Overview and takehome message on recent clinical trials in HNC radiotherapy

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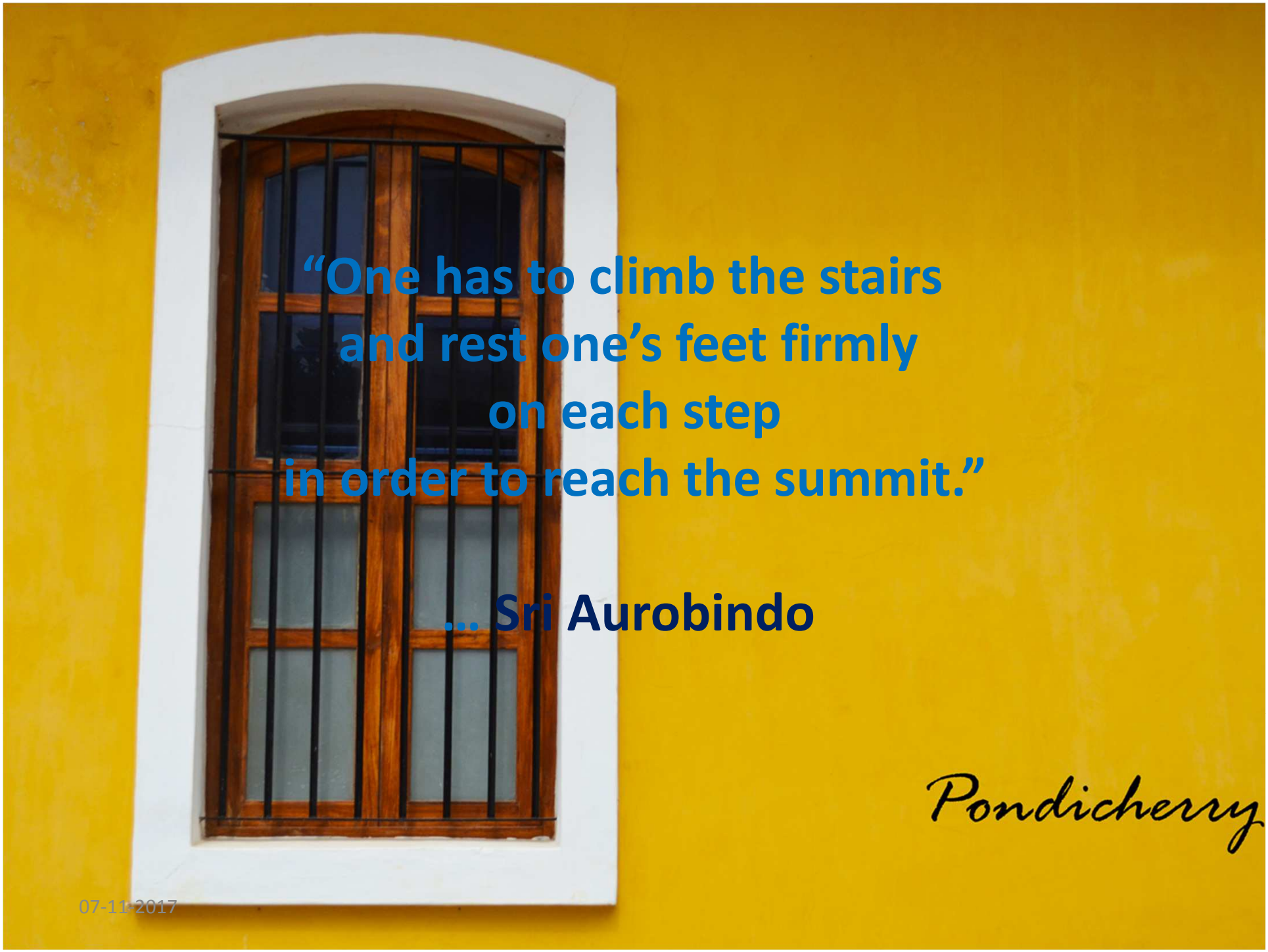
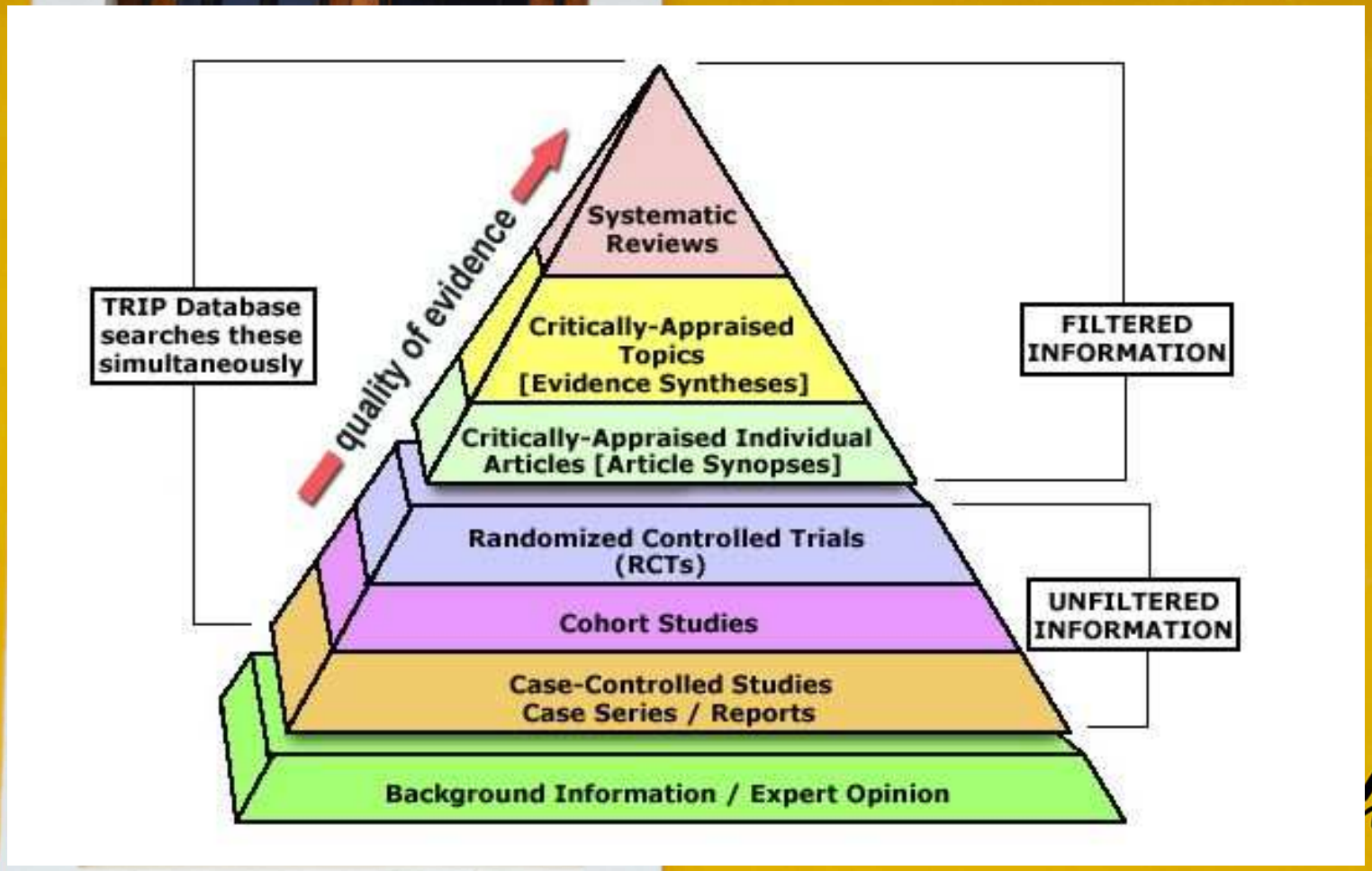

“One has to climb the stairs
and rest one’s feet firmly
on each step
in order to reach the summit.”
… Sri Aurobindo
Pondicherry

Levels of Evidence



Evidence Based Medicine

EBM is the "conscientious and explicit use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from clinical research"

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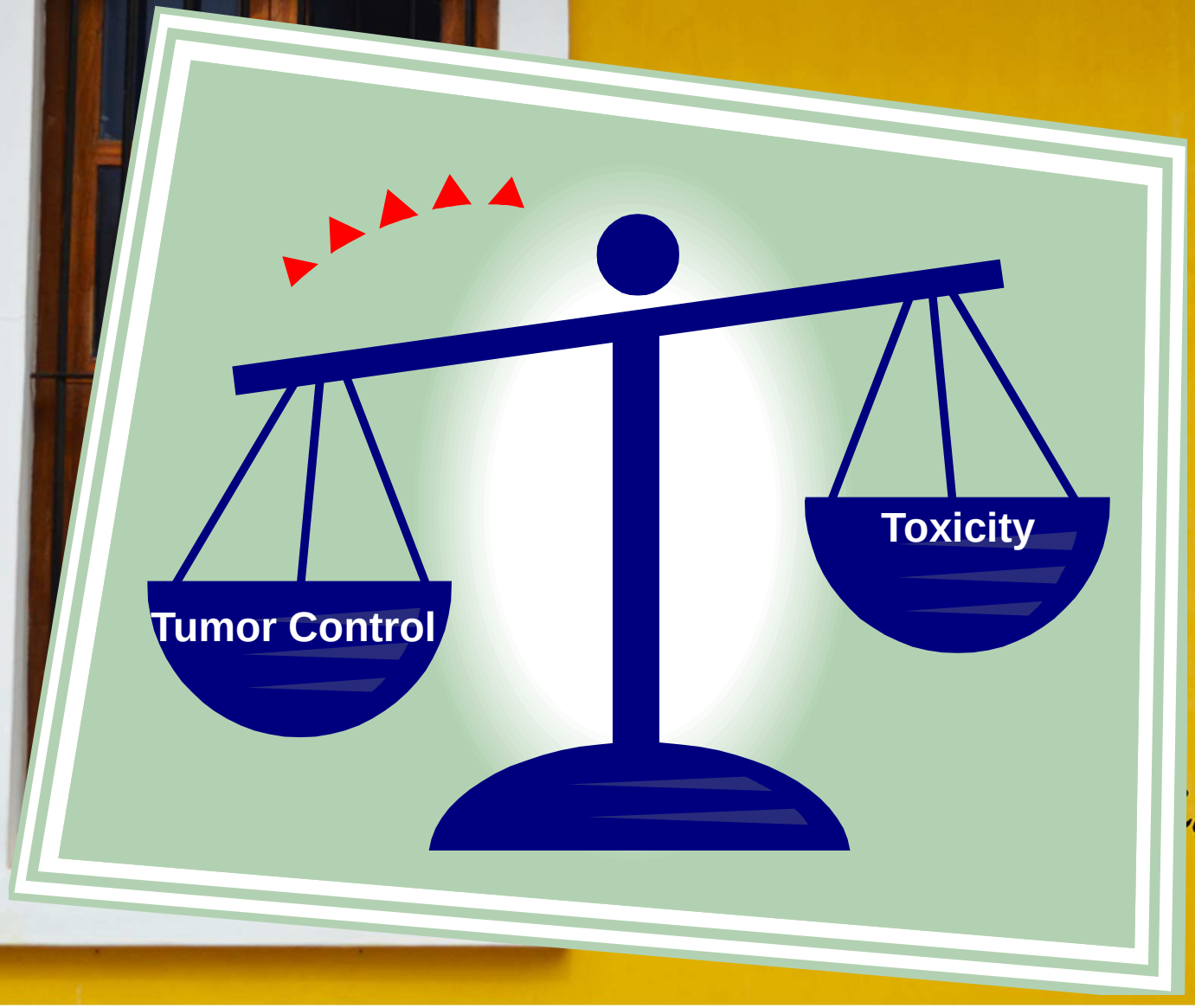
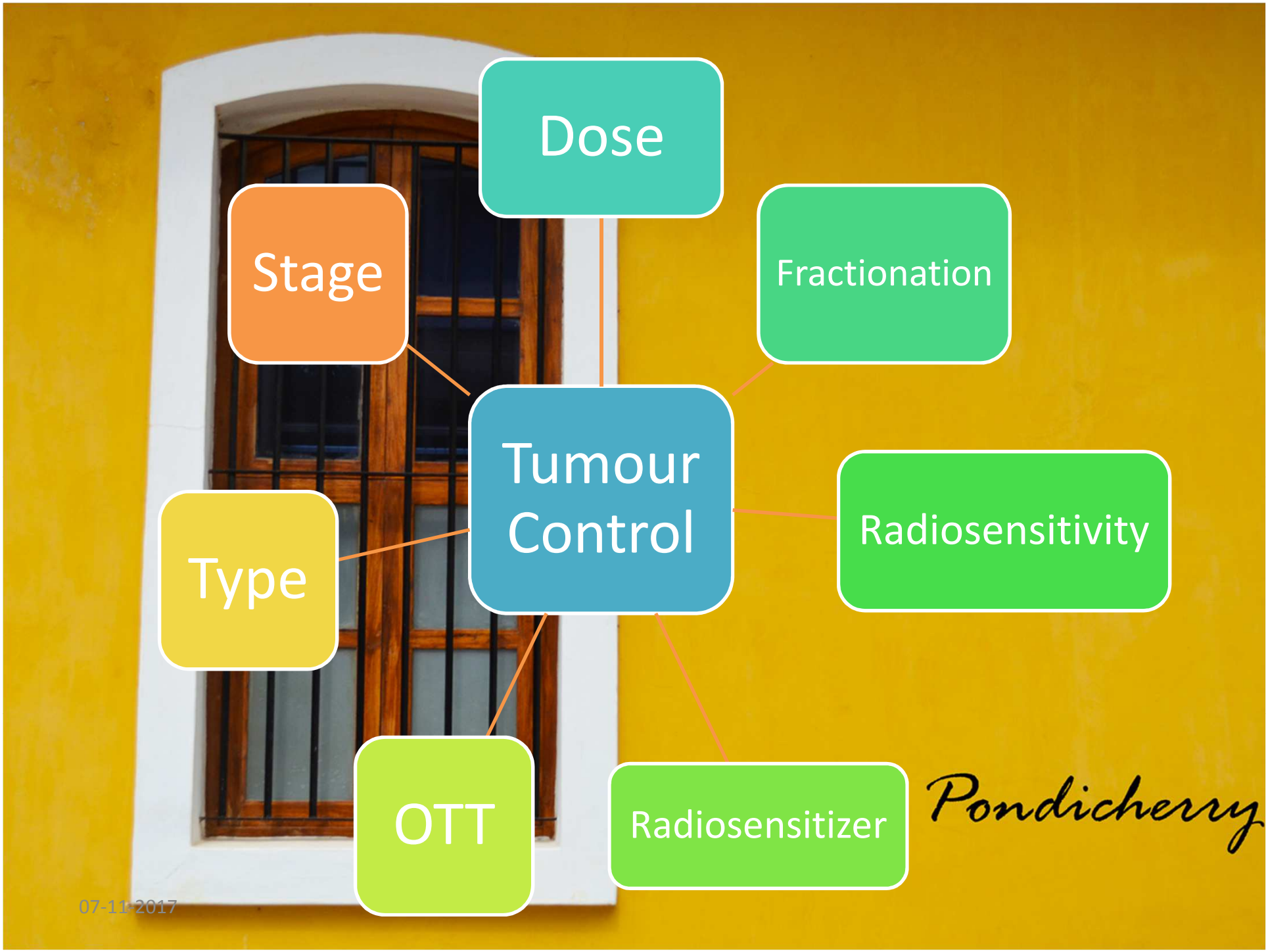
David Sackett

Key issues in Head and Neck Cancer




Dose
Stage
Fractionation
Tumour Control
Type
Radiosensitivity
OTT
Radiosensitizer
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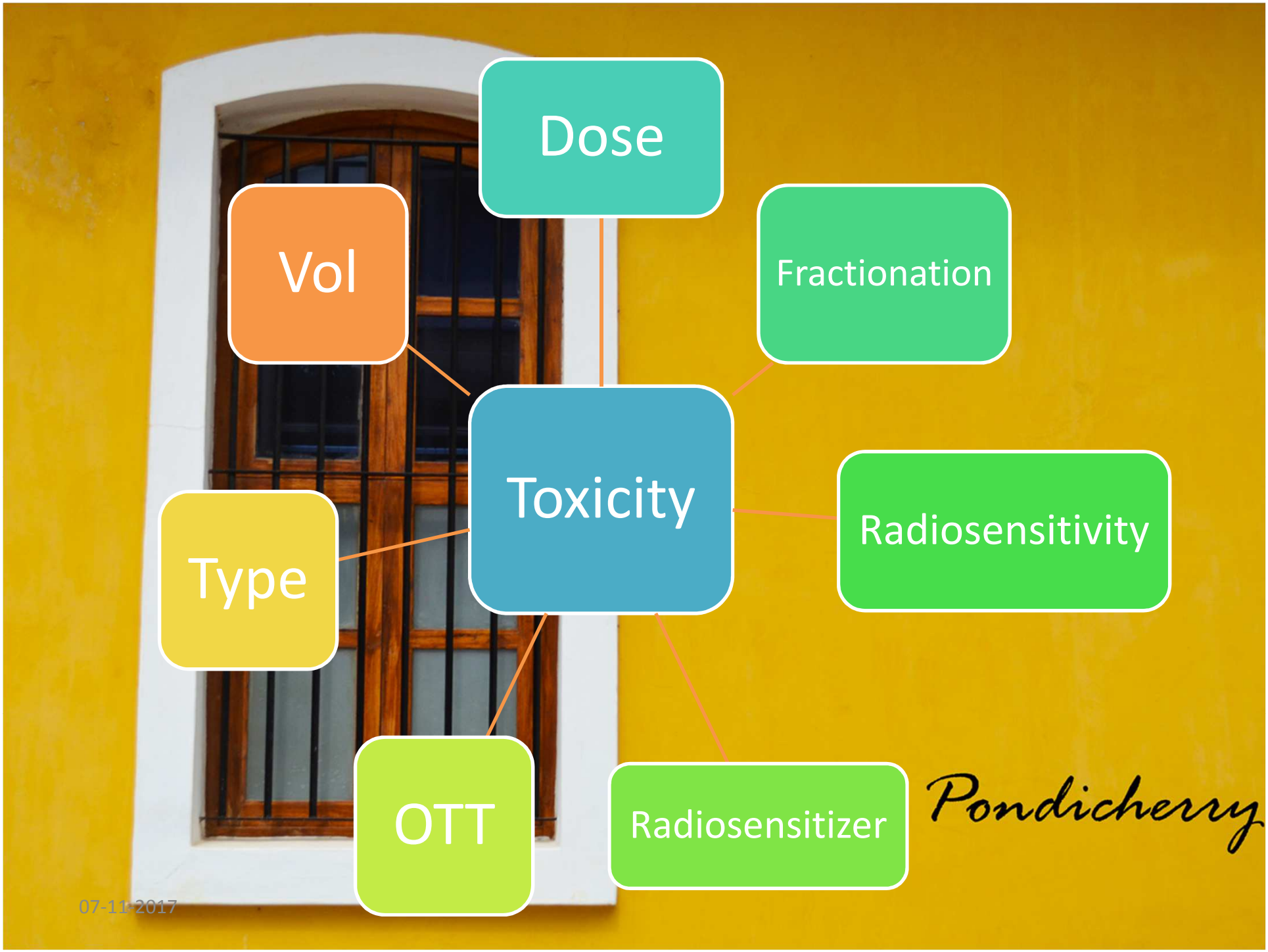
Dose
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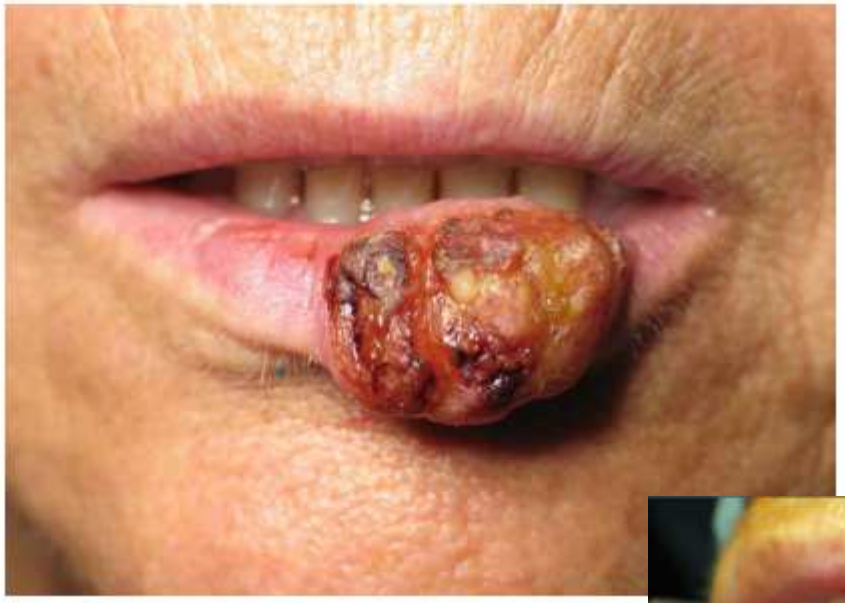
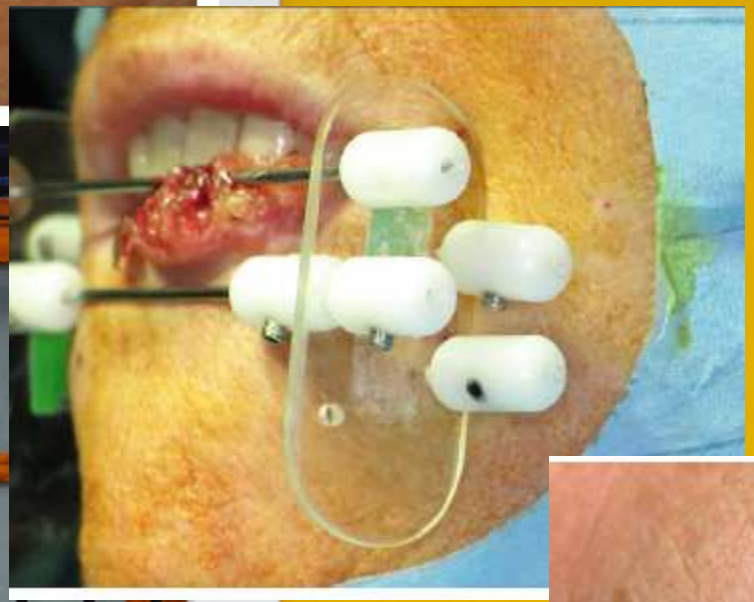
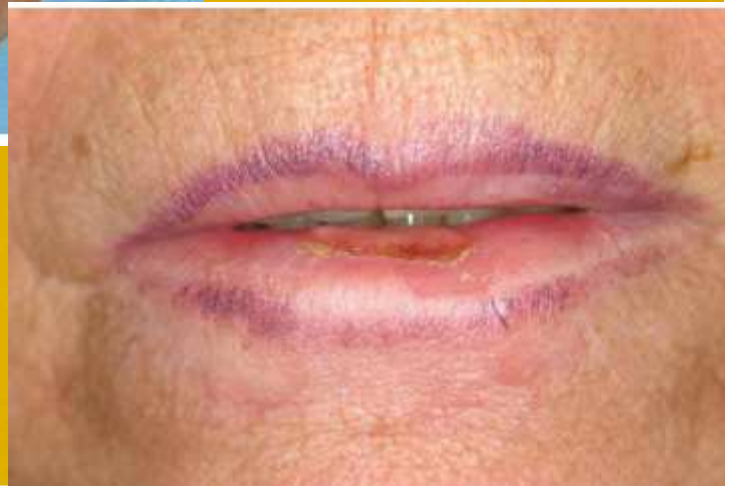


Lip lesion 2.5 cm
No palpable neck node



5 yr control rate 90-95%



Lartigeau 2013

Primary Brachytherapy

- Lips
- Oral cavity
- Nasopharynx
- Oropharynx

Original article

GEC-ESTRO ACROP recommendations for head & neck brachytherapy in squamous cell carcinomas: 1st update – Improvement by cross sectional imaging based treatment planning and stepping source technology

György Kovács [a,*,1], Rafael Martinez-Monge [b,1], Ashwini Budrukkar [c,1], Jose Luis Guinot [d,1], Bengt Johansson [e,1], Vratislav Strnad [f,1], Janusz Skowronek [g,h,1], Angeles Rovirosa [i,1], Frank-André Siebert [j,1], on behalf of the GEC-ESTRO Head & Neck Working Group

Radiotherapy Oncology, 2016

Head and neck brachytherapy

	# pts	Technique	Local control
Decroix	602	BT +/-EBI+/-Surg	76%
Haie	269	**BT**	87%
		EBI + BT	49%
Mazeron	121	**BT** 55-60 Gy	73%
		BT 65-75 Gy	92%
Wendt	103	**BT**	65%
		BT+ EBI <40 Gy	92%
		BT+ EBI >40 Gy	69%
		EBI	28%
Hareyama	130	BT	86%
		EBI + BT	
Shibuya	370	**BT**	75%
		BT + EBI	48%
Lefebvre	283	**BT**	83%
Pernot	448	BT	
		EBI + BT	68%
Matsura	173	**BT**	84 - 95%
		EBI + BT	74 - 80%
2500 Patients			65-95%

Lartigeau1.png

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Predictive Value of Tumor Thickness for Cervical Lymph-Node Involvement in Squamous Cell Carcinoma of the Oral Cavity

A Meta-analysis of Reported Studies

Shao Hui Huang, MSc[1,2], David Hwang, MB[2], Gina Lockwood, MMath[3], David P. Goldstein, MD[4,5], and Brian O'Sullivan, MD[2,4]

TT Cutoff Point	No. of Studies	No. of Observations at Lower Range of TT Cutoff Point	No. of $P_{LN}D$	NPV	FN-$P_{LN}D$ (1-NPV)	FN-$P_{LN}D$ L 95%	FN-$P_{LN}D$ U 95%
3 mm	4	113	6	94.7	5.3	1.9	14.0
4 mm	9	354	16	95.5	4.5	2.5	8.2
5 mm	6	181	30	83.4	16.6†	9.8	26.6
6 mm	4	362	47	87.0	13	3.7	36.4

NPV indicates negative predictive value; $P_{LN}D$, positive lymph node declaration.

*FN-$P_{LN}D$, percentage of patients with $P_{LN}D$ who fall below the TT cutpoint; FN-$P_{LN}D$ L 95% and FN-$P_{LN}D$ U 95%, lower and upper limit of 95% confidence interval for FN-$P_{LN}D$ respectively. FN-$P_{LN}D$ represents the percentage of patients with lymph node metastasis at the given TT cutoff. There was a significant trend for FN-$P_{LN}D$ as the TT cutoff point increased (test for trend, $P = .03$).

† When the TT cutoff point migrates from 4 mm to 5 mm, the rate of $P_{LN}D$ increased from 4.5% to 16.6% ($P = .007$).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer

Anil K. D'Cruz, M.S., D.N.B., Richa Vaish, M.S., Neeti Kapre, M.S., D.N.B., Mitali Dandekar, M.S., D.N.B., Sudeep Gupta, M.D., D.M., Rohini Hawaldar, B.Sc., D.C.M., Jai Prakash Agarwal, M.D., Gouri Pantvaidya, M.S., D.N.B., Devendra Chaukar, M.S., D.N.B., Anuja Deshmukh, M.S., D.L.O., D.O.R.L., Shubhada Kane, M.D., Supreeta Arya, M.D., D.N.B., D.M.R.D., Sarbani Ghosh-Laskar, M.D., D.N.B., Pankaj Chaturvedi, M.S., F.A.I.S., Prathamesh Pai, M.S., D.N.B., D.O.R.L., Sudhir Nair, M.S., M.Ch., Deepa Nair, M.S., D.N.B., D.O.R.L., and Rajendra Badwe, M.S., for the Head and Neck Disease Management Group

ABSTRACT

BACKGROUND

Whether patients with early-stage oral cancers should be treated with elective neck dissection at the time of the primary surgery or with therapeutic neck dissection after nodal relapse has been a matter of debate.

METHODS

In this prospective, randomized, controlled trial, we evaluated the effect on survival of elective node dissection (ipsilateral neck dissection at the time of the primary surgery) versus therapeutic node dissection (watchful waiting followed by neck dissection for nodal relapse) in patients with lateralized stage T1 or T2 oral squamous-cell carcinomas. Primary and secondary end points were overall survival and disease-free survival, respectively.

RESULTS

Between 2004 and 2014, a total of 596 patients were enrolled. As prespecified by the data and safety monitoring committee, this report summarizes results for the first 500 patients (245 in the elective-surgery group and 255 in the therapeutic-surgery group), with a median follow-up of 39 months. There were 81 recurrences and 50 deaths in the elective-surgery group and 146 recurrences and 79 deaths in the therapeutic-surgery group. At 3 years, elective node dissection resulted in an improved rate of overall survival (80.0%; 95% confidence interval [CI], 74.1 to 85.8), as compared with therapeutic dissection (67.5%; 95% CI, 61.0 to 73.9), for a hazard ratio for death of 0.64 in the elective-surgery group (95% CI, 0.45 to 0.92; P=0.01 by the log-rank test). At that time, patients in the elective-surgery group also had a higher rate of disease-free survival than those in the therapeutic-surgery group (69.5% vs. 45.9%, P<0.001). Elective node dissection was superior in most subgroups without significant interactions. Rates of adverse events were 6.6% and 3.6% in the elective-surgery group and the therapeutic-surgery group, respectively.

CONCLUSIONS

Among patients with early-stage oral squamous-cell cancer, elective neck dissection resulted in higher rates of overall and disease-free survival than did therapeutic neck dissection. (Funded by the Tata Memorial Centre; ClinicalTrials.gov number, NCT00193765.)

The authors' affiliations are as follows: Head Neck Services (A.K.D., R.V., N.K., M.D., G.P., D.C., A.D., P.C., P.P., S.N., D.N.), Department of Medical Oncology, Advanced Center for Treatment, Research and Education in Cancer (S.G.), Clinical Research Secretariat (R.H.), and the Departments of Radiation Oncology (J.P.A., S.G.-L.), Head Cytology (S.K.), Radio-diagnosis (S.A.), and Surgical Oncology (R.B.) — all at the Tata Memorial Centre, Mumbai, India. Address reprint requests to Dr. D'Cruz at the Tata Memorial Centre, Head and Neck Services, Parel, Mumbai, India 400012, or at docdcruz@gmail.com.

A complete list of members of the Head and Neck Disease Management Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 31, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1506007

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer

associated with node positivity. A marked increase in cumulative lymph-node positivity was observed with increasing depth of invasion from 3 mm (5.6%) to 4 mm (16.9%).

treated to prevent one relapse. A higher percentage of patients in the elective-surgery group received adjuvant radiotherapy on the basis of nodal indications, and the contribution of this factor to the improved rate of overall survival cannot be excluded. However, our trial was not designed to answer this question.

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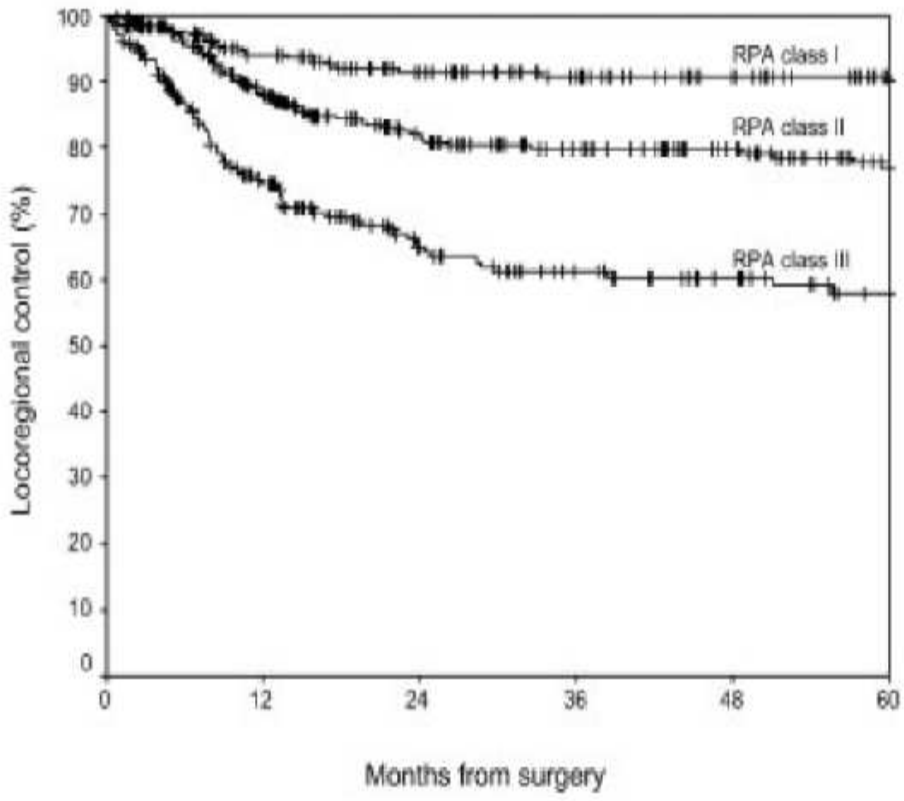
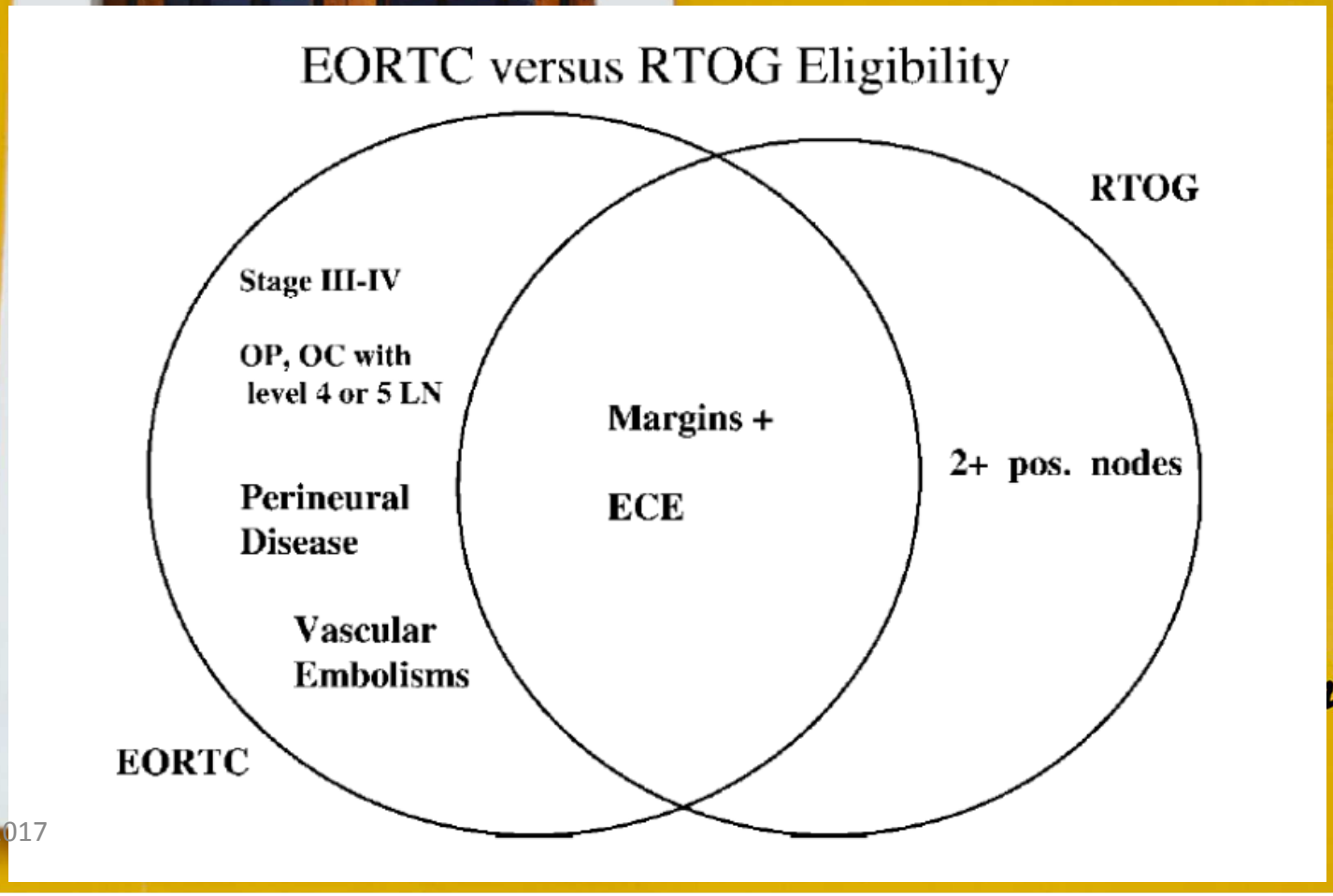
Post op RT (RPA class)

RPA class	Definition(s)
Class I (intermediate risk)	Free surgical margins and no extranodal spread
Class II (high risk)	T1, T2, and T4 tumors with close or positive surgical margins One lymph node metastasis with extranodal spread
Class III (very high risk)	T3 tumors with close or positive surgical margins Multiple lymph node metastases with extranodal spread N3 neck



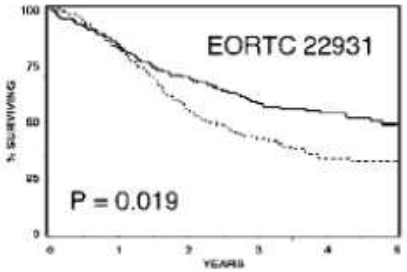
DEFINING RISK LEVELS IN LOCALLY ADVANCED HEAD AND NECK CANCERS: A COMPARATIVE ANALYSIS OF CONCURRENT POSTOPERATIVE RADIATION PLUS CHEMOTHERAPY TRIALS OF THE EORTC (#22931) AND RTOG (#9501)

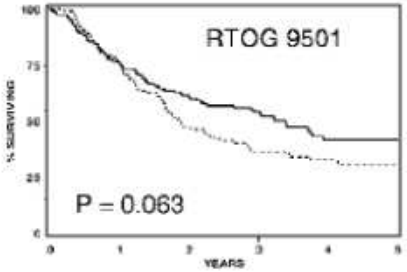
Jacques Bernier, MD, PhD,[1] Jay S. Cooper, MD,[2] T. F. Pajak, PhD,[3] M. van Glabbeke, Ir,[4] J. Bourhis, MD, PhD,[5] Arlene Forastiere, MD,[6] Esat Mahmut Ozsahin, MD, PhD,[7] John R. Jacobs, MD,[8] J. Jassem, MD,[9] Kie-Kian Ang, MD,[10] J. L. Lefèbvre, MD[11]



EORTC 22931+RTOG 9501

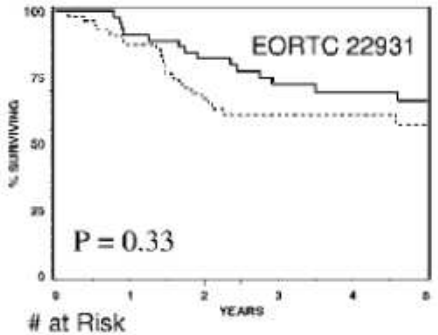
Overall Survival
Patients with positive margin and/or ECE

