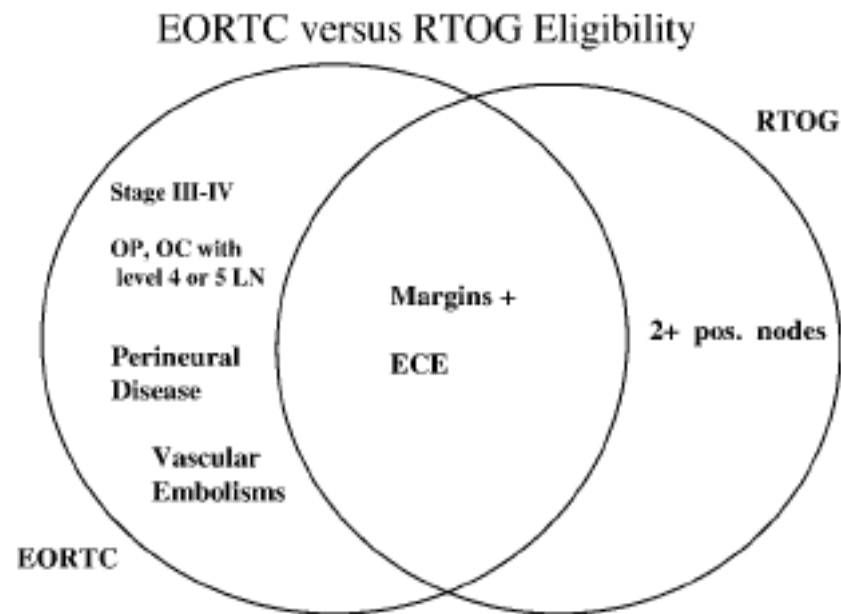
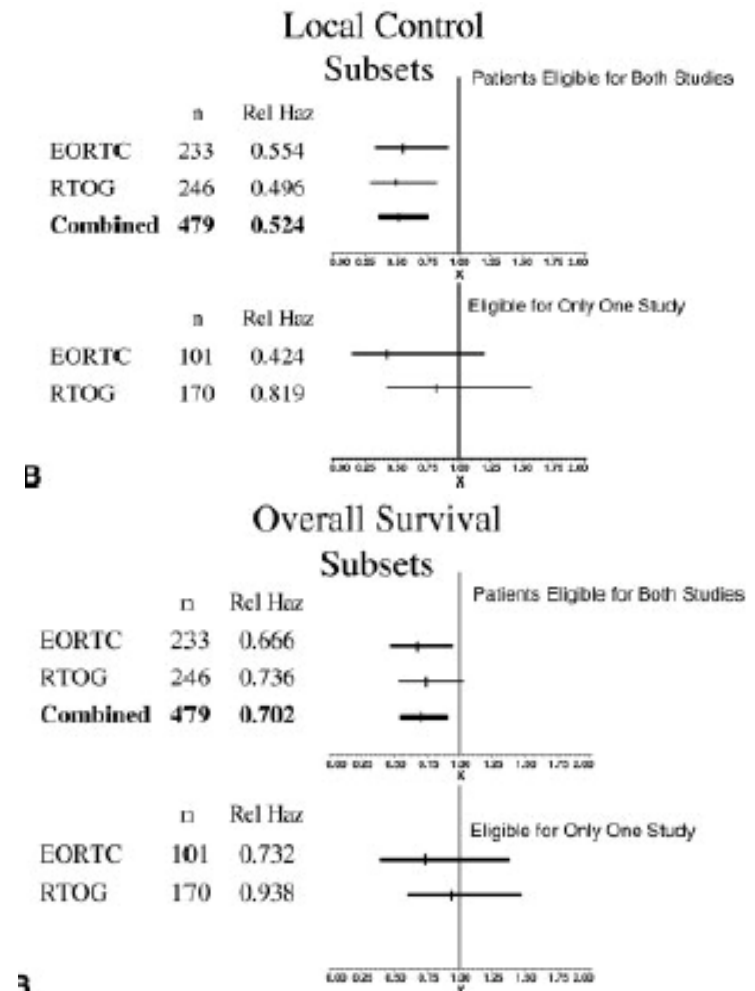


FIGURE 1. Eligibility criteria in EORTC 22931 and RTOG 9501 trials. OP, oropharynx; OC, oral cavity; LN, lymph node; ECE, extracapsular extension.

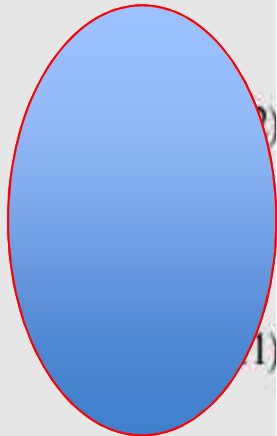
Bernier et al, Head & Neck 2005

Outcomes



Benefits of CTRT may not be sustained

Table 3 Overall survival by cause of death

	Assigned treatment	Failures	5-year estimate (95% CI)	10-year estimate (95% CI)	Hazard ratio (95% CI)
All patients					
Death from any cause*	RT	148	37.1 (30.4-43.8)	27.0 (20.5-33.5)	
	RT + CT	141	45.8 (38.8-52.7)	29.1 (22.3-35.8)	
Death from study cancer	RT	121	43.0 (35.8-50.2)	35.1 (27.7-42.5)	
	RT + CT	100	56.9 (49.6-64.1)	42.7 (34.6-50.7)	
Death not from study cancer	RT	27	83.7 (76.5-90.9)	74.1 (64.5-83.8)	
	RT + CT	41	78.5 (71.3-85.7)	65.6 (55.9-75.3)	
Patients who had involved margin(s) and/or extracapsular extension					
Death from any cause	RT	89	30.7 (22.0-39.4)	19.6 (11.5-27.7)	-
	RT + CT	91	42.5 (33.8-51.2)	27.1 (18.9-35.4)	0.76 (0.57-1.03)
Death from study cancer	RT	77	35.7 (26.4-45.1)	26.7 (17.1-36.2)	-
	RT + CT	67	53.4 (44.1-62.7)	37.4 (27.4-47.5)	0.66 (0.47-0.91)
Death not from study cancer	RT	12	82.7 (71.5-94.0)	69.8 (53.2-86.3)	-
	RT + CT	24	77.7 (68.5-87.0)	70.3 (59.5-81.2)	1.30 (0.65-2.61)

Summary recommendations



Type of intervention	Level 1 evidence (strong)	Level 2 evidence	Level 3 evidence (weak)
CTRT (cisplatin +RT)	Positive margins, ECS, fit for CTRT (age <70)		Close margins
RT		<p>T3.T4 disease; Node positive without ECS irrespective of nodal stations</p> <p>Positive margins, ECS, and NOT fit for CTRT</p>	LVI, Depth of invasion

Will AJCC 8 affect treatment?

