
Associazione
Italiana
Radioterapia
Oncologica
XXV CONGRESSO NAZIONALE
AIRO2015
PALACONGRESSI - Rimini, 7-10 novembre
Presidente AIRO
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Cynthia Aristei
Ernesto Maranzano
Radioterapia del cavo orale:
fattori predittivi e indicazioni al trattamento radiante
Ester Orlandi

Summary of role of ERT for OCC

	External Beam Radiotherapy (EBRT)
Primary setting	• Early disease when patient intolerant of surgery • Early disease when anticipated cosmetic consequence of surgery is a concern, especially for lip cancer involving commissure • Unresectable disease, usually combined with chemotherapy • Advanced disease for patients intolerant of surgery due to poor performance status or comobidities
Adjuvant setting	• Unfavorable pathological features • Combined with chemotherapy for positive resection margins and extracapsular nodal extension
Salvage setting	• Adjuvant treatment after salvage surgery • Primary treatment modality, usually combined with chemotherapy if further surgery is not feasible

Huang 2013

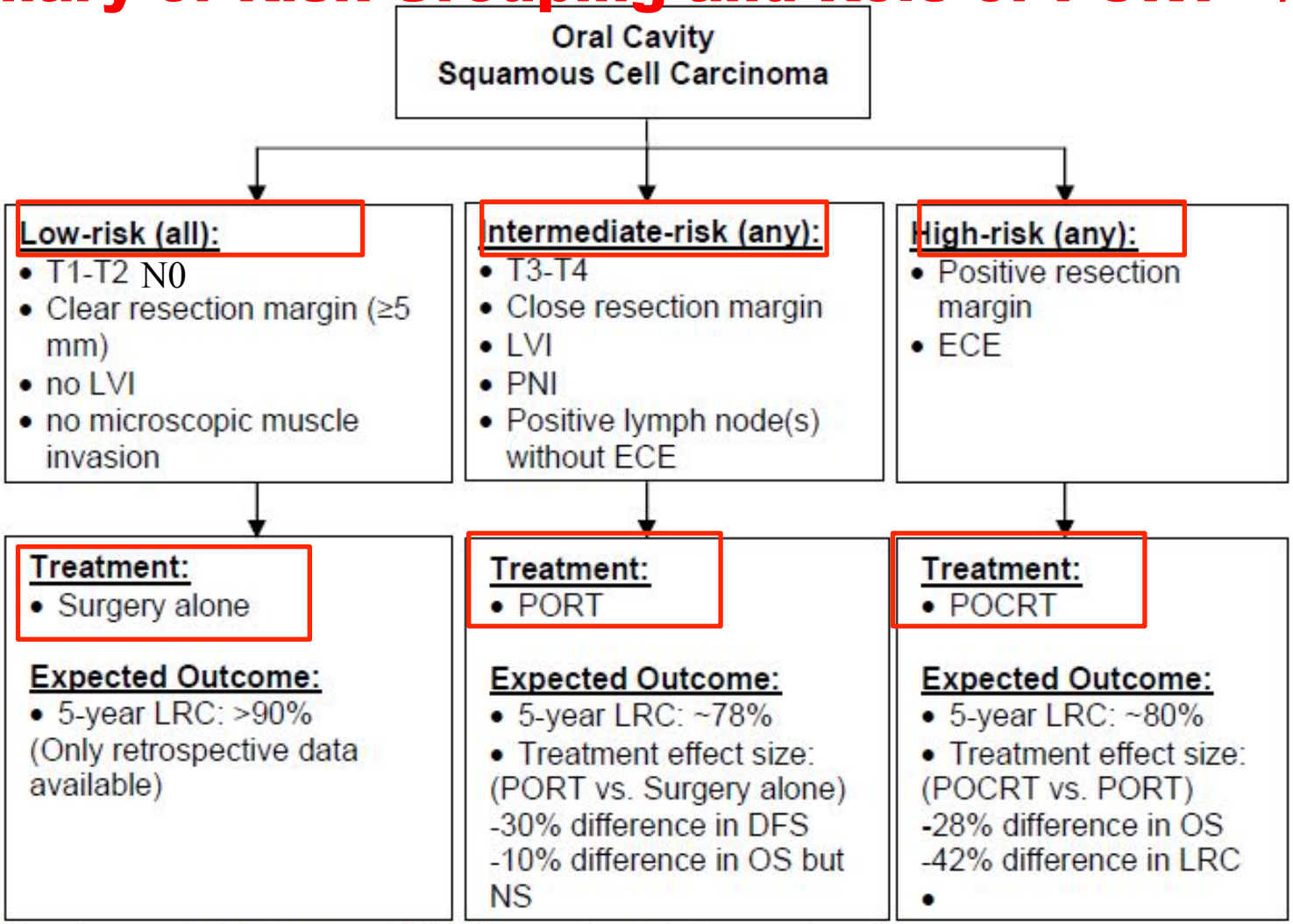
Role of Postoperative Radiotherapy (PORT)

- No large randomized trials confirming the added value of PORT after primary Surgery (S) compared to S alone.

  Misha RC 1996; Rodrigo JP 2009; Kokal WA 1988

- Most data come from retrospective series comparing the effect of PORT with historical information.

Summary of Risk Grouping and Role of PORT +/- CHT



Huang

2012

Low Risk patients

- Pathological stage I-II disease with sufficiently clear resection margins is generally considered low-risk and does not require PORT.

- Despite early diagnosis and treatment, almost 20 % of patients with early-stage (cT1-cT2N0) OSCC still die of their diseases.

  Brown 2012

- What are unfavorable prognostic factors?

  LVI
  PNI
  Depth/Pattern of invasion/growth
  Close margin
  Etc…

Contents lists available at ScienceDirect

Oral Oncology

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

Predictors of locoregional recurrence in early stage oral cavity cancer with free surgical margins

Tsai-Ying Huang [a], Lee-Ping Hsu [b,c], Yu-Hsuan Wen [b], Tung-Tsun Huang [b,c], Yu-Fu Chou [b], Chia-Fong Lee [b,c], Miao-Chun Yang [b], Yi-Kuo Chang [b], Peir-Rong Chen [b,c,*]

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100% of pts with N0 and pathological margin ≥ 5 mm

60% of pts received END
No RT
No CHT

Table 1
Patient characteristics.

Characteristics	*n*	Percentage
Total	148	
Gender		
Female	18	12.16
Male	130	87.87
Primary site		
Lip	24	16.22
Oral tongue	37	25.00
Gum/gingiva	8	5.41
Mouth of floor	2	1.35
Hard palate	4	2.70
Buccal Mucosa/retromolar trigone	73	49.32
T classification		
pT1	85	57.43
pT2	63	42.57
Differentiation		
Well	122	82.43
Moderate	26	17.57
Pathological characteristics		
Lympho-vascular permeation (−)	136	91.89
Lympho-vascular permeation (+)	12	8.11
Peri-neural infiltration (−)	139	93.92
Peri-neural infiltration (+)	9	6.08
Non-T4 muscular invasion (−)	108	72.97
Non-T4 muscular invasion (+)	40	27.02

Non -T4MI=Malignant cells observed micoroscopically in muscles excluding the extrinsic muscles and masseter muscles