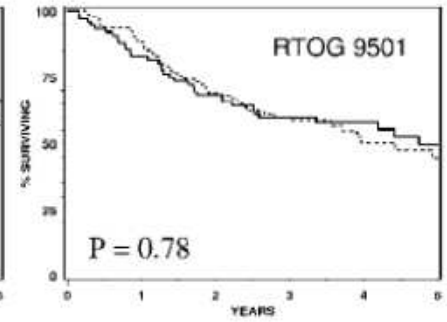




# at Risk						
Year	0	2	5	0	2	5
RCT ——	122	82	31	130	80	16
RT ---	111	59	16	116	55	11

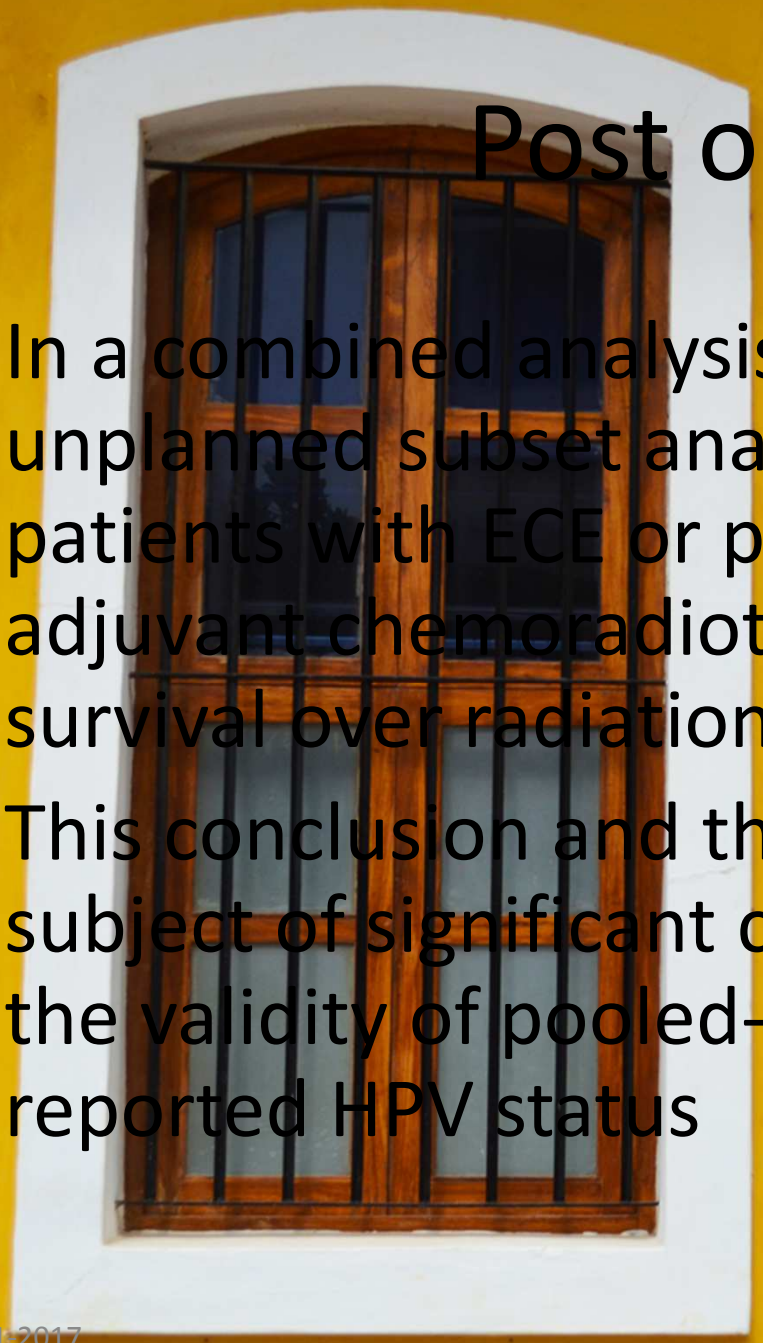
Overall Survival
Patients without positive margin and/or ECE





# at Risk						
Year	0	2	5	0	2	5
RCT ——	45	36	16	76	52	11
RT ---	56	34	15	94	65	14

Post op CTRT



- In a combined analysis of these two trials, an unplanned subset analysis found that for patients with ECE or positive margins, adjuvant chemoradiotherapy improved overall survival over radiation alone.
- This conclusion and these data have been the subject of significant controversy, including the validity of pooled-subsite analysis, lack of reported HPV status

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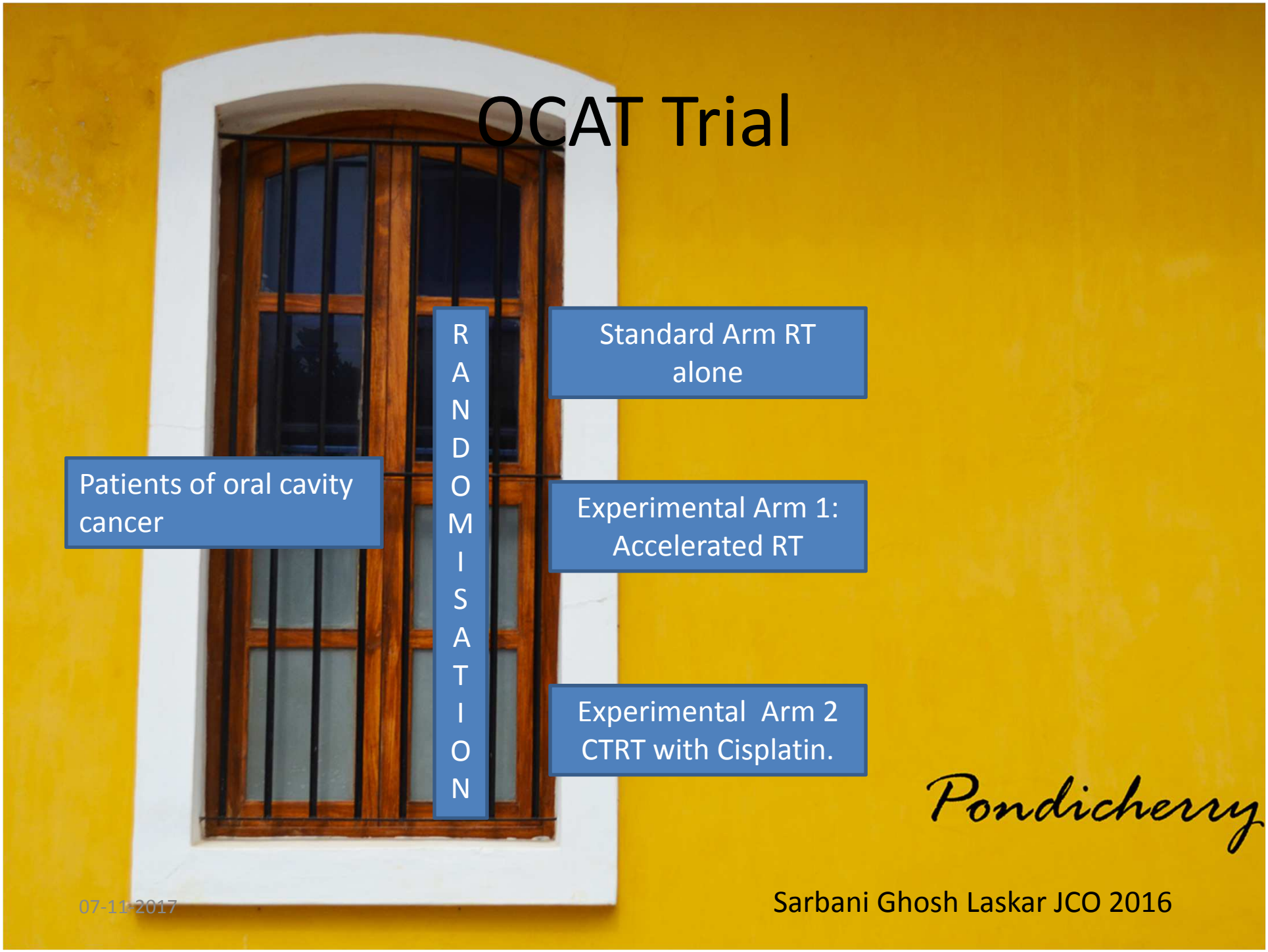
OCAT Trial

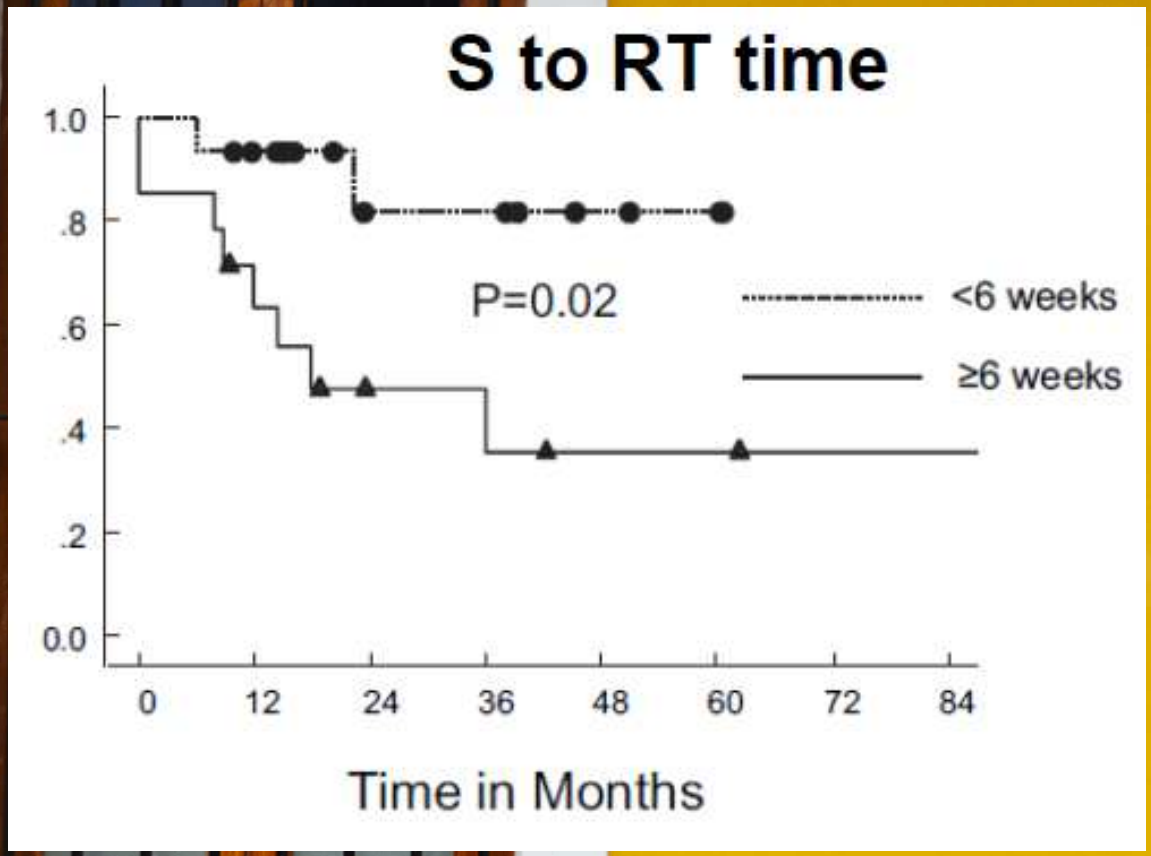


Sarbani Ghosh Laskar JCO 2016

Results OCAT

- The 5 year LRC comparable.
- Advanced T & N stage, tongue involvement, and ECE had poorer outcomes but with no significant difference in LRC or OS between the three arms even with these high risk features.
- Acute grade 3 or more (CTCAE Vr 3.0) skin and mucosal toxicity were comparable between arms.
- Intensification of adjuvant radiotherapy with concurrent chemotherapy or accelerated radiotherapy did not result in improved disease outcomes in resectable oral cavity cancers.

Time to radiotherapy after surgery



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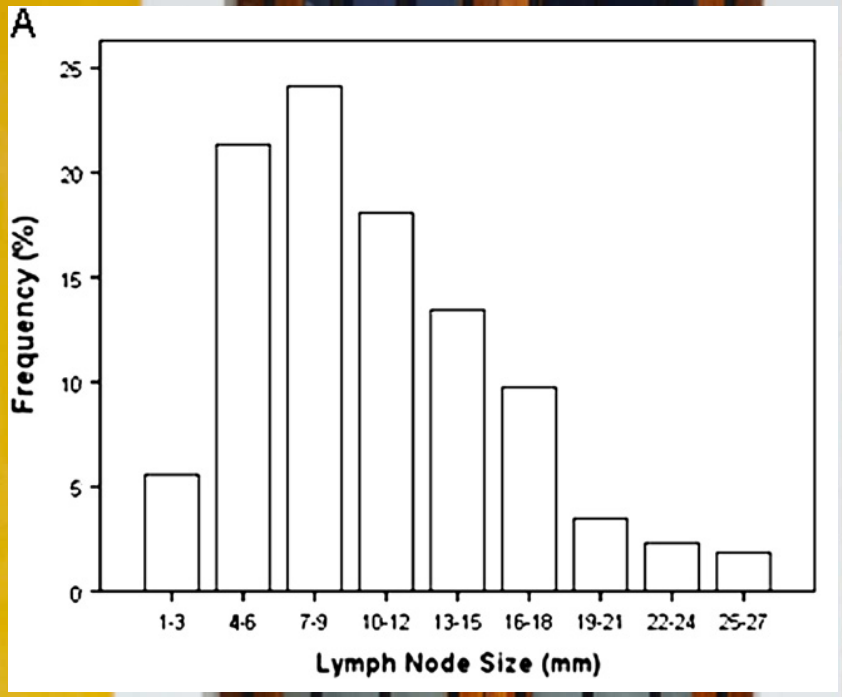
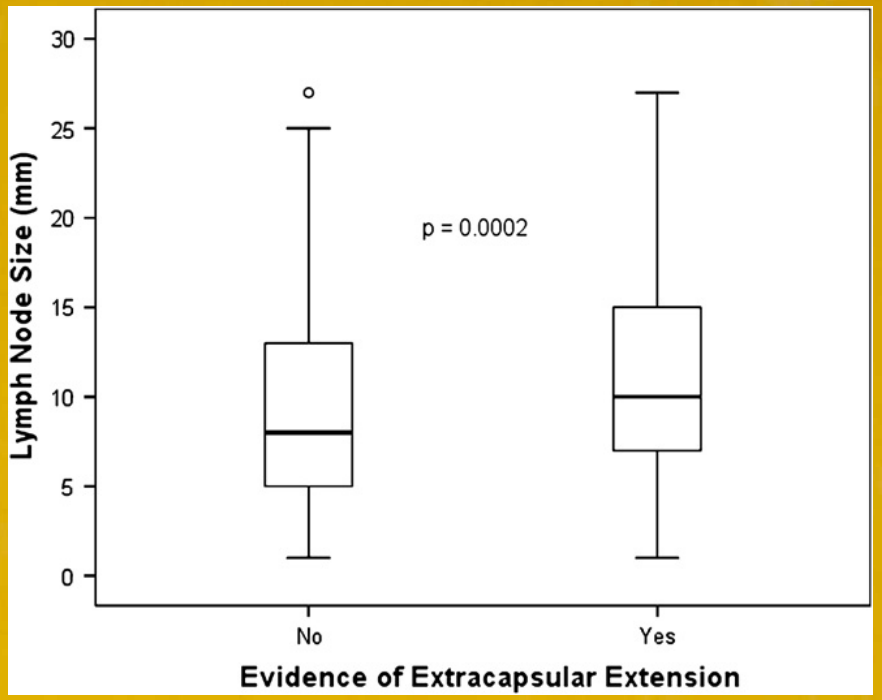
Daly IJROBP 2011

ECE and nodal size





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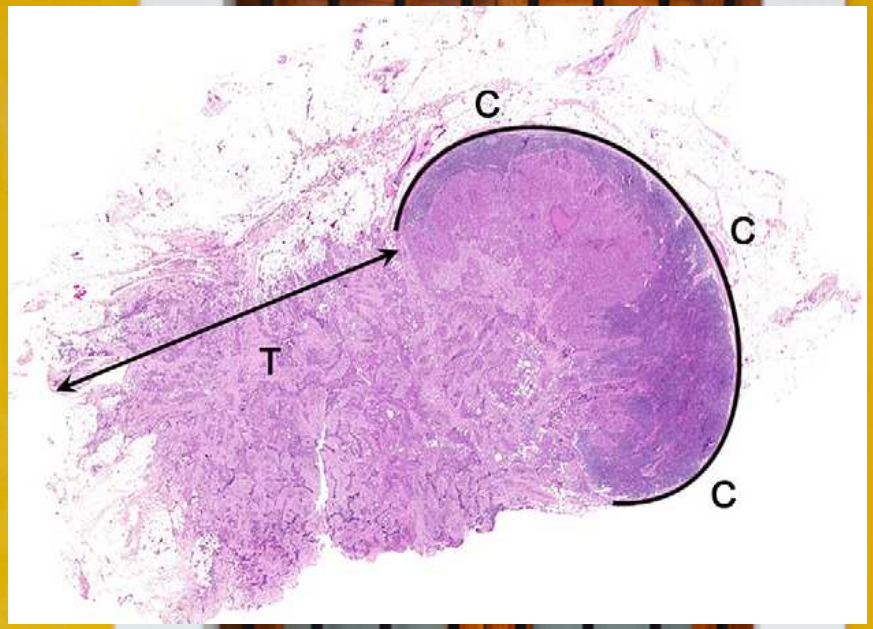
PIRUS GHADJAR IJROBP 2010

Extent of ECE



- The mean and median extent values of ECE were 1.8 and 1 mm
- ECE 5 mm in 97% and 3 mm in 91% of the 231 LN analyzed.
- The largest percentage of LN had an ECE of 1 mm (58%)
- In 17 (17%) patients, infiltration of the adjacent
- muscular fascia was observed, with mean and median extension values of 2.8 and 2.0 mm, respectively (range, 1–9 mm).

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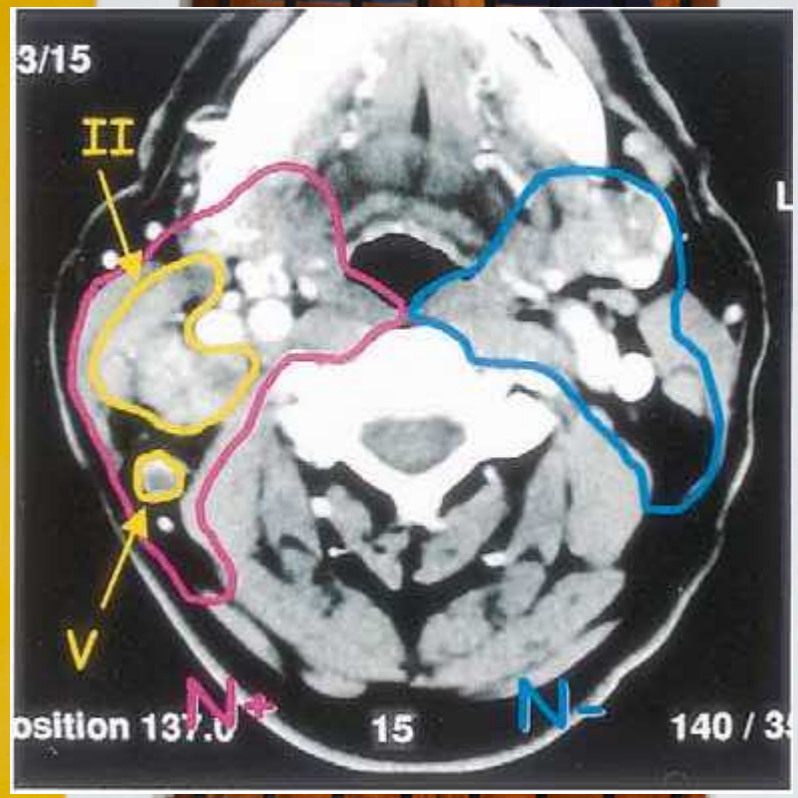
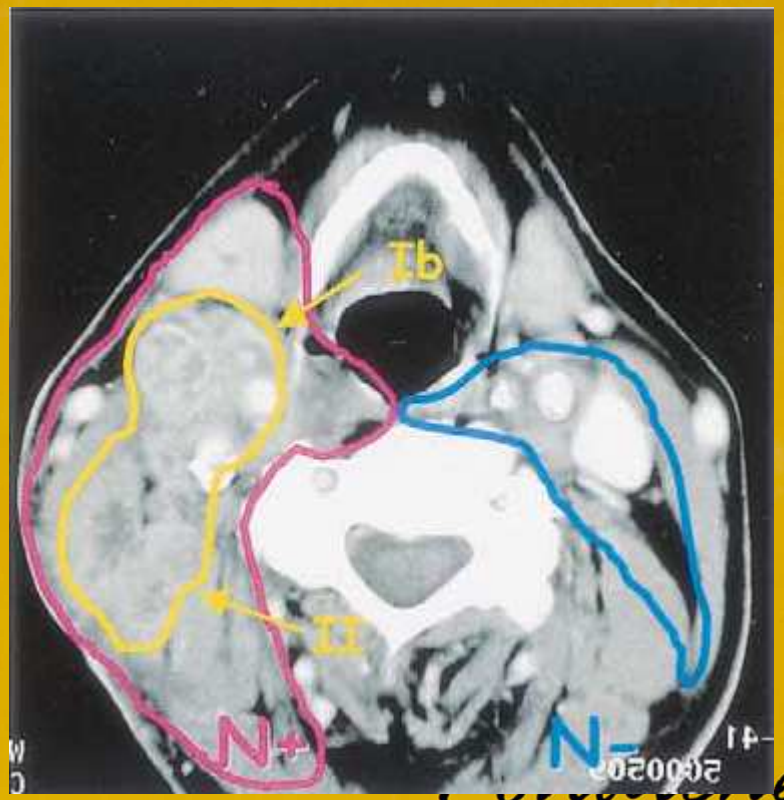
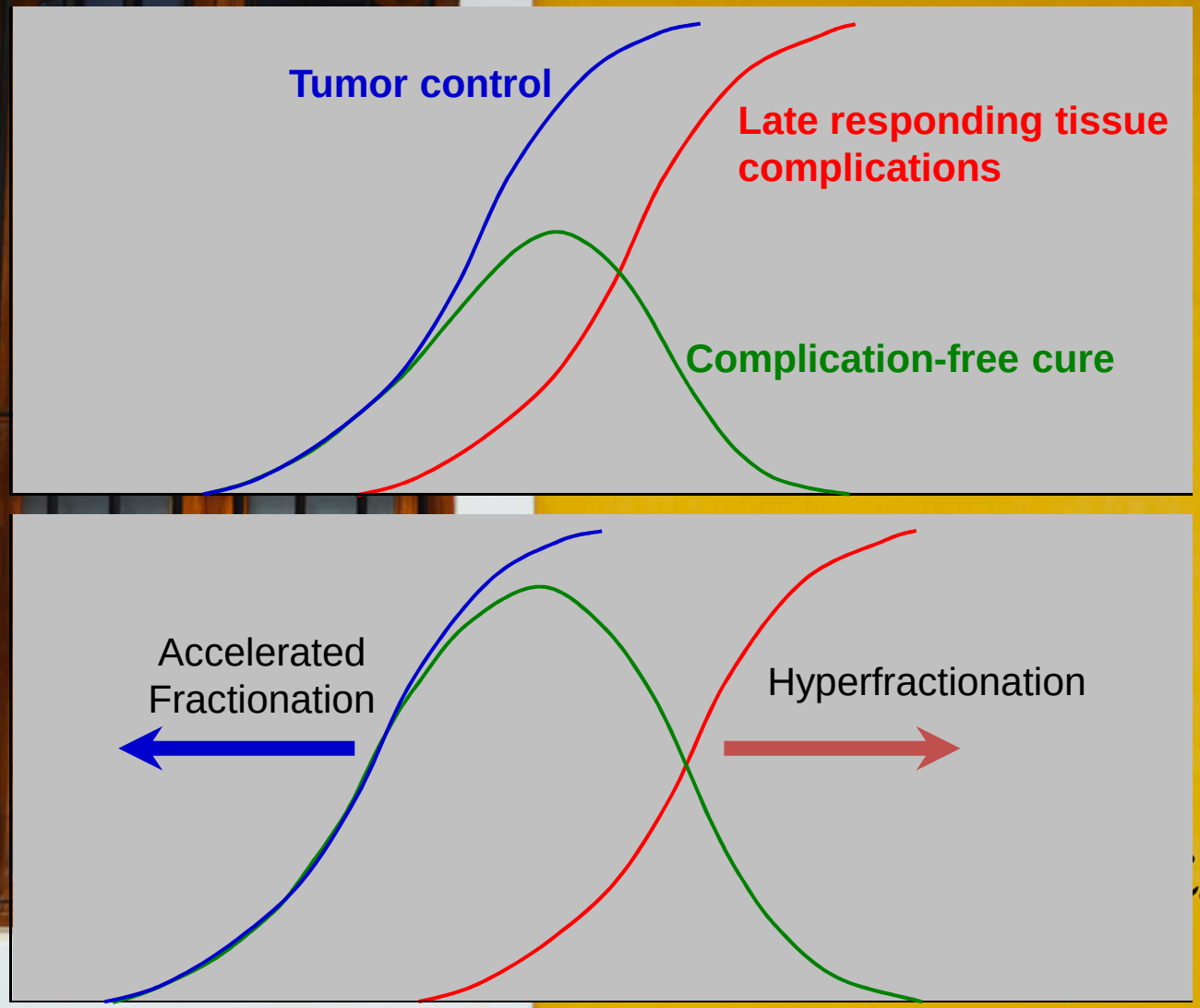
PIRUS GHADJAR IJROBP 2010

CTV in presence of ECE





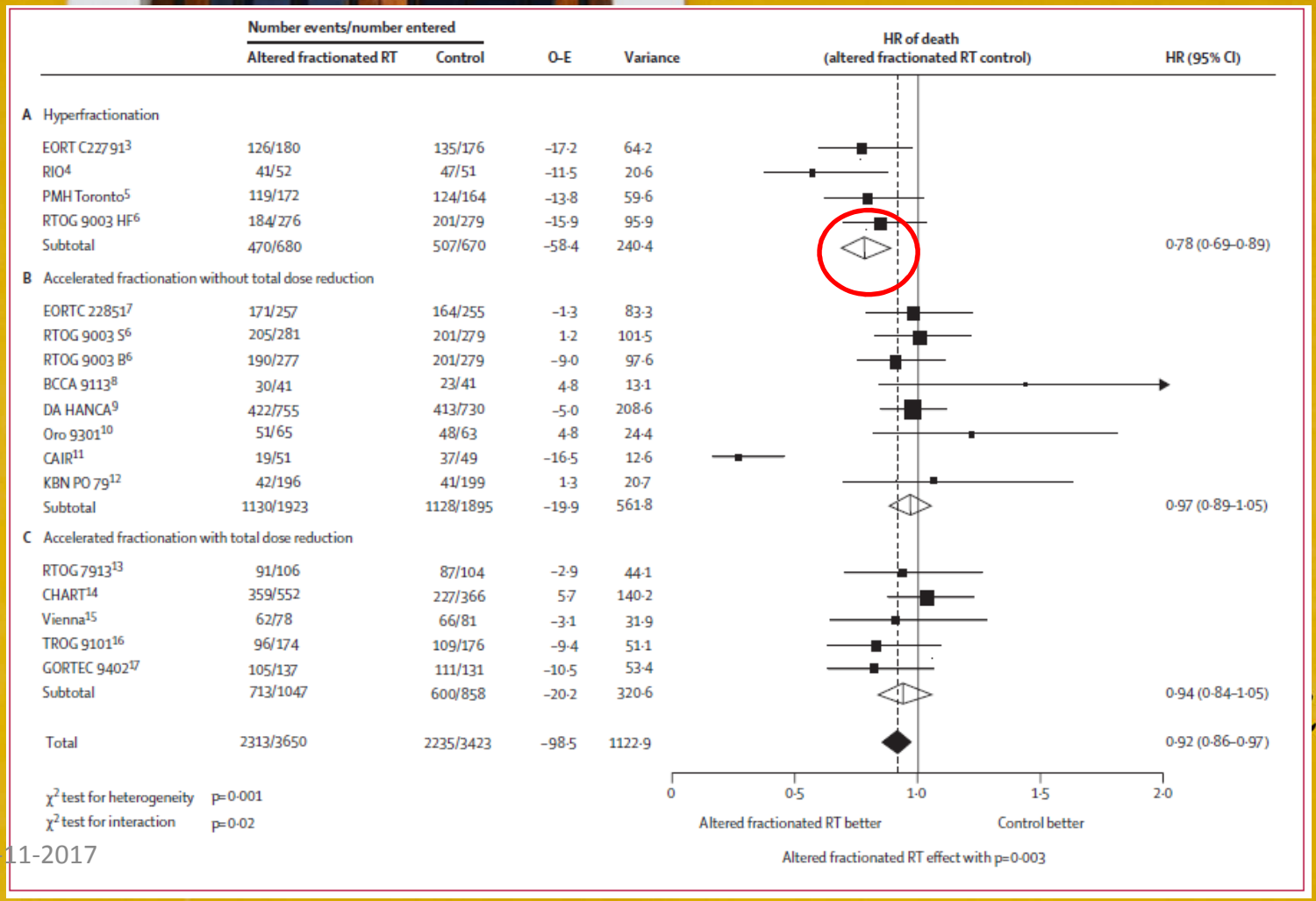
Altered fractionation



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



	Number events/number entered: Altered fractionated RT	Control	O-E	Variance	HR (95% CI)
A Hyperfractionation					
EORT C22791[3]	126/180	135/176	−17·2	64·2	
RIO[4]	41/52	47/51	−11·5	20·6	
PMH Toronto[5]	119/172	124/164	−13·8	59·6	
RTOG 9003 HF[6]	184/276	201/279	−15·9	95·9	
Subtotal	470/680	507/670	−58·4	240·4	0·78 (0·69–0·89)
B Accelerated fractionation without total dose reduction					
EORTC 22851[7]	171/257	164/255	−1·3	83·3	
RTOG 9003 S[6]	205/281	201/279	1·2	101·5	
RTOG 9003 B[6]	190/277	201/279	−9·0	97·6	
BCCA 9113[8]	30/41	23/41	4·8	13·1	
DA HANCA[9]	422/755	413/730	−5·0	208·6	
Oro 9301[10]	51/65	48/63	4·8	24·4	
CAIR[11]	19/51	37/49	−16·5	12·6	
KBN PO 79[12]	42/196	41/199	1·3	20·7	
Subtotal	1130/1923	1128/1895	−19·9	561·8	0·97 (0·89–1·05)
C Accelerated fractionation with total dose reduction					
RTOG 7913[13]	91/106	87/104	−2·9	44·1	
CHART[14]	359/552	227/366	5·7	140·2	
Vienna[15]	62/78	66/81	−3·1	31·9	
TROG 9101[16]	96/174	109/176	−9·4	51·1	
GORTEC 9402[17]	105/137	111/131	−10·5	53·4	
Subtotal	713/1047	600/858	−20·2	320·6	0·94 (0·84–1·05)
Total	2313/3650	2235/3423	−98·5	1122·9	0·92 (0·86–0·97)

HR of death (altered fractionated RT control)

0 0·5 1·0 1·5 2·0

Altered fractionated RT better — Control better

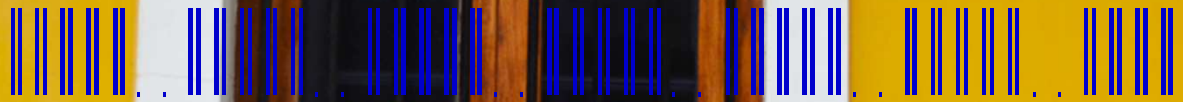
χ^2 test for heterogeneity p=0·001
χ^2 test for interaction p=0·02

Altered fractionated RT effect with p=0·003

RTOG 90-03, Phase III comparison of fractionation schedules in Stage III and IV SCC of oral cavity, oropharynx, larynx, hypopharynx (N = 1113)

Conventional

70 Gy - 35 fx - 7 wks



Hyperfractionated

81.6 Gy - 68 fx - 7 wks

Accelerated with split

67.2 Gy - 42 fx - 6 weeks (including 2-week split)

Accelerated with concomitant boost

72 Gy - 42 fx - 6 wks

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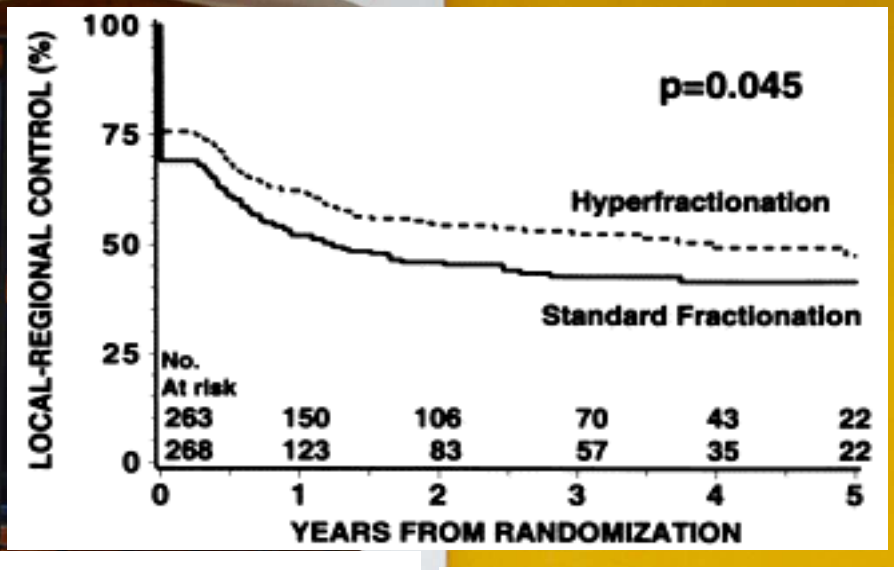
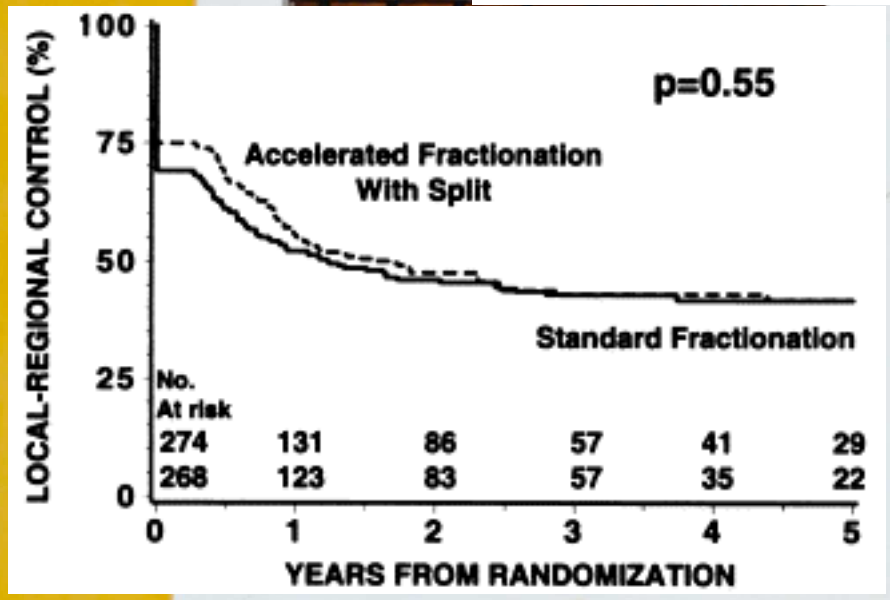
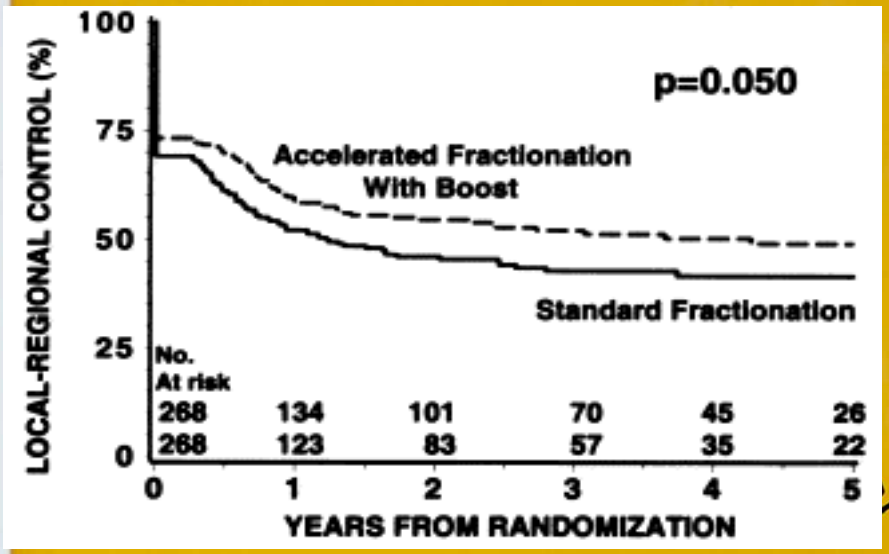
Int J Radiation Oncol Biol Phys, Vol. 89, No. 1, pp. 13–20, 2014

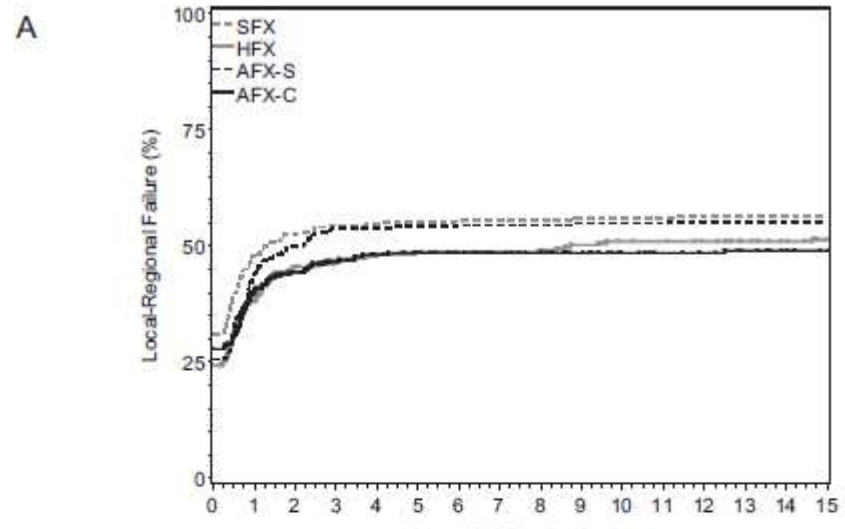
RTOG 90-03, loco-regional control

Fu 2000



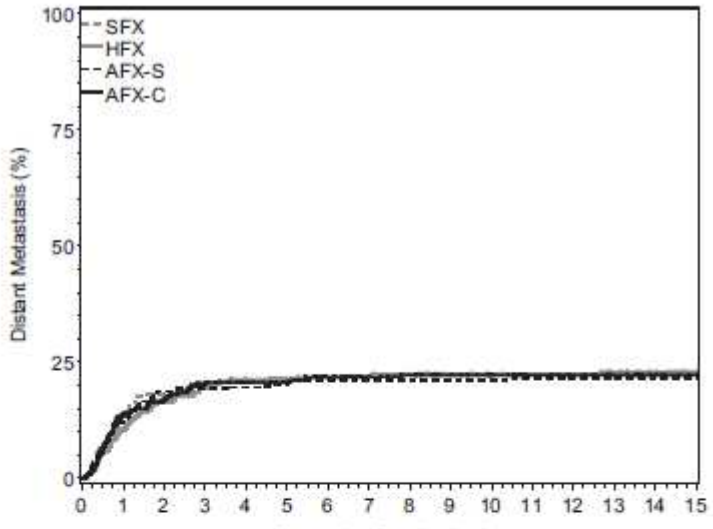






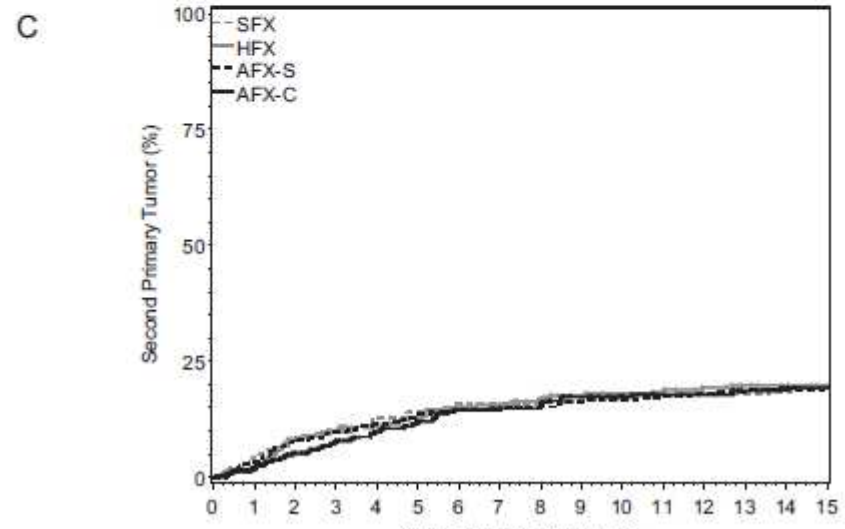
Patients at Risk

SFX	269	123	94	78	66	58	49	43	39	34	31	27	21	18	17	13
HFX	263	148	113	99	86	80	67	57	51	41	36	35	32	25	20	15
AFX-S	275	133	100	81	73	70	64	56	54	49	45	39	33	25	24	17
AFX-C	269	133	108	91	80	74	66	59	55	46	35	30	27	22	18	14