Prognostic factors may NOT be predictive of RT response

ICRO JIPMER Aug 2017



Neo- Adjuvant

Neo Adjuvant Taxanes

TAX 323

TPF induction

chemotherapy for 4
cycles followed by RT
better than PF
followed by RT-
improved local control
and improved overall
survival

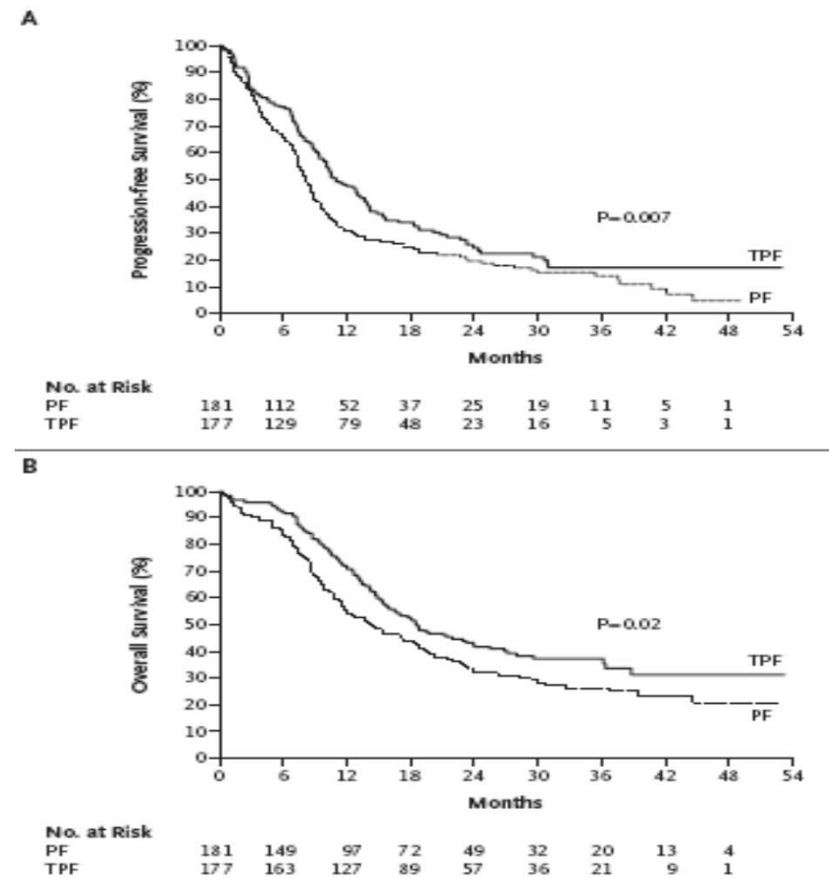


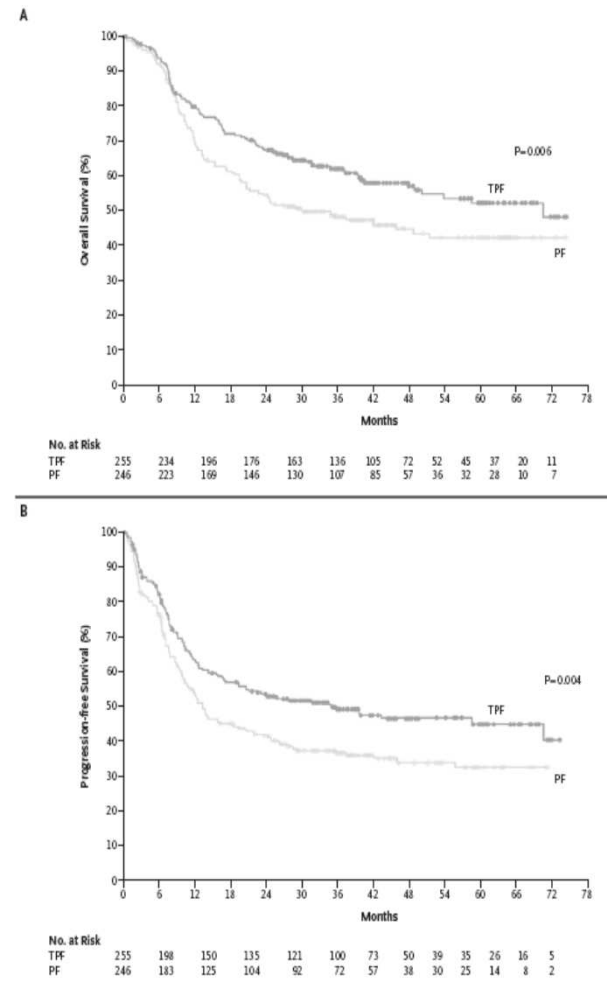
Figure 2. Effects of TPF and PF Therapy on Progression-free Survival (Panel A) and Overall Survival (Panel B).

TPF denotes docetaxel–cisplatin–fluorouracil, and PF cisplatin–fluorouracil.

TAX 324

TPF induction 3 cycles followed by CXRT vs PF plus CXRT

Improved OS (HR 0.7, $p=0.006$) and Local control ($p=0.04$)





Contents lists available at [ScienceDirect](#)

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Original article

Induction chemotherapy followed by concurrent radio-chemotherapy versus concurrent radio-chemotherapy alone as treatment of locally advanced squamous cell carcinoma of the head and neck (HNSCC): A meta-analysis of randomized trials

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Characteristics, treatment compared number of patients and risk of bias.

	Trial characteristics	Trial characteristics induction chemotherapy (IC)	Trial characteristics chemoradiotherapy (CRT)	Treatment compared number of patients	Risk of bias: excluded patients
Cohen [19]	Randomized	2 cycles of TPF	DFHX and hyperfractionated radiotherapy (2×1.5 Gy/d) \rightarrow 39/54/75 Gy (3D conformal RT or IMRT)	n = 285 site withdraw n = 5 IC-CRT: n = 142 CRT: n = 138	n = 12: (withdraw consent: n = 6, n = 1: ineligible, n = 5: site withdrawn)
Takacs-Nagy [18]	Randomized	2 cycles of TPF	3 \times Cis-DDP (d1, 22, 43) 5 \times 2 Gy/week \rightarrow 50/70 Gy ConPas-technique (conformal parotid sparing)	n = 63 3 patients died after IC IC-CRT: n = 30 CRT: n = 33	3 patients did not appear to the first treatment (IC-CRT)
Hitt [15]	Randomized	3 cycles of PF or TPF	3 \times Cis-DDP (d1, 22, 43) 5 \times 1.8–2.0 Gy/week \rightarrow 50/70 Gy	n = 439 IC (TPF)-CRT: n = 155 IC (PF)-CRT: n = 156 CRT: n = 128 (n = 10 did not receive treatment) n = 283 (155 + 128) received CRT \pm TPF N = 145	No patients were excluded, ITT analysis was performed
Haddad [14]	Randomized	3 cycles of TPF	IC-CRT-arm: NR; Docetaxel weekly for 4 weeks Accelerated Boost RT 6 weeks IC-CRT-arm: Carboplatin weekly Daily RT 7 weeks CRT-arm: 2 \times Cis-DDP (weekly for 4 weeks) Accelerated boost RT 6 weeks	IC-CRT: n = 70 CRT: n = 75	No patients were excluded
Ghi [20]	Randomized	3 cycles of TPF	Cis-DDP 20 mg/sqm d 1–4, 5 FU 800 mg/sqm week 1 and 6 RT: 70 Gy/2 Gy SD Cetuximab 250 mg/sqm weekly	n = 421 IC-CRT: n = 210 CRT: n = 211 n = 6 major violation n = 258 (129 + 129) received CRT \pm TPF	IC-CRT: n = 2 (major violation) CRT: n = 4 (major violation)