≠

Depth invasion

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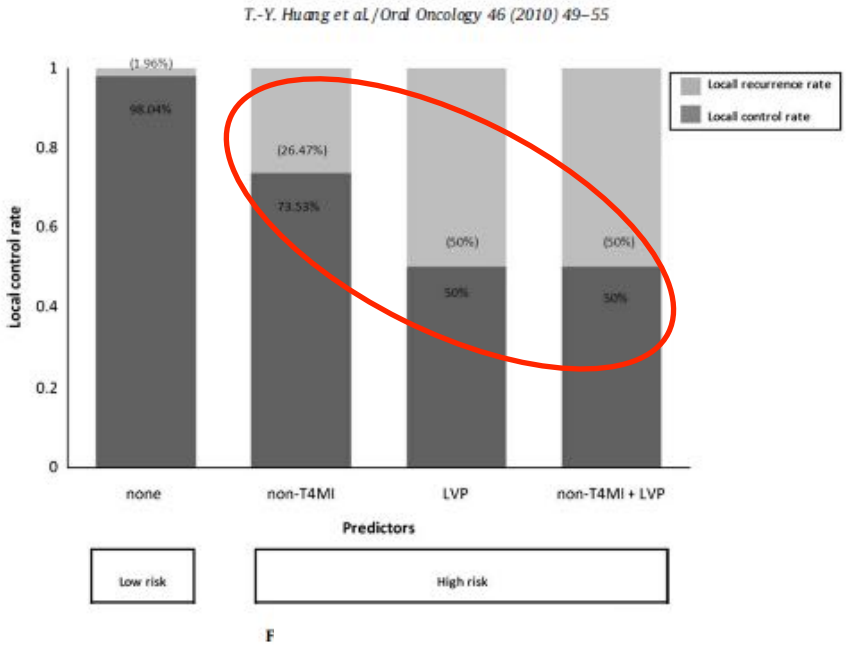
Table 5
Multivariate logistic regression analysis of recurrence at endpoint. LRR

Variable	*B*	*SE* (*B*)	Odds ratio (OR)	95% CI	*p*-value
Lympho-vascular permeation	2.37	0.88	10.75	(1.92–59.91)	$p = 0.007$
Peri-neural infiltration	−0.15	1.01	0.86	(0.12–6.24)	$p = 0.883$
Non-T4 muscular invasion	2.12	0.63	8.35	(2.45–28.44)	$p = 0.001$



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26-50% LRR

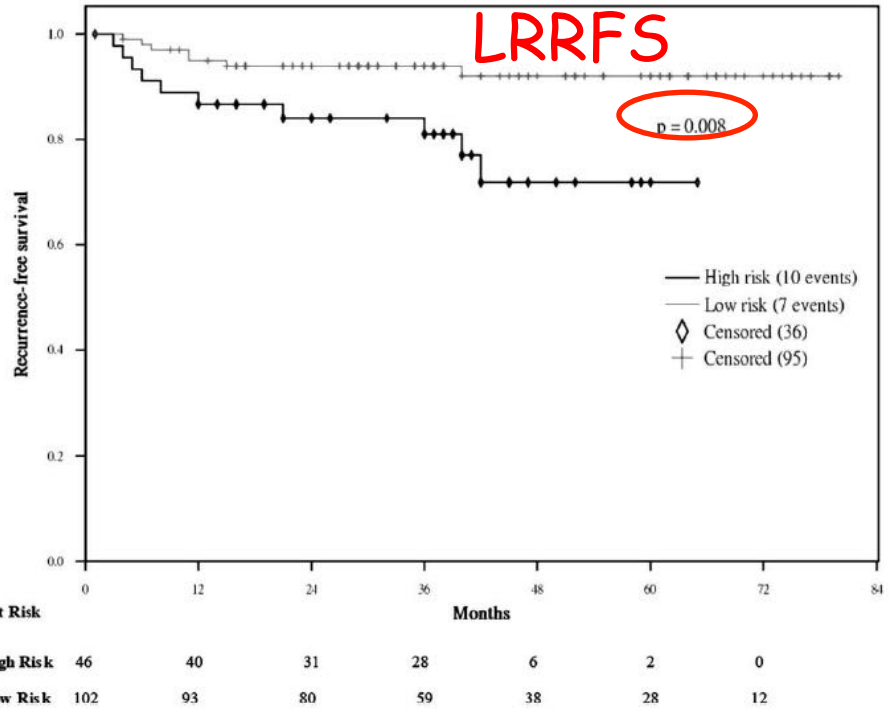

Figure 4 Recurrence-free survival curve by the Kaplan–Meier method.

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

CHUN-TA LIAO, M.D.,[*§§] JOSEPH TUNG-CHIEH CHANG, M.D., M.H.A.,[†§§] HUNG-MING WANG, M.D.,[‡§§] 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.[‡‡§§]

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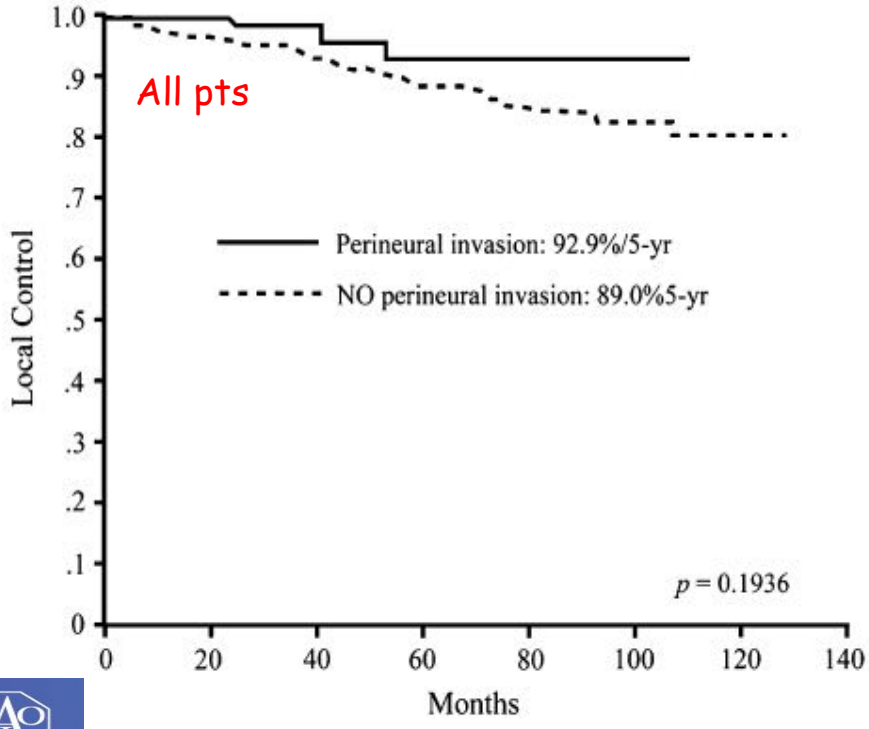
2008