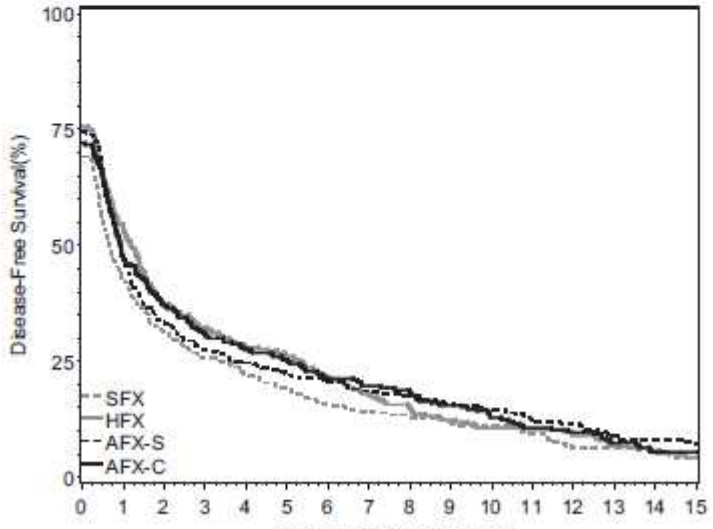
Patients at Risk

SFX	269	165	114	96	81	75	64	55	51	46	41	35	29	26	23	18
HFX	263	172	134	111	97	91	78	65	59	50	42	41	37	29	24	18
AFX-S	275	169	119	100	87	77	68	59	57	53	48	42	37	27	26	18
AFX-C	269	163	122	102	93	85	72	62	58	50	41	34	30	26	20	15



Patients at Risk

SFX	269	173	111	94	74	67	53	47	42	38	34	28	21	20	17	10
HFX	263	176	126	104	88	79	64	51	45	37	33	32	27	20	17	14
AFX-S	275	177	116	89	77	68	60	52	48	43	39	32	29	23	21	16
AFX-C	269	176	122	98	86	74	62	55	51	41	32	26	24	19	12	9

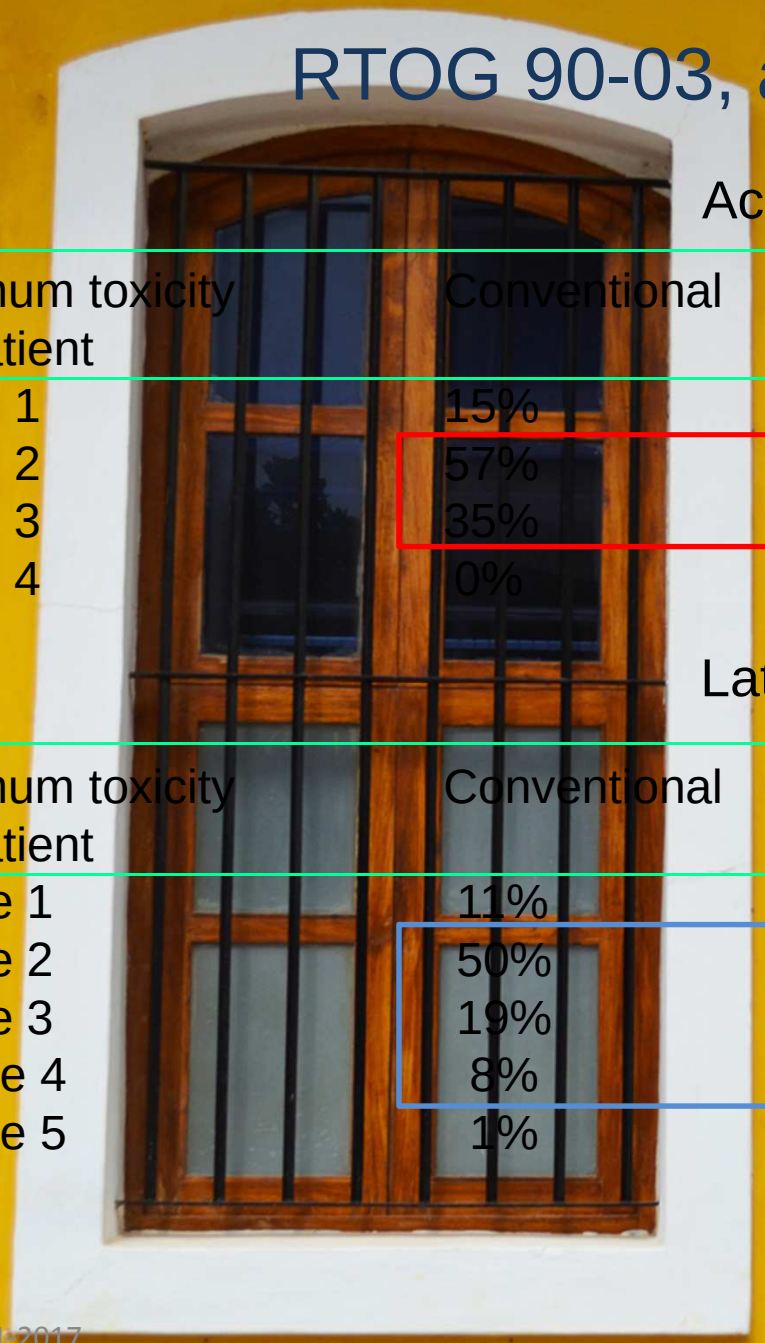


Patients at Risk

SFX	269	114	82	68	59	51	40	35	31	27	25	21	14	13	12	7
HFX	263	138	96	83	72	66	53	44	38	30	26	25	22	16	13	10
AFX-S	275	127	91	75	67	61	55	49	46	40	37	30	27	21	19	15
AFX-C	269	124	98	81	72	64	53	49	45	36	29	24	22	16	11	8

RTOG 90-03, adverse effects

Fu 2000



Acute

Maximum toxicity per patient	Conventional	Hyperfract	Concom Acc + boost	split
Grade 1	15%	4%	4%	7%
Grade 2	57%	39%	36%	41%
Grade 3	35%	54%	58%	49%
Grade 4	0%	1%	1%	2%

Late

Maximum toxicity per patient	Conventional	Hyperfract	Concom Acc + boost	split
Grade 1	11%	8%	7%	16%
Grade 2	50%	56%	44%	50%
Grade 3	19%	19%	29%	20%
Grade 4	8%	9%	8%	7%
Grade 5	1%	0%	1%	1%

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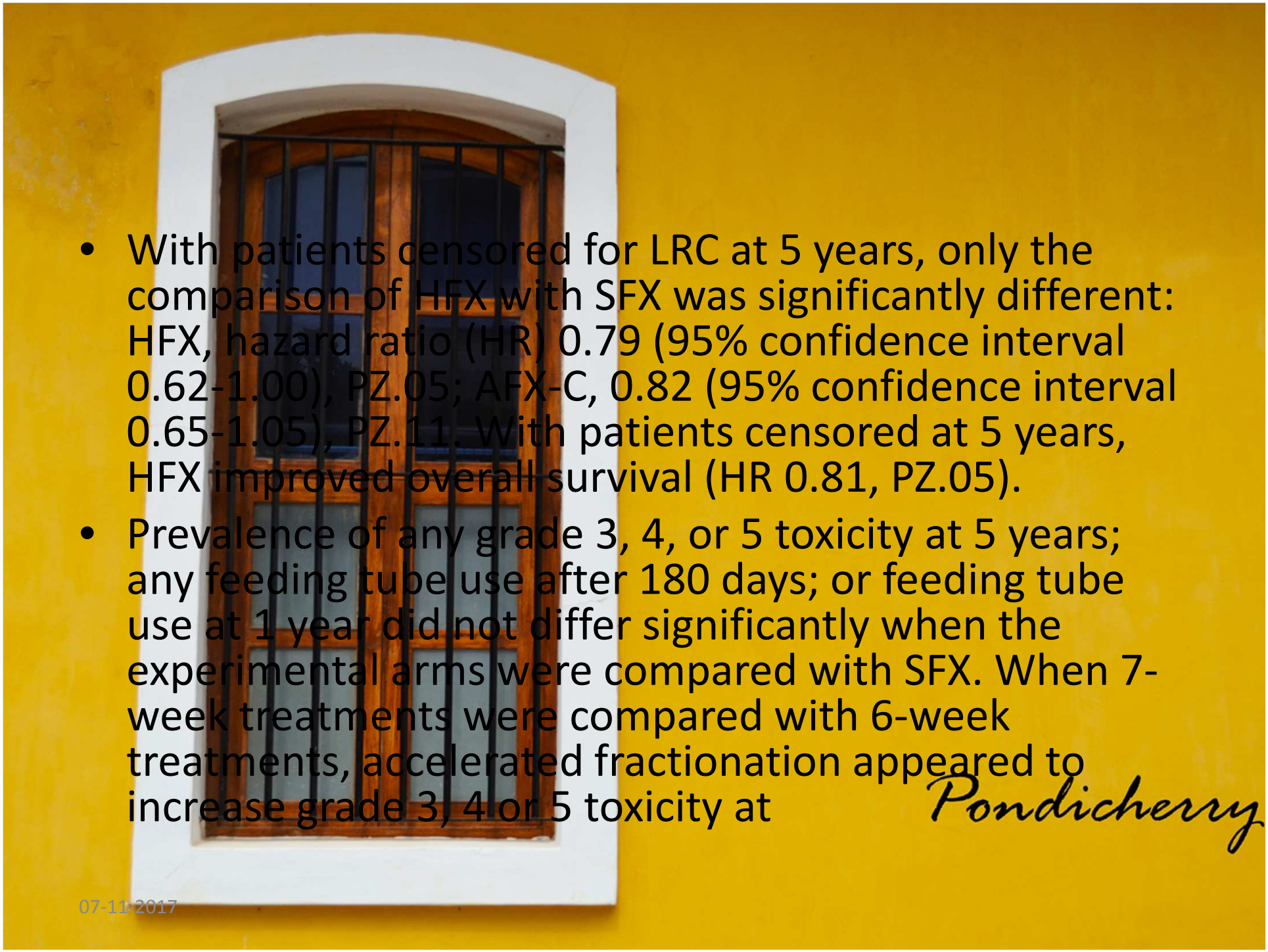
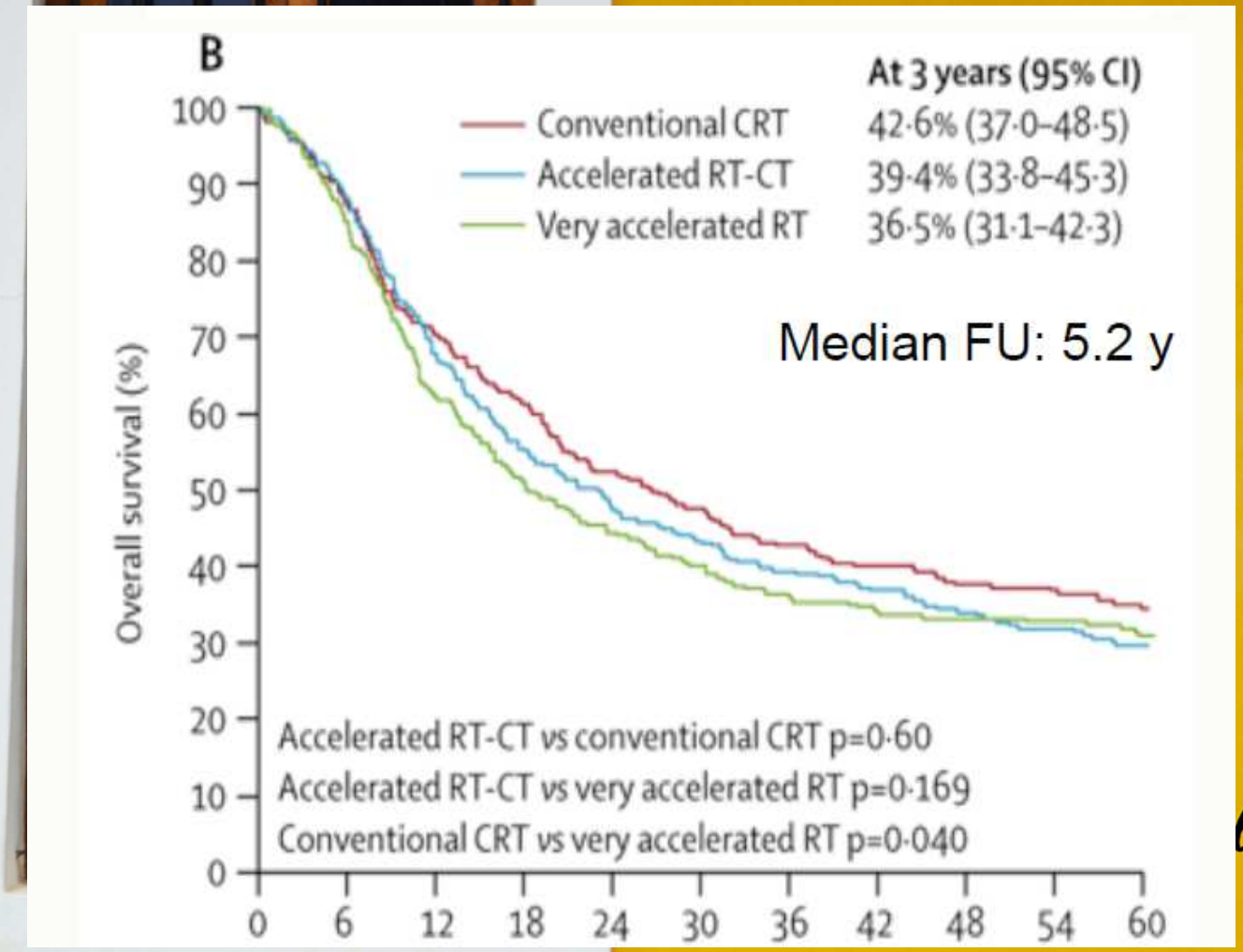


- With patients censored for LRC at 5 years, only the comparison of HFX with SFX was significantly different: HFX, hazard ratio (HR) 0.79 (95% confidence interval 0.62-1.00), PZ.05; AFX-C, 0.82 (95% confidence interval 0.65-1.05), PZ.11. With patients censored at 5 years, HFX improved overall survival (HR 0.81, PZ.05).
- Prevalence of any grade 3, 4, or 5 toxicity at 5 years; any feeding tube use after 180 days; or feeding tube use at 1 year did not differ significantly when the experimental arms were compared with SFX. When 7-week treatments were compared with 6-week treatments, accelerated fractionation appeared to increase grade 3, 4 or 5 toxicity at

GORTEC 9902 OS

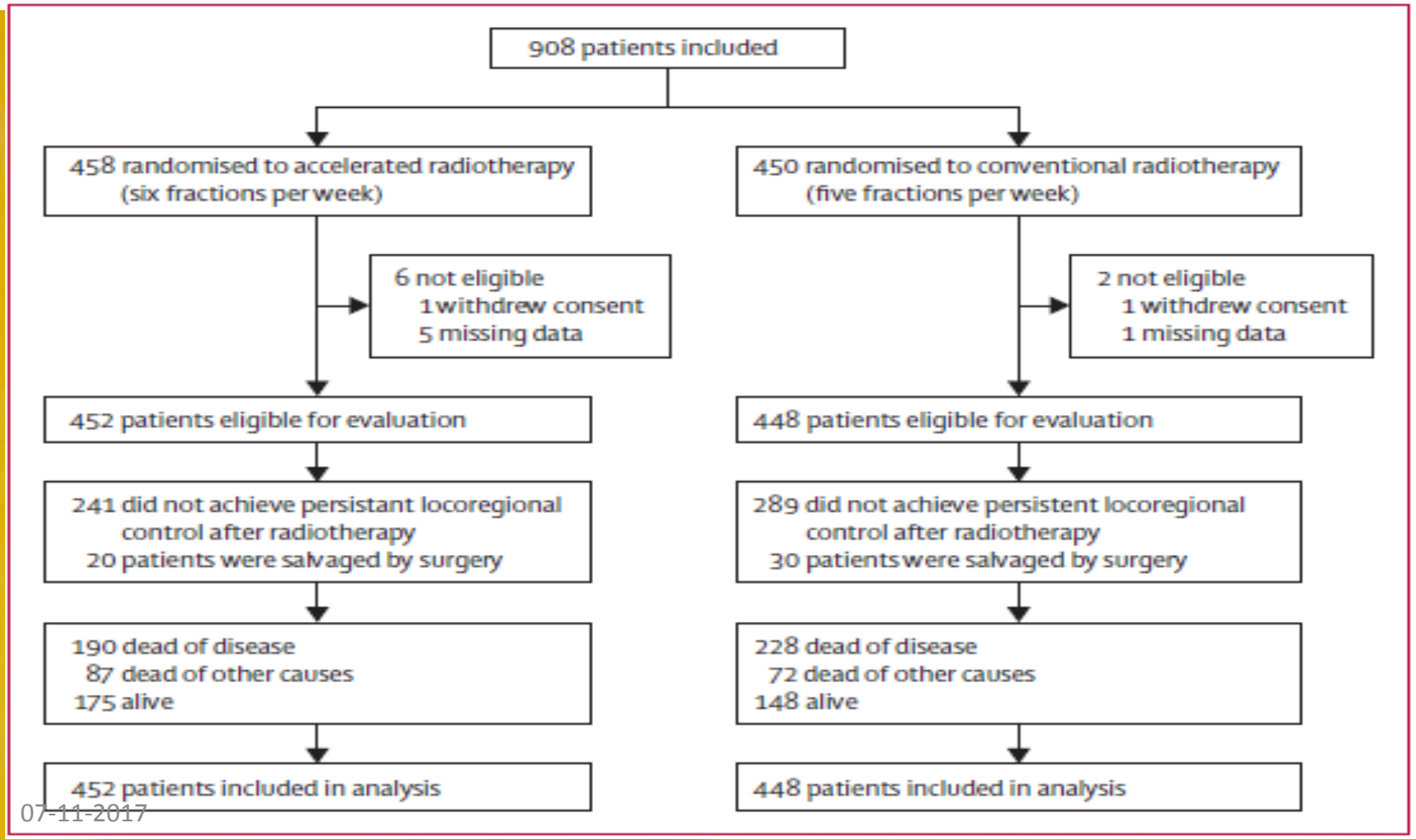


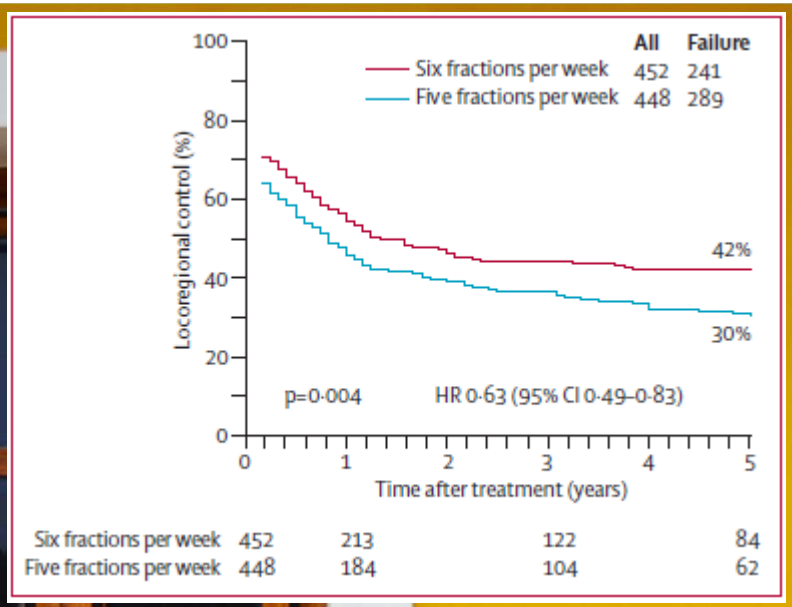
licherry

Bourhis Lancet Oncol 2012

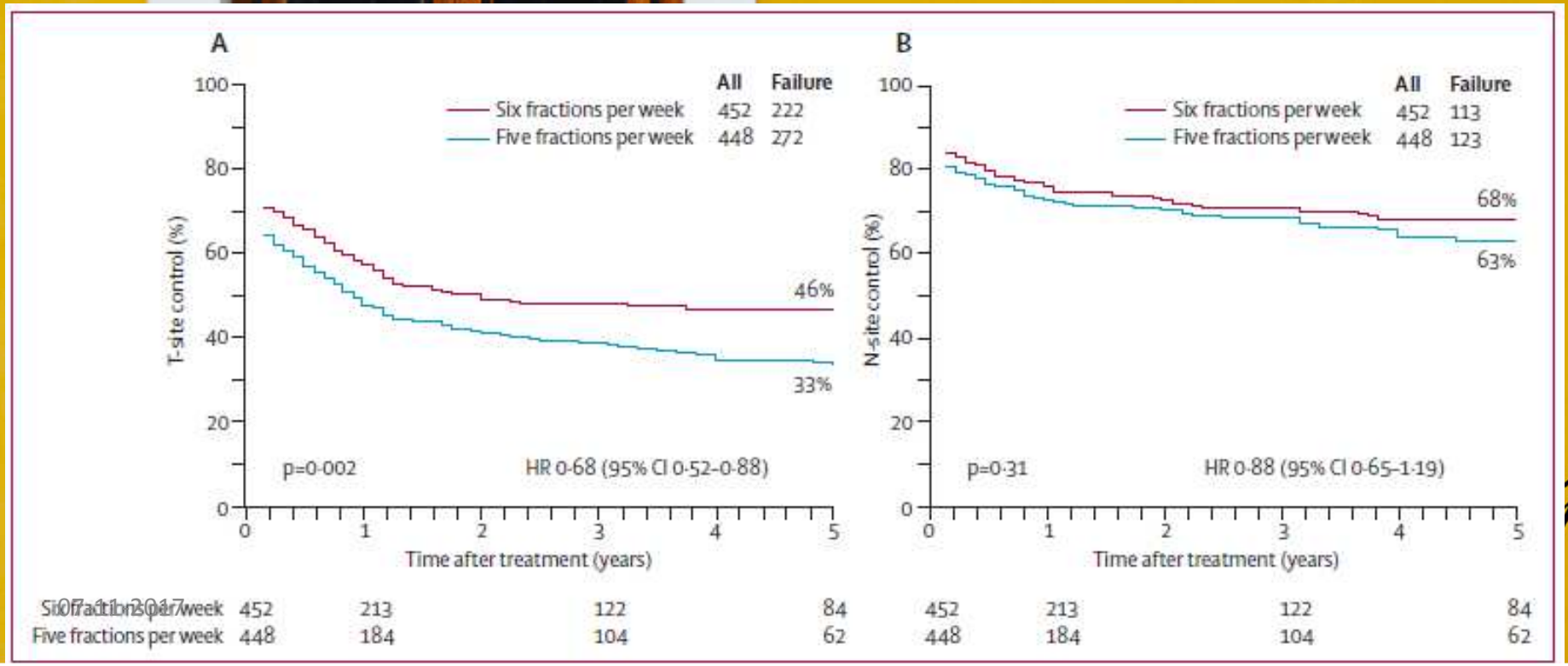
Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study): a randomised, multicentre trial

Jens Overgaard, Bidhu Kaylan Mohanti, Naseem Begum, Rubina Ali, Jai Prakash Agarwal, Maire Kuddu, Suman Bhasker, Hideo Tatsuzaki, Cai Grau

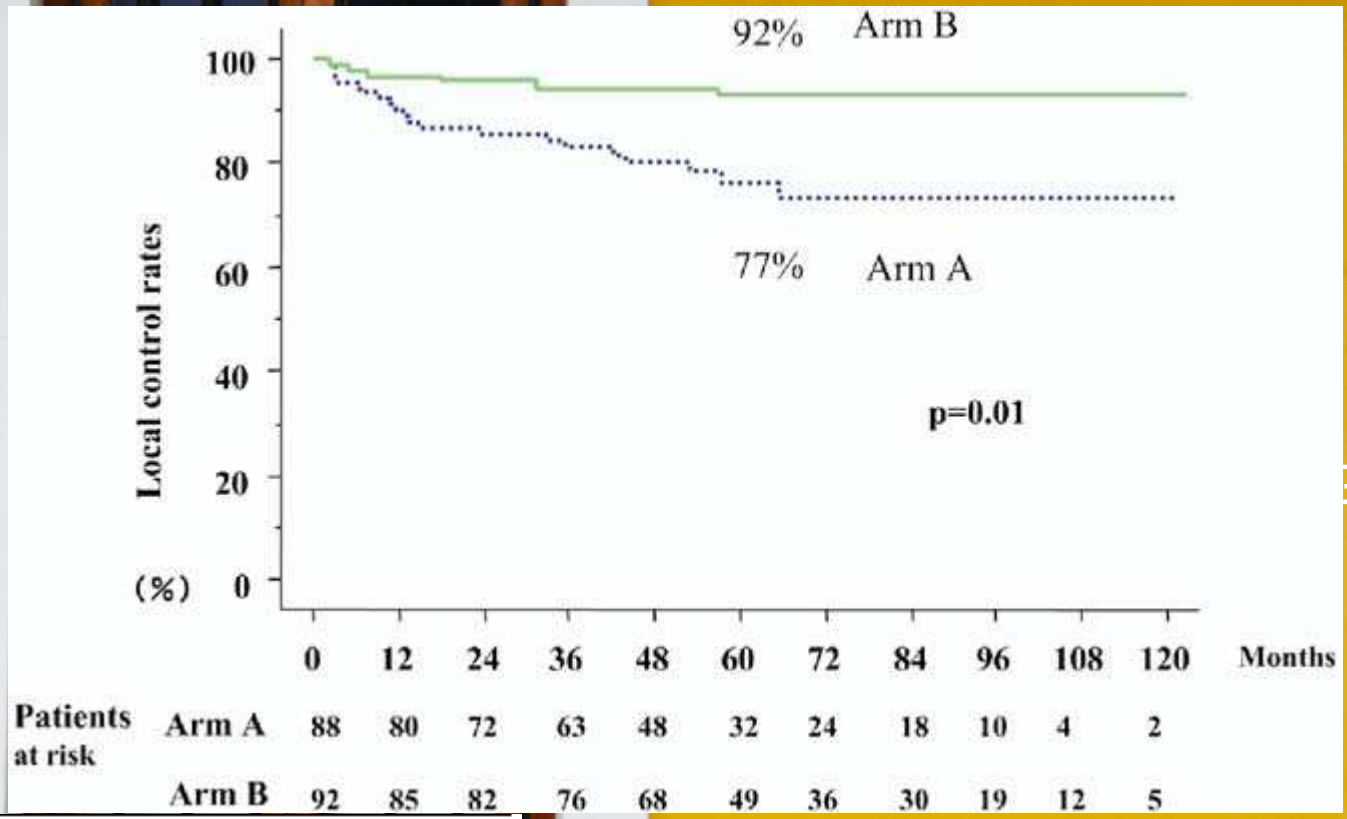




Locoregional control 5 days Vs 6 days schedule



Hypo-fractionation (RCT) in vocal cord



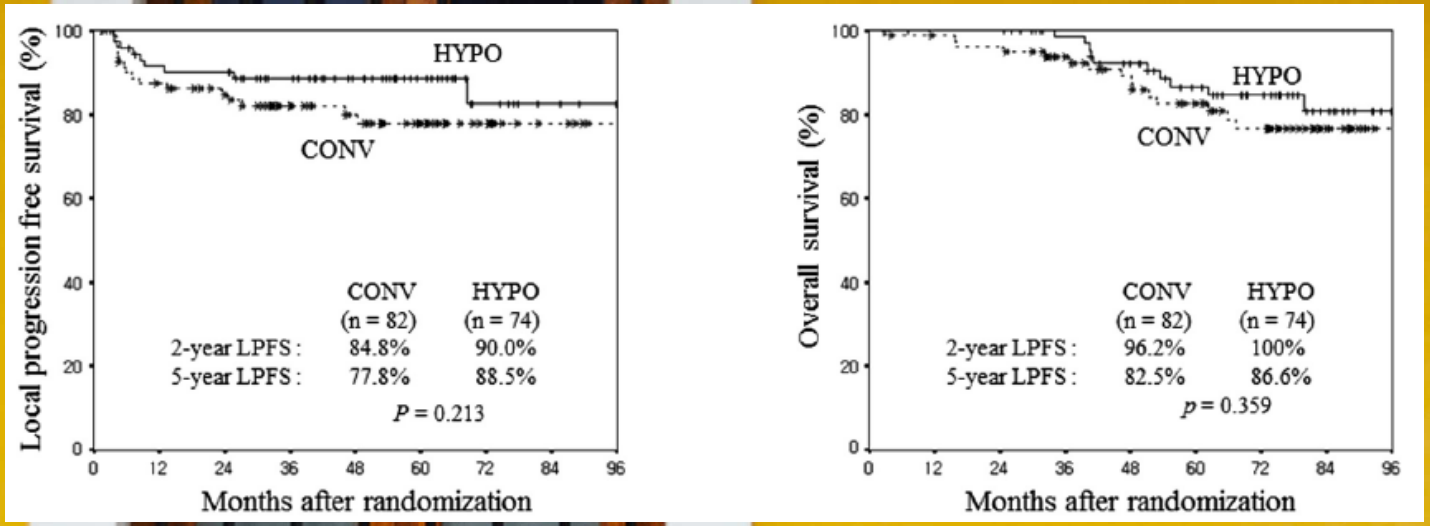
Gy/#

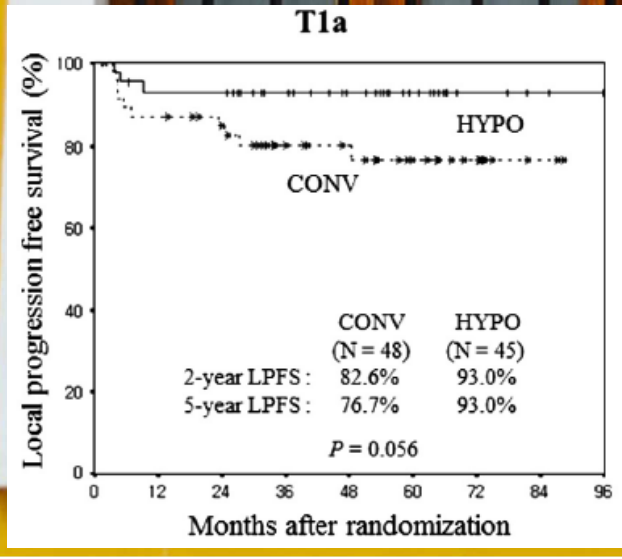
Arm	Tumor length <2/3 of glottis	Tumor length ≥2/3 of glottis
Arm A (2 Gy/fr)		
A-1 (n = 31)	60 Gy/30 fr/6 wk	
A-2 (n = 57)		66 Gy/33 fr/6.6 wk
Arm B (2.25 Gy/fr)		
B-1 (n = 31)	56.25 Gy/25 fr/5 wk	
B-2 (n = 61)		63 Gy/28 fr/5.6 wk

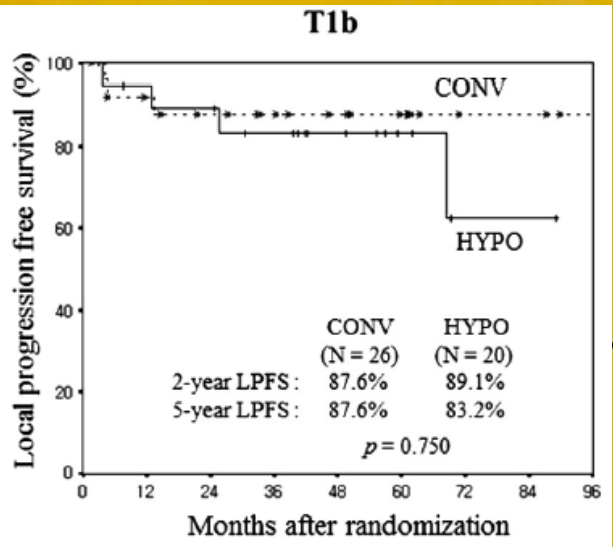
Pondicherry

Yamazaki et al IJROBP 2006

KROG 0201 (Vocal cord) N=156

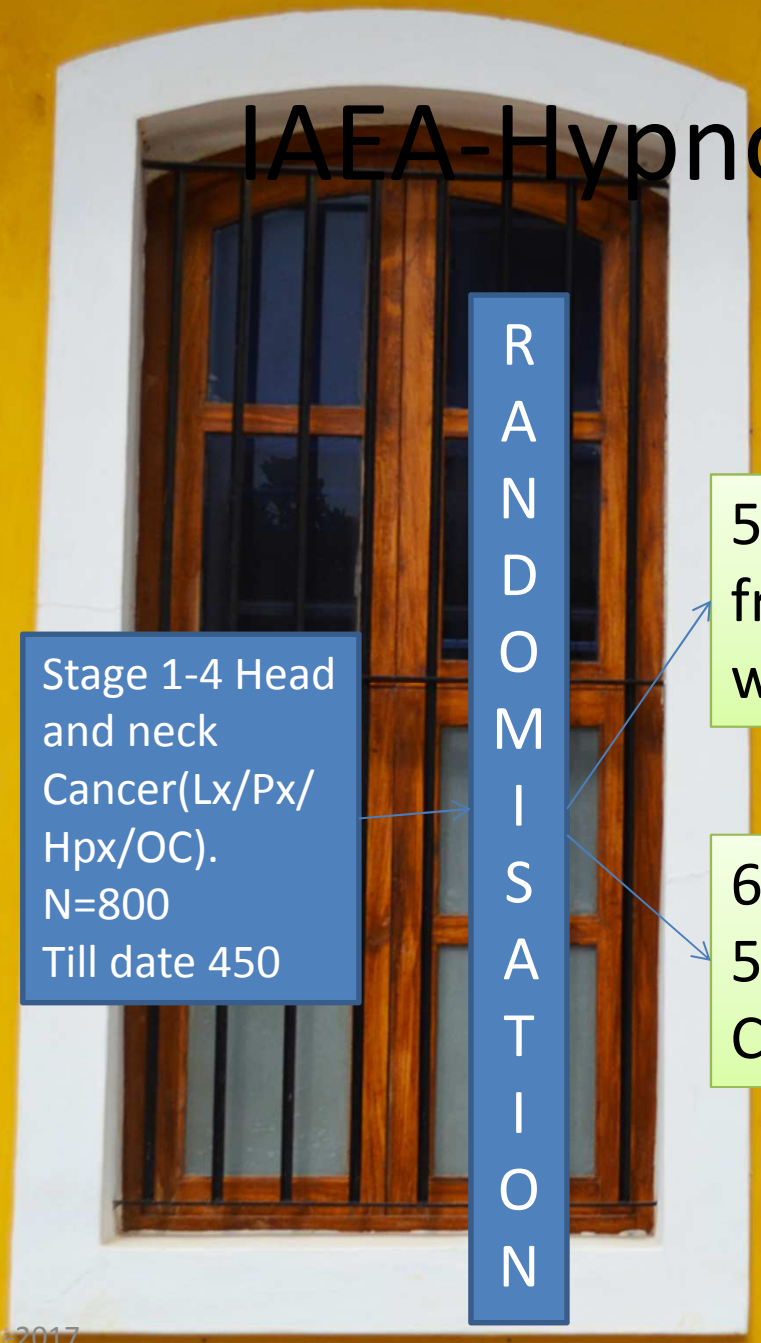






dicherry

IAEA-Hypno (on going)



Stage 1-4 Head and neck Cancer(Lx/Px/ Hpx/OC).
N=800
Till date 450

RANDOMISATION

55 Gy in 20 fractions / 4 wks +/- CCT

66 Gy/33# in 5 wks +/- CCT

Primary End point: Tumour control. Late Grade 2 toxicity.

Secondary End Pt: OS, DFS, Other Late toxicity, QOL

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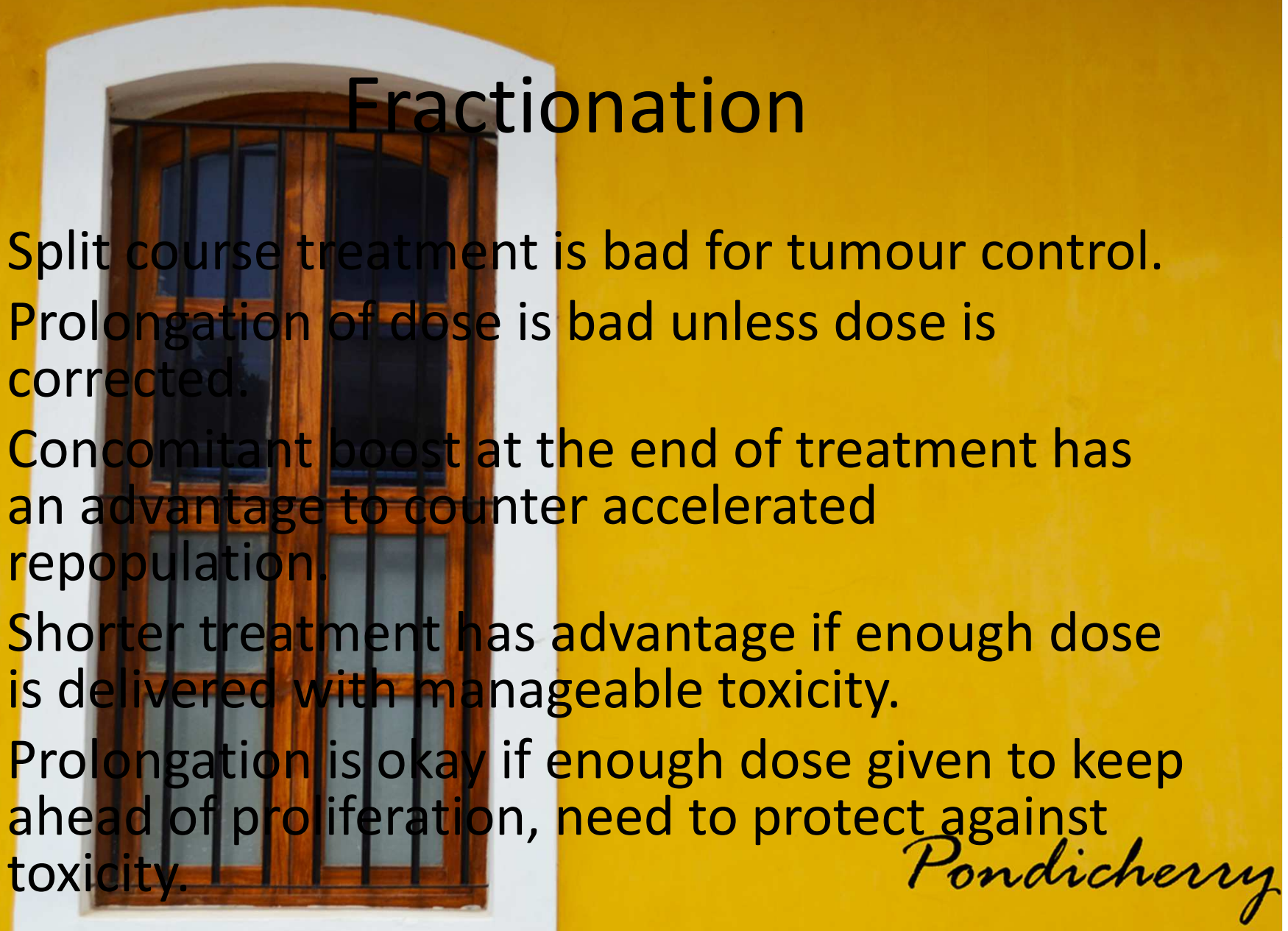
Courtesy: Gupta T, Agarwal JP.