TPF-CTRT versus CTRT

TPF→RT-CHX vs. RT-CHX in locally advanced head and neck cancer

Meta-analysis of randomized controlled trials: PFS

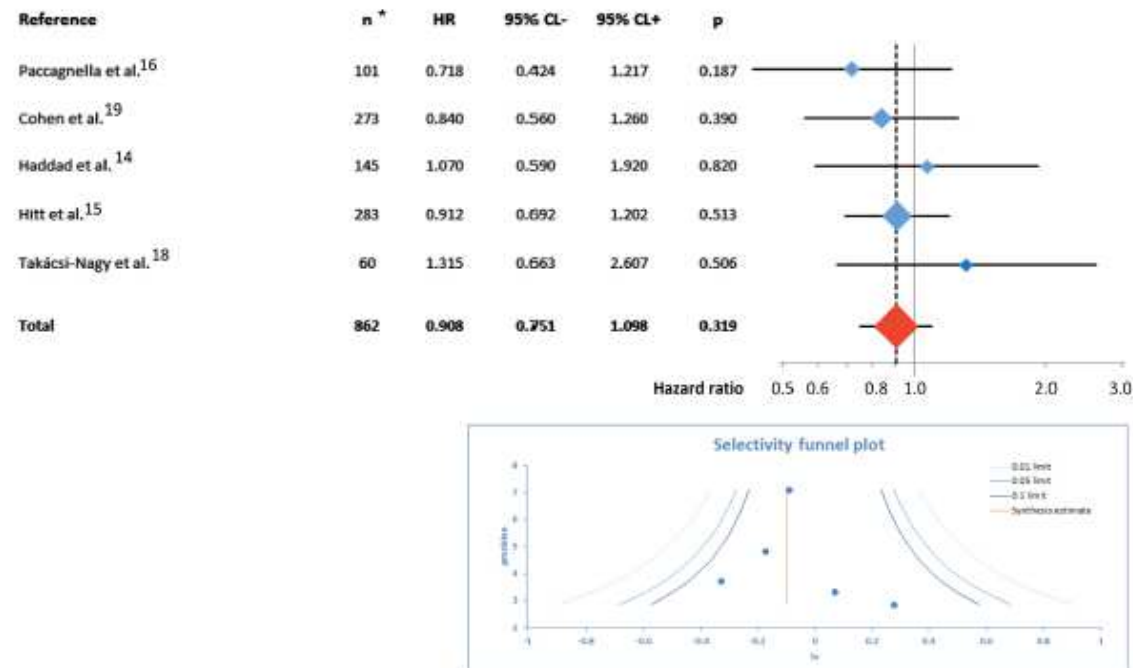


Fig. 2. Meta-analysis of randomized trials. Hazard ratios of induction CHX and concomitant RT-CHX versus RT-CHX alone are given for PFS.

Conclusion

- In general NACT does not seem to add a sustained survival benefit in comparison with cisplatin and CTRT
- Can be judiciously used in select patients depending on clinical stage, logistics and PS

Neoadjuvant Chemotherapy has

No role

in the routine management of oral cancers

Oral Cavity Cancers treated with Surgery has higher chance of cure...



Clinical Oncology (1998) 10:155–160
© 1998 The Royal College of Radiologists

**Clinical
Oncology**

Early Closure of a Randomized Trial: Surgery and Postoperative Radiotherapy Versus Radiotherapy in the Management of Intra-oral Tumours

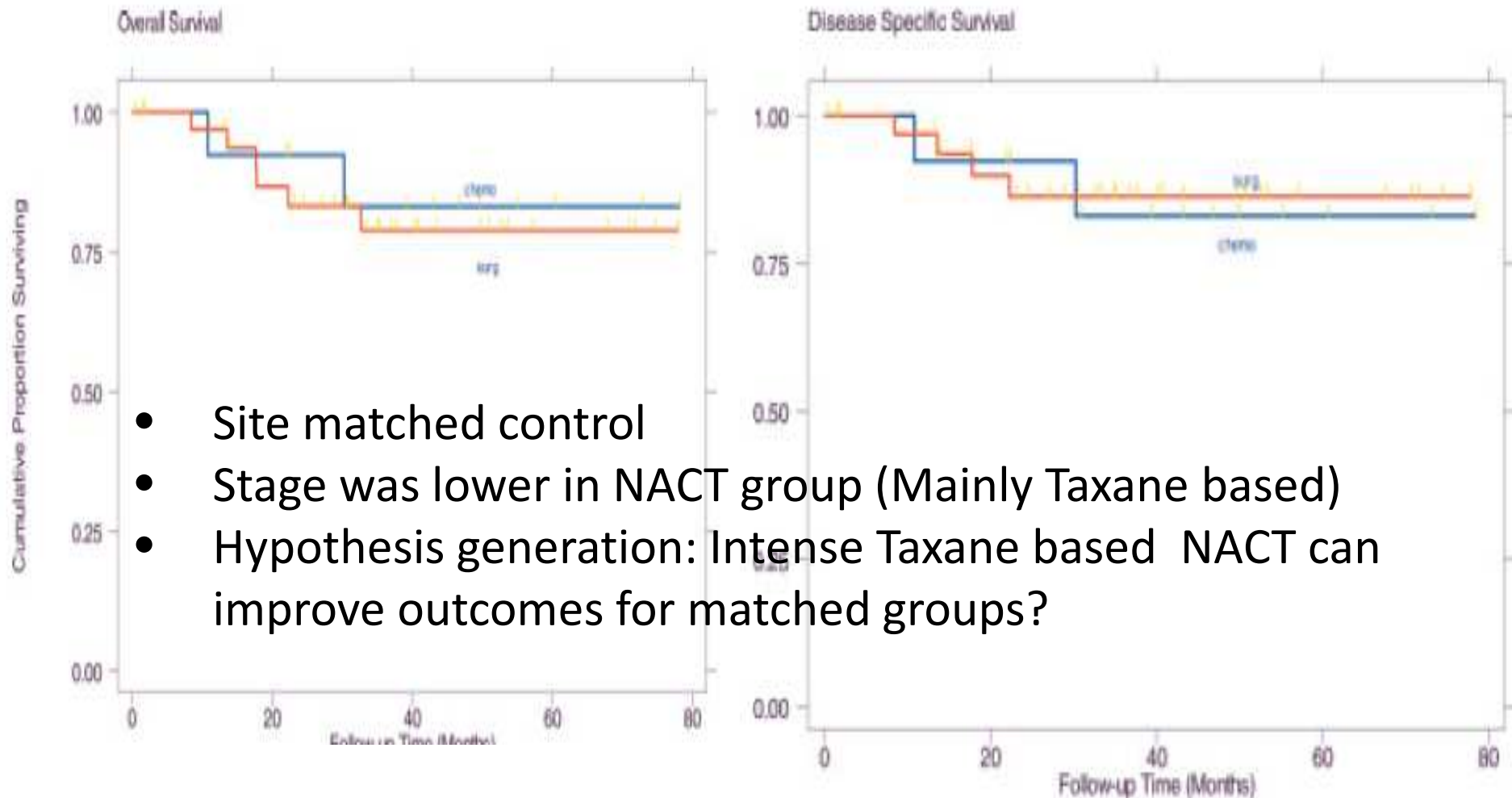
result, but, after 35 patients had been entered, the trial was closed prematurely with a marked difference in overall survival in favour of the combination arm ($P=0.0006$).