460 pts, 15% with PNI
Selected pts with pT3 and/or PNI received PORT



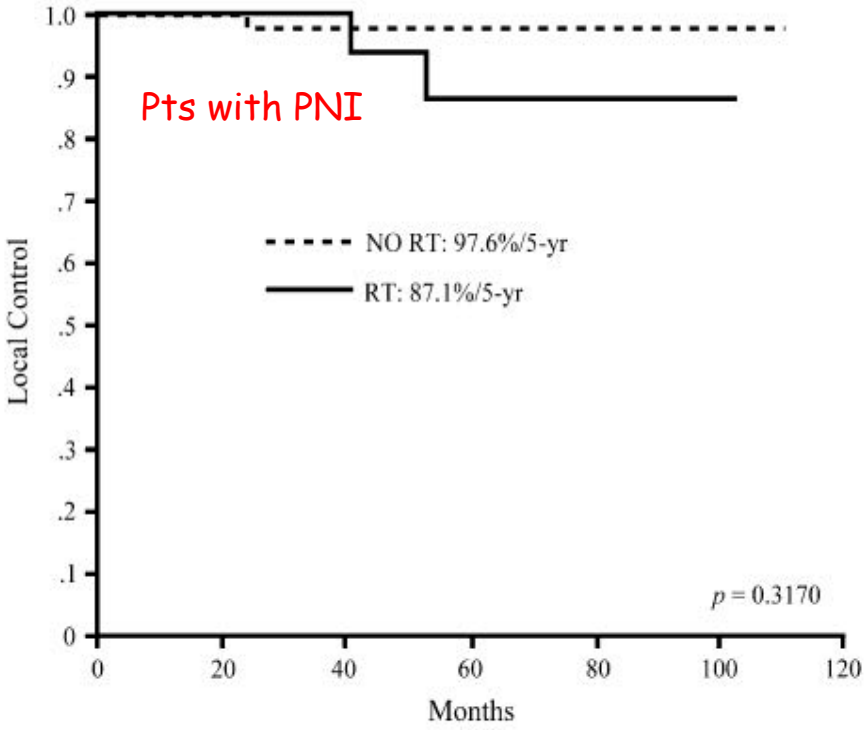


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Table 1. Clinical pathologic characteristics of the 460 patients with oral cavity squamous cell carcinoma

	Group A, no risk factors (n = 392)	Group B, perineural invasion (n = 68)	p
Sex, n			0.990
Male	63	63	
Female	29	5	
Age, n			0.289
≤40 years	92	12	
>40 years	300	56	
Cancer subsite, n			0.056
Tongue	180	41	
Mouth floor	15	1	
Lip	19	2	
Buccal	113	21	
Gum	37	0	
Hard palate	11	0	
Retromolar	17	3	
Differentiation, n			0.393
Well/moderate	382	65	
Poor	10	3	
Neck dissection, n			0.061
No	63	5	
Yes	329	63	
Pathologic tumor status, n			0.085
T1–2	323	50	
T3	69	18	
Tumor depth, n			< 0.001
<10 mm	289	30	
≥10 mm	99	38	
Treatment modality, n			< 0.001
Surgery	343	44	
Surgery plus radiotherapy	49	24	
Local recurrence, n			0.118
No	351	65	
Yes	41	3	
Neck recurrence, n			0.043
No	355	56	
Yes	37	12	
Distant metastases, n			0.590
No	382	67	
Yes	10	1	
Second primary tumors, n			0.337
No	315	58	

10%

35%

Liao 2008

242 OCC pts , 60% T1-T2, 50% receiving PORT

TABLE 8. Comparison of POI, Lymphocytic Response, and Perineural Invasion

Variable	Local Recurrence	Regional Metastasis	Overall Survival
PPOI 4	NS	NS	95% CI 1.07, 3.60 $P = 0.024$
PPOI 5	NS	NS	95% CI 1.78, 8.38 $P = 0.001$
WPOI 4	WPOI 4 vs. 5 95% CI 0.86, 5.01 $P = 0.015$	NS	HR 2.0 95% CI 1.62, 8.77 $P = 0.004$
WPOI 5		NS	HR 6.4 95% CI 2.43, 13.97 $P = 0.001$
Lymphocytic response, weak or none	95% CI 1.47, 9.21 $P = 0.005$	NS	HR 6.2 95% CI 2.88, 14.18 $P = 0.001$
Perineural invasion <1 mm	NS	NS	HR 2.3 95% CI 1.36, 3.95 $P = 0.002$
Perineural invasion >1 mm	95% CI 1.43, 7.89 $P = 0.005$	NS	HR 1.9 95% CI 1.42, 4.81 $P = 0.039$

NS, not significant; HR, hazard ratio.

POI= pattern of tumor invasion;at the tumor host interface
WPOI= worst POI
Lymphoid infiltrate at the tumor host interface

→ Growth Pattern

TABLE 9. Proposed Risk Assessment for Oral Squamous Cell Carcinoma

	Point Assignment for Risk Scoring		
Histologic Variable	**0**	**1**	**3**
Perineural invasion	None	Small nerves	Large nerves
Lymphocytic infiltrate at interface	Continuous band	Large patches	Little or none
WPOI at interface	1 or 2 or 3	4	5

Risk Score (sum of all point assignments)	Risk for local Recurrence	Overall Survival Probability	Adjuvant Treatment Recommendations
Score = 0	Low	Good	No local disease-free benefit seen for adjuvant RT
1 or 2	Intermediate	Intermediate	No local disease-free benefit seen for adjuvant RT
3 to 9	High	Poor	RT regardless of 5 mm margins

Brandwein –Gensler 2007

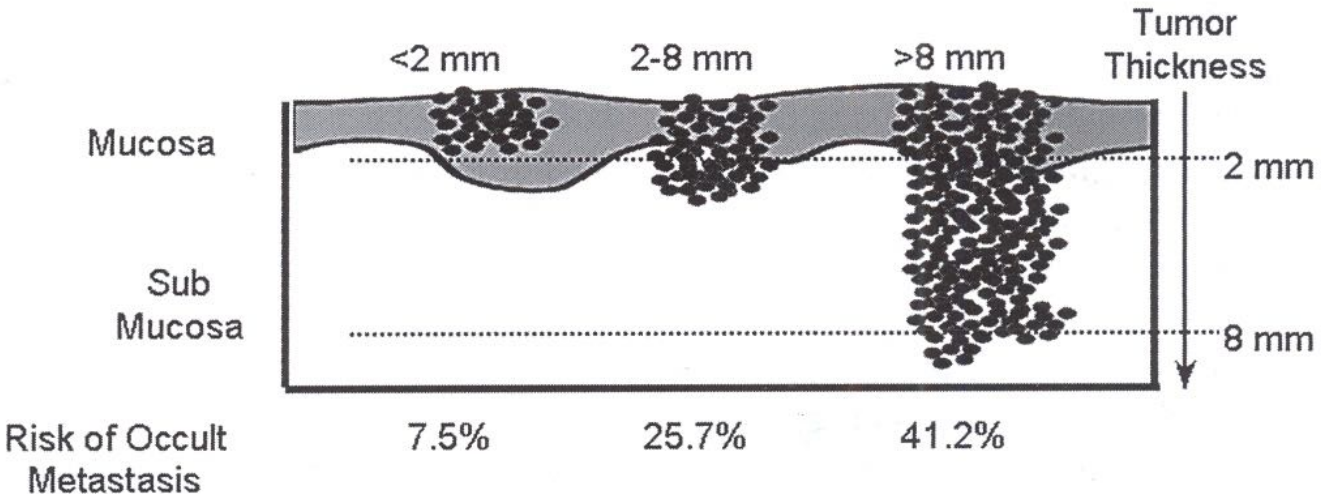
Head and Neck Pathol (2013) 7:211–223
DOI 10.1007/s12105-012-0412-1

ORIGINAL PAPER

Validation of the Risk Model: High-Risk Classification and Tumor Pattern of Invasion Predict Outcome for Patients with Low-Stage Oral Cavity Squamous Cell Carcinoma