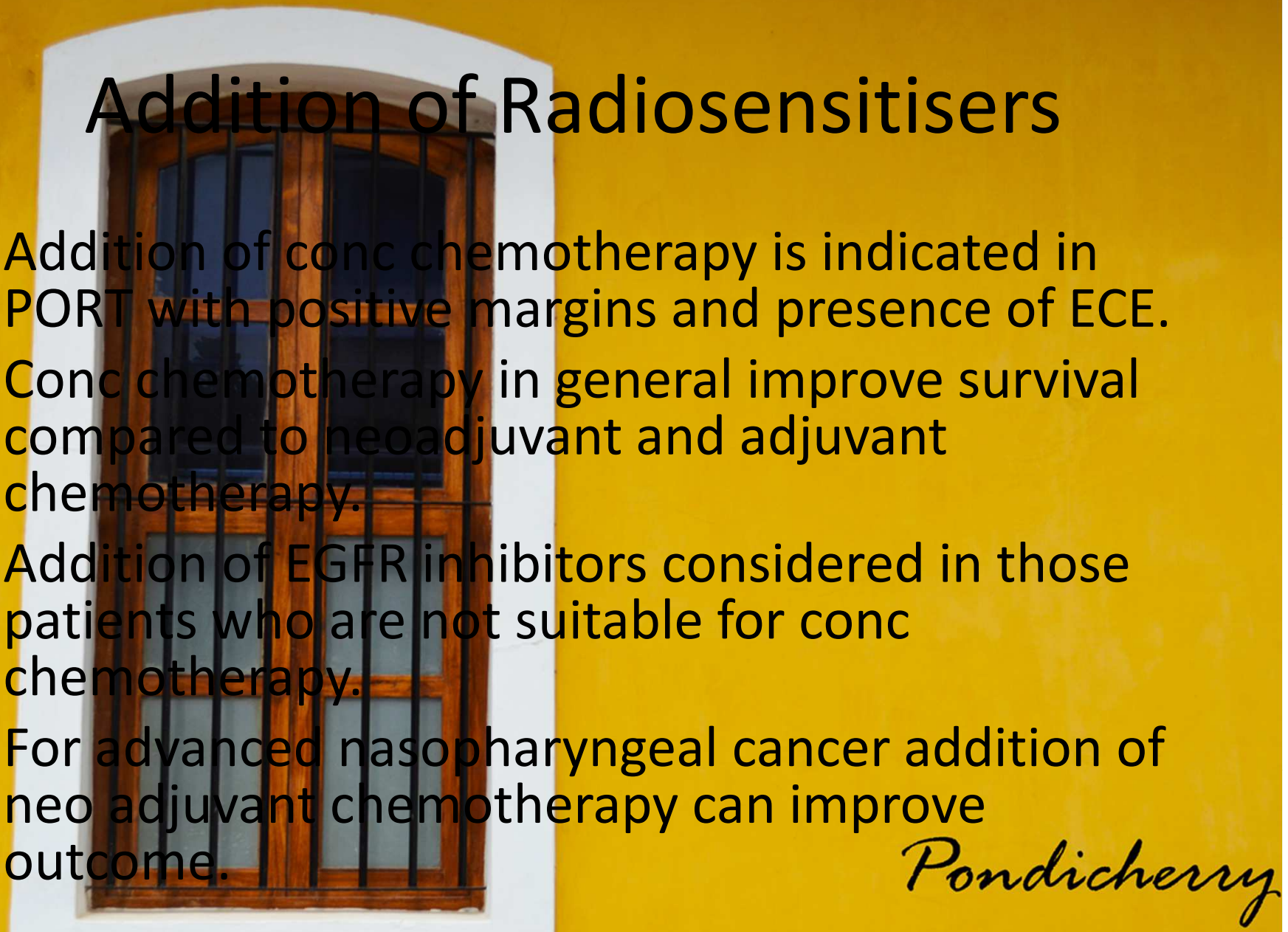
Fractionation

- Split course treatment is bad for tumour control.
- Prolongation of dose is bad unless dose is corrected.
- Concomitant boost at the end of treatment has an advantage to counter accelerated repopulation.
- Shorter treatment has advantage if enough dose is delivered with manageable toxicity.
- Prolongation is okay if enough dose given to keep ahead of proliferation, need to protect against toxicity.



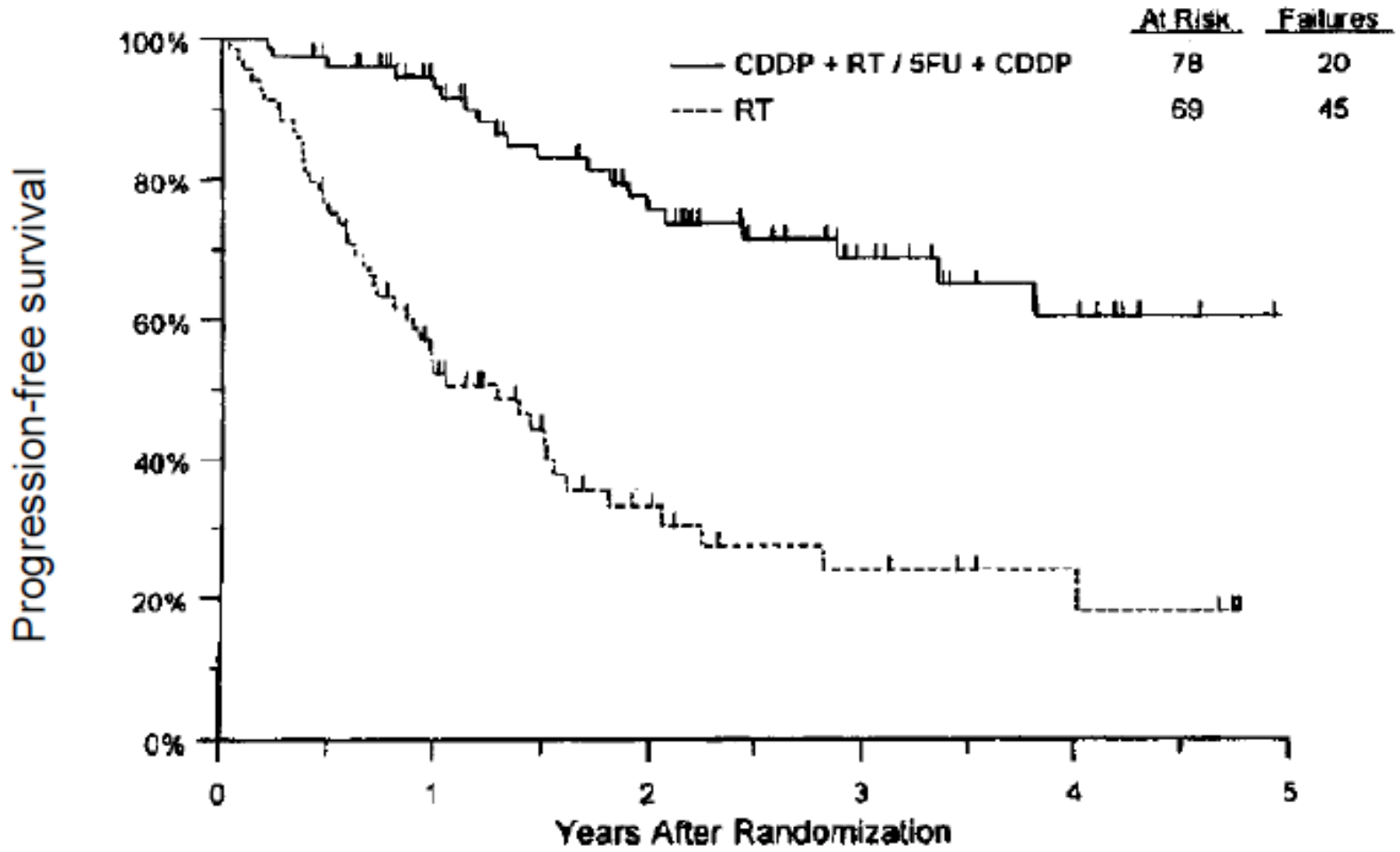
Addition of Radiosensitisers

- Addition of conc chemotherapy is indicated in PORT with positive margins and presence of ECE.
- Conc chemotherapy in general improve survival compared to neoadjuvant and adjuvant chemotherapy.
- Addition of EGFR inhibitors considered in those patients who are not suitable for conc chemotherapy.
- For advanced nasopharyngeal cancer addition of neo adjuvant chemotherapy can improve outcome.

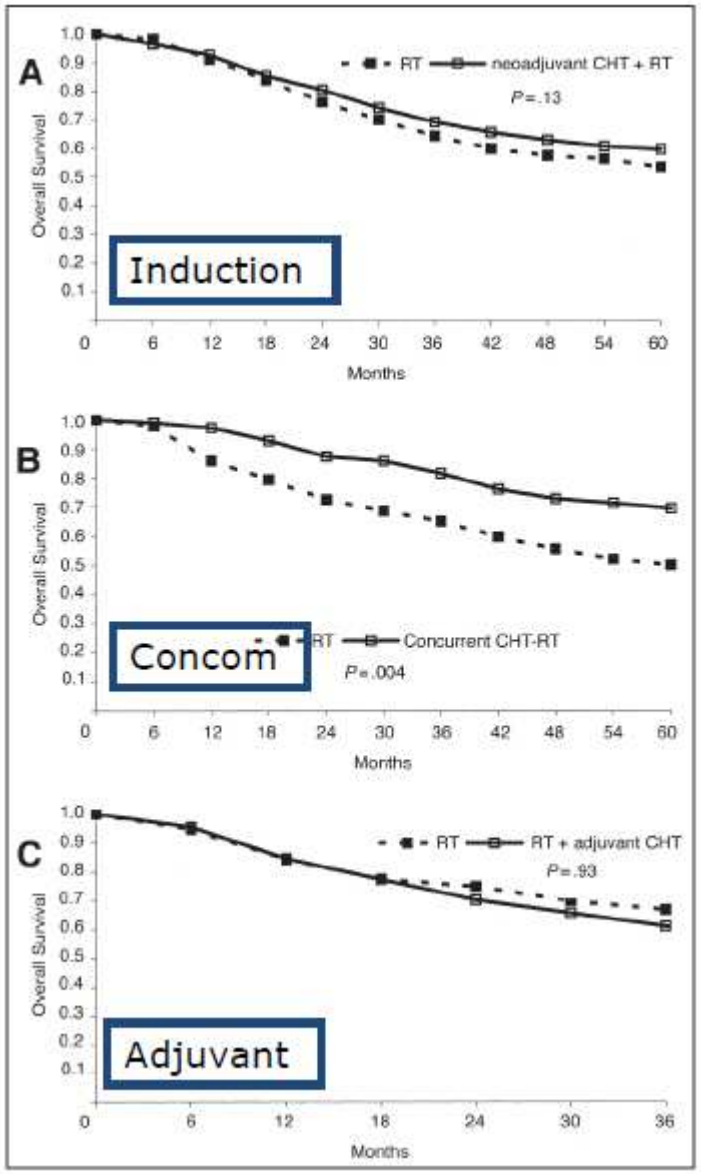


NPC RT ±chemo (cis + adj cis-FU)

Intergroup 0099 (n=147)



Al-Sarraf et al, JCO 1998

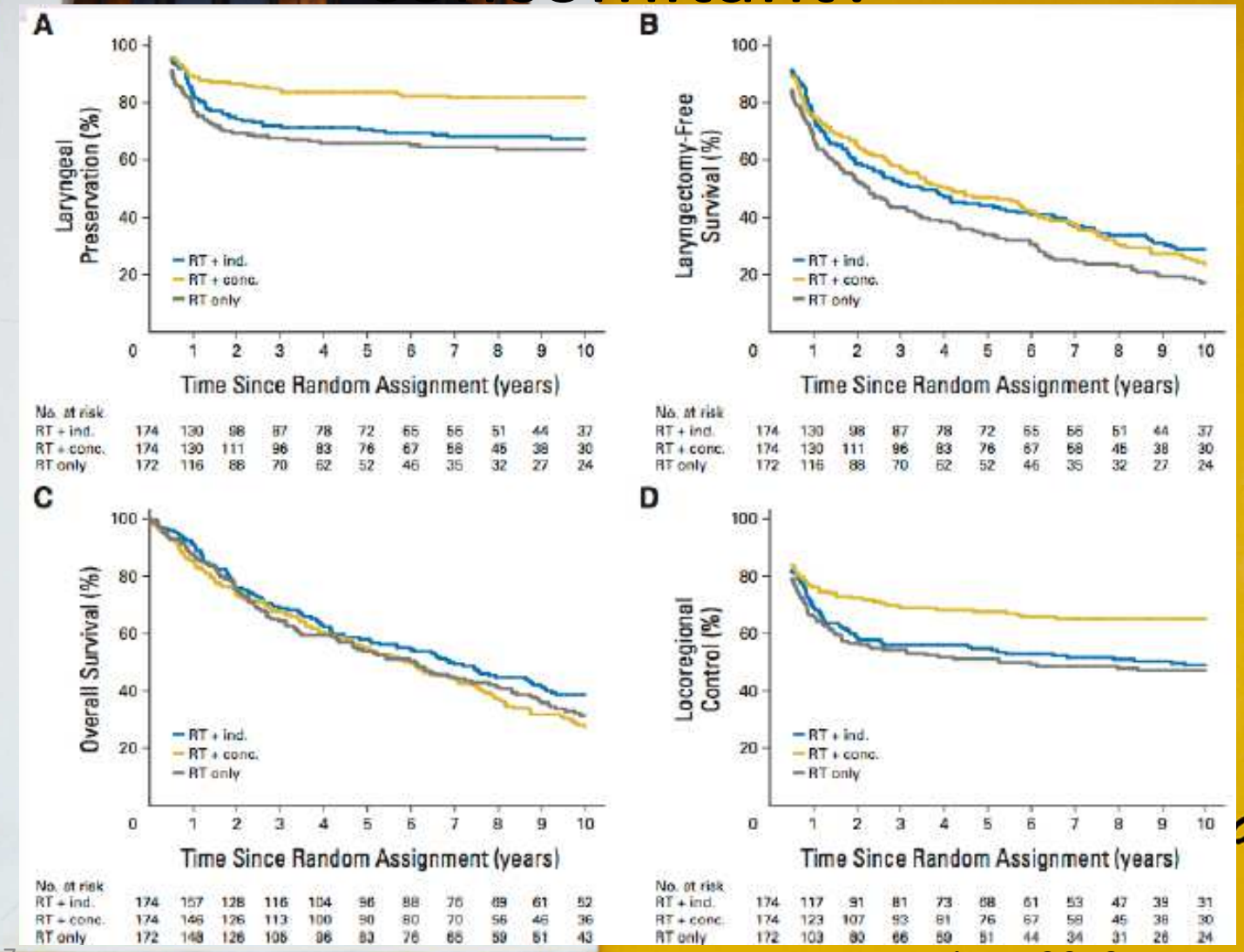


NPC
Meta-analysis
n = 2,455

survival benefit of 20% after 5 years

Langendijk JCO 2004

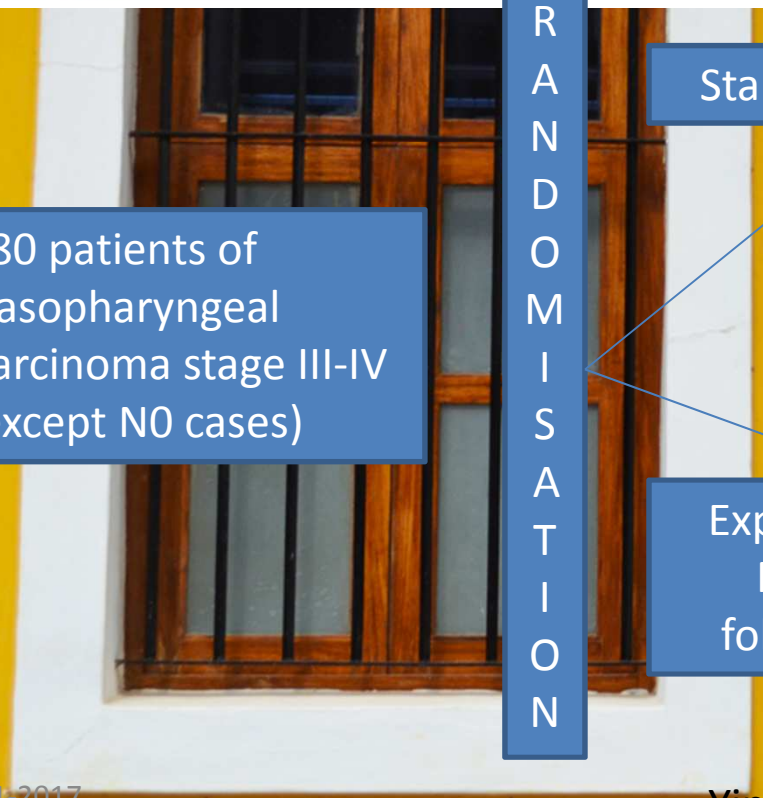
Chemotherapy: Induction or concomitant?



Forastiere, 2013

Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial

Ying Sun*, Wen-Fei Li*, Nian-Yong Chen*, Ning Zhang*, Guo-Qing Hu*, Fang-Yun Xie*, Yan Sun*, Xiao-Zhong Chen, Jin-Gao Li, Xiao-Dong Zhu, Chao-Su Hu, Xiang-Ying Xu, Yuan-Yuan Chen, Wei-Han Hu, Ling Guo, Hao-Yuan Mo, Lei Chen, Yan-Ping Mao, Rui Sun, Ping Ai, Shao-Bo Liang, Guo-Xian Long, Bao-Min Zheng, Xing-Lai Feng, Xiao-Chang Gong, Ling Li, Chun-Ying Shen, Jian-Yu Xu, Ying Guo, Yu-Ming Chen, Fan Zhang, Li Lin, Ling-Long Tang, Meng-Zhong Liu, Jun Ma



480 patients of Nasopharyngeal Carcinoma stage III-IV (except N0 cases)

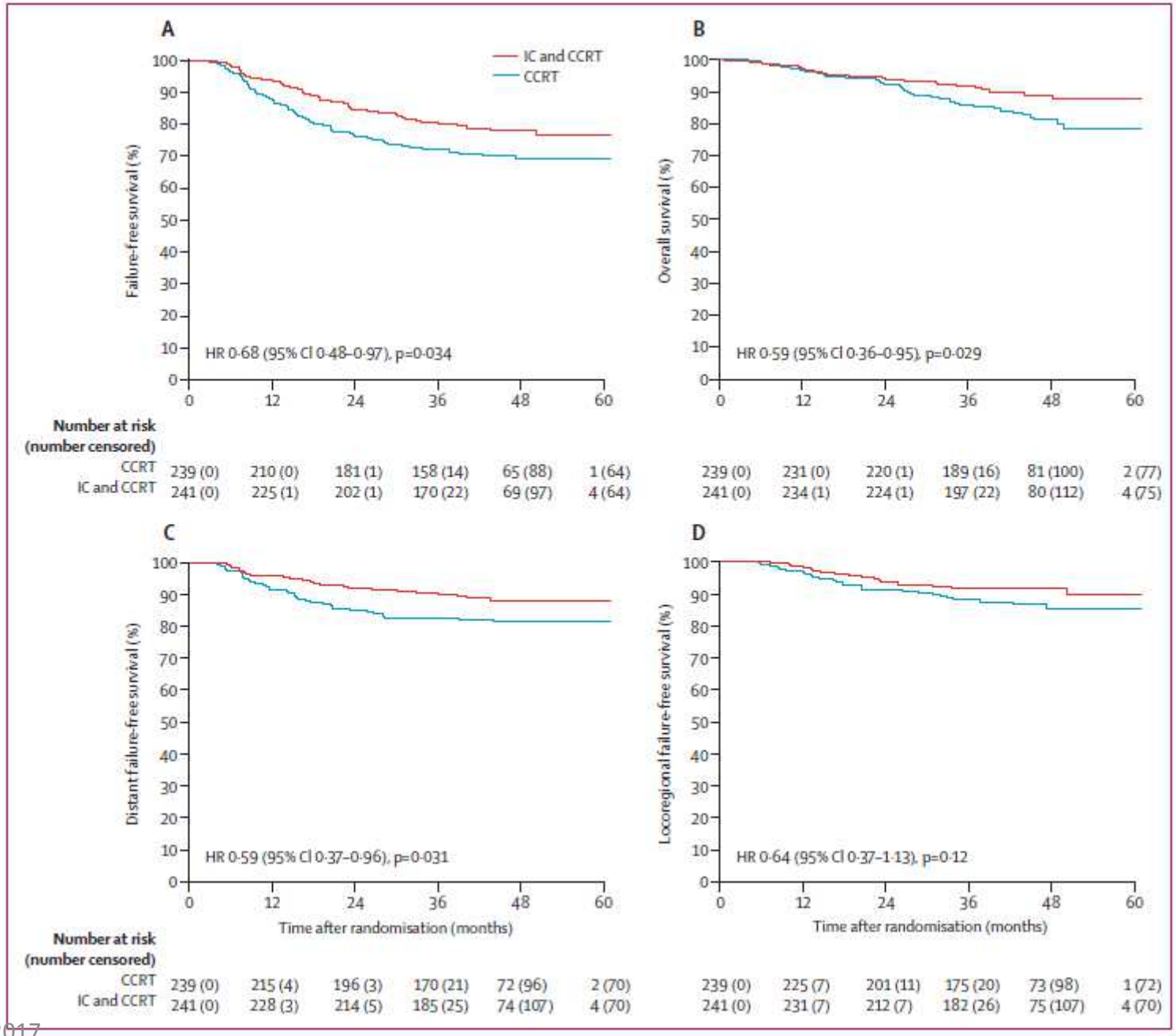
RANDOMISATION

Standard Arm CTRT

Experimental Arm NACT(3# TPF) followed by CTRT

Pondicherry

Ying Sun ***Lancet Oncol*** **2016; 17: 1509–20**



Ying Sun ***Lancet Oncol* 2016; 17: 1509–20**

Toxicity profile

	Induction chemotherapy plus concurrent chemoradiotherapy group (n=239)		Concurrent chemoradiotherapy group (n=238)		p value*	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Any†	132 (55%)	42 (18%)	125 (53%)	3 (1%)	0·55	<0·0001
Haematological						
Neutropenia	64 (27%)	37 (15%)	16 (7%)	1 (<1%)	<0·0001	<0·0001
Febrile neutropenia	5 (2%)	2 (1%)	0	0	0·061	0·50
Neutropenic infection	1 (<1%)	0	0	0	1·00	..
Leucopenia	86 (36%)	12 (5%)	40 (17%)	1 (<1%)	<0·0001	0·0020
Anaemia	4 (2%)	0	5 (2%)	0	0·75	..
Thrombocytopenia	5 (2%)	1 (<1%)	2 (1%)	0	0·45	1·00
Non-haematological						
Stomatitis (mucositis)	96 (40%)	2 (1%)	82 (34%)	2 (1%)	0·20	1·00
Vomiting	52 (22%)	4 (2%)	45 (19%)	0	0·44	0·12
Nausea	46 (19%)	4 (2%)	40 (17%)	0	0·49	0·12
Dry mouth	13 (5%)	..‡	13 (5%)	..‡	0·99	..
Dermatitis	8 (3%)	1 (<1%)	10 (4%)	0	0·62	1·00
Oesophagitis, dysphagia, or odynophagia	5 (2%)	0	9 (4%)	0	0·27	..
Hepatoxicity	7 (3%)	0	2 (1%)	0	0·18	..
Allergic reaction	2 (1%)	0	0	0	0·50	..

Data are n or n (%). *p values were calculated with the χ^2 test (or Fisher's exact test). †No grade 3–4 nephrotoxicity, ototoxicity, or neurotoxicity was recorded. ‡According to the Common Terminology Criteria for Adverse Events (version 3.0) dry mouth has only grade 1–3.

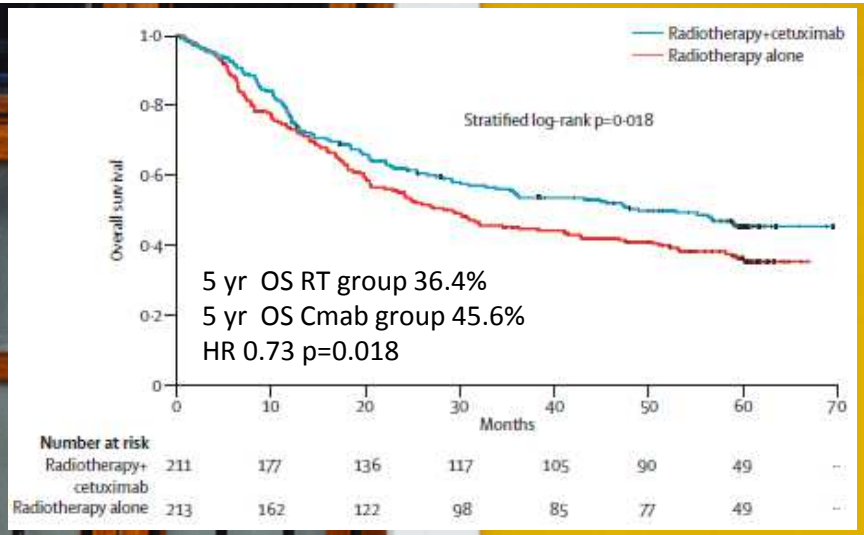
Table 4: **Cumulative adverse events during treatment by maximum grade per patient during treatment**

Ying Sun ***Lancet Oncol*** **2016; 17: 1509–20**

Rx Intensification : Biological

Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival

James A Bonner, Paul M Harari, Jordi Giralt, Roger B Cohen, Christopher U Jones, Ranjan K Sur, David Raben, Jose Baselga, Sharon A Spencer, Junming Zhu, Hagop Youssoufian, Eric K Rowinsky, K Kian Ang



5 yr OS RT group 36.4%
5 yr OS Cmab group 45.6%
HR 0.73 p=0.018

Updated Five year overall survival (Median follow up 60 months)

Pondicherry

Bonner J et al lancet 2010

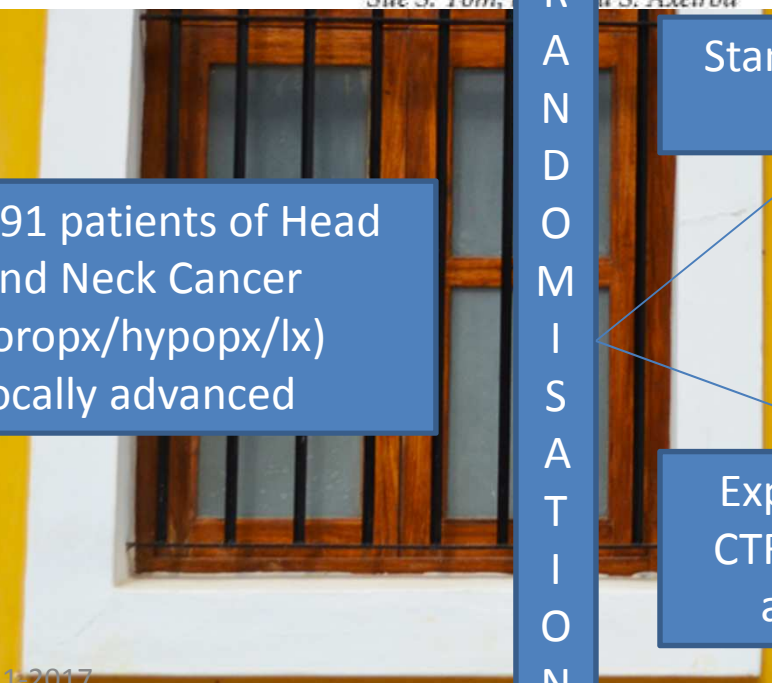
VOLUME 32 · NUMBER 27 · SEPTEMBER 20 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Trial of Concurrent Accelerated Radiation Plus Cisplatin With or Without Cetuximab for Stage III to IV Head and Neck Carcinoma: RTOG 0522

K. Kian Ang,† Qiang Zhang, David I. Rosenthal, Phuc Felix Nguyen-Tan, Eric J. Sherman, Randal S. Weber, James M. Galvin, James A. Bonner, Jonathan Harris, Adel K. El-Naggar, Maura L. Gillison, Richard C. Jordan, Andre A. Ko... ade L. Thorstad, Andy Trotti, Jonathan J. Beitler, Adam S. Garden, William J. Spanos,† Sue S. Yom, ... a S. Axelrod



891 patients of Head and Neck Cancer (oropx/hypopx/lx) locally advanced

RANDOMISATION

Standard Arm CTRT(Cisplatin)

Experimental Arm CTRT with Cisplatin and Cetiximab

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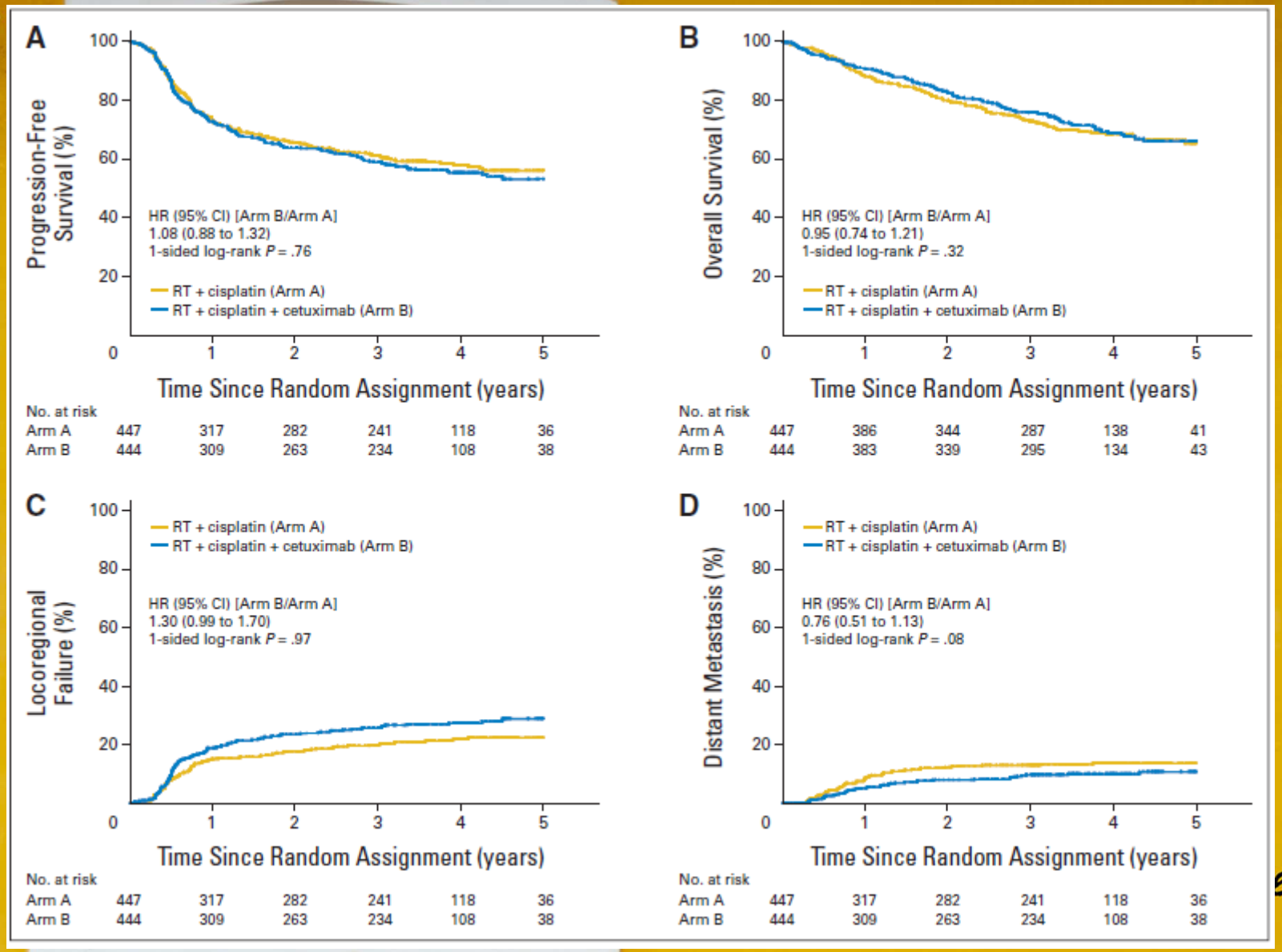
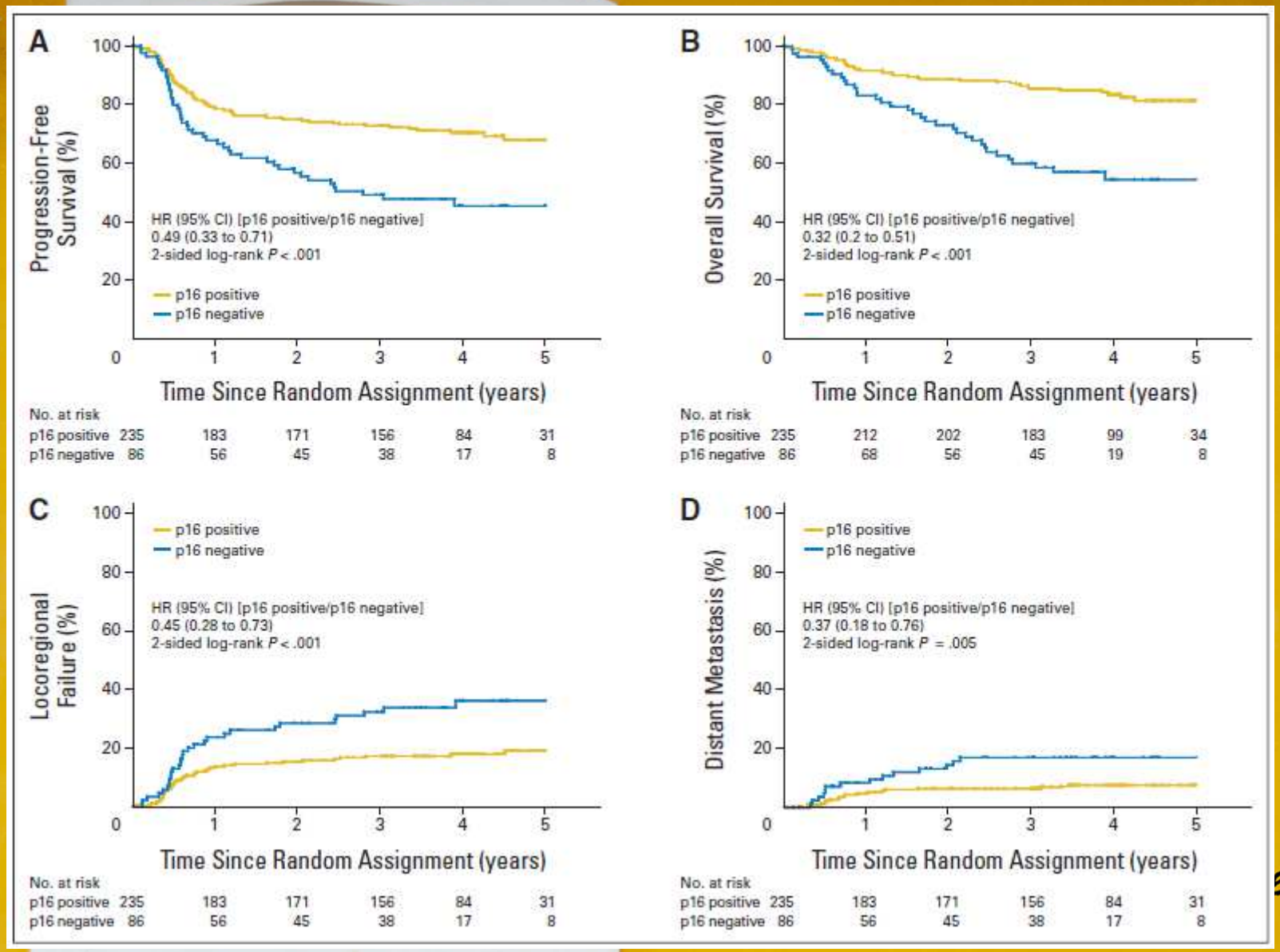
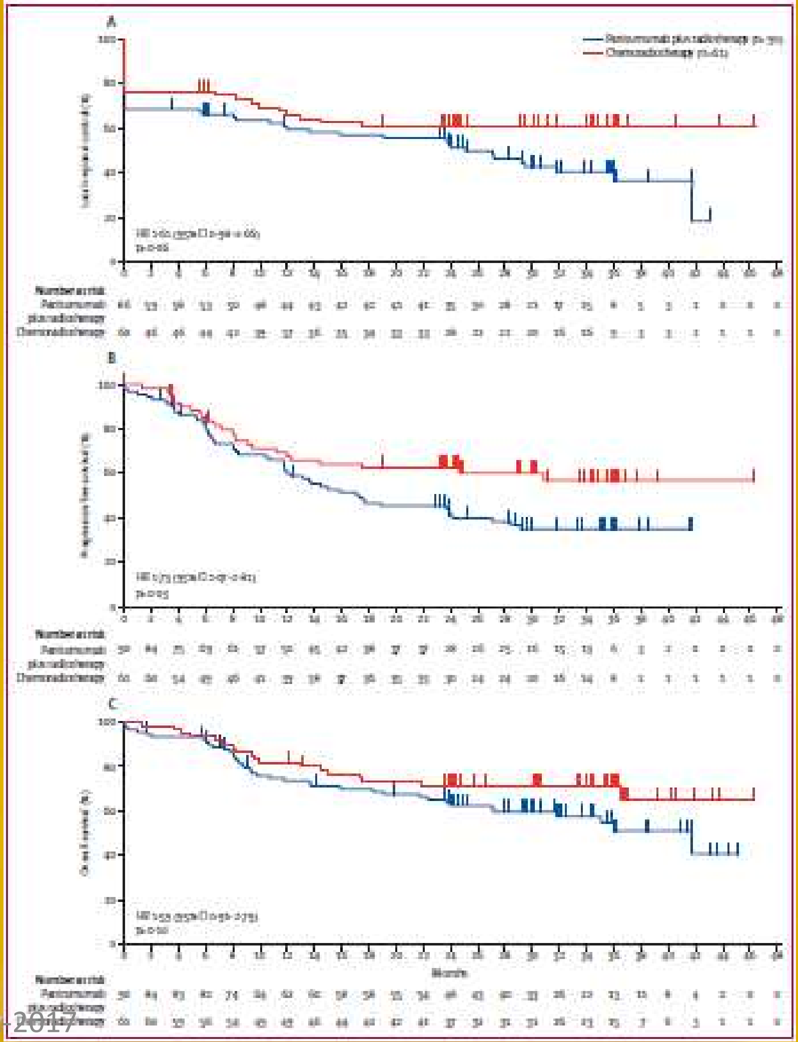

A
Progression-Free Survival (%)
100
80
60
40
20
0
1
2
3
4
5
HR (95% CI) [Arm B/Arm A]
1.08 (0.88 to 1.32)
1-sided log-rank P = .76
RT + cisplatin (Arm A)
RT + cisplatin + cetuximab (Arm B)
Time Since Random Assignment (years)
No. at risk
Arm A 447 317 282 241 118 36
Arm B 444 309 263 234 108 38
B
Overall Survival (%)
HR (95% CI) [Arm B/Arm A]
0.95 (0.74 to 1.21)
1-sided log-rank P = .32
RT + cisplatin (Arm A)
RT + cisplatin + cetuximab (Arm B)
Time Since Random Assignment (years)
No. at risk
Arm A 447 386 344 287 138 41
Arm B 444 383 339 295 134 43
C
Locoregional Failure (%)
RT + cisplatin (Arm A)
RT + cisplatin + cetuximab (Arm B)
HR (95% CI) [Arm B/Arm A]
1.30 (0.99 to 1.70)
1-sided log-rank P = .97
Time Since Random Assignment (years)
No. at risk
Arm A 447 317 282 241 118 36
Arm B 444 309 263 234 108 38
D
Distant Metastasis (%)
RT + cisplatin (Arm A)
RT + cisplatin + cetuximab (Arm B)
HR (95% CI) [Arm B/Arm A]
0.76 (0.51 to 1.13)
1-sided log-rank P = .08
Time Since Random Assignment (years)
No. at risk
Arm A 447 317 282 241 118 36
Arm B 444 309 263 234 108 38