At this analysis, carried out 23 months after trial closure, the survival difference between the two arms remains statistically significant for all causes of mortality ($P=0.001$; relative death rate = 0.24; 95% CI 0.10–0.59).

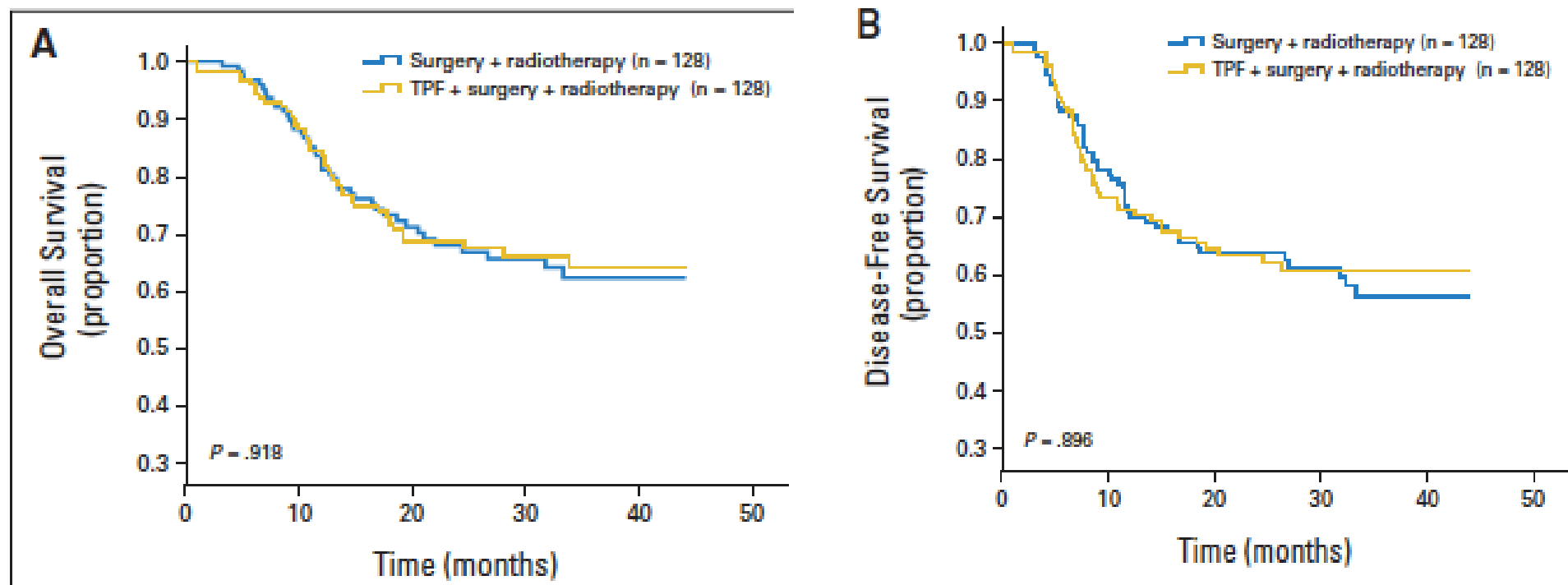
NEOADJUVANT CHEMOTHERAPY FOR SQUAMOUS CELL CARCINOMA OF THE ORAL TONGUE IN YOUNG ADULTS: A CASE SERIES

Head Neck 27: 748–756, 2005

TER



Randomized Phase III Trial of Induction Chemotherapy With Docetaxel, Cisplatin, and Fluorouracil Followed by Surgery Versus Up-Front Surgery in Locally Advanced Resectable Oral Squamous Cell Carcinoma



- Post hoc analysis N2 disease ?? Better with TPF?

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



European Journal of Cancer (2015) 51, 2596–2603

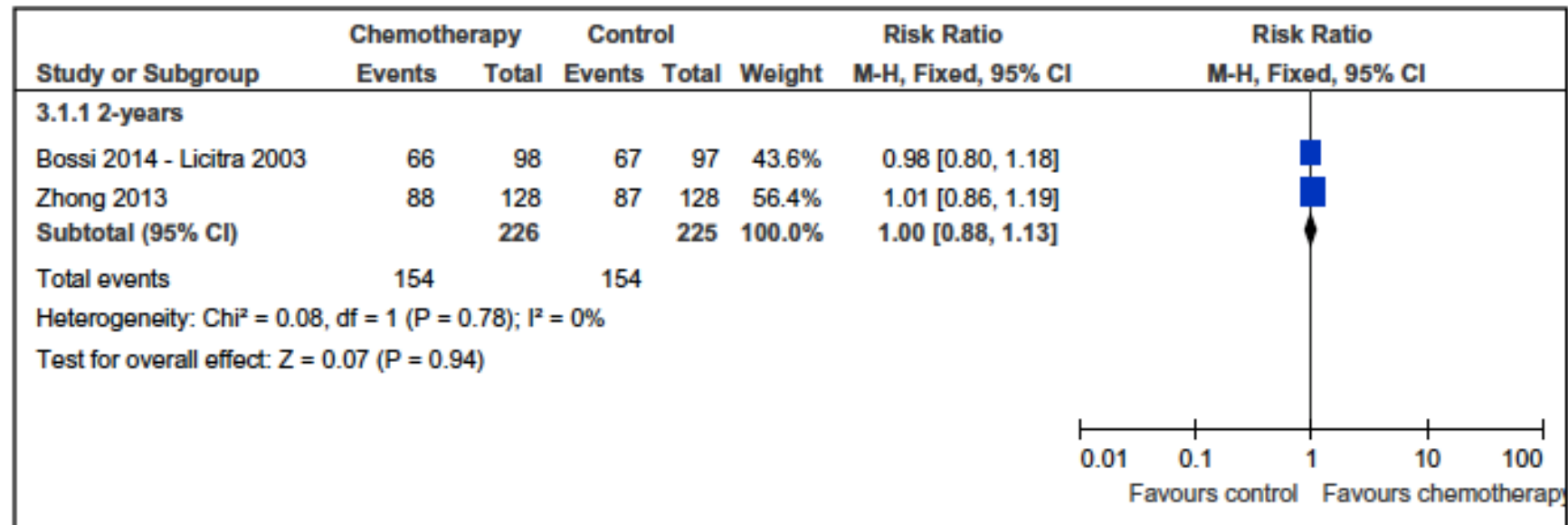


Fig. 4. Forest plot of comparison: Chemotherapy \times Control (no chemotherapy). Outcome: overall survival.