Yufeng Li · Shuting Bai · William Carroll · Dan Dayan · Joseph C. Dort · Keith Heller · George Jour · Harold Lau · Carla Penner · Michael Prystowsky · Eben Rosenthal · Nicolas F. Schlecht · Richard V. Smith · Mark Urken · Marilena Vered · Beverly Wang · Bruce Wenig · Abdissa Negassa · Margaret Brandwein-Gensler

Depht invasion



Huang 2009

IDENTIFICATION OF A HIGH-RISK GROUP AMONG PATIENTS WITH ORAL CAVITY SQUAMOUS CELL CARCINOMA AND pT1–2N0 DISEASE

CHUN-TA LIAO, M.D.,*† CHIEN-YU LIN, M.D.,†‡ KANG-HSING FAN, M.D.,*‡ HUNG-MING WANG, M.D.,*§ SHU-HANG NG, M.D.,*‖ LI-YU LEE, M.D.,†¶ CHUEN HSUEH, M.D.,†¶ I-HOW CHEN, M.D.,*† SHIANG-FU HUANG, M.D.,*† CHUNG-JAN KANG, M.D.,*† AND TZU-CHEN YEN, M.D, PH.D.†#

*Department of Otorhinolaryngology, Head and Neck Surgery, †Department of Head and Neck Oncology Group, §Department of Hema-Oncology, ‖Department of Diagnostic Radiology, ¶Department of Pathology, and #Nuclear Medicine and Molecular Imaging Center, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; and ‡Department of Radiation Oncology, Chang Gung Memorial Hospital and Graduate Institute of Clinical Medical Sciences of Chang Gung University, Taoyuan, Taiwan

387 pts receiving S on primary tumor and ND

Table 2. Multivariate analysis of 5-year control and survival rates ($n = 387$)

Characteristics	Local control	Neck control	Distant metastasis	Disease-free survival	Disease-specific survival	Overall survival
Poor differentiation						
p	NS	0.002	NS	0.009	< 0.001	NS
HR (95% CI)		4.727 (1.809–12.353)		3.105 (1.329–7.253)	6.092 (2.280–16.281)	
Tumor depth ≥4 mm						
p	NS	0.015	NS	0.007	0.037	NS
HR (95% CI)		3.679 (1.285–10.530)		2.476 (1.286–4.770)	3.109 (1.073–9.008)	
Lymphatic invasion						
p	NS	NS	NS	NS	NS	< 0.001
HR (95% CI)						16.459 (3.930–69.928)

Abbreviations: NS = not significant; HR = hazard ratio; CI = confidence interval.

Intermediate Risk patients

- Three randomized trials (pts staged III and IV), only one including the OC (buccal mucosa) exclusively.

- Kokal WA, 1988: OC, larynx, and pharynx cancer pts; surgery alone (n = 27); surgery +PORT(n = 24). 100% of pts with clear margins. RT dose: median dose 50 Gy. No significant differences in either LRC or OS were noted between the two treatment arms.

- Rodriguo JP , 2004: 1/42 pts with OCC; 100% of pts with clear mergins; RT dose: 50-60 Gy. PORT does not LRC and OS compared to S alone.

Intermediate Risk patients

Table 1. Characteristics of patients entered in the study

	Surgery alone	Post-operative radiation
Number	60	80
Median age (years)	48	46
Sex M/F	39/21	47/33
TNM		
T3–4 N0M0	35 (58)	24 (30)
T3–4N1–2bM0	25 (41.6)	56 (70)
Histopathology		
Differentiation		
Well	19 (31.6)	20 (25)
Moderate	34 (56.6)	48 (60)
Poor	7 (11.6)	12 (15)
Nodal involvement	23 (38)	33 (41)
Perinodal disease	8 (13)	11 (13.75)
Perineural invasion	6 (10)	11 (13.75)
Post-operative morbidity	22 (36.6)	17 (21.25)

NS = Not significant, values in parentheses are percentages.

Mishra 1996

100% of pts with OCC and clear margins
Median RT dose:60 Gy

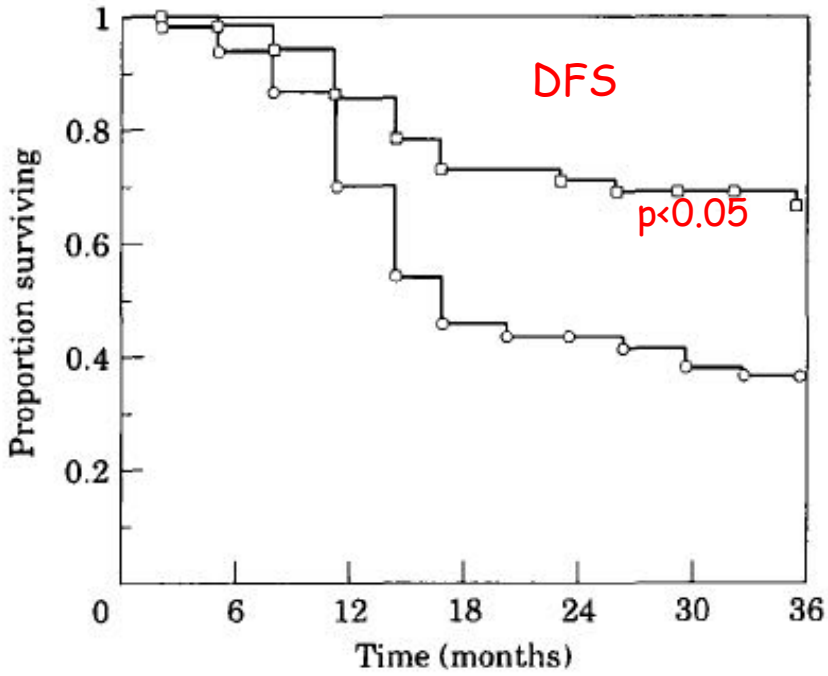


Fig. 1. Actuarial disease-free survival rates in the surgery alone (○) and post-operative radiotherapy (□) groups.

Table 2
Comparison of surgery alone with surgery and postoperative radiotherapy (PORT) for T3–4 and stage III–IV disease. Data are number (%). *OCC*

First author, reference, and institution	Year	No	Surgery	PORT	Local recurrence		Regional recurrence		Total recurrence		Salvage		Overall survival	
					Surgery	PORT	Surgery	PORT	Surgery	PORT	Surgery	PORT	Surgery	PORT
Designated comparative studies for surgery compared with PORT														
Mishra[17] Orissa, India	1996	119	50	69 (58)	15 (30)	8 (12)	8 (16)	10 (15)	23 (46)	18 (26)	15 (65)	14 (78)	42 (84)	65 (94)
Dixit[10] Ahmedabad	1998	78	47	31 (40)	–	–	–	–	34 (72)	16 (52)	–	–	–	–
Magge[11] Pittsburgh	2003	54	21	33 (61)	0	2 (6)	–	–	–	–	–	–	–	–
Outcome studies with incidental surgery compared with PORT														
Loree[15] MSK	1990	45	25	20 (44)	8 (32)	7 (35)	6 (24)	4 (15)	–	–	–	–	21 (84)	10 (50)
Franceschi[18] MSK	1993	86	24	62 (72)	–	–	–	–	–	–	–	–	10 (42)	18 (29)
Carvalho[9] Sao Paulo	2003	724	372	352 (49)	66 (18)	61 (17)	40 (11)	33 (9)	125 (34)	115 (33)	–	–	–	–
Totals		1106	539	567 (51)	89/468 (19)	78/474 (16)	54/447 (12)	47/441 (11)	182/469 (39)	149/452 (33)	15 (65)	14 (78)	73/99 (74)	93/151 (62)

Dixit: PORT advantageous in terms of LRC if close surgical margins, positive node, and bone invasion.