A
Progression-Free Survival (%)
100
80
60
40
20
0
1
2
3
4
5
HR (95% CI) [p16 positive/p16 negative]
0.49 (0.33 to 0.71)
2-sided log-rank P < .001
p16 positive
p16 negative
Time Since Random Assignment (years)
No. at risk
p16 positive 235 183 171 156 84 31
p16 negative 86 56 45 38 17 8
B
Overall Survival (%)
HR (95% CI) [p16 positive/p16 negative]
0.32 (0.2 to 0.51)
2-sided log-rank P < .001
p16 positive
p16 negative
Time Since Random Assignment (years)
No. at risk
p16 positive 235 212 202 183 99 34
p16 negative 86 68 56 45 19 8
C
Locoregional Failure (%)
HR (95% CI) [p16 positive/p16 negative]
0.45 (0.28 to 0.73)
2-sided log-rank P < .001
p16 positive
p16 negative
Time Since Random Assignment (years)
No. at risk
p16 positive 235 183 171 156 84 31
p16 negative 86 56 45 38 17 8
D
Distant Metastasis (%)
HR (95% CI) [p16 positive/p16 negative]
0.37 (0.18 to 0.76)
2-sided log-rank P = .005
p16 positive
p16 negative
Time Since Random Assignment (years)
No. at risk
p16 positive 235 183 171 156 84 31
p16 negative 86 56 45 38 17 8

Panitumumab plus radiotherapy versus chemoradiotherapy in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-2): a randomised, controlled, open-label phase 2 trial

Jordi Giralt, Jose Trigo, Sandro Nuyts, Mehmet Ozsahin, Krzysztof Skladowski, Georges Hatoum, Jean-François Daisne, Alejandro César Yunes Ancona, Anthony Cmelak, Ricard Mesía, Alicia Zhang, Kelly S Oliner, Ari VanderWalde

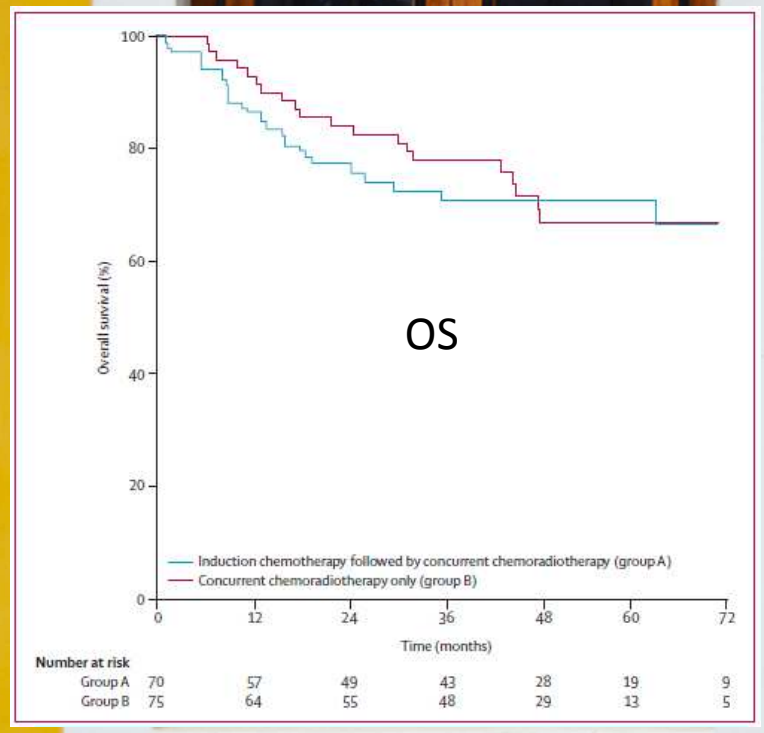


CTRT with Cisplatin is still standard of care

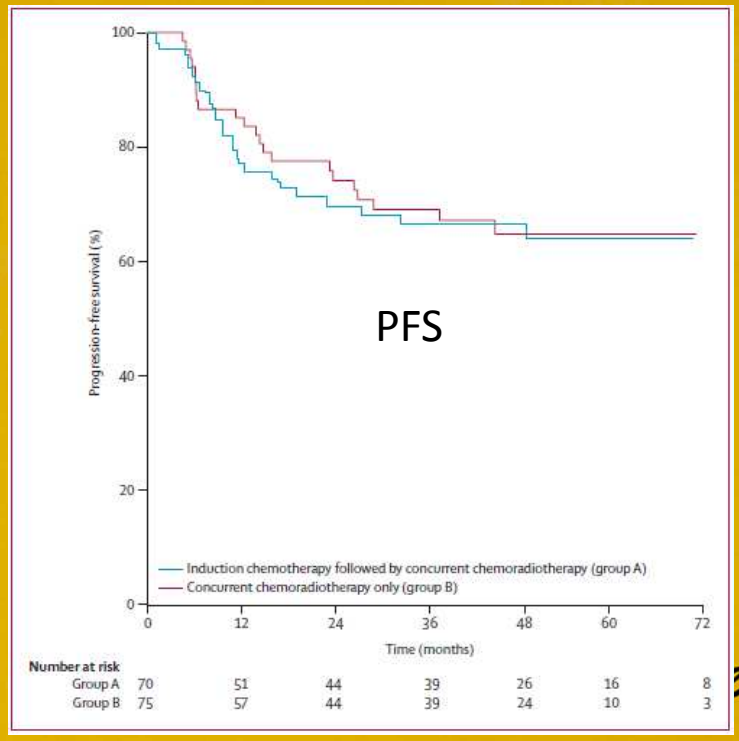
Pondicherry

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



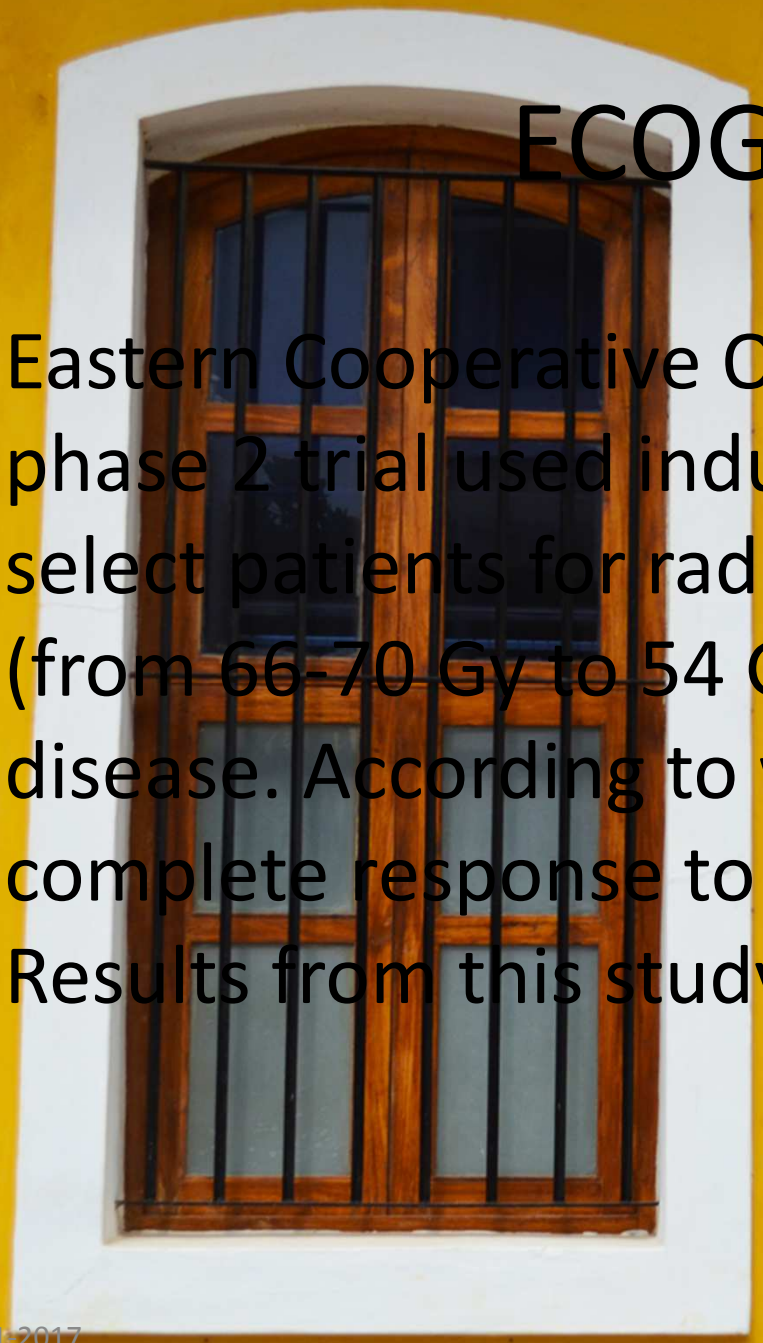
OS



PFS

ECOG 1308

- Eastern Cooperative Oncology Group 1308 phase 2 trial used induction chemotherapy to select patients for radiation dose modification (from 66-70 Gy to 54 Gy) for HPV positive disease. According to whether they achieved a complete response to induction therapy. Results from this study are currently pending.



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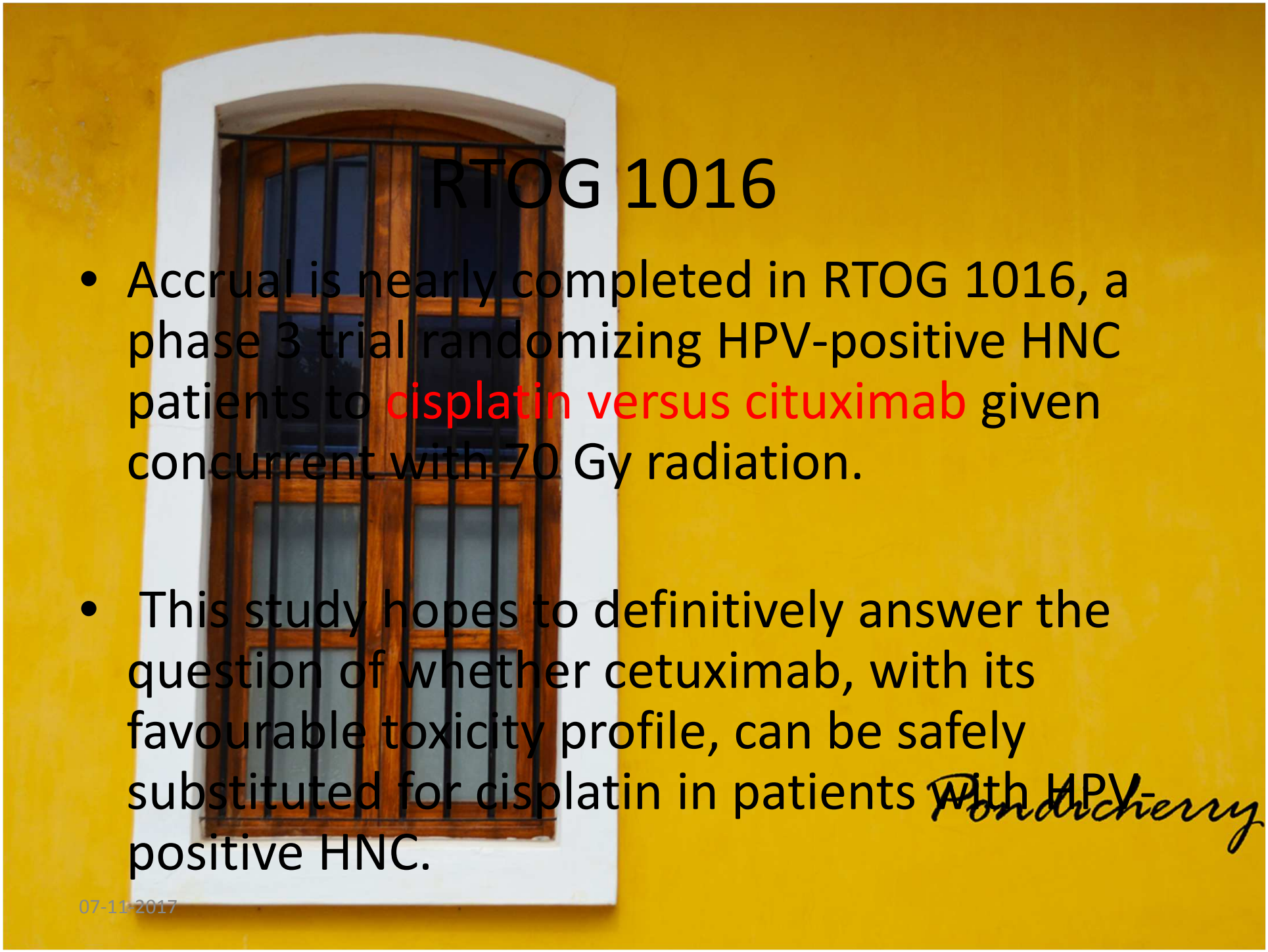

RTOG 1016

- Accrual is nearly completed in RTOG 1016, a phase 3 trial randomizing HPV-positive HNC patients to cisplatin versus cituximab given concurrent with 70 Gy radiation.

- This study hopes to definitively answer the question of whether cetuximab, with its favourable toxicity profile, can be safely substituted for cisplatin in patients with HPV-positive HNC.

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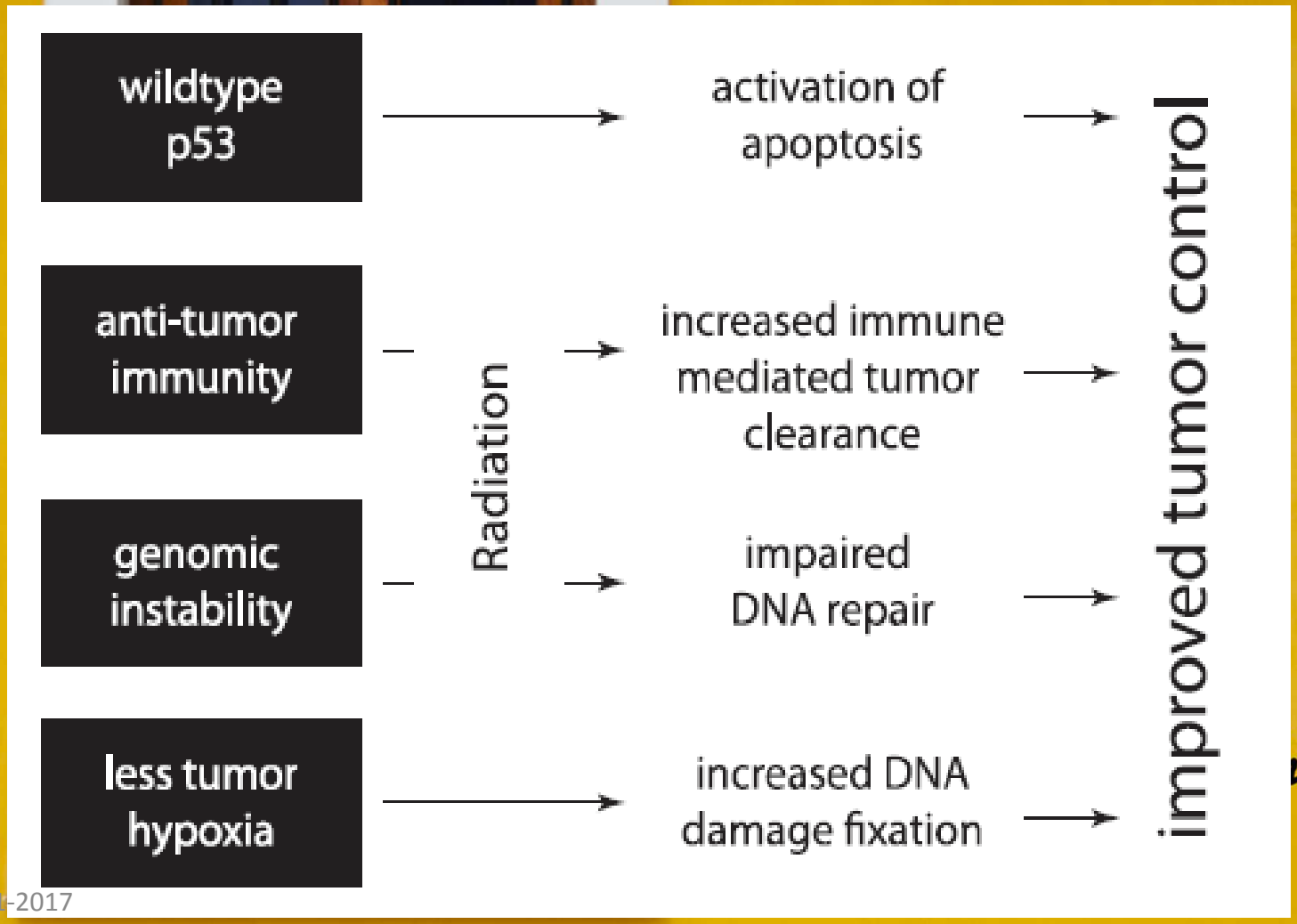
Ongoing trials

Table 3 Ongoing trials for patients with human papillomavirus-positive squamous cell carcinoma of the head and neck

Type	n	Group/institution	ClinicalTrials.gov identifier	Trial design
Phase 2	83*	ECOG	NCT01084083	Neoadjuvant chemotherapy and response-adapted radiation (54 or 66-70 Gy) + cetuximab
Phase 2	50	North Shore Long Island Jewish Health System	NCT01525927	Neoadjuvant TPF and response-adapted radiation (60 Gy) ± concurrent chemotherapy
Phase 2	50	University of California, Davis	NCT01716195	Neoadjuvant chemotherapy followed by paclitaxel + response-adapted radiation (50 or 60 Gy)
Phase 2	36	University of Michigan	NCT01663259	Weekly cetuximab + radiation (70 Gy)
Phase 2	40	University of North Carolina	NCT01530997	Radiation with weekly cisplatin followed by supra-selective neck dissection
Phase 3	706	RTOG	NCT01302834	Randomized to cetuximab versus cisplatin with concurrent radiation (70 Gy in 6 wk)
Phase 3	365	Mount Sinai School of Medicine	NCT01706939	Weekly carboplatin/cetuximab + 56 Gy versus weekly carboplatin + 70 Gy
Phase 2	337	ECOG	Pending	Transoral resection − risk-adapted postoperative RT (0 versus 50 versus 60 versus 66 Gy with weekly cisplatin)
Phase 3	496	Washington University	NCT01687413	Postoperative radiation (60 Gy) ± weekly cisplatin

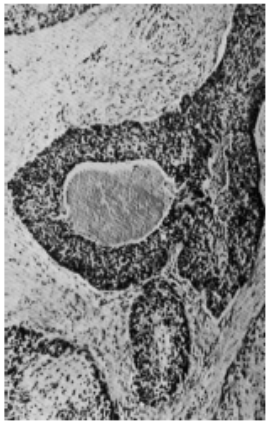
WHY HPV +ve patients do well??

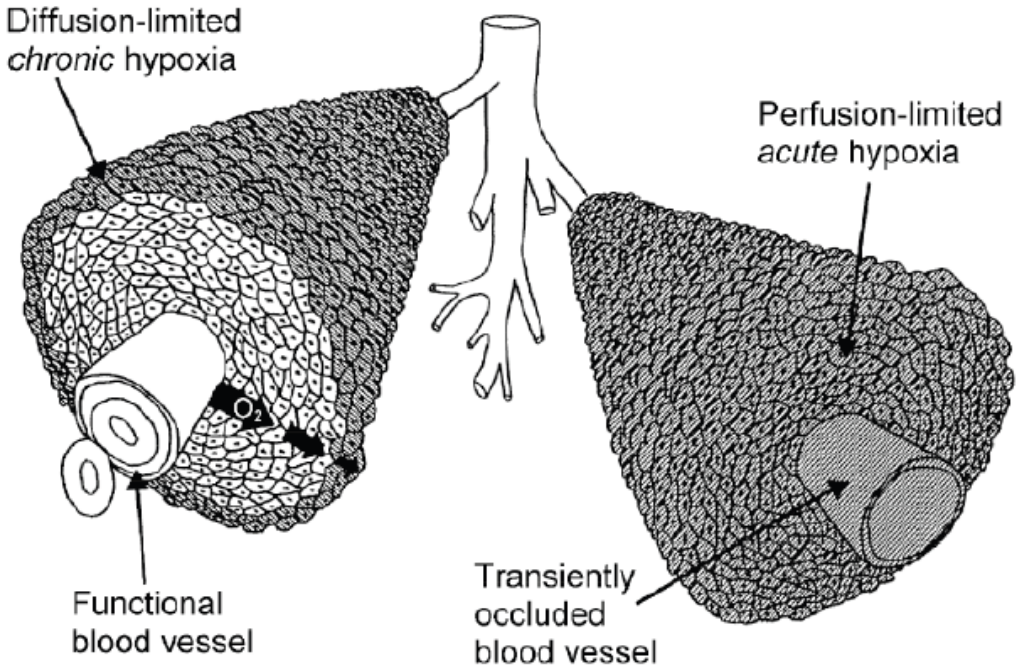


Hypoxia

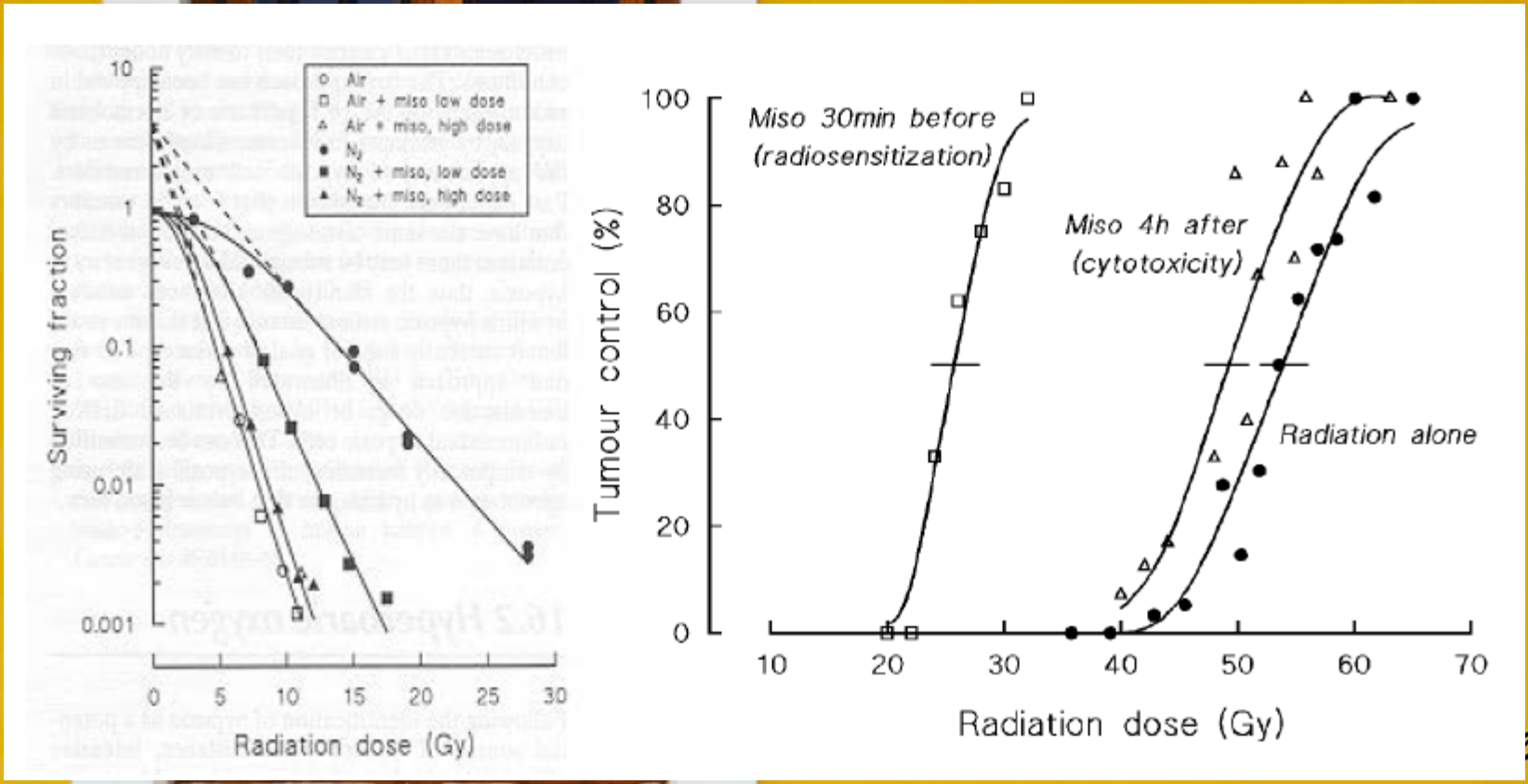
Thomlinson & Gray 1955

Cord structure in lung cancer (150 µm)

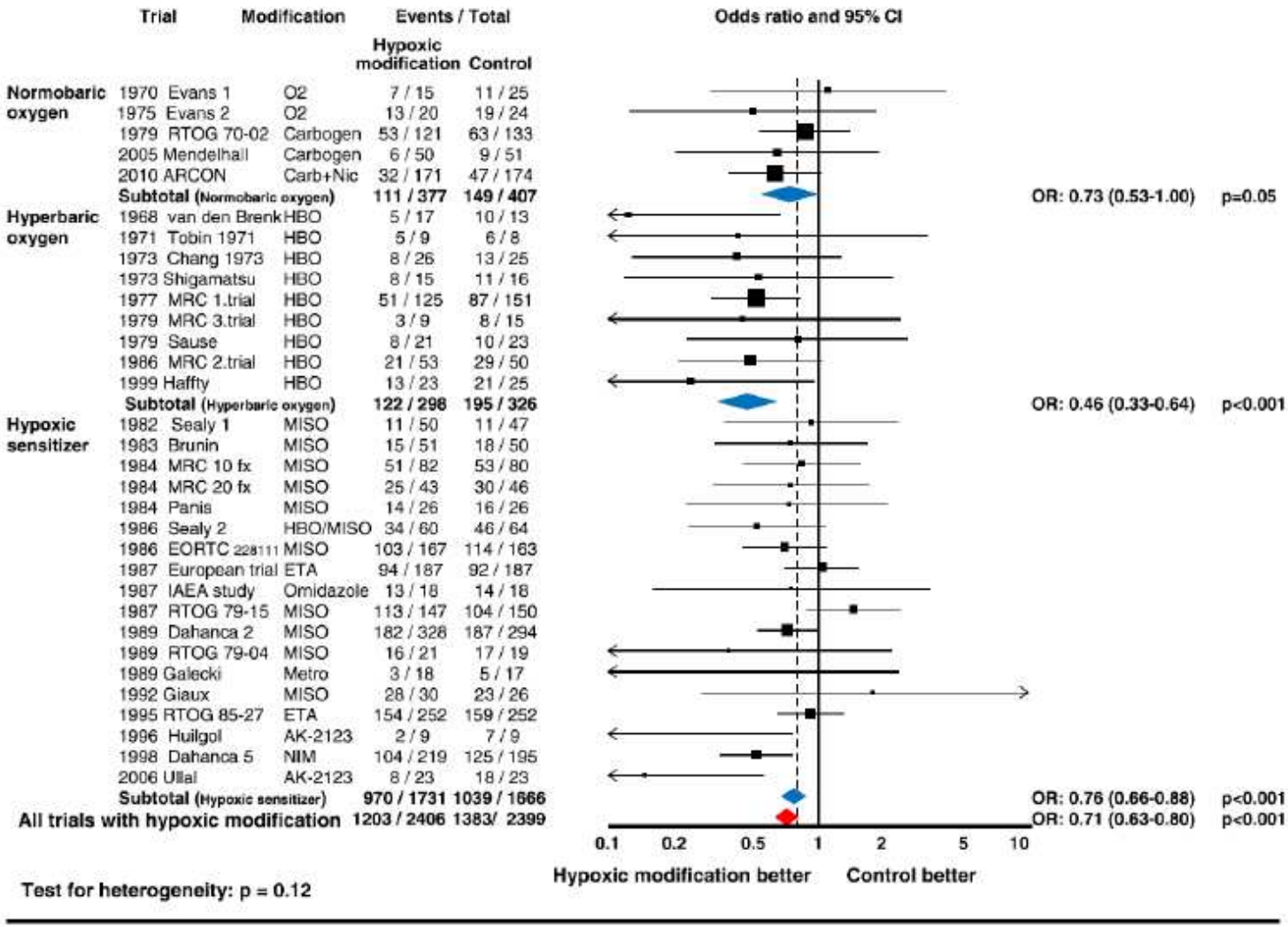




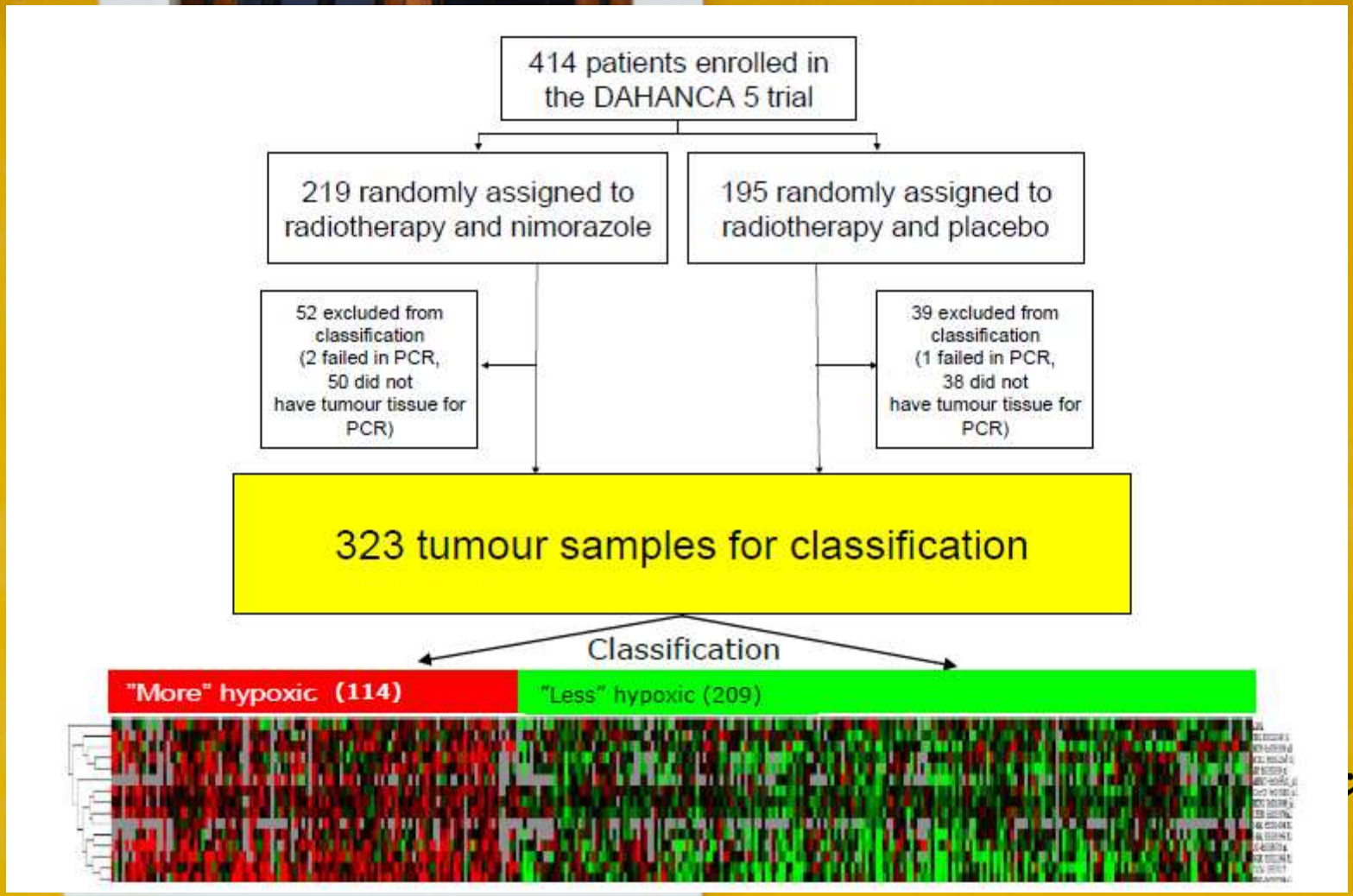
Hypoxic cell sensitizer



Hypoxic modifier: Overgaard 2011

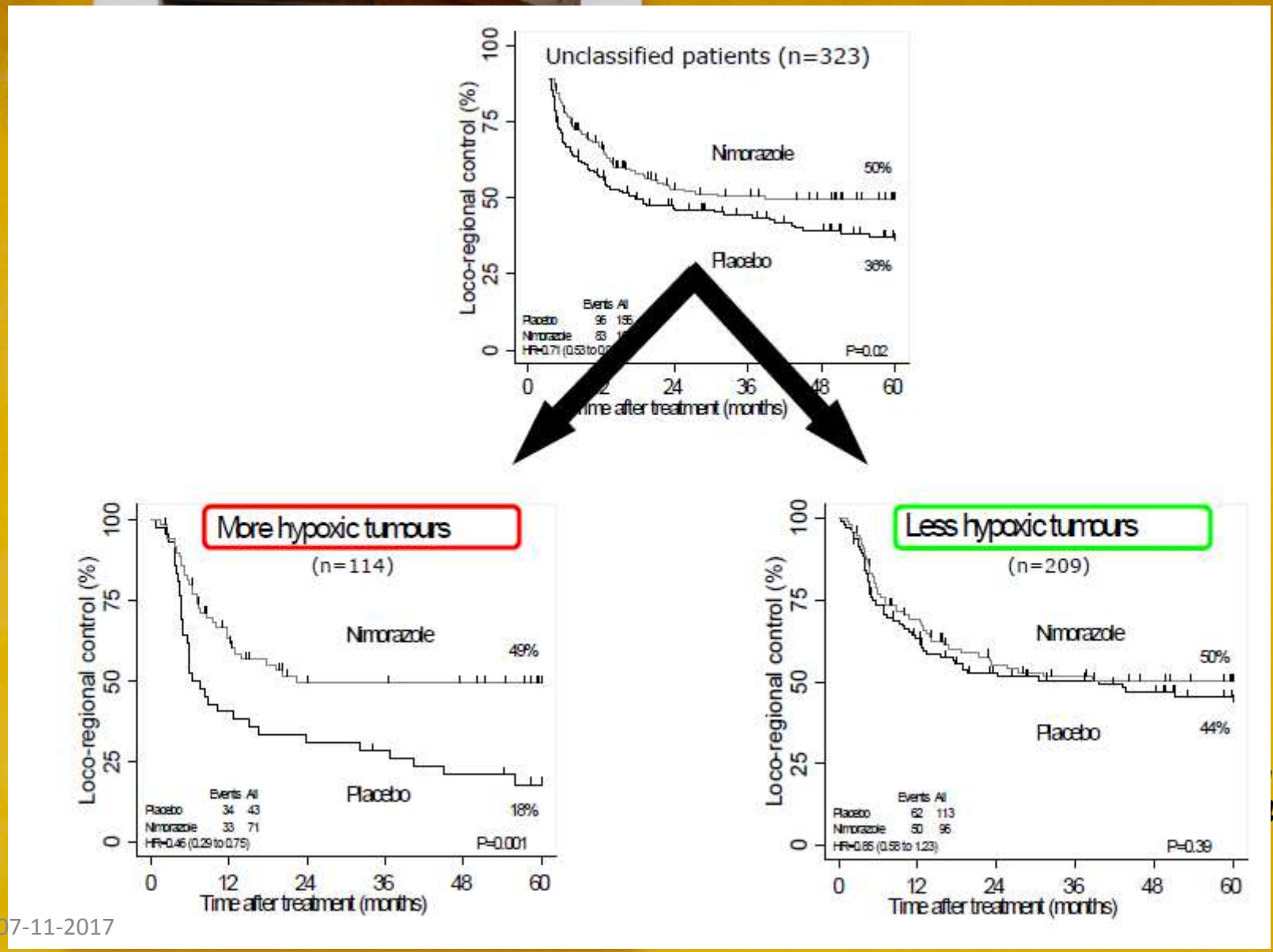


Hypoxic Classifier



Toustrup K Radiothe Oncol 2012

Effect of hypoxia



Accelerated fractionated RT+ Cisplatin+ Nimorazole

TNM stage (UICC 2002)

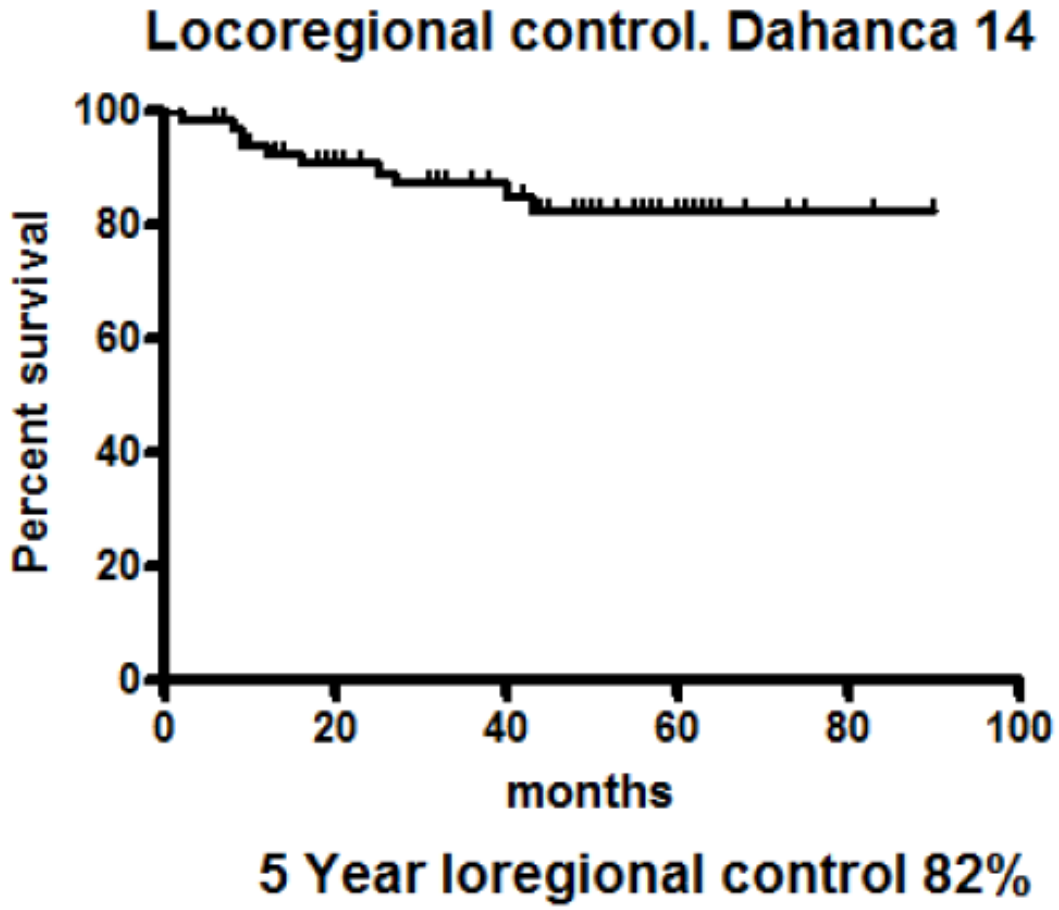
Stage 1	:7
Stage 2a	: 3
Stage 2b	: 11
Stage 3	:26
Stage 4a	: 17
Stage 4b	: 7

Patient Demography:

- 71 patients were included from jan 1. 2003 to dec 31. 2008
- 46 males and 25 females
- Median age 49 years (r 17-79)

Histopathology

·Keratinizing high differentiated	: 1
•Keratinizing moderate differentiated	: 2
·Keratinizing low differentiated	: 11
•Non keratinizing undifferentiated	: 46
·Non keratinizing differentiated	: 10
•Other	: 1

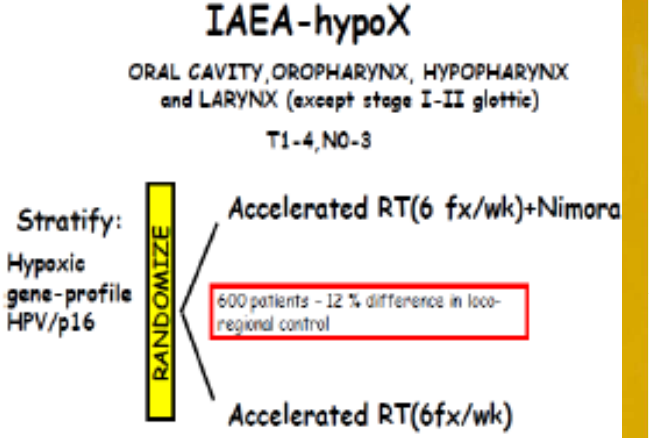


DAHANCA14, Bentzen et al, ESTRO 2011

On going validation studies

IAEA-HypoX

- Randomized phase III; accelerated radiotherapy ± Nimorazole
  - hypoxia gene expression and HPV/p16
  - Eastern Europe, Asia
  - Recruitment opened 2012

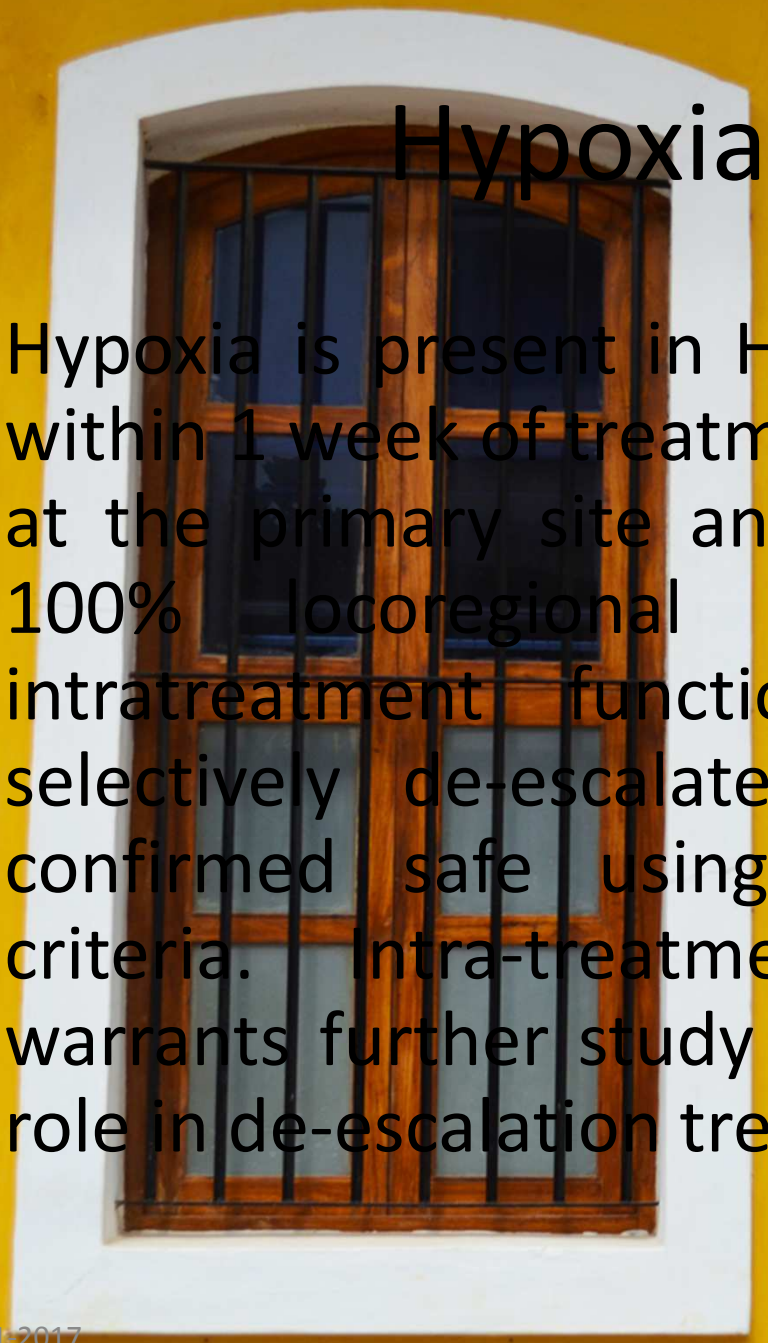


Intergroup EORTC - ROG HNCG 1219 DAHANCA

- Randomized phase III; accelerated chemoradiotherapy ± Nimorazole
  - hypoxia gene expression and HPV/p16
  - Europe, Canada
  - Recruitment starting 2013

Hypoxia in HPV+

- Hypoxia is present in HPV+ tumors, but resolves within 1 week of treatment in 48% of cases either at the primary site and/or Lymph node(s). Our 100% locoregional control suggests that intratreatment functional imaging used to selectively de-escalate node(s) to 60Gy was confirmed safe using our stringent imaging criteria. Intra-treatment functional imaging warrants further study to determine its ultimate role in de-escalation treatment strategies.