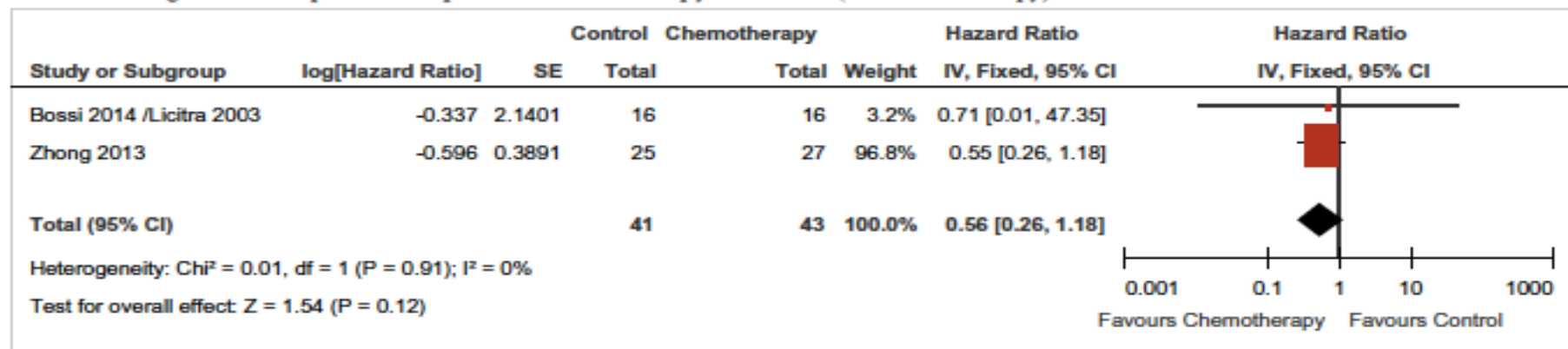
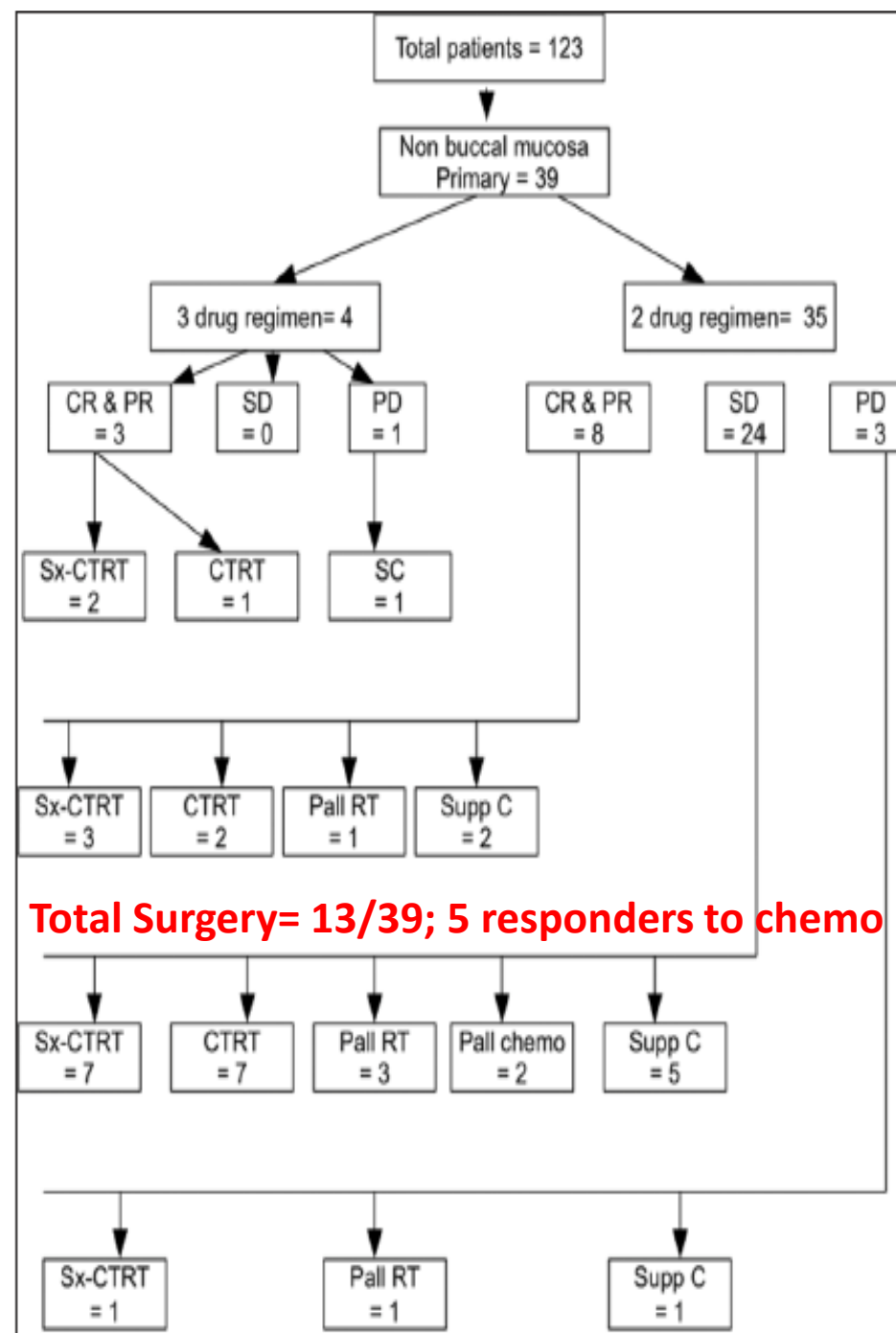
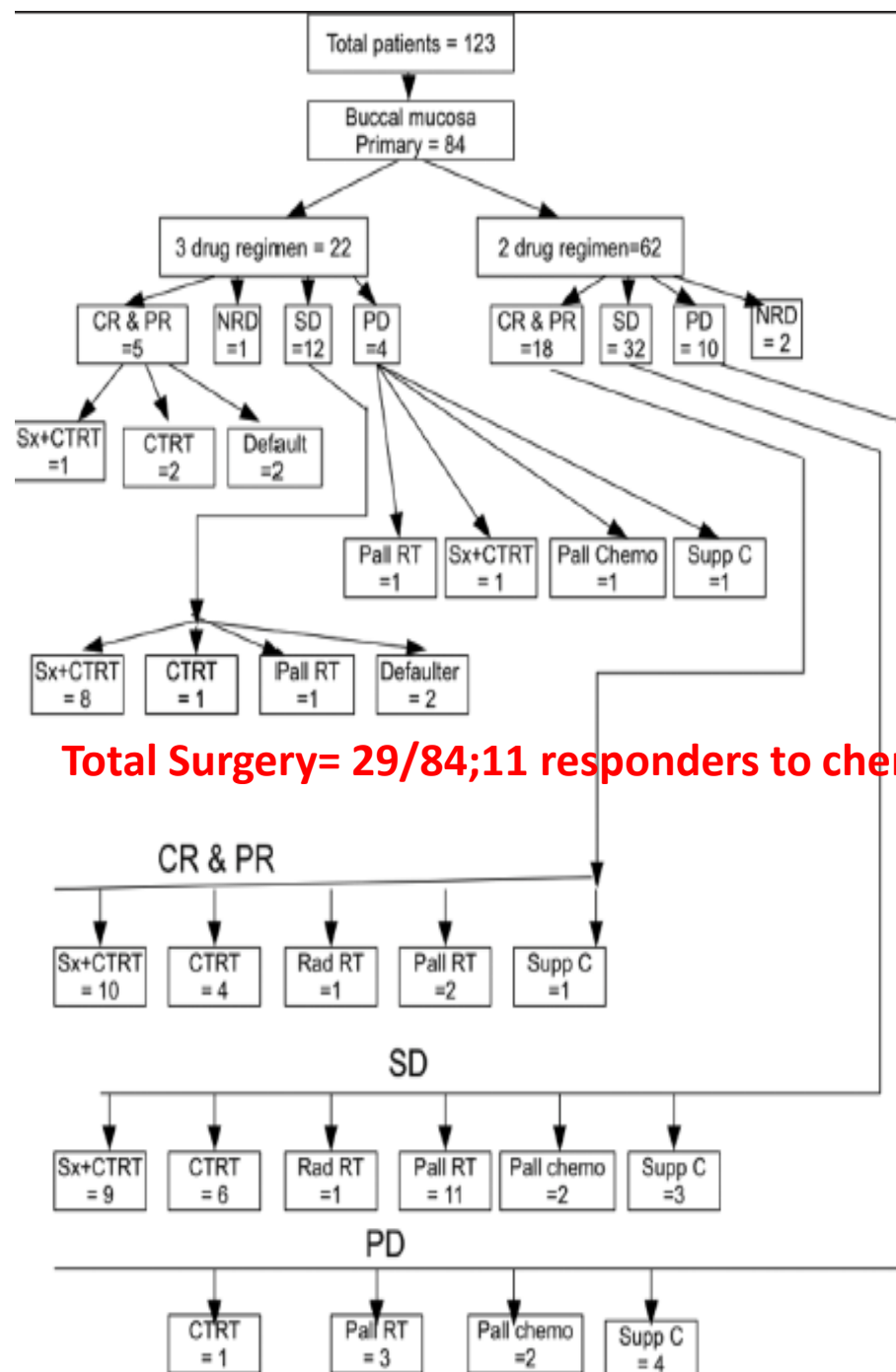