Magge: for T3-T4 a little benefit in terms of LC (1-10%) with PORT.

Loree : a trend toward lower recurrence rates was noted in pts with positive surgical margins receiving PORT compared to pts receiving RT alone.

Franceschi : In pts group with pN+, RC was significantly increased for patients receiving PORT compared to pts receiving RT alone.

Brown 2012

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Review

2010

Postoperative strategies after primary surgery for squamous cell carcinoma of the head and neck ☆

Johannes A. Langendijk [a,*], Alfio Ferlito [b], Robert P. Takes [c], Juan P. Rodrigo [d], Carl Suárez [d], Primo Strojan [e], Missak Haigentz Jr. [f], Alessandra Rinaldo [b]

11 papers

LRC was significantly better with S plus PORT compared to after surgery.

In most series a significant benefit on OS was found also.

Table 1 Factors from relevant literature that different authors have recommended in the d operative radiotherapy

Author	Year	Risk of recurrence
		Intermediate
Laramore	1992	Stage 3–4, Stage 2–4 (hypopharynx
Peters	1993	Scoring system based on stage, margins, perineural invasion, Nodal status, ECS, Direct invasion to muscle, skin, nerve, vessel, carotid, base of skull
Ang	1996–2001	One of Site, mucosal margin +ve Perineural invasion, >=2 nodes, >2 nodal groups, nodal size
Majoufre	1999	PN+ Stage 3–4
Muriel	2001	Radical neck dissection, clear margins N0 neck
Bastit	2001	Close margin, N+
De Stafani	2000	Extension to soft tissues of neck, pN+, Poorly differentiated, Perineural or perivascular invasion
Shah	2000	Close margins (<5 mm), T3-4, Perineural or perivascular invasion, Poorly differentiated, Site, Multicenter primary, >4 positive nodes
Rosenthal	2002	T3-4, invasion of cartilage or bone or soft tissues of the neck, Perineural or perivascular invasion, >=pN2a
Langendijk	2003	One of: >1 nodal level, Perineural invasion, Stage 3–4
Present study		Close margins (<5 mm), Unfavourable pattern, pN+ pstage 3–4

All HN sites

Margin status?

pT3?

How many factors should be considered?

How many pathological nodes should be considered?

Brown 2009

Surgical margin

- The status of the surgical resection is an important predictor of outcome, both LC and OS .

- The most widely accepted definition of a close margin is tumor within 5 mm of the inked resection margin (in formalin fixed surgical specimens), in general not including premalignant change at the margin . Two mm inked margins as cut off for the close margin definition could be sufficient.

- Close margins had a similar impact on the incidence and pattern of local recurrence as involved margins (38%-80%).

Jones 1994, Lore 1990, Kademani 2005, Spiro 1999, Sutton 2003, Herman 2015, Binahmed 2007

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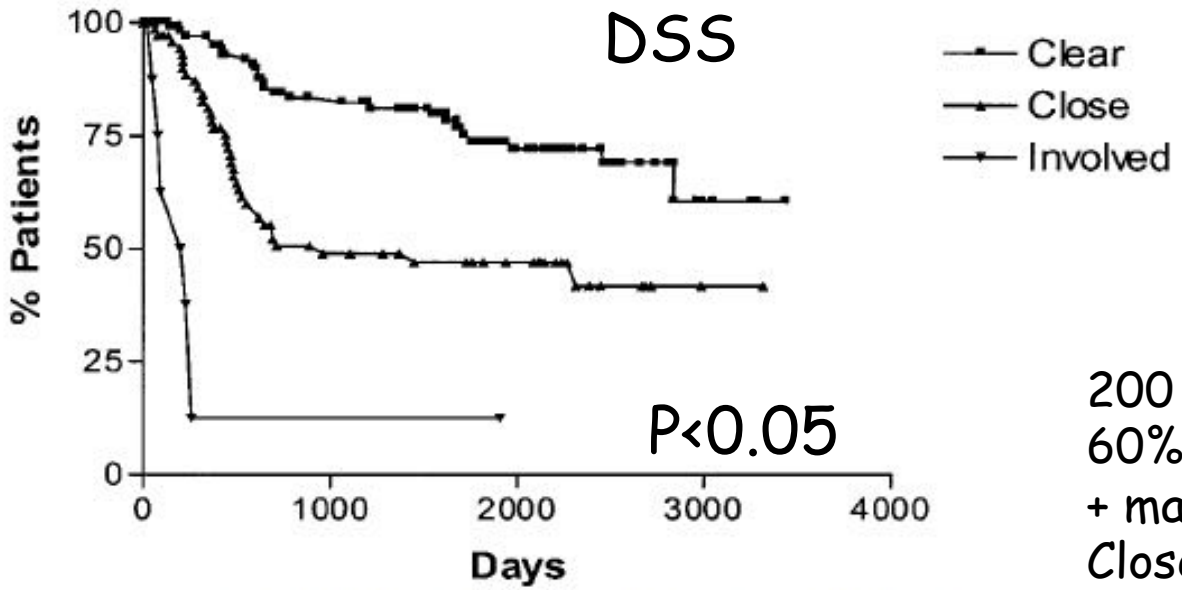

Fig. 1. Kaplan–Meier curve to show disease specific survival.

200 pts
60% with St III-IV
+ margins: 10% of pts
Close margins: 42% of pts
PORT for N+>2, ECE+,R1
(median TD 60 Gy)

Table 4. Cox regression analysis of survival data

	Relative risk of death	*P* value
Involved margin	11.61	0.0013
Close margin	2.66	0.02
N positive	2.15	0.063
ECS	1.22	0.64
Vascular perm'n	1.48	0.48
HMG Score	1.32	0.96
T Diameter	1.03	0.039
T Site	0.90	0.80
Perineural inv'n	0.67	0.33

PORT+CHT
PORt alone

Sutton 2003

Prognostic Impact of Intraoperative Microscopic Cut-Through on Frozen Section in Oral Cavity Squamous Cell Carcinoma

2010

Jennifer P. Guillemaud, MD, BSc, Rajan S. Patel, MBChB, MD, FRCS (ORL-HNS), David P. Goldstein, MD, FRCSC, Kevin M. Higgins, MD, MSc, FRCSC, and Danny J. Enepekides, MD, FRCSC

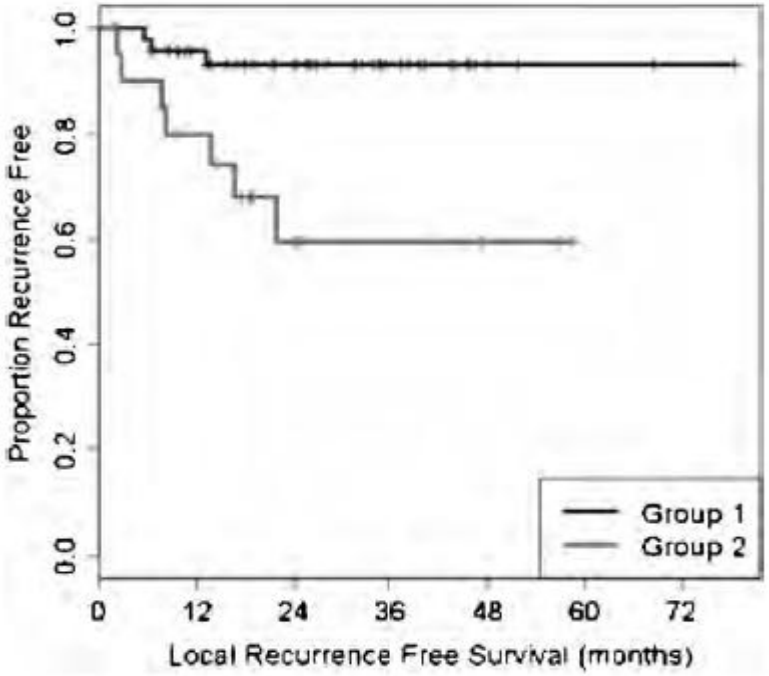

Figure 2. Kaplan-Meier analysis for local disease control by margin group (significant log-rank *p* value = .003).