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Phase III randomised trial

Radiotherapy and Oncology 122 (2017) 171–177

Reduction of the dose of radiotherapy to the elective neck in head and neck squamous cell carcinoma; a randomized clinical trial. Effect on late toxicity and tumor control

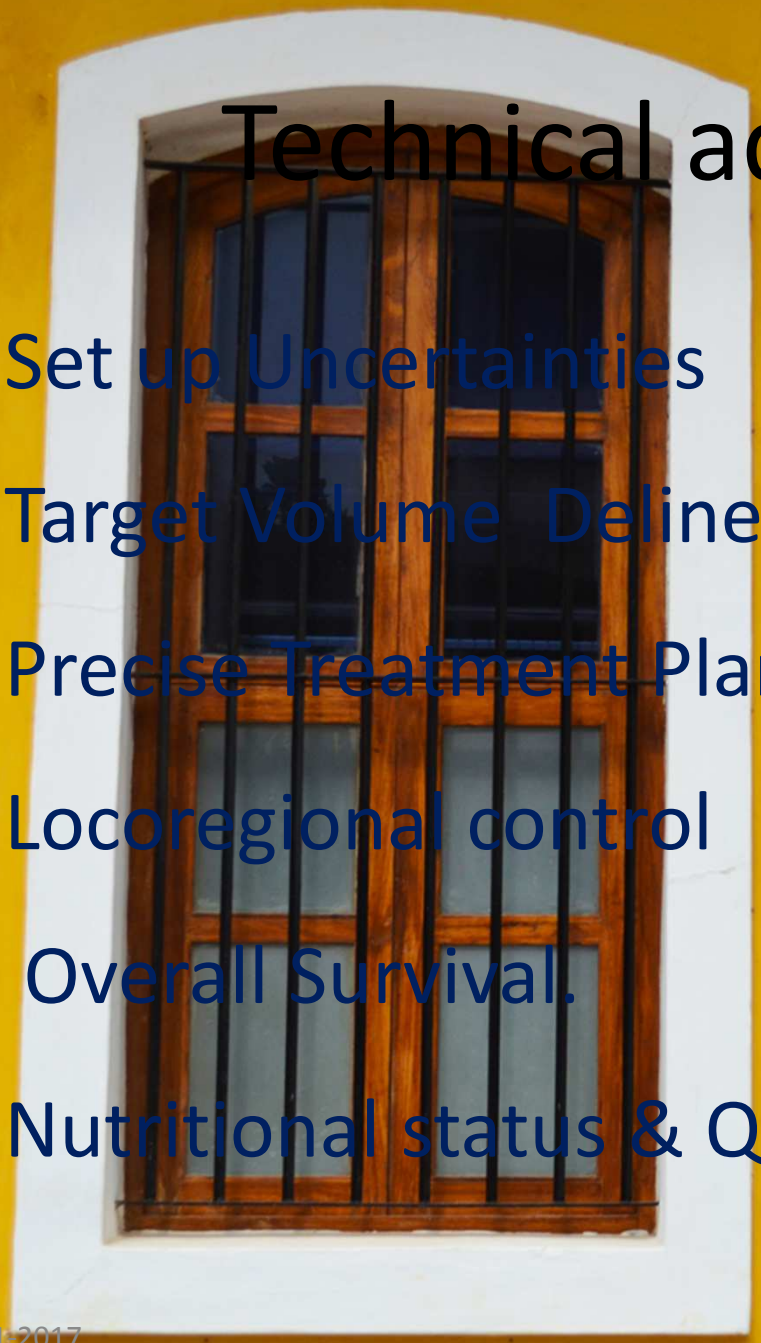
Daan Nevens [a,*], Fréderic Duprez [b], Jean Francois Daisne [c], Ruveyda Dok [d], Ann Belmans [e], Mia Voordeckers [f], Danielle Van den Weyngaert [g], Wilfried De Neve [b], Sandra Nuyts [a]

[a] Department of Radiation Oncology, KU Leuven – University of Leuven, University Hospitals Leuven; [b] Department of Radiotherapy, Ghent University Hospital; [c] Department of

200 patients were randomized in two groups of elective neck irradiation 50 Gy Vs 40 Gy by IMRT technique

- Trend towards less dysphagia at 6 months.
- Significant less salivary gland toxicity >= Grade 1 at 6 months(p=0.01) and 18 months(p=0.03)
- No difference of local control at 2 yrs.

Technical advancement



- Set up Uncertainties
- Target Volume Delineation
- Precise Treatment Planning & Delivery
- Locoregional control
- Overall Survival.
- Nutritional status & Quality of life

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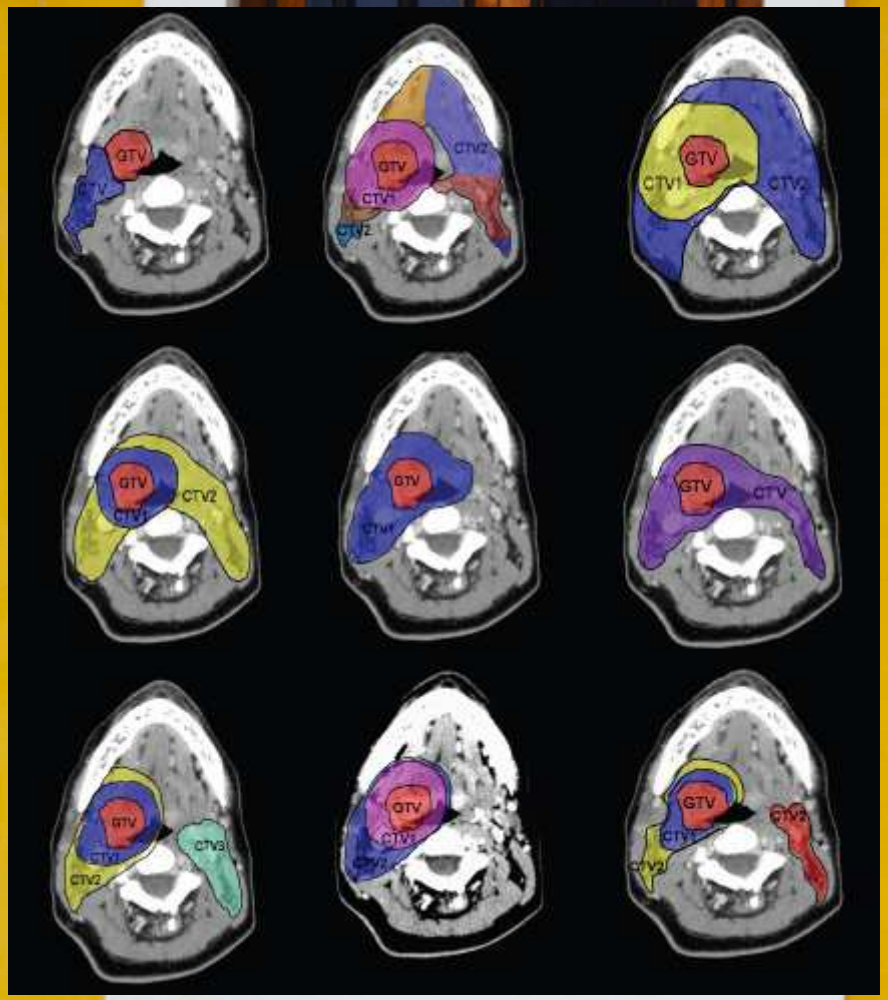
Delineation



Harari et al 2004

Grégoire V et al Radiother Oncol 2000;56:135–50.

Grégoire V et al, Radiother Oncol 2003;69:227–36.

Grégoire V et al, Radiother Oncol 2013.

RTOG contouring guideline

www.dahanca.dk

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Priority	OAR	Constraint OAR	Constraint PRV
"ABSOLUTE" (priority above target coverage)	Brain stem	Dmax ≤ 54Gy	Dmax ≤ 60Gy
	Spinal cord	Dmax ≤ 45Gy	Dmax ≤ 50Gy
"MUST" (priority not neccesarily above target coverage)	Anterior eye	Dmax ≤30 Gy	Dmax ≤ 35 Gy
	Optic chiasm and nerve	Dmax ≤ 54Gy	Dmax ≤ 60Gy
	Retina	Dmax ≤ 45 Gy	Dmax ≤ 50 Gy
"SHOULD" (good evidence for sparing)	Cochlea	Dmean ≤ 45 and D95% ≤ 55 Gy	
	Parotid glands	1) Contralateral parotid: Dmean ≤ 20 Gy 2) Both parotidś: Dmean ≤ 26 Gy	
	Mandible	Hotspots should be avoided	
"CAN" (less evidence for sparing, or less important morbidity or other uncertainties)	Pituitary gland	Dmean < 30 Gy	
	Brain	Dmax ≤ 60Gy	
	Submandibular glands	Dmean ≤ 35Gy	
	Oral cavity	Dmean ≤ 30Gy (non-involved part)	
	Lips	Dmean ≤ 20Gy	
	Larynx	Dmean ≤ 44 Gy	
	Thyroid	Dmean < 40 Gy	
	Oesohagus	Dmean ≤ 30Gy	

Adopted from www.dahanca.dk

Xerostomia

- The consensus has been reached that xerostomia can be substantially reduced by limiting the mean parotid gland dose to <26–30 Gy as a planning criterion.
- By reducing the mean dose to at least one parotid gland, salivary function can be partially preserved, and it improves gradually over time.
- However, the improvement in objective parotid function as measured by salivary flow is not always accompanied with improved patient-reported xerostomia. symptoms reported by patients are more suggestive of its true severity.
- Under stimulated status, 60–65% of saliva is produced by the parotid glands, 20–30% by the submandibular glands (SMGs), and 2–5% by the sublingual glands. non-stimulated state, the SMGs contribute up to 90% of the salivary output

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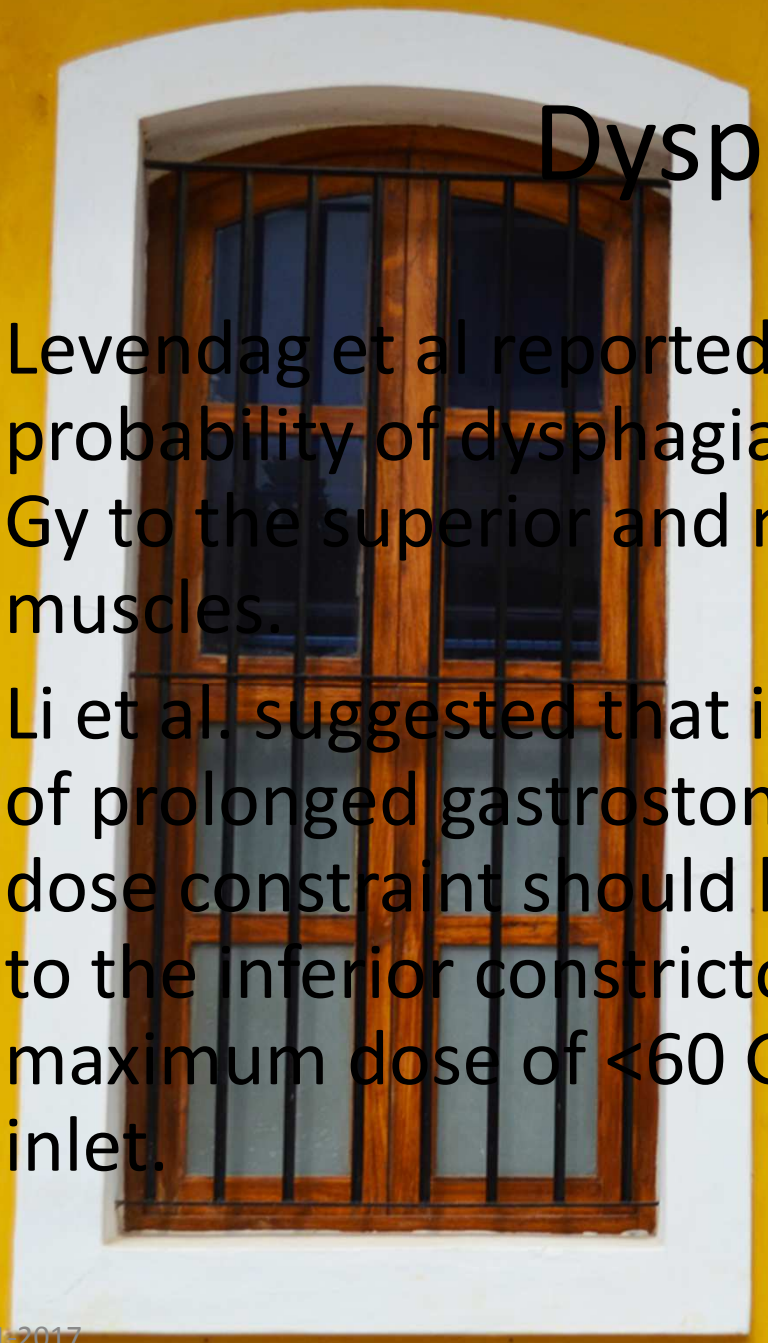
Wang XS, Eisbruch A: Journal of Radiation Research, Vol. 57, No. S1, 2016, pp. i69–i75

Dysphagia

- Levendag et al reported a 19% increase in the probability of dysphagia with every additional 10 Gy to the superior and middle constrictor muscles.
- Li et al. suggested that in order to reduce the risk of prolonged gastrostomy feeding tube use, the dose constraint should be a mean dose of <55 Gy to the inferior constrictor muscle, and a maximum dose of <60 Gy to the cricopharyngeal inlet.



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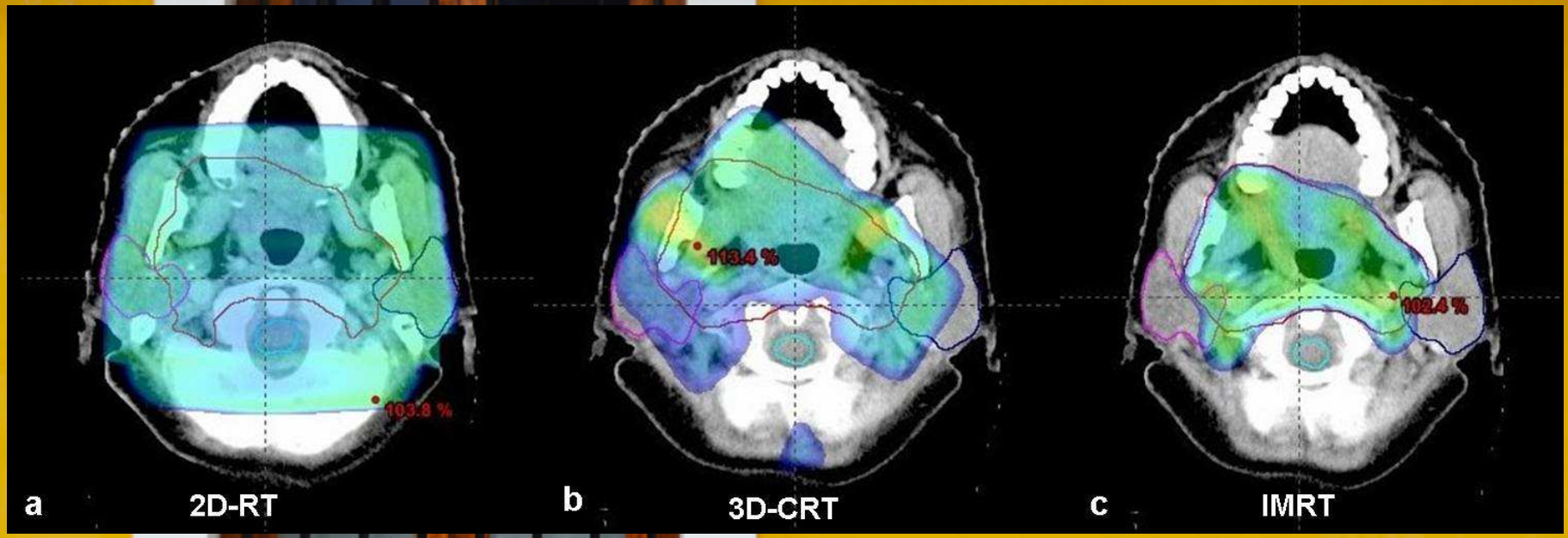
Progressive conformation of dose



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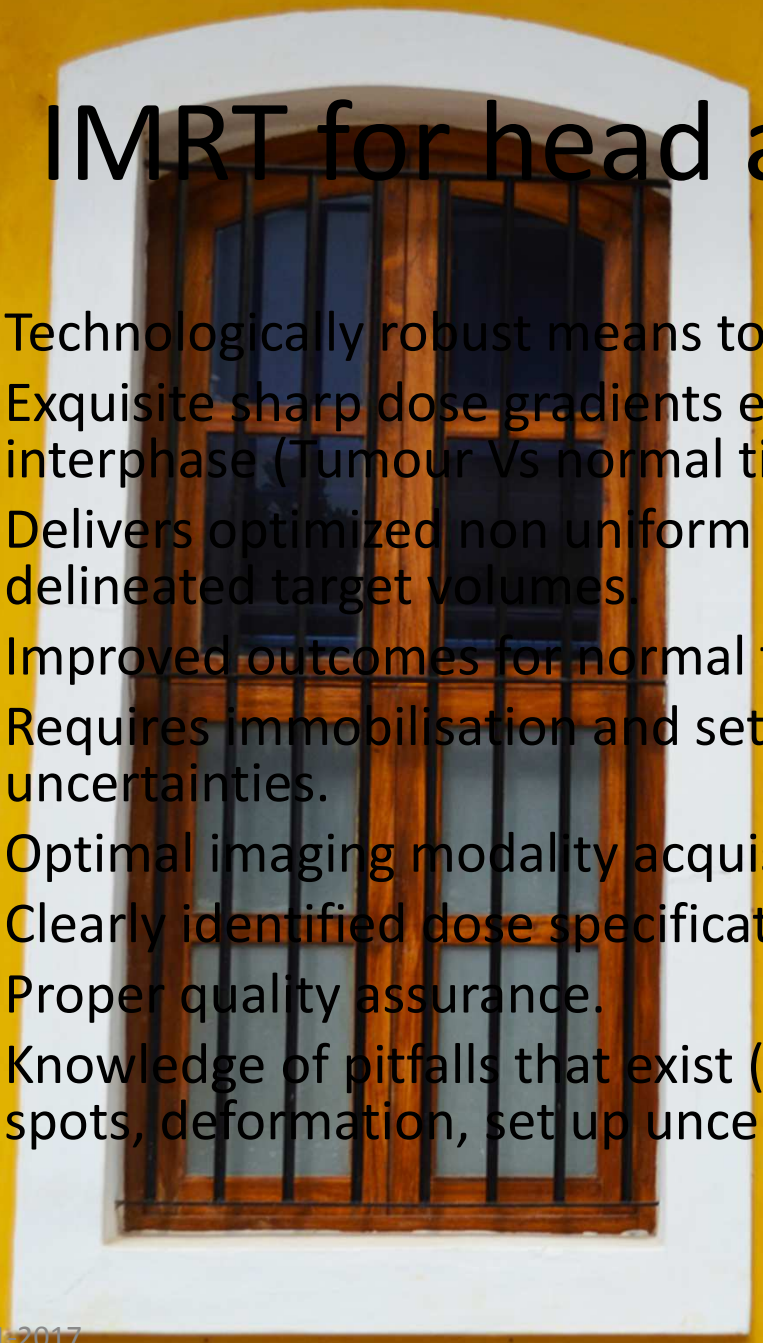
IMRT for head and neck cancer



- Technologically robust means to improve dose delivery:
- Exquisite sharp dose gradients especially in areas of crucial interphase (Tumour Vs normal tissue)
- Delivers optimized non uniform beam intensities to precisely delineated target volumes.
- Improved outcomes for normal tissues.
- Requires immobilisation and set-up issues and knowledge of uncertainties.
- Optimal imaging modality acquisition and registration.
- Clearly identified dose specification and prescription.
- Proper quality assurance.
- Knowledge of pitfalls that exist (poor dilineation, hot and cold spots, deformation, set up uncertainties etc)

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CLINICAL INVESTIGATION

MULTI-INSTITUTIONAL TRIAL OF ACCELERATED HYPOFRACTIONATED INTENSITY-MODULATED RADIATION THERAPY FOR EARLY-STAGE OROPHARYNGEAL CANCER (RTOG 00-22)

Table 3. Acute toxicity Grade ≥2 for 67 patients (%)

	Grade		
	2	3	4
Gastrointestinal	46	31	4
Dysphagia	37	15	0
Mucositis	31	25	1
Esophagitis	3	0	0
Dry mouth	49	0	0
Salivary gland changes	42	0	0
Taste disturbance	16	0	0
Nausea	6	3	0
Vomiting	3	3	0
Dehydration	12	1	0
Anorexia	0	3	3
Other	0	1	0
Skin	21	10	0
Pain	16	4	0
Pulmonary	1	1	0
Blood	0	4	0
Constitutional symptoms	28	0	0
Auditory	1	0	0
Infection febrile neutropenia	1	0	0
Neurology	1	0	0

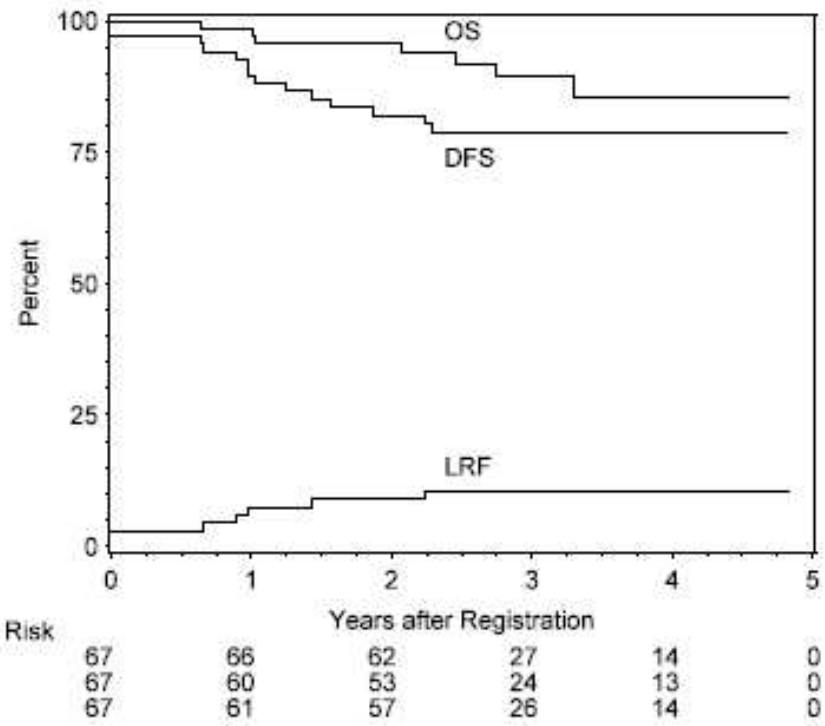


Fig. 1. Kaplan-Meier estimates of overall survival (OS) and disease-free survival (DFS) and cumulative incidence of local-regional failure (LRF).

Eisbruch et al, IJROBP 2009

XEROSTOMIA AND QUALITY OF LIFE AFTER INTENSITY-MODULATED RADIOTHERAPY VS. CONVENTIONAL RADIOTHERAPY FOR EARLY-STAGE NASOPHARYNGEAL CARCINOMA: INITIAL REPORT ON A RANDOMIZED CONTROLLED CLINICAL TRIAL

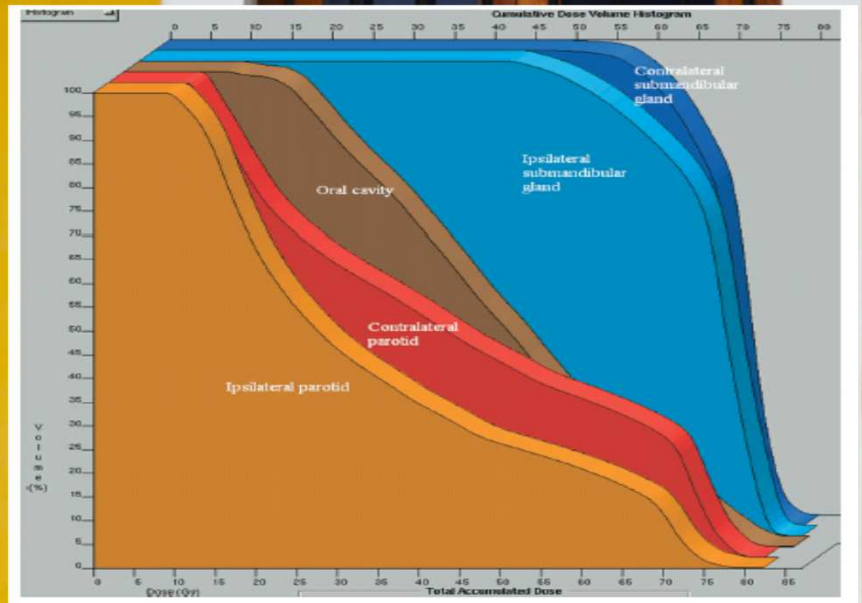


Fig. 1. Dose–volume histogram of the salivary glands for an intensity-modulated radiotherapy patient.

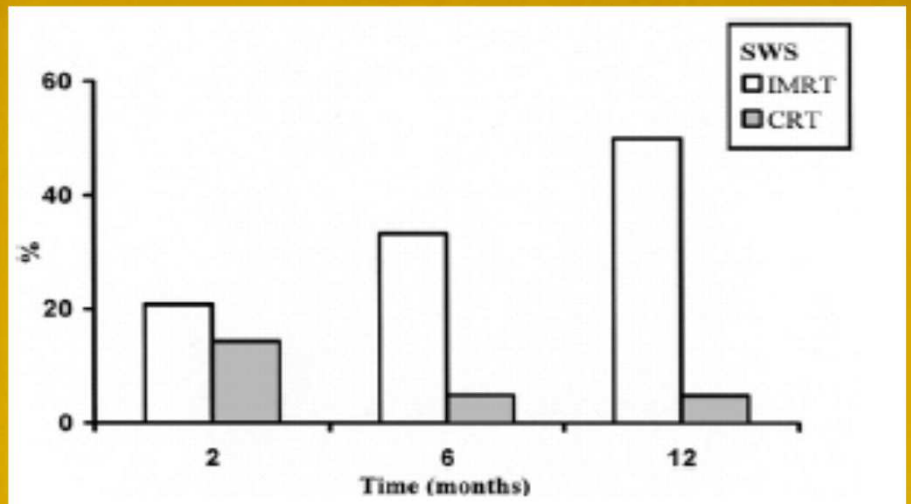


Fig. 2. Intensity-modulated radiotherapy (IMRT) and conventional radiotherapy (CRT) patients (%) who had recovered at least 25% of preradiotherapy stimulated whole salivary (SWS) flow at 2, 6, and 12 months postradiotherapy.

Conclusions: IMRT was significantly better than CRT in terms of parotid sparing and improved QoL for early-stage disease. The findings support the case for assessment of health-related QoL in relation to head-and-neck cancer using a site-specific approach. © 2006 Elsevier Inc.

Pow et al, IJROBP 2006

Prospective Randomized Study of Intensity-Modulated Radiotherapy on Salivary Gland Function in Early-Stage Nasopharyngeal Carcinoma Patients

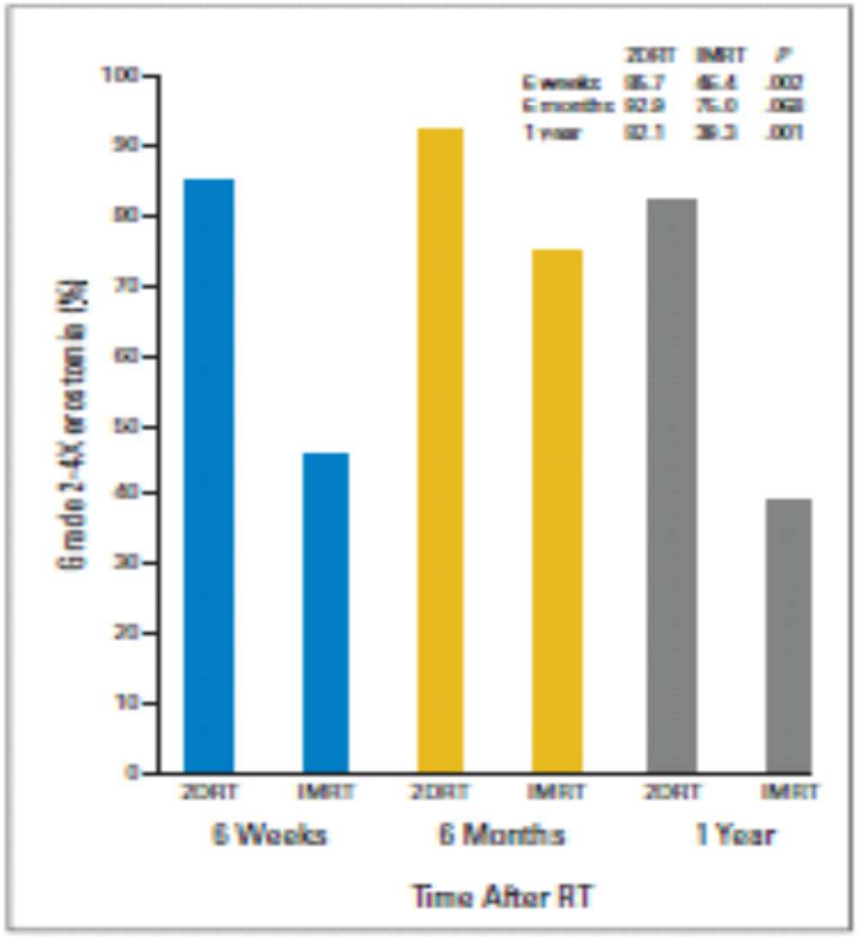


Fig 2. Histogram showing the incidence of Radiation Therapy Oncology Group (RTOG)/European Organisation for the Research and Treatment of Cancer (EORTC) grade 2 to 4 xerostomia in patients treated by two-dimensional radiation therapy (2DRT) and intensity-modulated radiation therapy (IMRT).

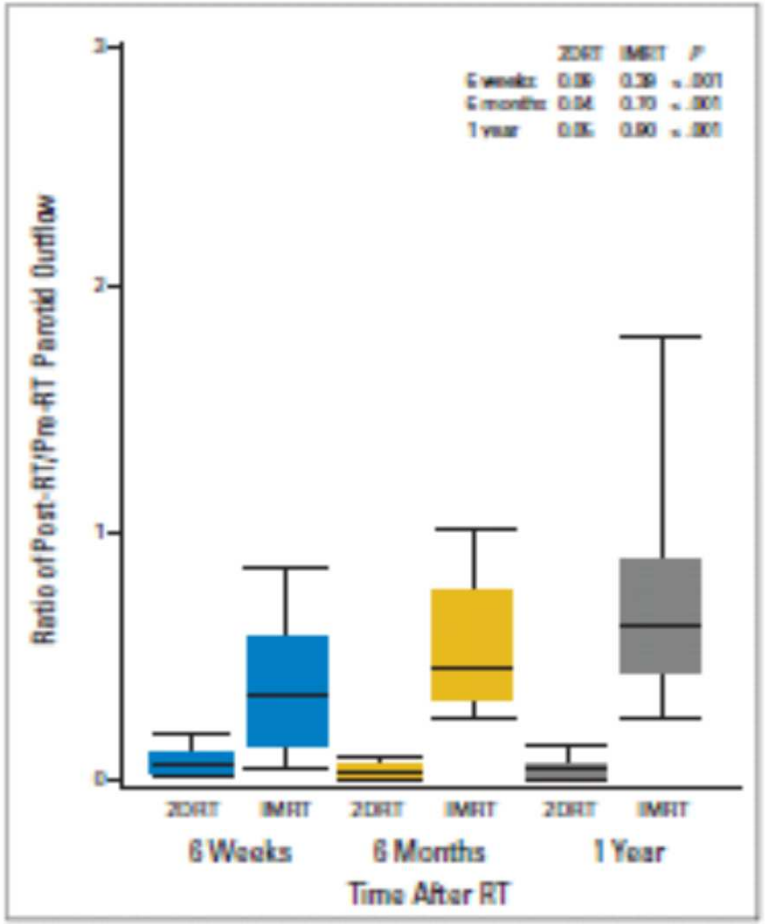
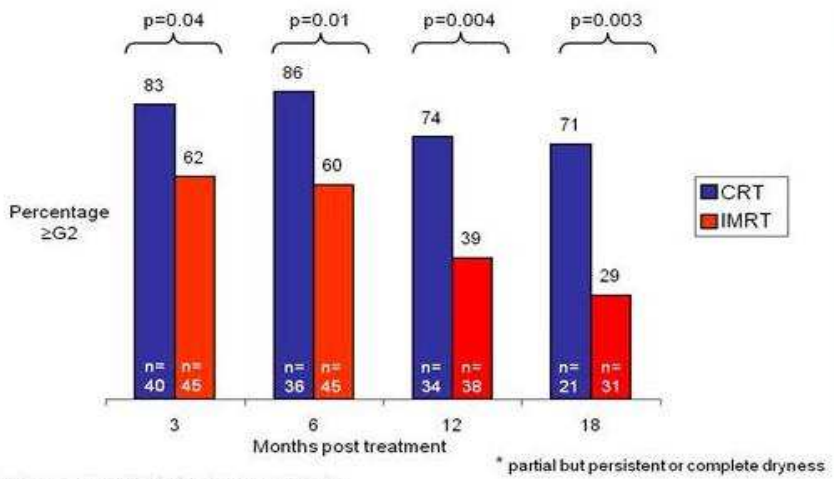


Fig 3. Changes in fractional stimulated parotid flow rate (SPFR) after two-dimensional radiation therapy (2DRT) and intensity-modulated radiation therapy (IMRT). Spread of data denoted by box whiskers plot: box limits represent 25 and 75 percentiles, line within box median, whisker ends 1 and 99 percentiles; comparison of means denoted in inserts.