Fig. 6. Forest plot of comparison: Chemotherapy \times Control (no chemotherapy). Outcome: disease-free survival for cN2 patients.

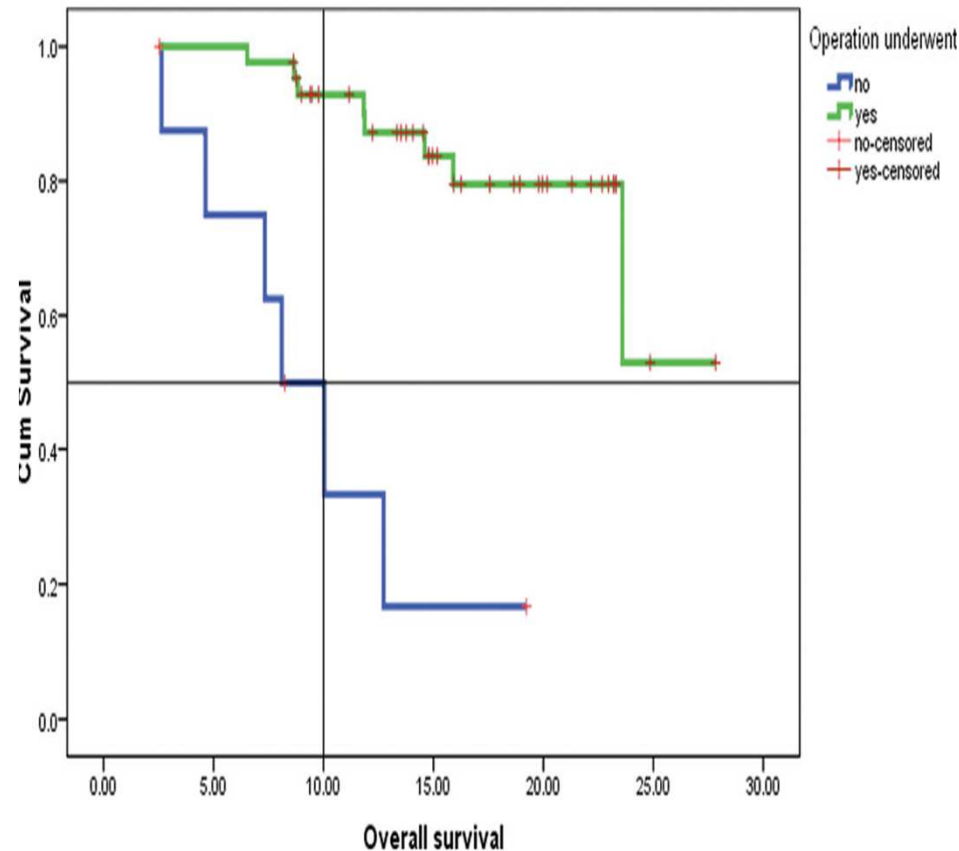
Induction chemotherapy in technically unresectable locally advanced oral cavity cancers: Does it make a difference?