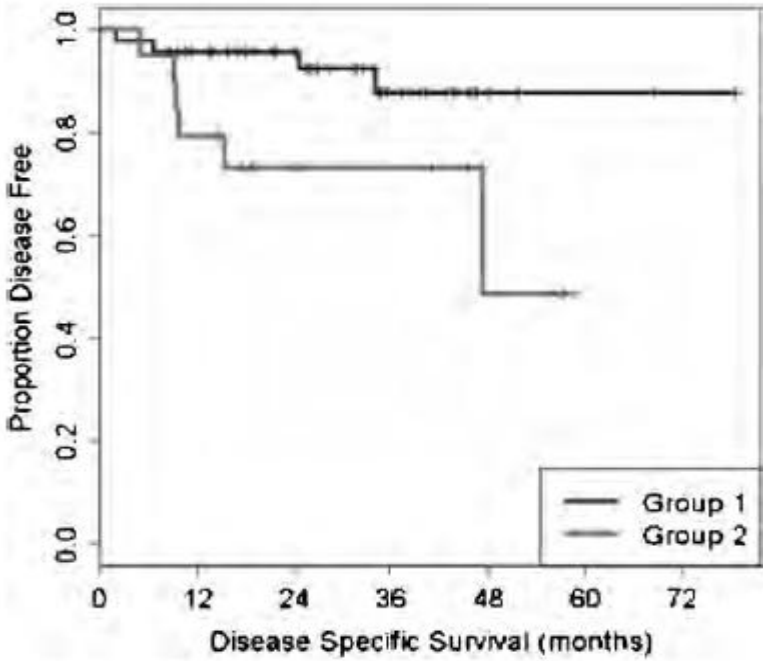

Figure 1. Kaplan-Meier analysis for disease-specific survival by margin group (significant log-rank *p* value = .03).

65 pts
65% of pts
St III/IV

Group 1= 40 pts with negative margins on both frozen and permanent section
Group 2: 20 pts with initially pos margins on frozen section which were revised to negative margins

Ann Surg Oncol (2011) 18:2569–2578
DOI 10.1245/s10434-011-1616-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEAD AND NECK ONCOLOGY

Identification of a High-Risk Subgroup of Patients with Resected pT3 Oral Cavity Cancer in Need of Postoperative Adjuvant Therapy

Chun-Ta Liao, MD[1,2], Chien-Yu Lin, MD[2,3], Kang-Hsing Fan, MD[2,3], Shiang-Fu Huang, MD[1,2], I-How Chen, MD[1,2], Chung-Jan Kang, MD[1,2], Hung-Ming Wang, MD[2,4], Shu-Hang Ng, MD[2,5], Chuen Hsueh, MD[2,6], Li-Yu Lee, MD[2,6], Chih-Hung Lin, MD[2,7], and Tzu-Chen Yen, MD, PhD[2,8]

119 pts pN0, 42 PORT, 77 surgery alone

PORT alone

TABLultivariable analyses of 5-year control and survival rates in pT3N0 OSCC patients

Characte cs	Local control *P*; HR, (95% CI)	Neck control *P*; HR, (95% CI)	Distant metastases *P*; HR, (95% CI)	Disease-free survival *P*; HR, (95% CI)	Disease-specific survival *P*; HR, (95% CI)
Tumor depth ≥10 mm	0.038; 1.245 (1.013–1.531)	NS	NS	0.013; 1.167 (1.033–1.319)	0.020; 5.741 (1.312–25.112)
Tumor depth ≥13 mm	NS	NS	0.033; 9.719 (1.196–79.005)	NS	NS

HR indic azard ratio, *95% CI* 95% confidence interval

PORT+CHT

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High risk patients

Table 2
Definition of risk groups based on RPA (Langendijk, 2005) and outcome.

RPA class	Definition	Outcome after 5 years			
		Loco-regional control (%)	Metastasis-free interval (%)	Disease-free survival (%)	Overall survival (%)
Class I intermediate risk	Free surgical margins and no extranodal spread	92	92	65	67
Class II high-risk	T1, T2 and T4 tumours with close or positive surgical margins or one lymph node metastasis with extranodal spread	78	80	47	50
Class III very high-risk	T3 tumours with close or positive surgical margins or multiple lymph node metastases with extranodal spread or N3	58	68	32	50

Positive and close surgical margins
and or
ECE+

Langendijk 2005

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]

Conclusions. Subject to the usual caveats of retrospective subgroup analysis, our data suggest that in locally advanced head and neck cancer, microscopically involved resection margins and extracapsular spread of tumor from neck nodes are the most significant prognostic factors for poor outcome. The addition of concomitant cisplatin to postoperative radiotherapy improves outcome in patients with one or both of these risk factors who are medically fit to receive chemotherapy. © 2005

Close margins were included
RTOG 60+/-6 Gy
EORTC 66 GY

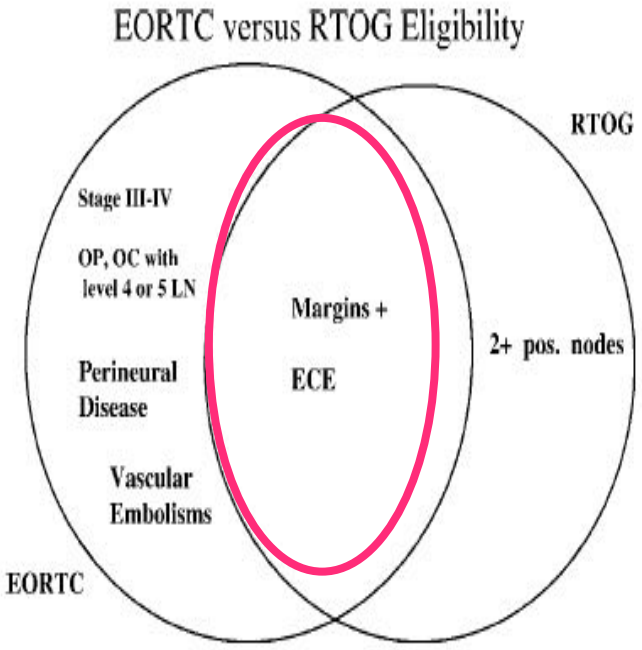

FIGURE 1. Eligibility criteria in EORTC 22931 and RTOG 9501 trials. OP, oropharynx; OC, oral cavity; LN, lymph node; ECE, extracapsular extension.

Head Neck 27: 843–850, 2

PRECISELY DEFINING HIGH-RISK OPERABLE HEAD AND NECK TUMORS BASED ON RTOG #85-03 AND #88-24: TARGETS FOR POSTOPERATIVE RADIOCHEMOTHERAPY?

pN≥2

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group 1, fewer than two involved nodes, no extracapsular spread of tumor, and uninvolved surgical margins; group 2, at least two involved nodes or extracapsular spread of tumor, but uninvolved surgical margins; group 3, microscopically involved surgical margins.