Kam et al, J Clin Oncol 2006

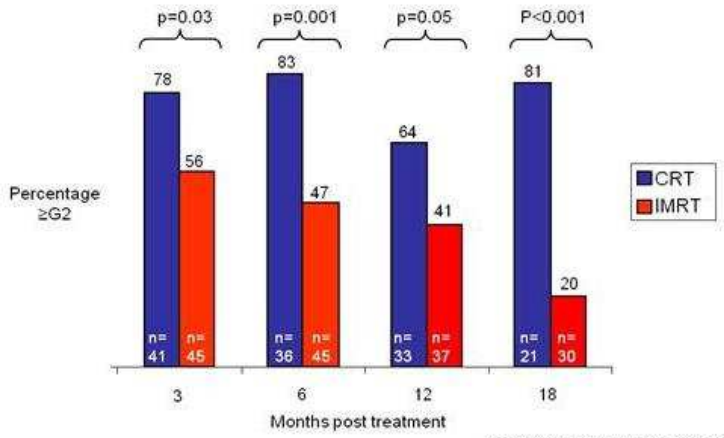
LENT SOM Subjective Xerostomia* rates



* partial but persistent or complete dryness

First Results of the PARSPORT Trial, Proc ASCO 2009

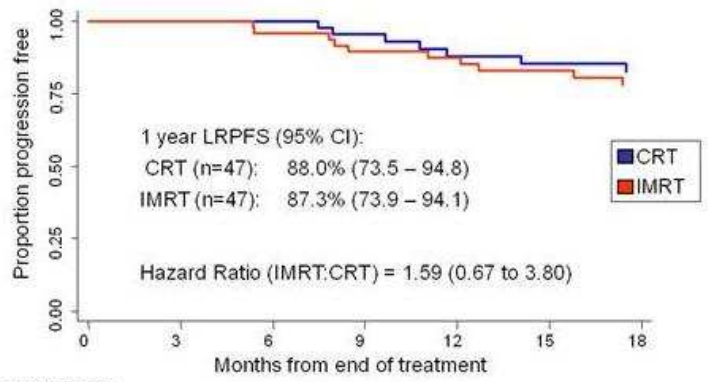
RTOG Subjective Salivary Gland toxicity ≥G2*



*Moderate or complete dryness of mouth poor or no response on stimulation

First Results of the PARSPORT Trial, Proc ASCO 2009

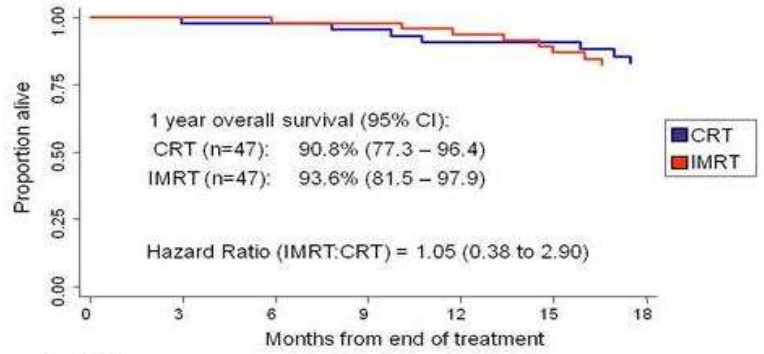
Loco-Regional Progression Free Survival (LRPFS)



n events/at risk				
CRT	0/47	0/45	5/36	2/28
IMRT	0/47	2/46	4/41	6/30

First Results of the PARSPORT Trial, Proc ASCO 2009

Overall Survival



n events/at risk				
CRT	0/47	1/44	3/40	3/32
IMRT	0/47	1/47	2/45	5/34

First Results of the PARSPORT Trial, Proc ASCO 2009

PARSPORT: Nutting et al, Lancet Oncol 2010

Significant reduction in acute salivary gland toxicity

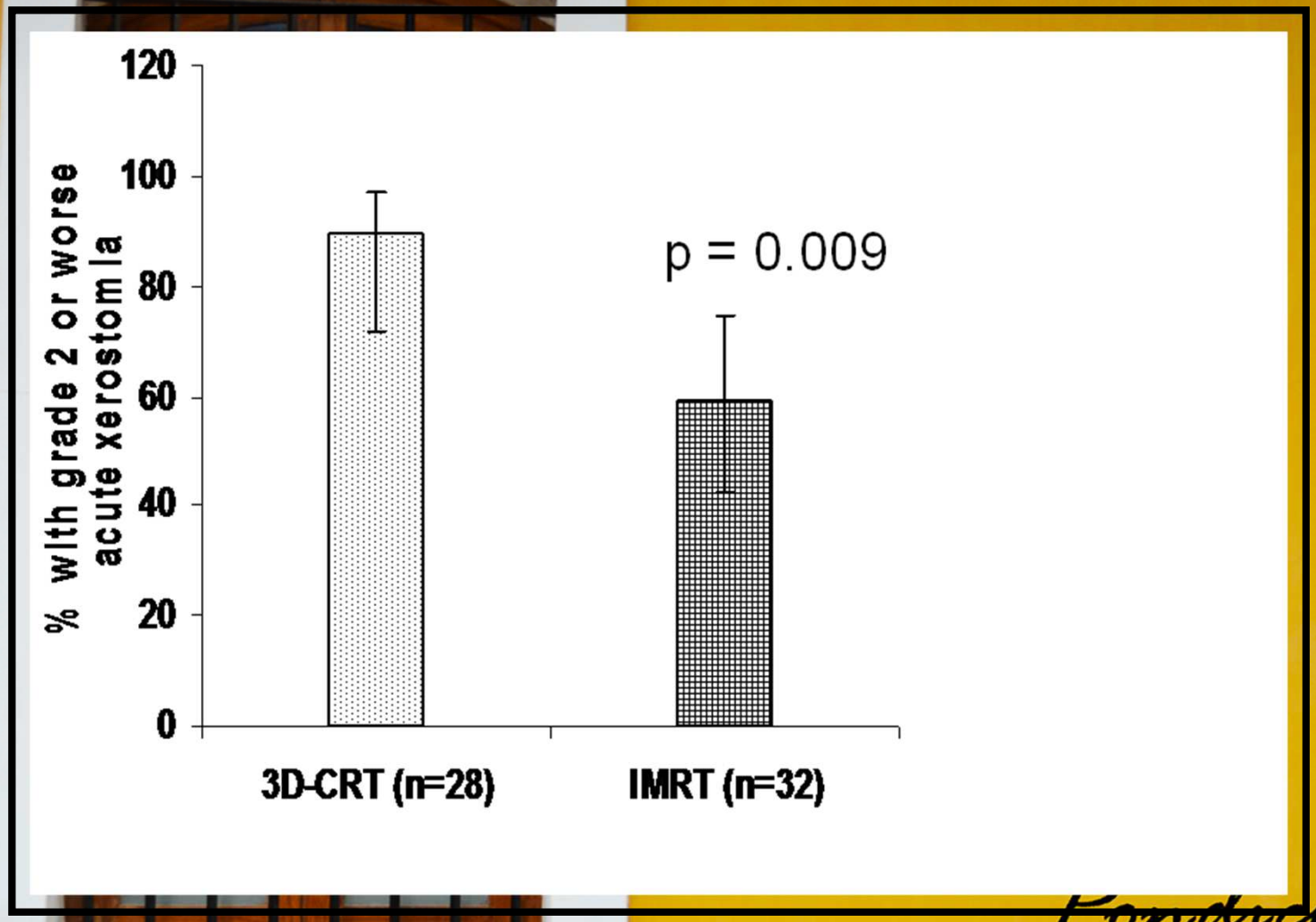


Fig. 2. Proportion of patients with grade 2 or worse acute salivary gland toxicity in 3D-CRT and IMRT arms (error bars represent 95% CIs).

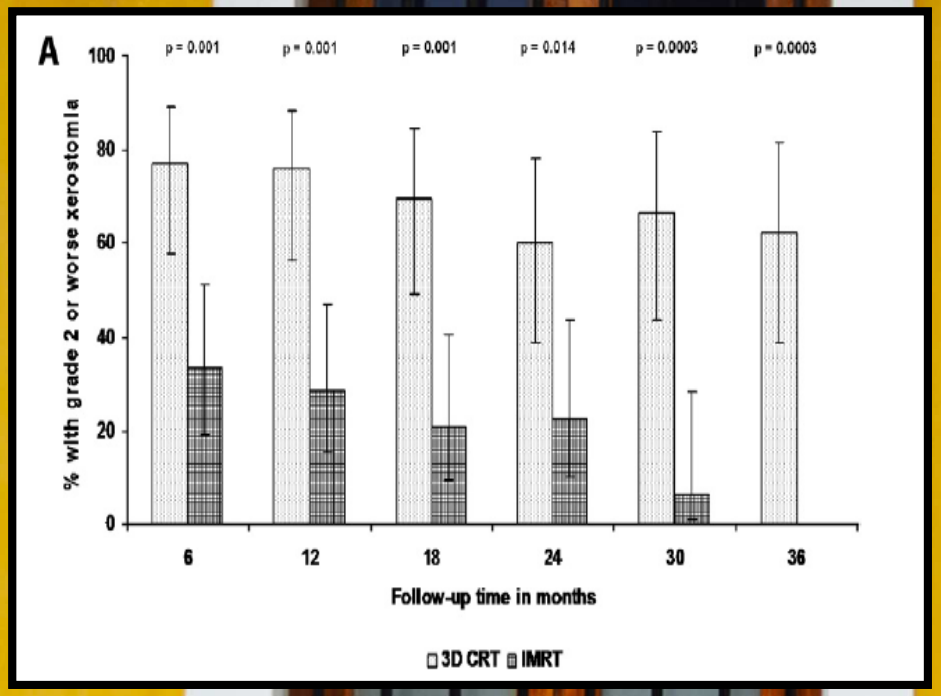
Tejpal Gupta, Radiotherapy Oncol

Table 2
Comparison of acute toxicity of radiotherapy between the two arms.

Toxicity	3D-CRT ($n = 28$)	IMRT ($n = 32$)	p-Value
Acute salivary toxicity			
Grade 0	0 (0%)	1 (3%)	
Grade 1	3 (11%)	12 (38%)	
Grade 2	25 (89%)	19 (59%)	0.03
Acute dermatitis			
Grade 1	1 (3.5%)	2 (6%)	
Grade 2	22 (78.5%)	28 (88%)	
Grade 3	5 (18%)	2 (6%)	0.35
Acute mucositis			
Grade 1	2 (7%)	7 (22%)	
Grade 2	22 (78.5%)	23 (71%)	
Grade 3	4 (14.5%)	2 (6%)	0.20
Acute dysphagia			
Grade 0	1 (3.5%)	1 (3%)	
Grade 1	7 (25%)	12 (37.5%)	
Grade 2	20 (71.5%)	16 (50%)	
Grade 3	0 (0%)	3 (9.5%)	0.21
Weight loss			
No weight loss	2 (7%)	3 (9.5%)	
<10% weight loss	16 (57%)	24 (75%)	
⩾10% weight loss	10 (36%)	5 (15.5%)	0.2

Tejpal Gupta, Radiotherapy Oncol

Comparison of late toxicity



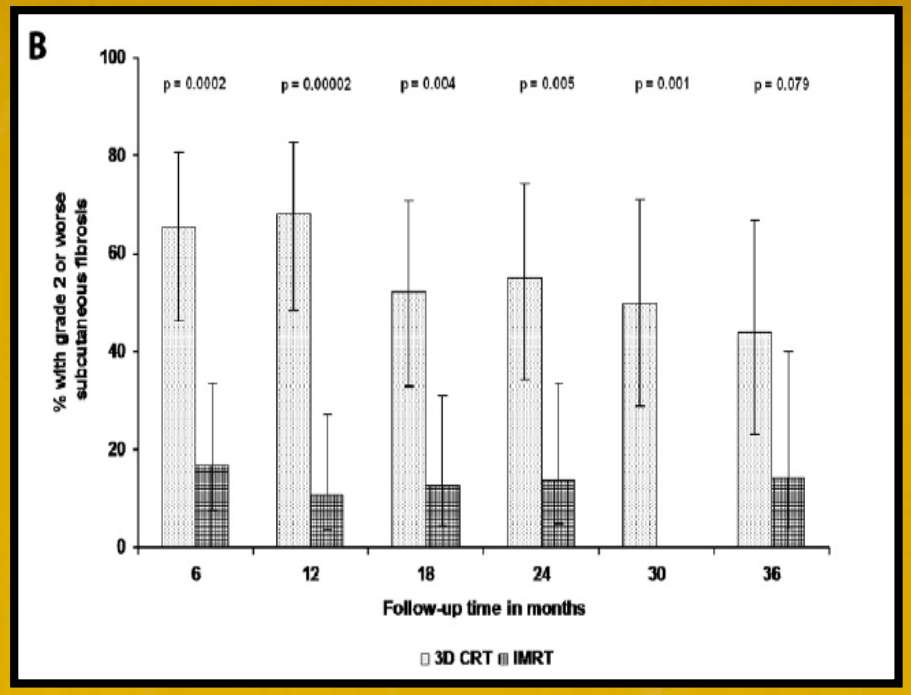
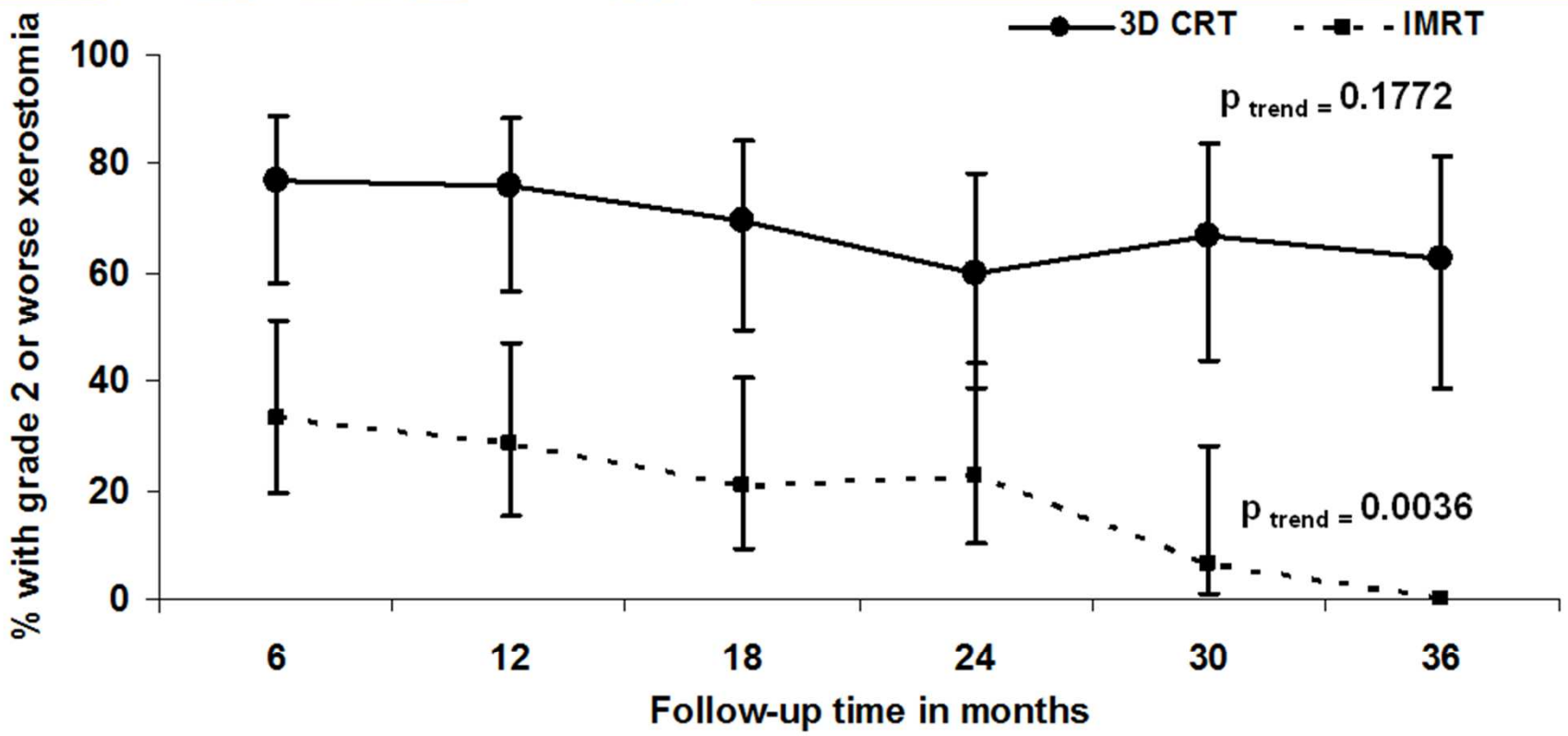


Fig. 3. Proportion of patients with grade 2 or worse late xerostomia (A) and subcutaneous fibrosis (B) in either arm at pre-specified intervals (error bars represent 95% CIs). Note the statistically significant *p*-value favoring IMRT at all time points.

Recovery of salivary function over time



No. at risk						
3D-CRT	26	25	23	20	18	16
IMRT	30	28	24	22	16	14

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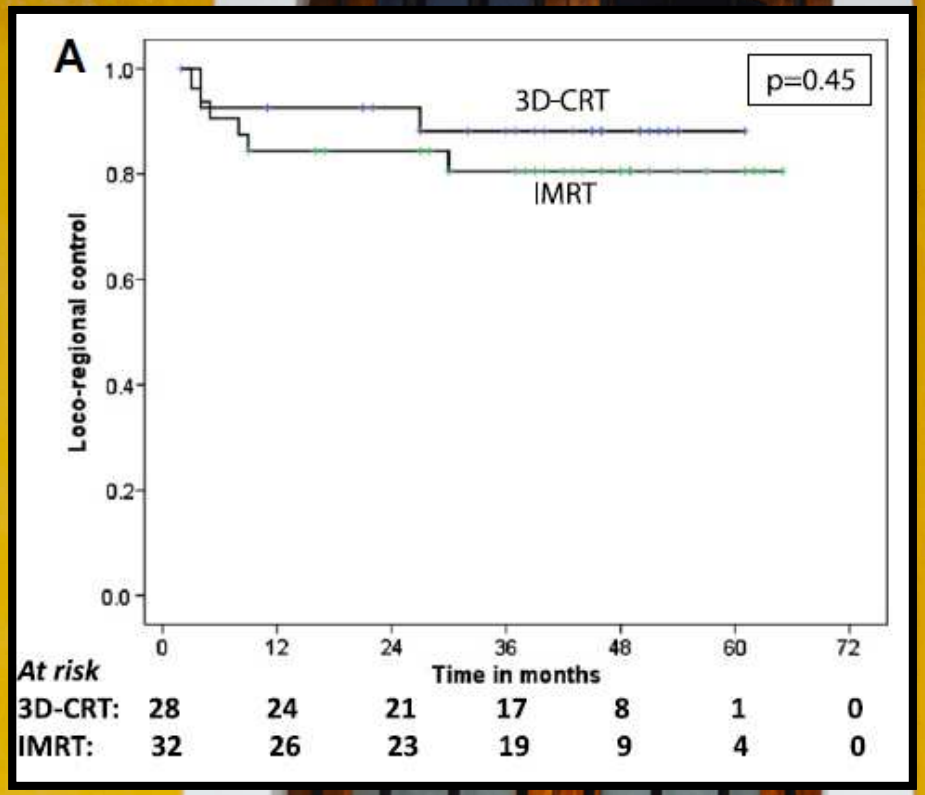
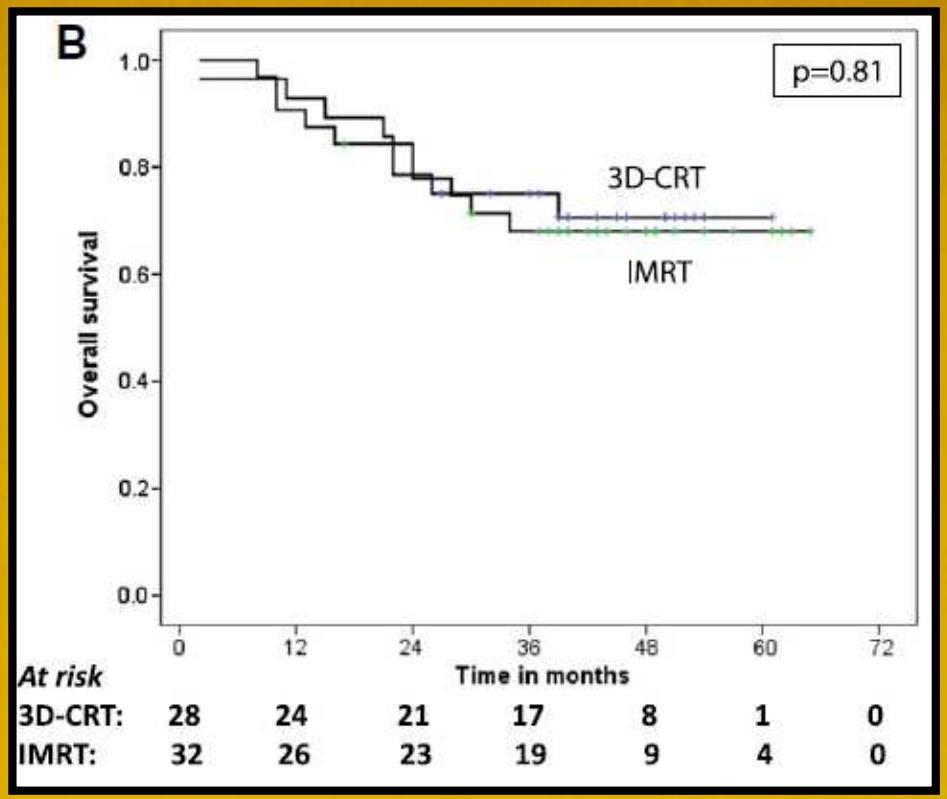
No difference in disease outcomes





Median FU: 40 months (IQR = 26-50 months)

Fig. 4. Kaplan–Meier estimates of loco-regional control (A) and overall survival (B) by randomization arm.

Tejpal Gupta, Radiotherapy Oncol

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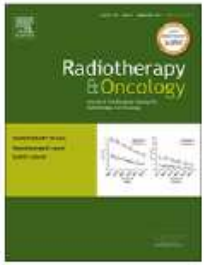


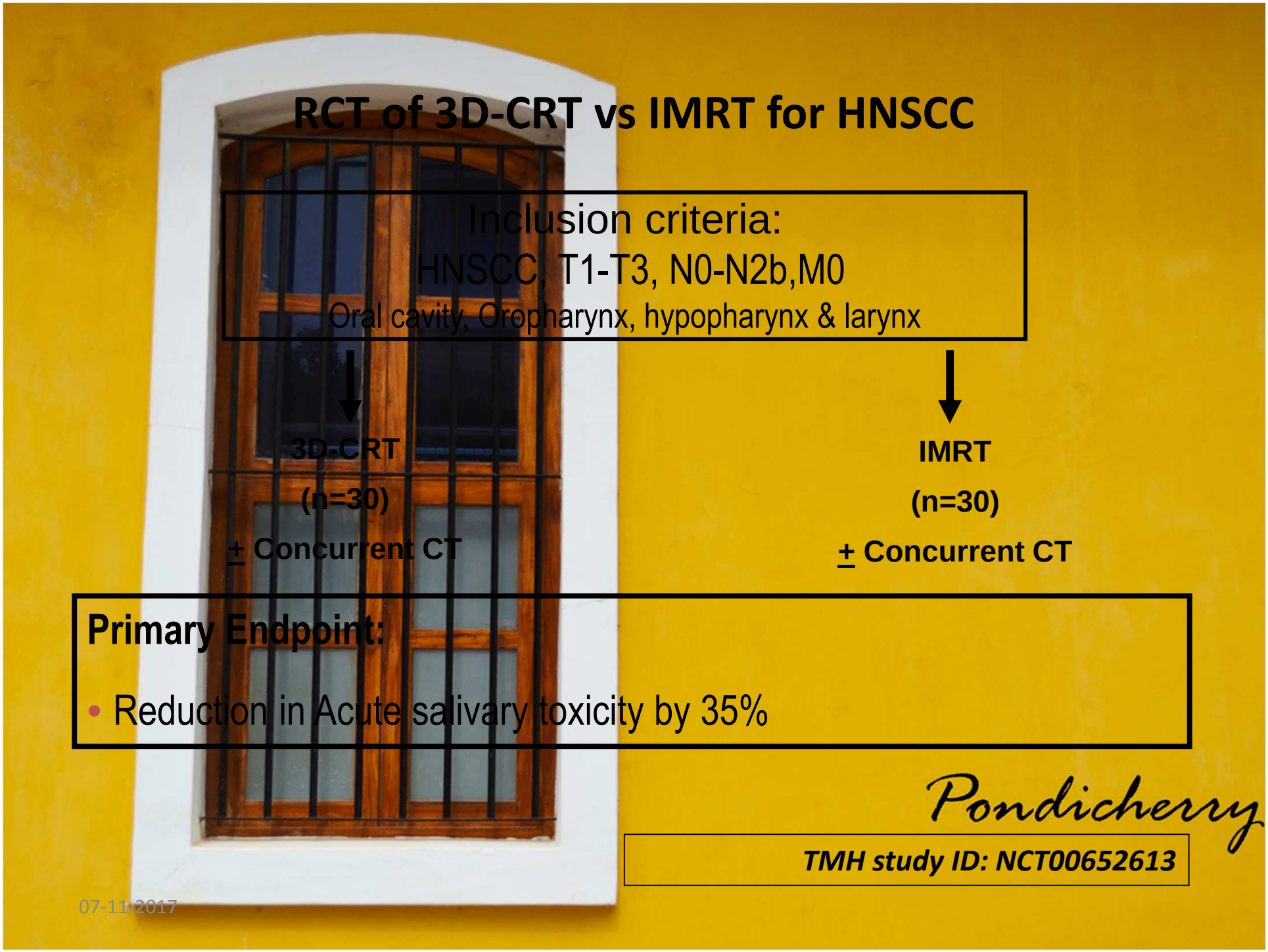
Phase III randomised trial

Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: A randomized controlled trial ☆

Tejpal Gupta [a,*], JaiPrakash Agarwal [b], Sandeep Jain [a], Reena Phurailatpam [a], Sadhana Kannan [a], Sarbani Ghosh-Laskar [b], Vedang Murthy [a], Ashwini Budrukkar [b], Ketayun Dinshaw [b], Kumar Prabhash [b], Pankaj Chaturvedi [b], Anil D'Cruz [b]

[a] *Advanced Centre for Treatment, Research & Education in Cancer (ACTREC), Tata Memorial Centre, Navi Mumbai, India;* [b] *Tata Memorial Hospital (TMH), Tata Memorial Centre, Navi Mumbai, India*

Conclusion: IMRT significantly reduces the incidence and severity of xerostomia compared to 3D-CRT in curative-intent irradiation of HNSCC.



RCT of 3D-CRT vs IMRT for HNSCC

Inclusion criteria:

HNSCC, T1-T3, N0-N2b,M0

Oral cavity, Oropharynx, hypopharynx & larynx

3D-CRT

(n=30)

± Concurrent CT

IMRT

(n=30)

± Concurrent CT

Primary Endpoint:

- Reduction in Acute salivary toxicity by 35%

Pondicherry

TMH study ID: NCT00652613

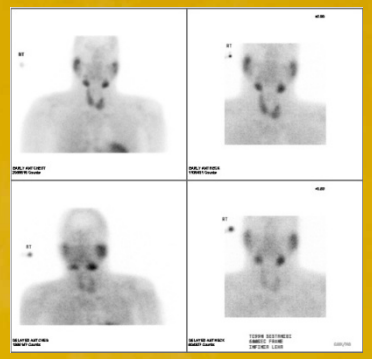
Salivary Function

Methods used:

- Xerostomia related QOL analysis: EORTC QLQ H&N35
- Sialometry
- Salivary Scintigraphy

Estimation done:

- At pre-RT, 2 , 6, 12 months and then yearly evaluation

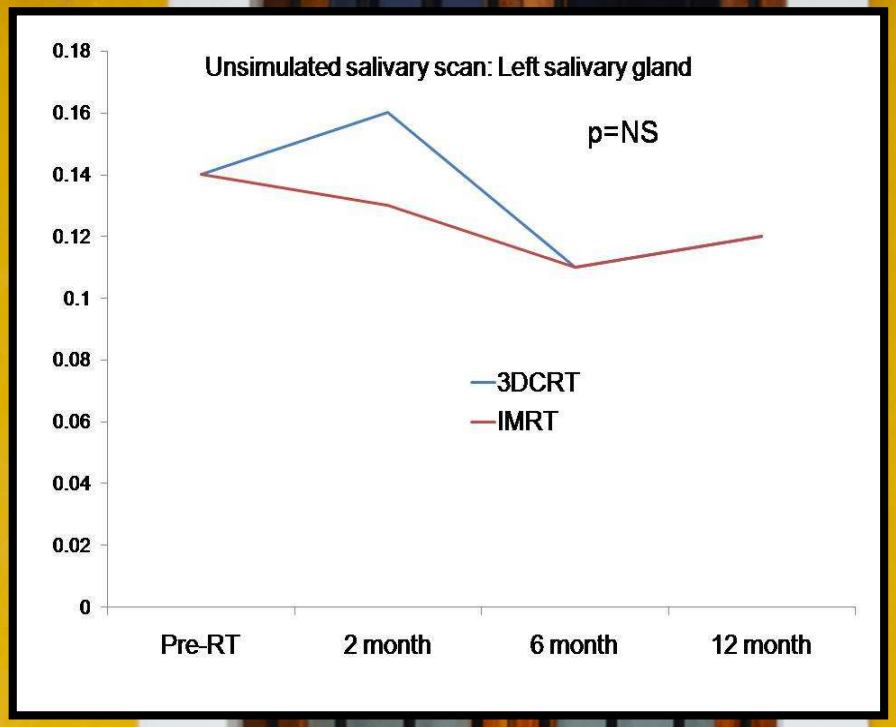


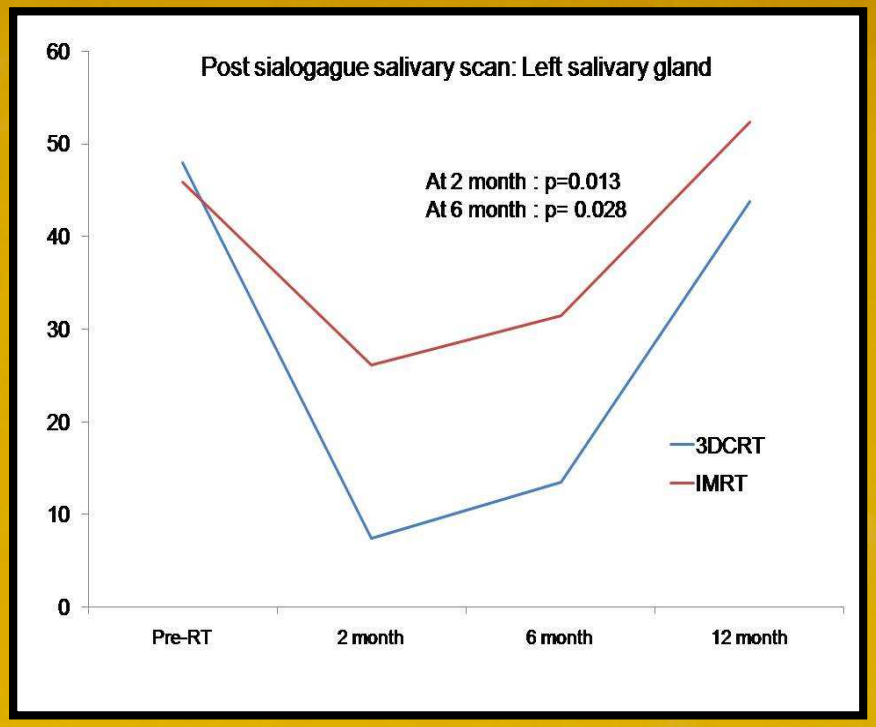
Analysis done:

- Estimation of salivary function by scintigraphy (stimulated & unstimulated)
- Correlation of dose & salivary function
- Correlation of QOL and salivary scan findings

Pondicherry

Impact of RT technique on salivary function: contralateral parotid gland





No significant difference in unstimulated salivary function.

Significant preservation of post-sialogogue function with IMRT

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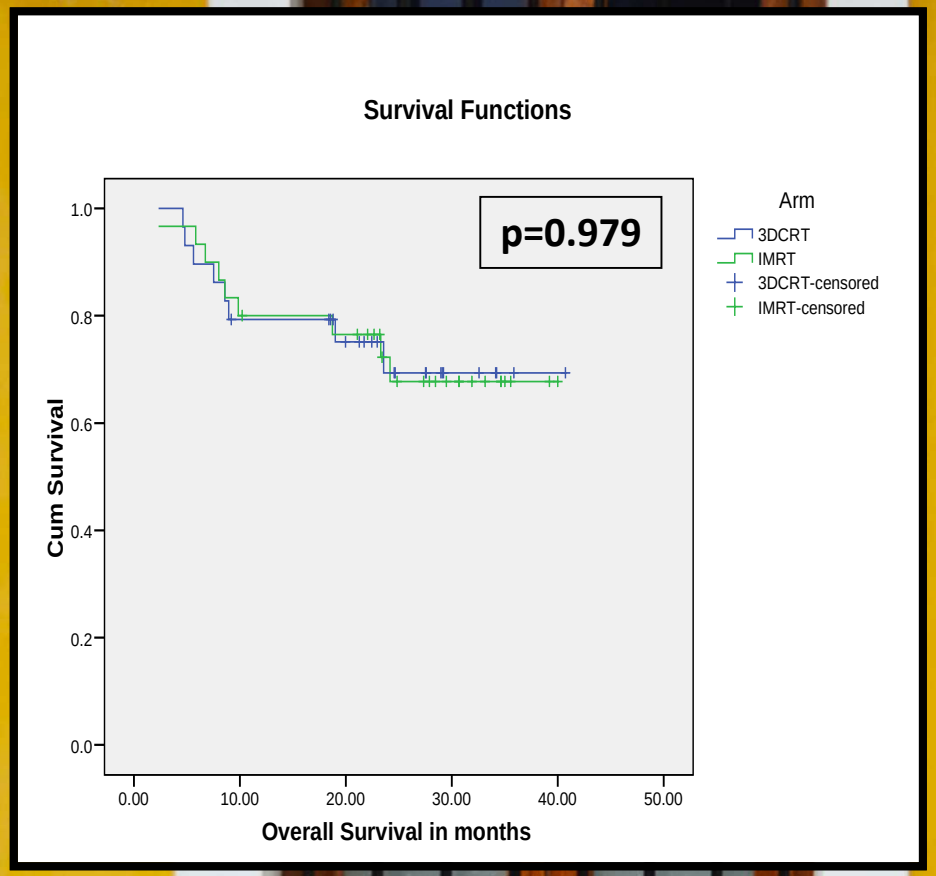
Ghosh-Laskar et al (unpublished data)

No difference in overall survival



	Deaths by arm	
	3D-CRT (N=30)	IMRT (N=30)
Oropharynx	5	6
Larynx	1	1
Hypopharynx	2	2
Total Deaths (n)	**8**	**9**

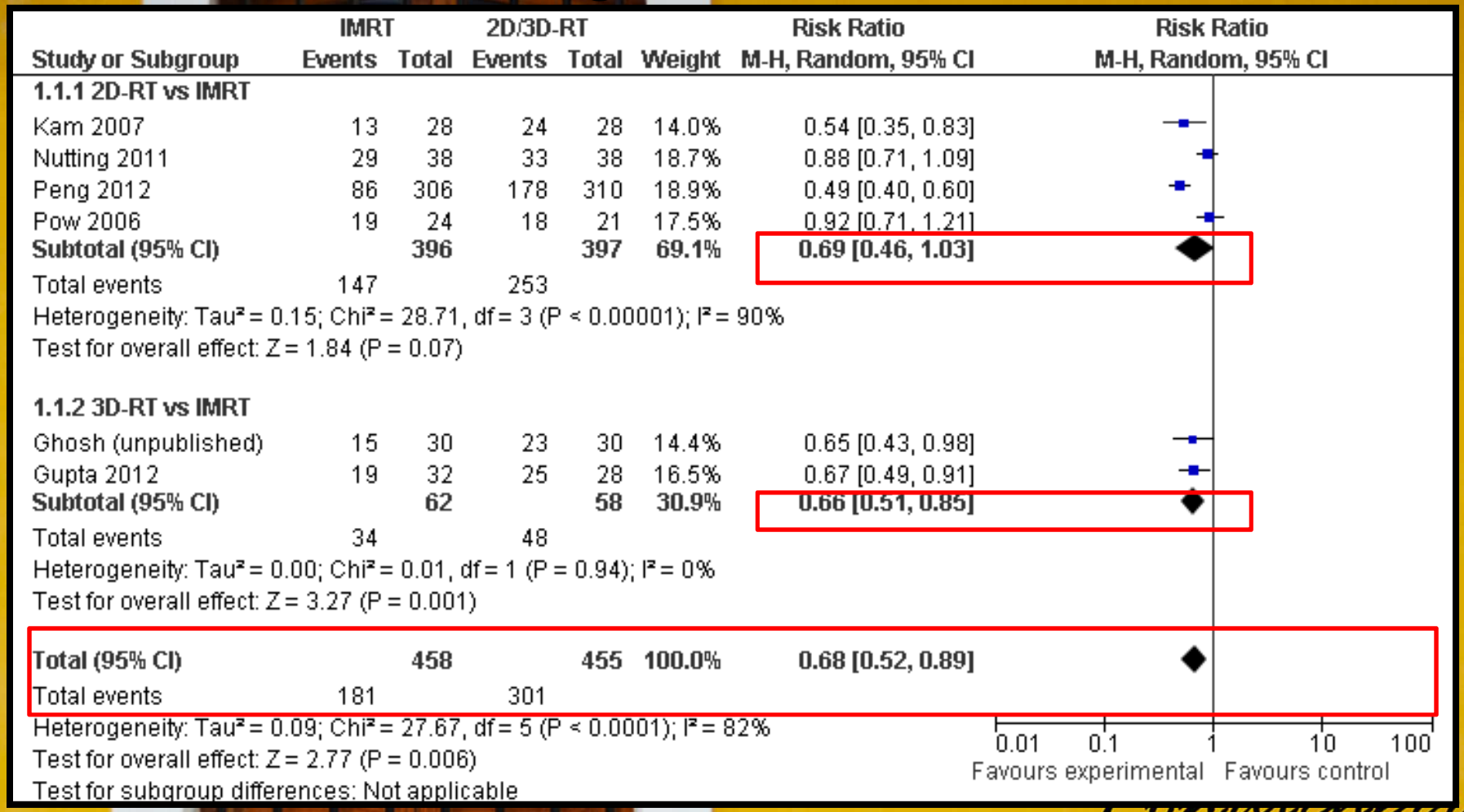
Median FU: 23.4 months
Range: 2-40 months