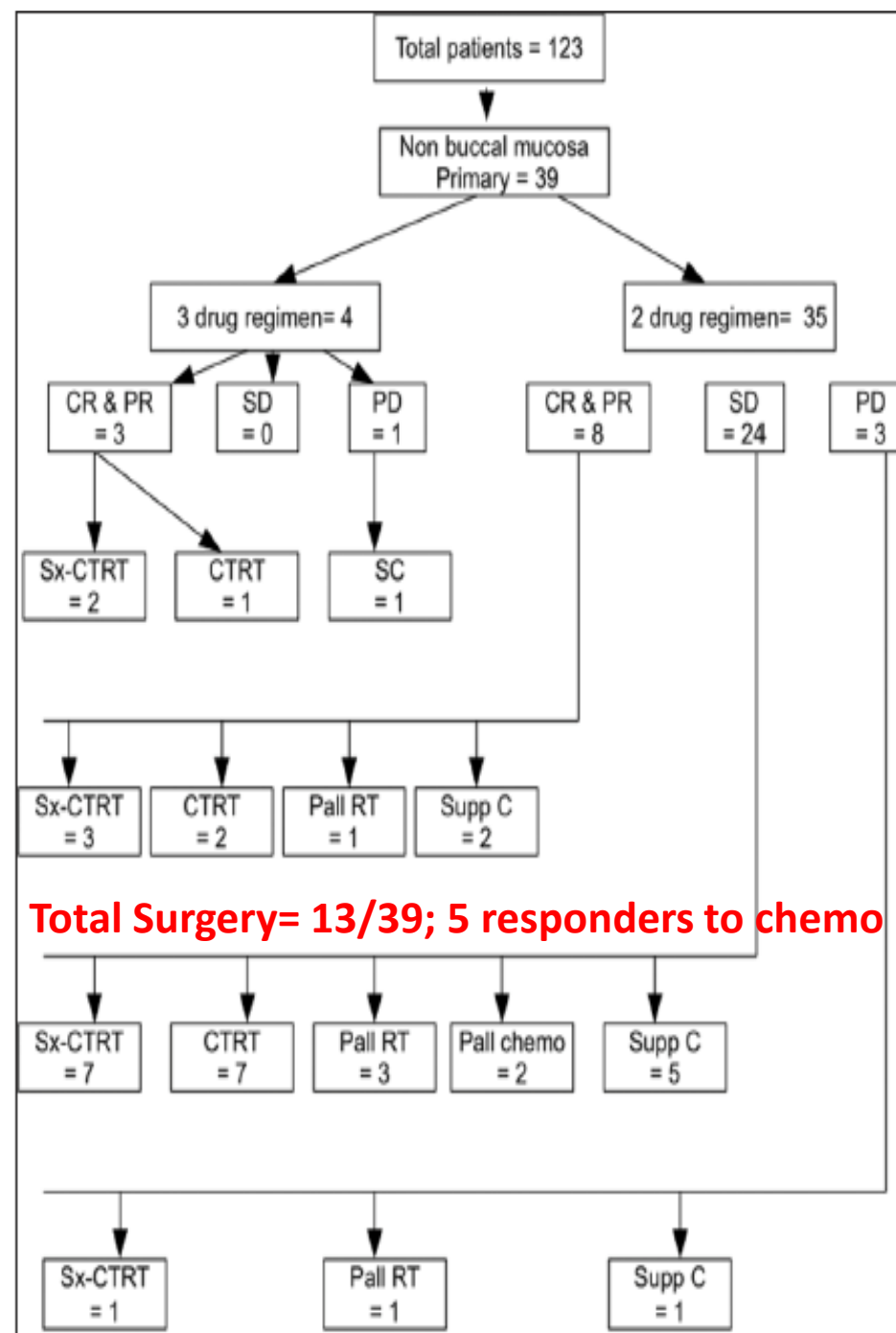
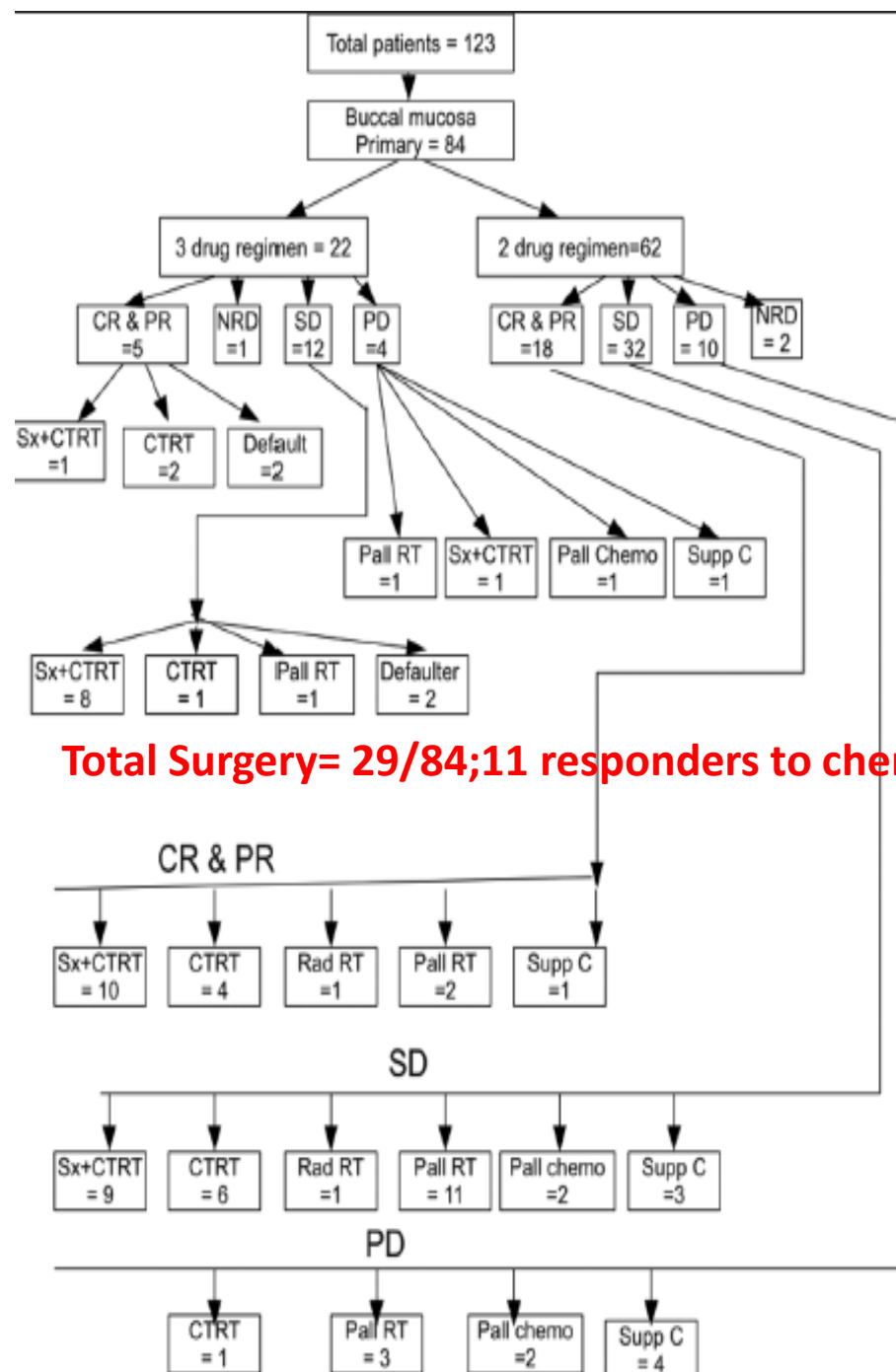
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Indian Journal of Cancer | January-March 2013 | Volume 50 | Issue 1



post NACT ($P = 0.0001$). **CONCLUSION:** Induction chemotherapy was effective in converting technically unresectable oral cavity cancers to operable disease in approximately 40% of patients and was associated with significantly improved overall survival in comparison to nonsurgical treatment.





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

Oral Oncology 50 (2014) 1000–1004



Results: 721 patients with stage IV oral-cavity cancer received NACT. 310 patients (43%) had sufficient reduction in tumour size and underwent surgical resection. Of the remaining patients, 167 received chemoradiation, 3 radical radiation and 241 palliative treatment alone. The locoregional control rate at 24 months was 20.6% for the overall cohort, 32% in patients undergoing surgery and 15% in patients undergoing non surgical treatment ($p = 0.0001$). The median estimated OS in patients undergoing surgery was 19.6 months (95% CI, 9.59–25.21 months) and 8.16 months (95% CI 7.57–8.76) in patients treated with non surgical treatment ($p = 0.0001$).