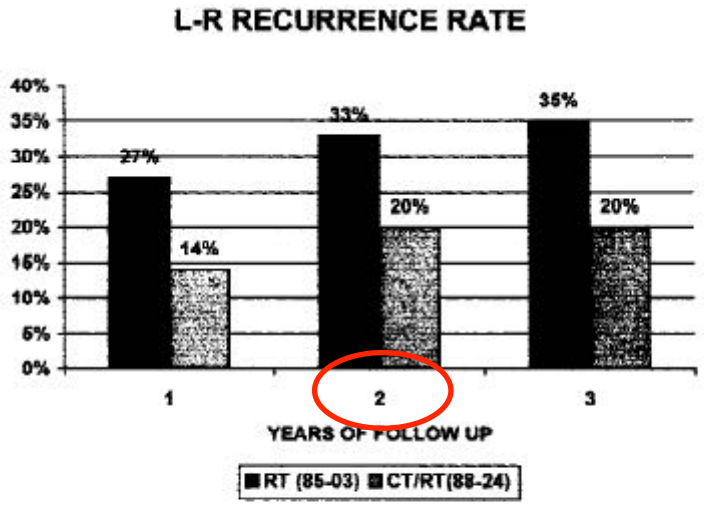

FIGURE 1. Local-regional recurrence rates in high-risk patients (groups 2 and 3) treated by surgery and radiotherapy alone (Radiation Therapy Oncology Group [RTOG] #85-03) versus surgery and chemotherapy/radiotherapy (RTOG #88-24).

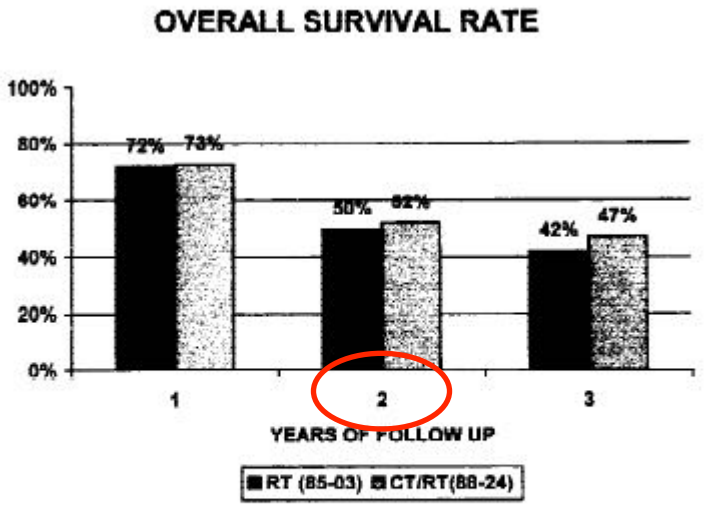

FIGURE 2. Survival rates in high-risk patients (groups 2 and 3) treated by surgery and radiotherapy alone (Radiation Therapy Oncology Group [RTOG] #85-03) versus surgery and chemotherapy/radiotherapy (RTOG #88-24).

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

Indication for CHT if > 3?

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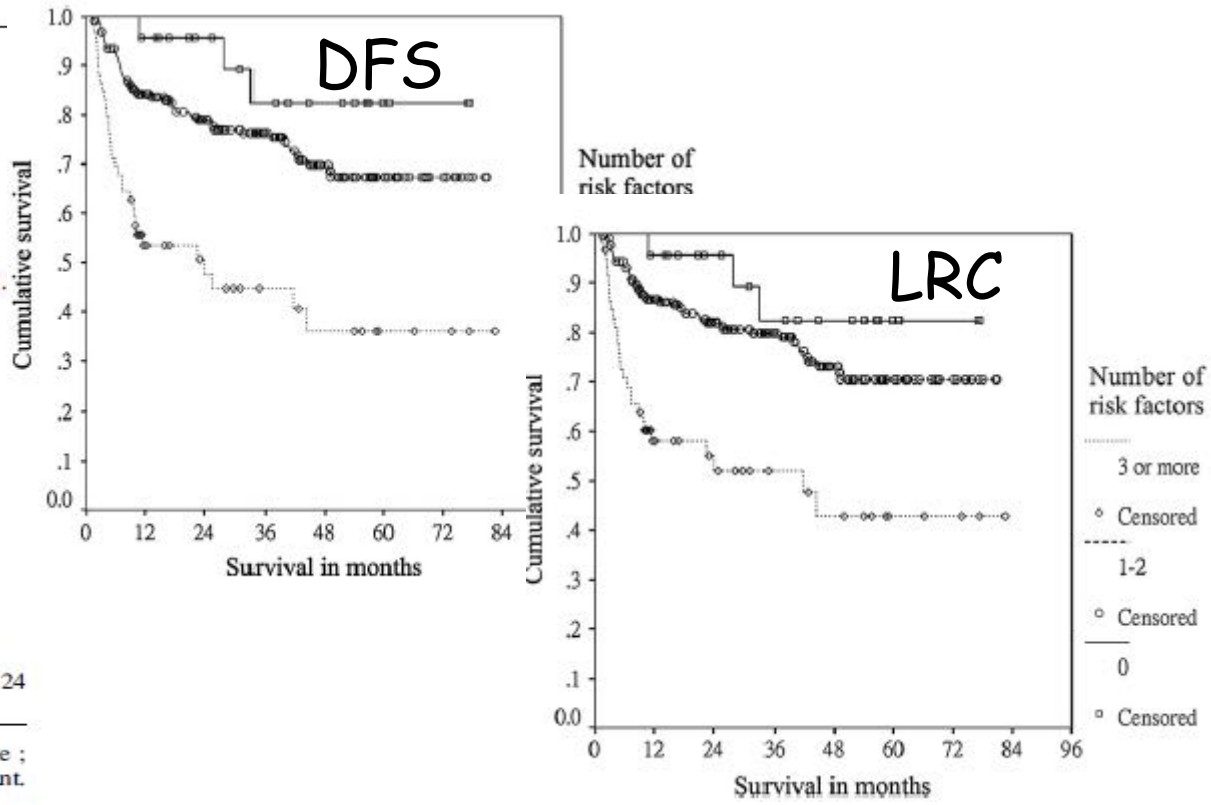
Table 2. Risk factors in univariate and multivariate analysis

	3-year recurrence-free survival	Univariate analysis	Multivariate analysis
Differentiation			
Poor	31%	$p < 0.01$	NS
Well or moderate	72%		
Perineural invasion			
Yes	60%	$p = 0.03$	NS
No	74%		
Lymphatic invasion			$p = 0.01$
Yes	40%	$p < 0.01$	HR = 5.21
No	72%		95% CI: 1.53-17.
Bone invasion			
Yes	63%	$p = 0.03$	NS
No	74%		
Location			
HR/RMT	53%	$p = 0.01$	NS
Other	74%		
Invasion depth			
≥ 10 mm	66%	$p < 0.01$	NS
< 10 mm	83%		
Margin distance			
< 4 mm	60%	$p = 0.03$	NS
≥ 4 mm	73%		
Number of risk factors			$p < 0.01$
0	82%	$p < 0.001$	HR = 11.96
1–2	76%		95% CI: 1.58-90.24
≥ 3	45%		

Abbreviations: HR/RMT = hard palate and retromolar trigone ; HR = hazard ratio ; CI = confidence interval ; NS = not significant.