Pondicherry

Ghosh-Laskar et al Head Neck 2015

Meta-analysis on IMRT in HNC

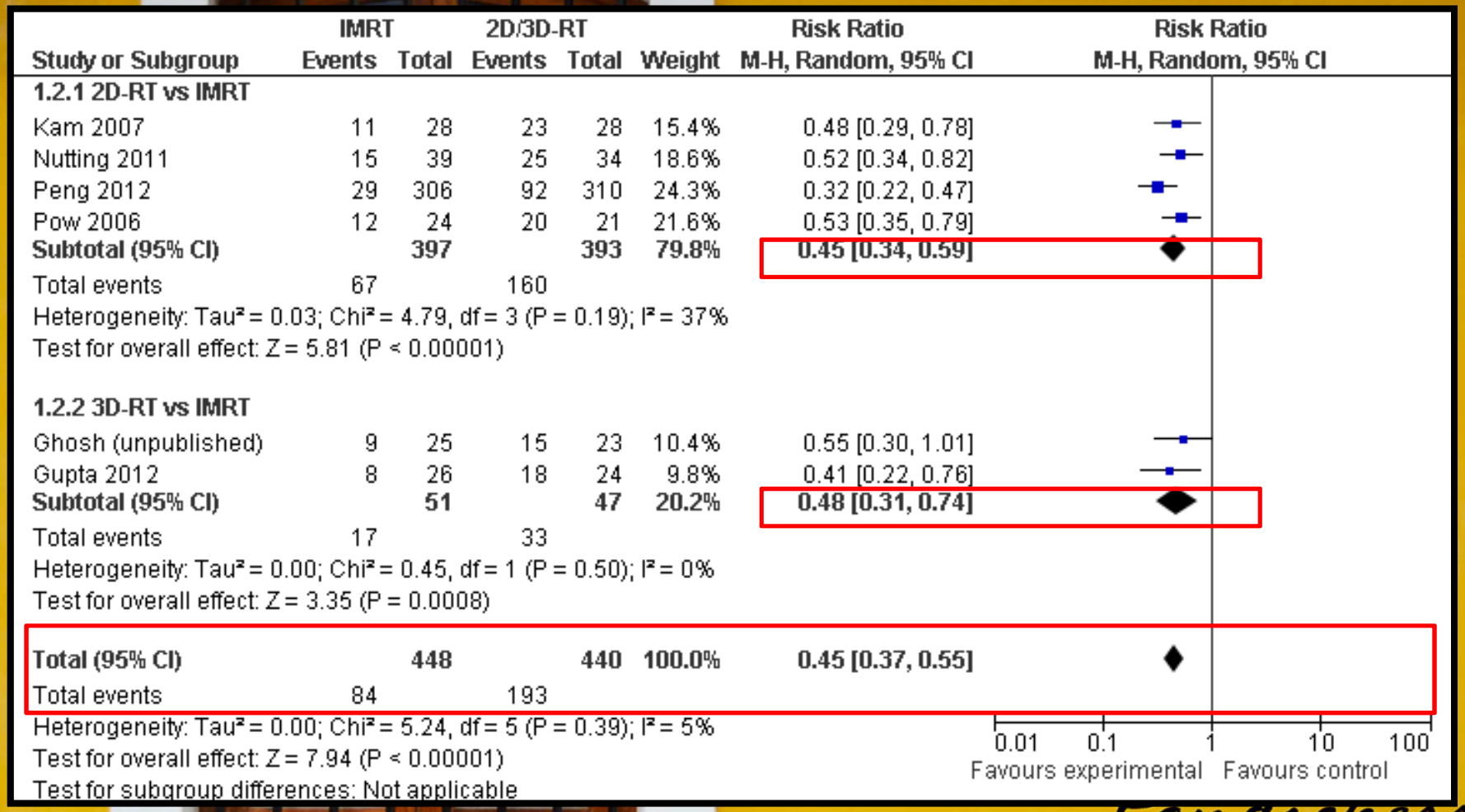
Acute ≥grade 2 xerostomia



Overall significant reduction in acute grade 2 or worse xerostomia

Courtesy: Dr Tejpal Gupta

Late ≥grade 2 xerostomia

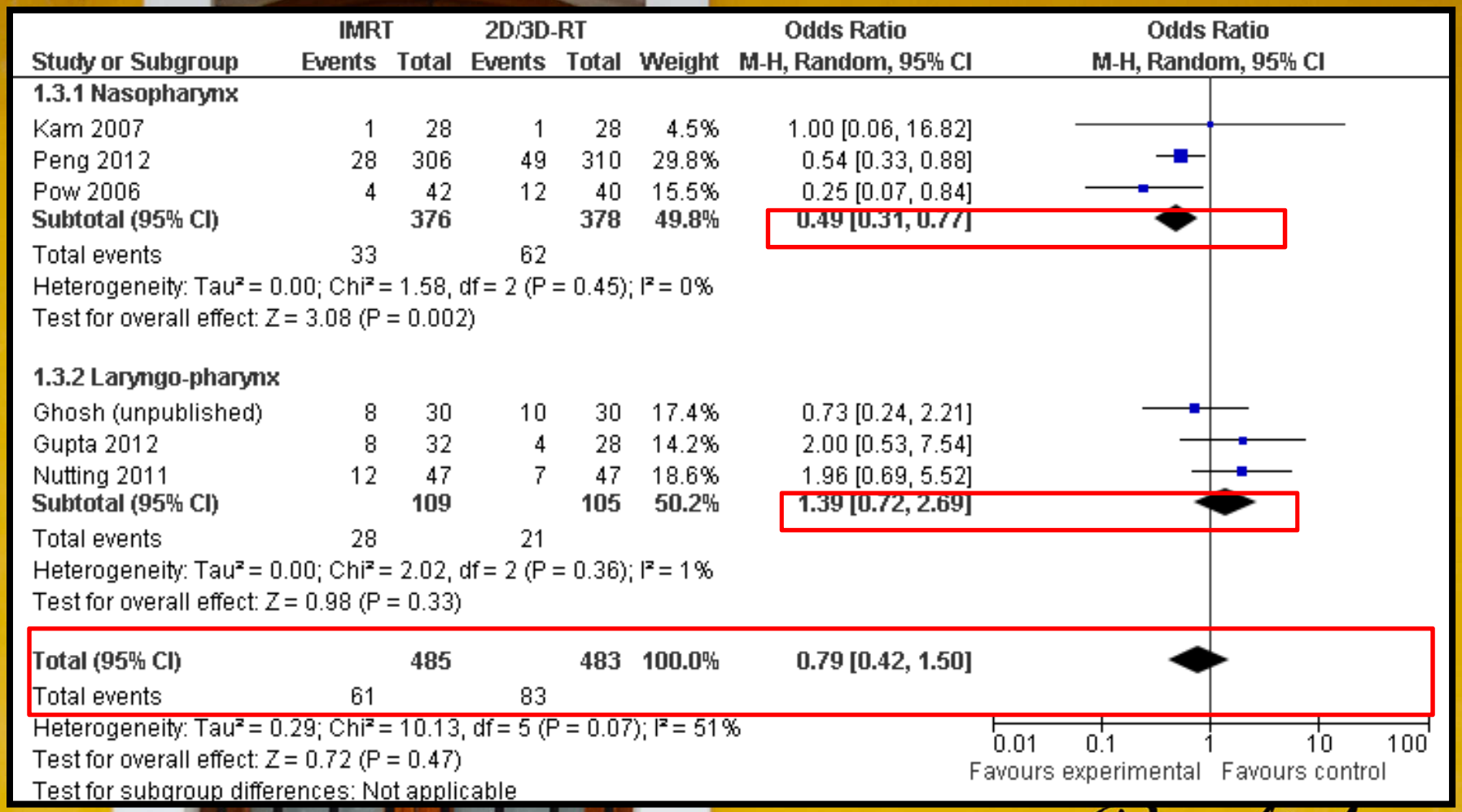


Study or Subgroup	IMRT Events	IMRT Total	2D/3D-RT Events	2D/3D-RT Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 2D-RT vs IMRT						
Kam 2007	11	28	23	28	15.4%	0.48 [0.29, 0.78]
Nutting 2011	15	39	25	34	18.6%	0.52 [0.34, 0.82]
Peng 2012	29	306	92	310	24.3%	0.32 [0.22, 0.47]
Pow 2006	12	24	20	21	21.6%	0.53 [0.35, 0.79]
Subtotal (95% CI)		**397**		**393**	**79.8%**	**0.45 [0.34, 0.59]**
Total events	67		160			
Heterogeneity: Tau² = 0.03; Chi² = 4.79, df = 3 (P = 0.19); I² = 37%						
Test for overall effect: Z = 5.81 (P < 0.00001)						
1.2.2 3D-RT vs IMRT						
Ghosh (unpublished)	9	25	15	23	10.4%	0.55 [0.30, 1.01]
Gupta 2012	8	26	18	24	9.8%	0.41 [0.22, 0.76]
Subtotal (95% CI)		**51**		**47**	**20.2%**	**0.48 [0.31, 0.74]**
Total events	17		33			
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 3.35 (P = 0.0008)						
Total (95% CI)		**448**		**440**	**100.0%**	**0.45 [0.37, 0.55]**
Total events	84		193			
Heterogeneity: Tau² = 0.00; Chi² = 5.24, df = 5 (P = 0.39); I² = 5%						
Test for overall effect: Z = 7.94 (P < 0.00001)						
Test for subgroup differences: Not applicable						

Unequivocal and consistent evidence of reduced late xerostomia with IMRT

Courtesy: Dr Tejpal Gupta

Loco-regional control



Study or Subgroup	IMRT Events	IMRT Total	2D/3D-RT Events	2D/3D-RT Total	Weight	Odds Ratio M-H, Random, 95% CI
1.3.1 Nasopharynx						
Kam 2007	1	28	1	28	4.5%	1.00 [0.06, 16.82]
Peng 2012	28	306	49	310	29.8%	0.54 [0.33, 0.88]
Pow 2006	4	42	12	40	15.5%	0.25 [0.07, 0.84]
Subtotal (95% CI)		**376**		**378**	**49.8%**	**0.49 [0.31, 0.77]**
Total events	33		62			
Heterogeneity: Tau² = 0.00; Chi² = 1.58, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 3.08 (P = 0.002)						
1.3.2 Laryngo-pharynx						
Ghosh (unpublished)	8	30	10	30	17.4%	0.73 [0.24, 2.21]
Gupta 2012	8	32	4	28	14.2%	2.00 [0.53, 7.54]
Nutting 2011	12	47	7	47	18.6%	1.96 [0.69, 5.52]
Subtotal (95% CI)		**109**		**105**	**50.2%**	**1.39 [0.72, 2.69]**
Total events	28		21			
Heterogeneity: Tau² = 0.00; Chi² = 2.02, df = 2 (P = 0.36); I² = 1%						
Test for overall effect: Z = 0.98 (P = 0.33)						
Total (95% CI)		**485**		**483**	**100.0%**	**0.79 [0.42, 1.50]**
Total events	61		83			
Heterogeneity: Tau² = 0.29; Chi² = 10.13, df = 5 (P = 0.07); I² = 51%						
Test for overall effect: Z = 0.72 (P = 0.47)						
Test for subgroup differences: Not applicable						

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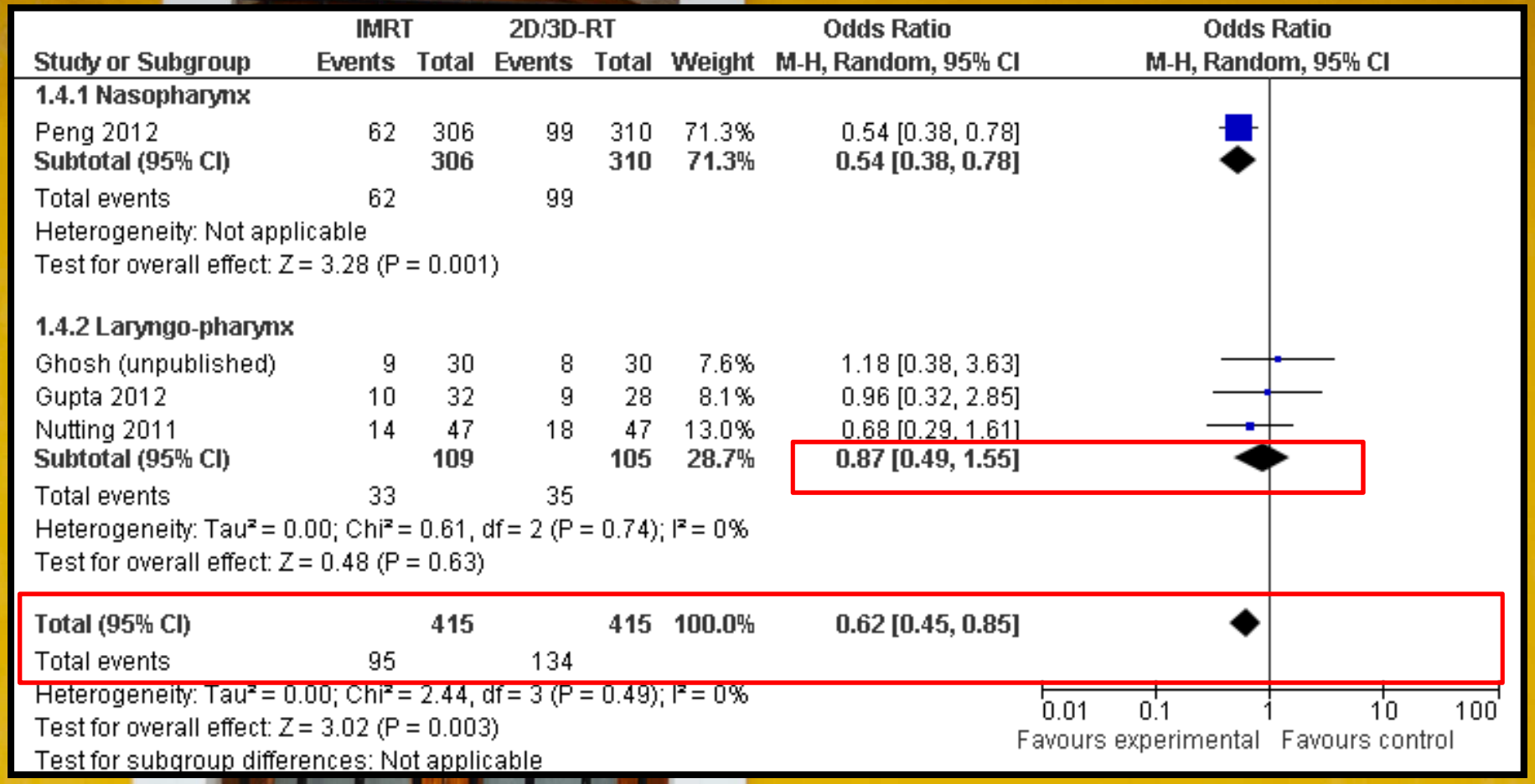
Courtesy: Dr Tejpal Gupta

Overall survival



Overall survival better with IMRT (more so in nasopharyngeal cancers)

Largely driven by results of the large nasopharynx trial

Courtesy: Dr Tejpal Gupta

Quality-of-life

1. QOL results formally reported in only 3 of the 6 RCTs
2. Different instruments used in different studies (SF36, EORTC, XQ)
3. Difficult to pool & meta-analyze such data
4. Global QOL not significantly different between 2D/3D-RT and IMRT
5. Most QOL domains either better or similar to conventional RT
6. Only fatigue was worse with IMRT (as reported in PARSPORT)
7. Xerostomia-specific QOL better preserved with IMRT in all 3 studies
8. Patient-reported outcomes & QOL worse than physician-rated outcomes

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Courtesy: Dr Tejpal Gupta

Which is the best system for Head-Neck IMRT?

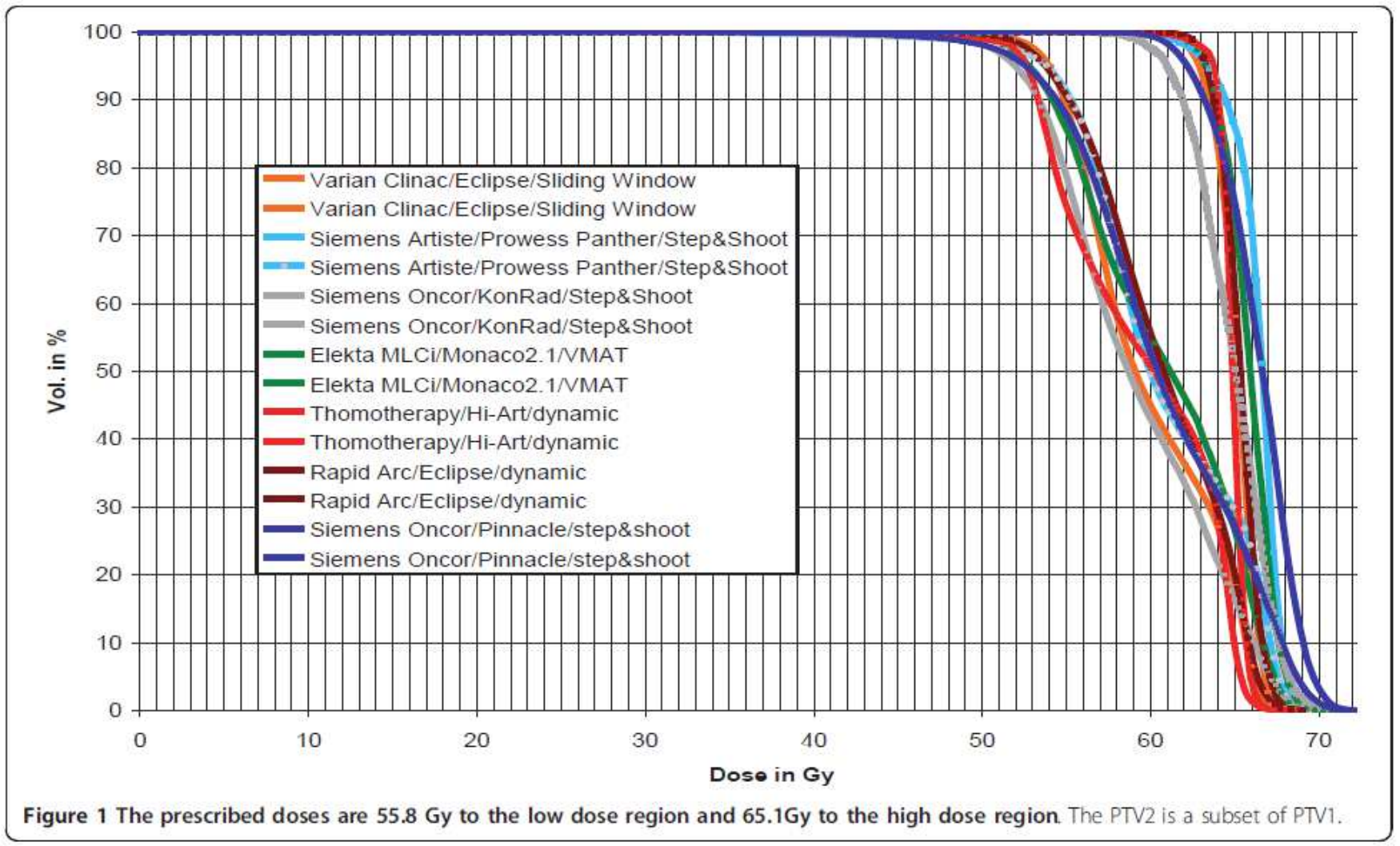


Figure 1 The prescribed doses are 55.8 Gy to the low dose region and 65.1Gy to the high dose region. The PTV2 is a subset of PTV1.

Is there any 'impact' of IMRT on QOL?

Study	Mean parotid dose in gray (Gy)				Benefit from IMRT		
	IMRT		RT		Xerostomia	Functional	QoL
			Conventional	Conformal			
Pow [15]	Ipsilateral	42 Gy (4.7; 31.3–51.2)	n.a	–	–	Yes	No
Mean (SD; range)	Contralateral	41.3 Gy (5.4; 33.1–51.8)					
Vergeer [17]	Ipsilateral	28.7 Gy (11.9)	Bilateral	–	Yes	Yes	Yes
Mean (SD)	Contralateral	23.3 Gy (11.2)	43.0 Gy				
Jabbari [11]	Ipsilateral	50 Gy (38.7–67.8)	Bilateral	–	Yes[a]	–	Yes[a]
Mean (Range)	Contralateral	21.8 Gy (14–35.5)	55.0 Gy				
Fang [9]	n.a		n.a	n.a	–	Yes[b]	Yes[b]
Fang [8]	Right	47.64 Gy (23.42–63.55)	–	Bilateral	–	No[c]	No[c]
Mean (Range)	Left	46.84 Gy (21.44–64.37)		60.0 Gy			
	Bilateral	33.7 Gy					
	Mean dose < 30 Gy:						
Graff [10]	For one or both parotids in 63.5% of patients		n.a	–	–	Yes	No
Mean	For both parotids in 23.8% of patients						
	Mean dose < 26 Gy:						
	For one or both parotids in 34.9% of patients						
McMillan [13]	Right	38.4 Gy (29.6–46.1)	–	–	–	–	–
Mean (range)	Left	40.4 Gy (29.7–53.4)					
Scrimger [16]	Total Parotid Volume	27.1 Gy (16.5)	–	–	–	–	–
Mean (SD)	Spared Parotid Volume	18.4 Gy (10.5)					
Lin [12]	n.a		–	–	–	–	–
	Right spared parotid volume	22.8 Gy (17.8–27.8)	–	–	–	–	–
Parliament [14]	Left spared parotid volume	20.9 Gy (17.9–24)					
Mean (Range)	Total Parotid Volume	30.0 Gy (26.9–33.1)					
Nutting [ASCO 2009]	Ipsilateral	45 Gy	Ipsilateral 60 Gy	–	Yes	–	n.a[d]
Mean	Contralateral	26 Gy	Contralateral 60 Gy				

Scott-Brown M et al, Radiother Oncol 2010

The Role of IMRT in Head & Neck Cancer: Guideline Recommendations

B. O'Sullivan, R.B. Rumble, P. Warde,
and members of the IMRT Indications Expert Panel

cancer care ontario
program in evidence-based care

RECOMMENDATIONS AND KEY EVIDENCE

If the reduction of xerostomia and improved quality of life are the main outcomes of interest, then IMRT is the recommended treatment for all nasopharyngeal, oropharyngeal, hypopharyngeal, laryngeal, oral cavity, and unknown primary cancers where lymph node regions requiring inclusion in the treatment volume would result in irreparable damage to salivary function if 2D EBRT or 3D EBRT were used due to their inability to maintain salivary doses within their tolerance limits (<26 Gy mean dose). The data provided are applicable to locally advanced disease but are equally applicable to early-stage disease and rare sites (e.g. salivary gland tumours) requiring RT that would otherwise damage these normal structures. In addition, these principles hold for skin malignancy where advantages in sparing normal tissue while achieving target coverage are also relevant.

If treatment-related outcomes (local control, overall survival) are the main outcomes of interest, there are no randomized data to support or refute a recommendation of IMRT over 2D EBRT or 3D EBRT in any head and neck site. However, NPC should ordinarily be treated with IMRT based on treatment-related outcomes as should nasal and paranasal sinus cancer.

Report Date: January 12, 2011

Summary interpretation

1. IMRT significantly reduces incidence of ≥grade 2 xerostomia (both acute & late)
2. Benefit is more pronounced and consistent for late xerostomia (1-year)
3. Benefit is regardless of the site or technique of conventional radiotherapy
4. Significant reduction in xerostomia does not translate into better global QOL
5. However, xerostomia-related domains better preserved or recovered with IMRT
6. IMRT may not improve loco-regional control compared to 2D/3D-RT
7. Improvement in loco-regional control & survival maybe dependent upon site
8. Patients with nasopharyngeal cancers stand to benefit most with IMRT
9. IMRT likely to be more cost-effective than 2D/3D-RT (cost per QALY saved)

Courtesy: Dr Tejpal Gupta

Proton therapy

Table 1 (*continued*)

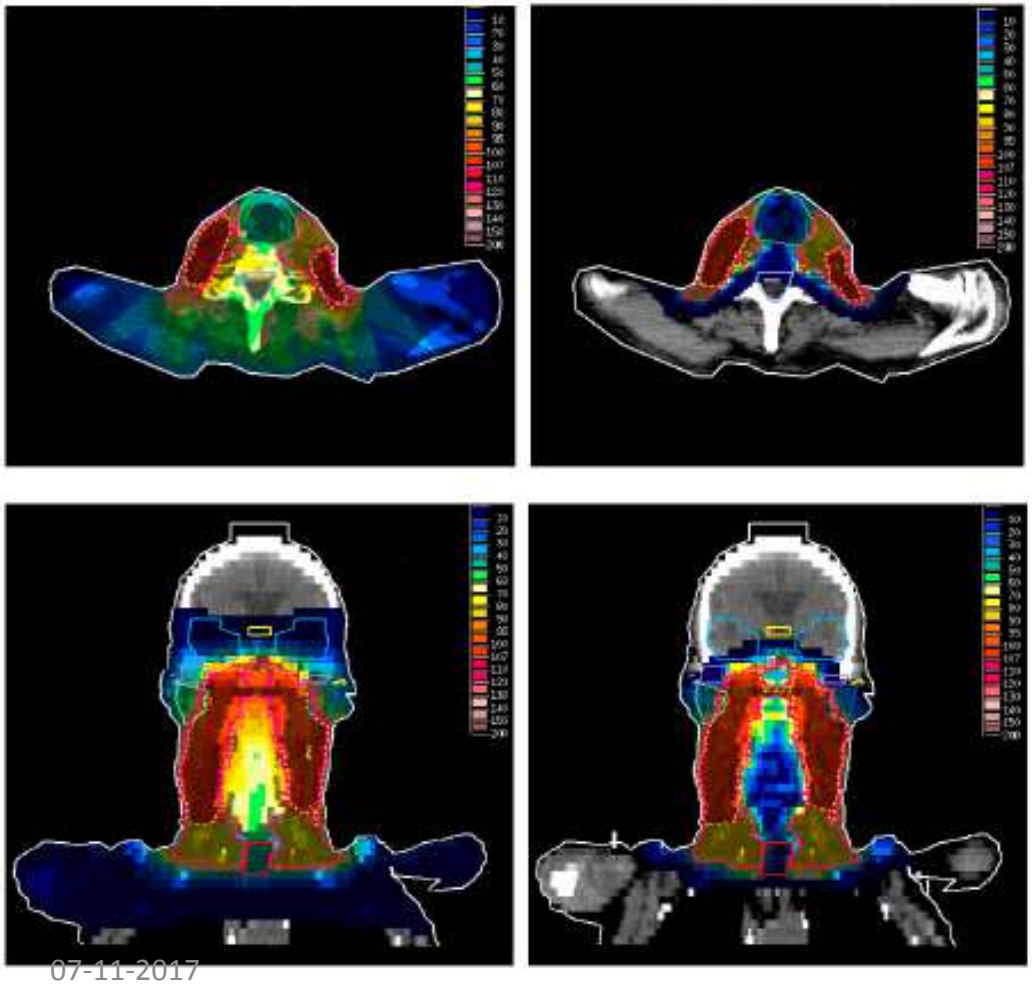
Study	N	Site	Treatment	Outcome	Toxicity	Conclusion
Oropharynx						
Slater et al (2005) prospective, nonrandomized	29	Stage II/IV oropharyngeal cancer	Accelerated proton-photon RT 75.9 CGE in 45 fractions.	5-y LRC 84% 5-y DFS 65%	Aggressive nutritional and anesthetic support needed, 3 patients with late grade 3 toxicity.	Protons used as concomitant boost with photons allows for an accelerated treatment with more tolerable toxicity profile
Other head and neck sites						
Zenda et al (2011), prospective nonrandomized	14	Mucosal melanoma of head and neck	PBR 60 Gy in 15 fractions	3-y LC 86% 3-y OS 58%	21% had grade 3 acute mucositis, 2 patients had decreased visual acuity	Proton therapy has promising LC benefits for mucosal melanoma
Tokuuye et al (2004), retrospective review	33	Head and neck cancers, not resected	17 with PBR alone, 16 with proton-photon, median 75 CGE in 3 CGE fractions	5-y LC 74% 5-y PFS 29% 5-y OS 44%	18% treatment-related acute and late toxicity >grade 3	PBR offers high control rates compared with conventional in unresectable head and neck cancer, but late toxicities were seen in high-dose areas perhaps because of large fraction size

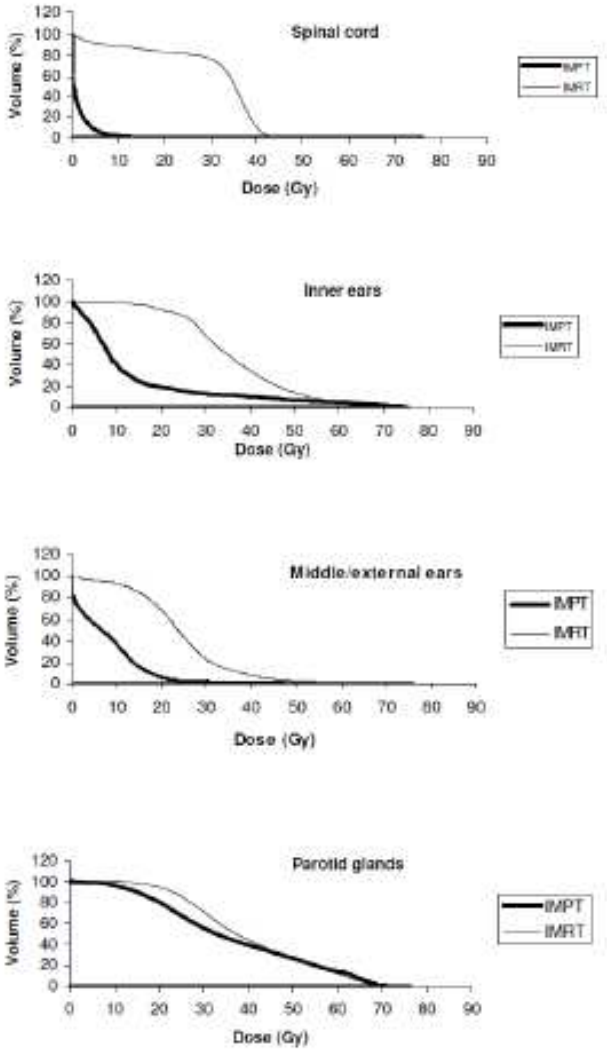
Abbreviations: BID = twice daily; CGE = cobalt-Gray-equivalent; cis-etop = cisplatin-etoposide; CNS = central nervous system; CR = complete response; CSF = cerebrospinal fluid; CSS = chordoma-specific survival; DFS = disease-free survival; DM = distant metastasis; DVH = dose-volume histogram; EBRT = external beam radiation therapy; Gy = Gray; IMPT = intensity modulated proton therapy; LC = local control; MRI = magnetic resonance imaging; OS = overall survival; PBR = proton beam radiation; PFS = progression-free survival; RT = radiation therapy.

Int J Radiation Oncol Biol Phys, Vol. 89, No. 2, pp. 292–302, 2014

Proton (IMPT)

IMRT IMPT





Taheri-Kadkhoda et al, Radiat Oncol 2008

Heavy ion therapy

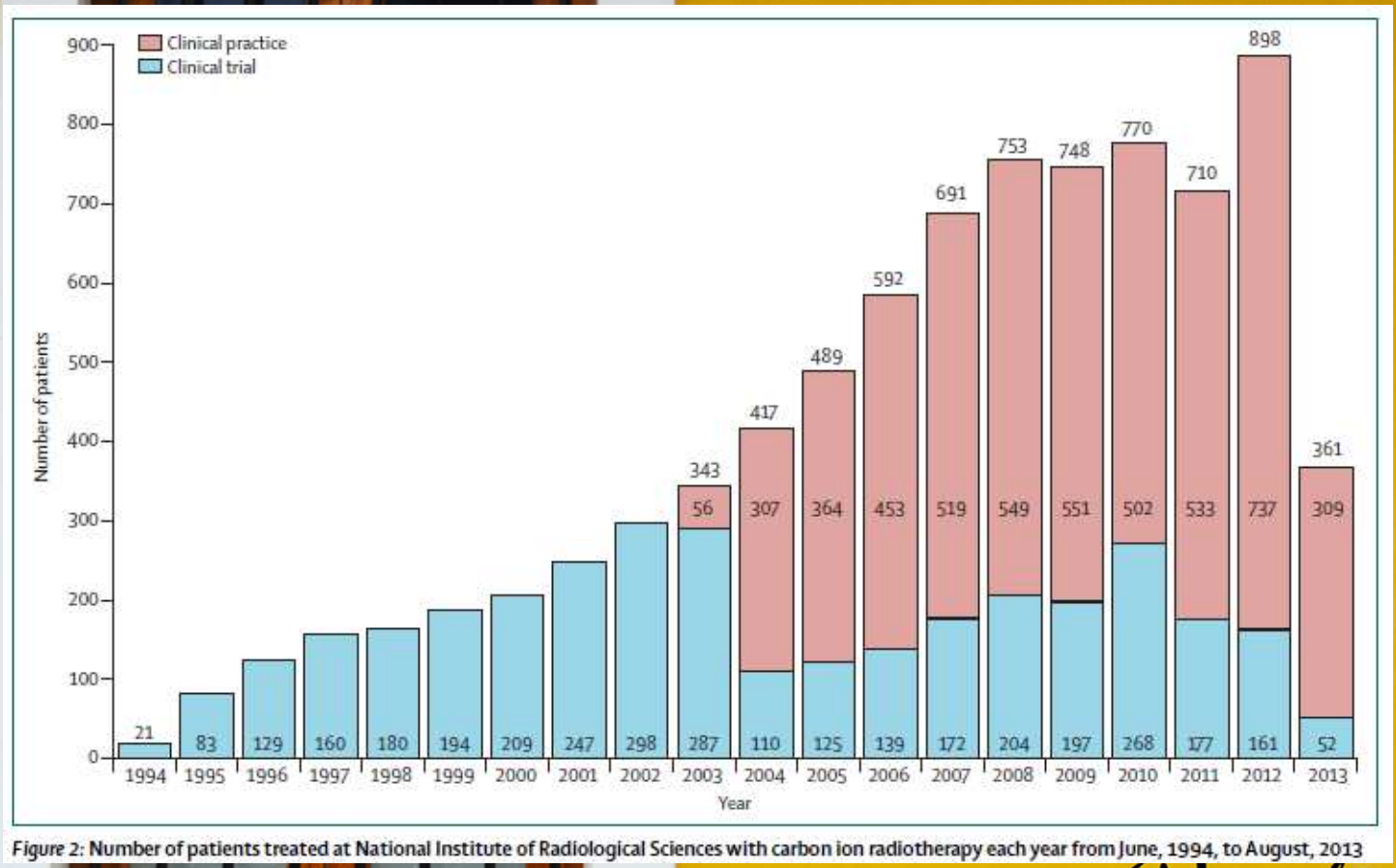


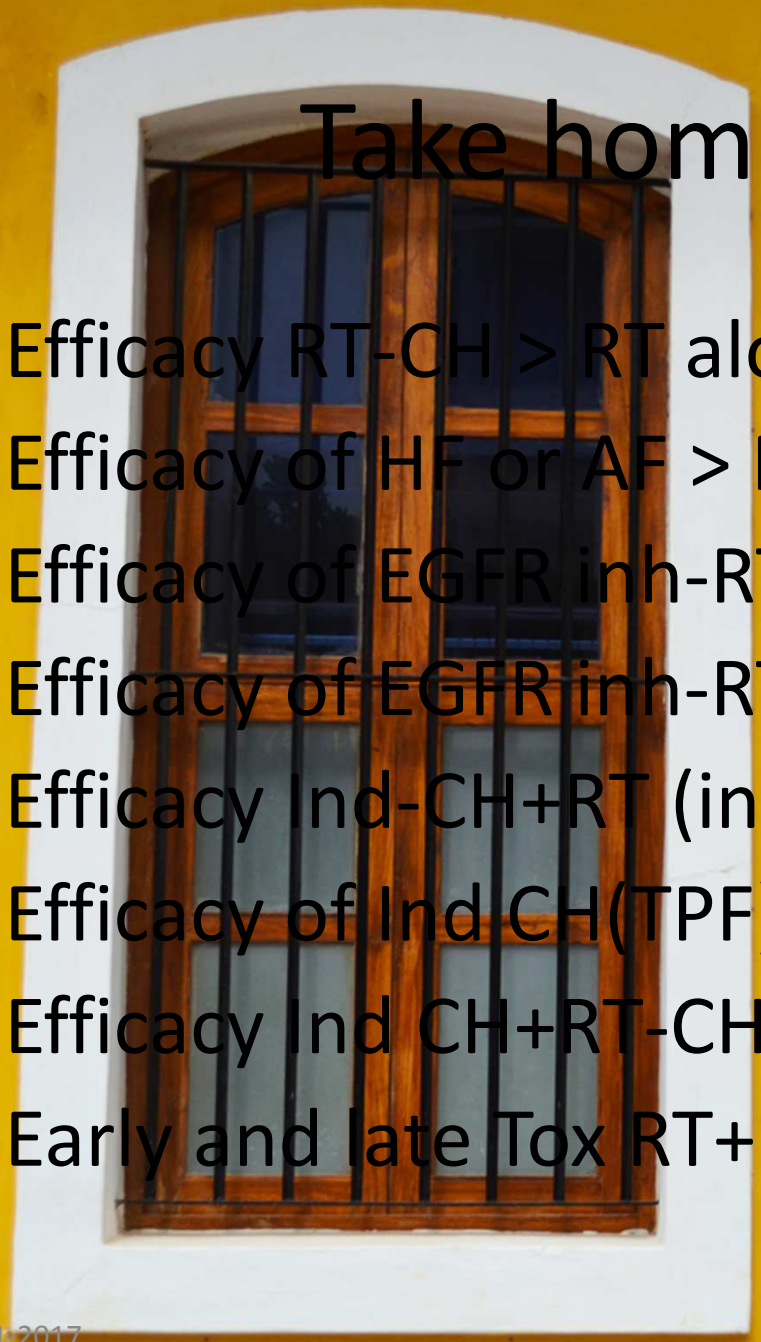
Figure 2: Number of patients treated at National Institute of Radiological Sciences with carbon ion radiotherapy each year from June, 1994, to August, 2013

Pondicherry

Mostly used for mucosal melanoma and adenoid cystic carcinoma.

Take home message

- Efficacy RT-CH > RT alone.
- Efficacy of HF or AF > RT alone.
- Efficacy of EGFR inh-RT> RT alone.
- Efficacy of EGFR inh-RT-CH < RT-CH.
- Efficacy Ind-CH+RT (in responders)= TL+RT
- Efficacy of Ind CH(TPF)> Ind-CH (PF)
- Efficacy Ind CH+RT-CH= RT-CT (except Npx)
- Early and late Tox RT+…> RT alone.



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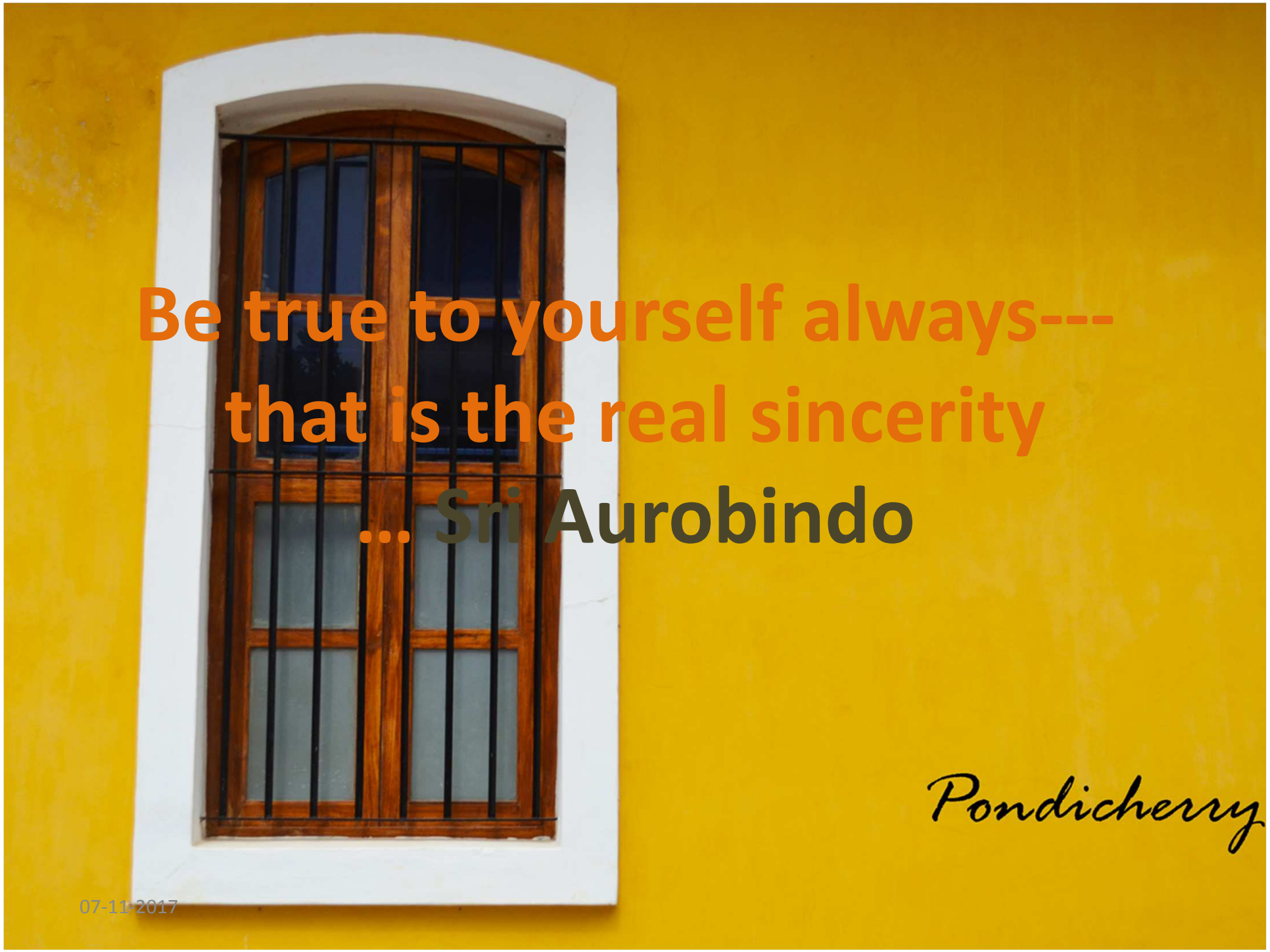
Be true to yourself always---
that is the real sincerity
... Sri Aurobindo
Pondicherry


Thank You
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