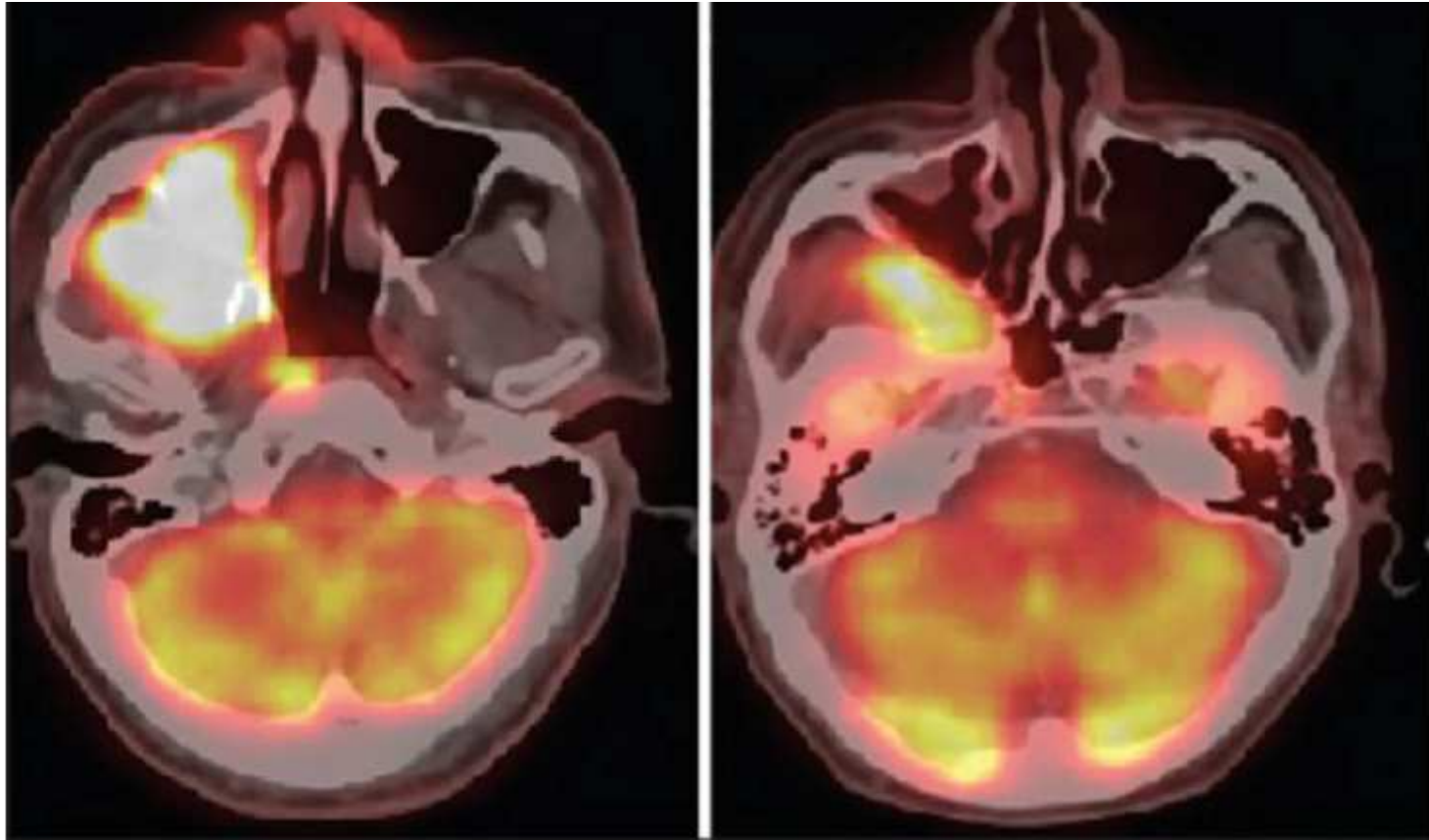
Unblinded assessor; Retrospective study...



ment. We used clinical and radiological response to decide respectability. We also categorised the response according to the RECIST criteria. On reviewing the data, we found that nearly 30% of patients with stable disease according to RECIST could undergo successful resection. After review of the scans, it was seen that several patients had a decrement more than 10% which was sufficient

the volume of the tumour [30]. This reaffirms our belief that the decision to operate should be made on both clinical and radiological grounds.

Regression post chemo is not concentric and centripetal...



Pre- and post-neoadjuvant chemotherapy positron emission tomography-computed tomography scan showing

Neoadjuvant chemotherapy in oral cancers: Selecting the right patients

Indian J Med Paediatr Oncol. 2015 Jul-Sep; 36(3): 148–153.

Tata Medical Center Data (Aug 2011-Sept 2015)



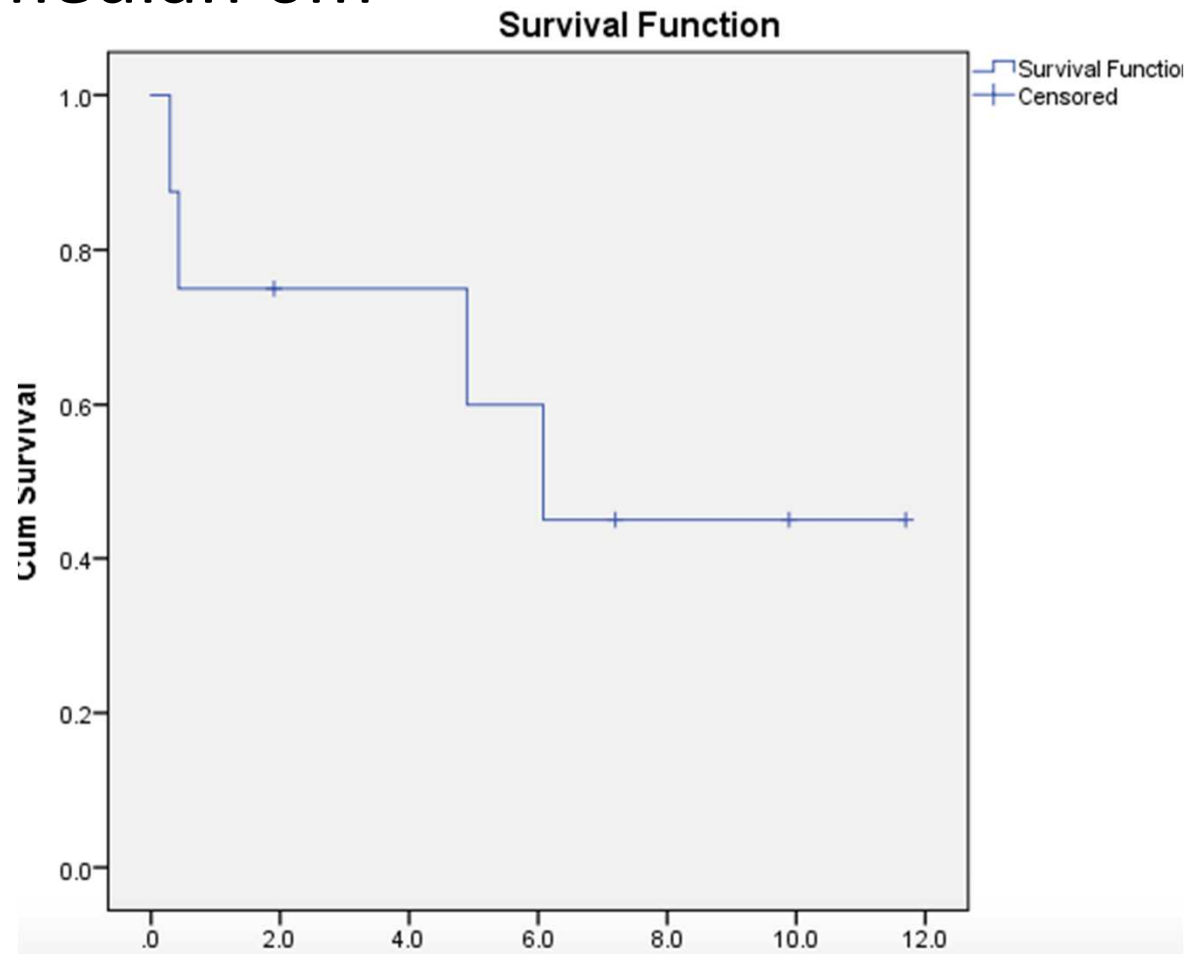
- 8 patients with unresectable Oral Cavity tumours received NACT (2 oral tongue)
- Median age 52yrs
- 6 Stage IVA, 2 IVB
- 2 or more cycles: 6patients, 6 TPF, 1 Pacli-Carbo
- 2patients were admitted (10 days each with sepsis)

Further to NACT

- 6 received radical treatment
- Only 1 had surgery +RT, 4 CTRT, 1 RT alone
(NACT to CTRT delay 33days)
- >1 cycles of chemo- 6 patients

Survival

- 1 patient disease free- The one who had Surgery
- OS- median 6m



Neoadjuvant Chemotherapy has

No role

in the **routine** management of oral cancers

ICRO JIPMER Aug 2017

Thank You