302 pts, PORT alone (54-66 Gy)



Time factors

- Interval beetween surgery and PORT
- Overall treatment time of radiation (OTT)
- Total treatment package (TTP)

Time from surgery to PORT

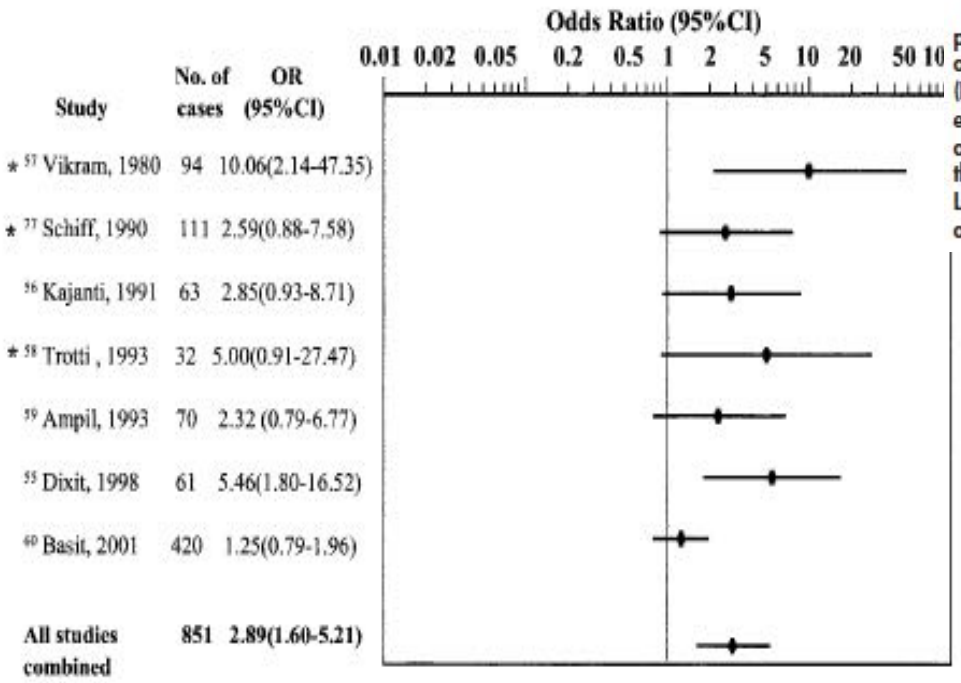
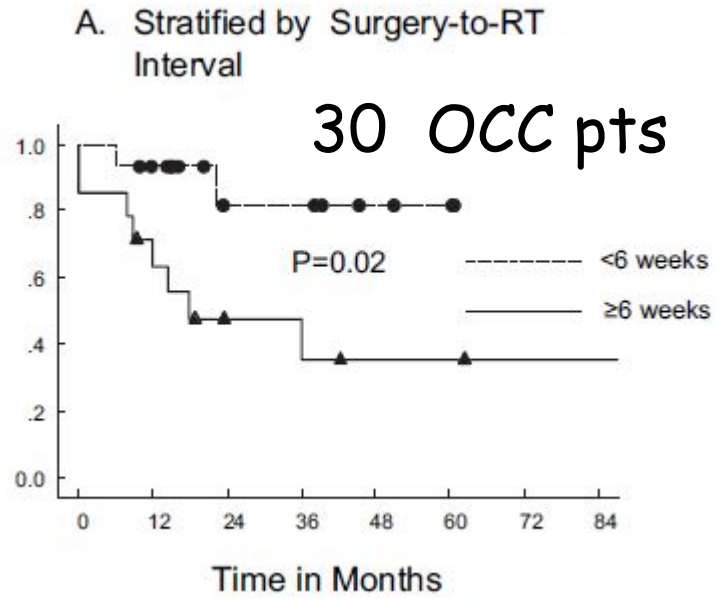


Fig 4. Associations between delay in postoperative radiotherapy (RT) for head and neck cancer and local recurrence rates (LRRs). LRRs in patients treated with postoperative RT more than 6 weeks after surgery are compared with the rates observed in those treated within 6 weeks of surgery. Low-quality studies are indicated by an asterisk.

Huang J, *JCO* 2003



Local control stratified by (A) surgery-to-RT interval (<6 weeks vs. ≥6 weeks)

Daly 2011

Therefore, no arbitrary time limit has been scientifically established during which PORT must begin, or beyond which PORT has been shown not to have an effect (5). In essence, high risk cases should still be considered in circumstances where there has been delay in initiating radiotherapy due to the grave consequences of loco-regional recurrence that might be prevented by the use of adjuvant treatment.

Huang 2012
Peters 1993

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POSTOPERATIVE RADIOTHERAPY IN SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY: THE IMPORTANCE OF THE OVERALL TREATMENT TIME

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Table 2. Results of the multivariate analysis with regard to locoregional control

Variable	Score	Regression coefficient (b)	SE (b)	*p* Value	RR	95% CI
Risk group	(Intermediate risk = 0, high risk = 1)	0.98	0.37	0.008	2.7	(1.3–5.4)
Overall treatment time radiotherapy				0.01		
6–7 weeks	Compared with <6 weeks	0.57	0.49	0.24	1.8	(0.7–4.6)
7–8 weeks	Compared with <6 weeks	0.94	0.50	0.06	2.6	(0.9–7.0)
>8 weeks	Compared with <6 weeks	1.58	0.53	0.003	4.8	(1.7–13.7)

Note: Only the factors significantly associated with local-regional recurrence (LRR) are shown. No significant association was found for interval between surgery and radiotherapy, sex, age, and total dose.

Table 4. Results of the multivariate analysis with regard to the overall survival

Variable	Score	Regression coefficient (b)	SE (b)	*p* Value	RR	95% CI
Risk group	(Intermediate risk = 0, high risk = 1)	0.67	0.23	0.003	2	(1.3–3.1)
Overall treatment time radiotherapy				0.018		
6–7 weeks	Compared with <6 weeks	0.71	0.32	0.02	2.0	(1.1–3.8)
7–8 weeks	Compared with <6 weeks	0.96	0.33	0.004	2.6	(1.4–5.0)
>8 weeks	Compared with <6 weeks	1.10	0.37	0.003	3.0	(1.4–6.2)

Note: Only the factors significantly associated with LRR are shown. No significant association was found for interval between surgery and radiotherapy and total dose at the high-risk area.

OTT and RT fractionation

Table 3
Overview of RCT's comparing altered fractionation with conventional fractionation in the postoperative setting (no CT)

Author	Treatment arms	Number	3-Year loco-regional control			3-Year overall survival		
			CF (%)	AF (%)	p-Value	CF (%)	AF (%)	p-Valu
Ang	63 Gy in 7 weeks versus 63 Gy in 5 weeks	152	62	76	p = 0.11	34	50	p = 0.0
Sanguineti	60 Gy in 6 weeks versus 63 Gy in 5 weeks	236	78	80	p = 0.52	64	67	p = 0.3
Awwad	60 Gy in 6 weeks versus 46.2 Gy in 12 days	100	57	88	p = 0.01	46	60	p = 0.2
Suwinski	63 Gy in 7 weeks versus 63 Gy in 5 weeks	279	64	70	p = 0.32	55	52	p = 0.2

- AF beneficial when delay in starting radiotherapy (Sanguineti 2005)

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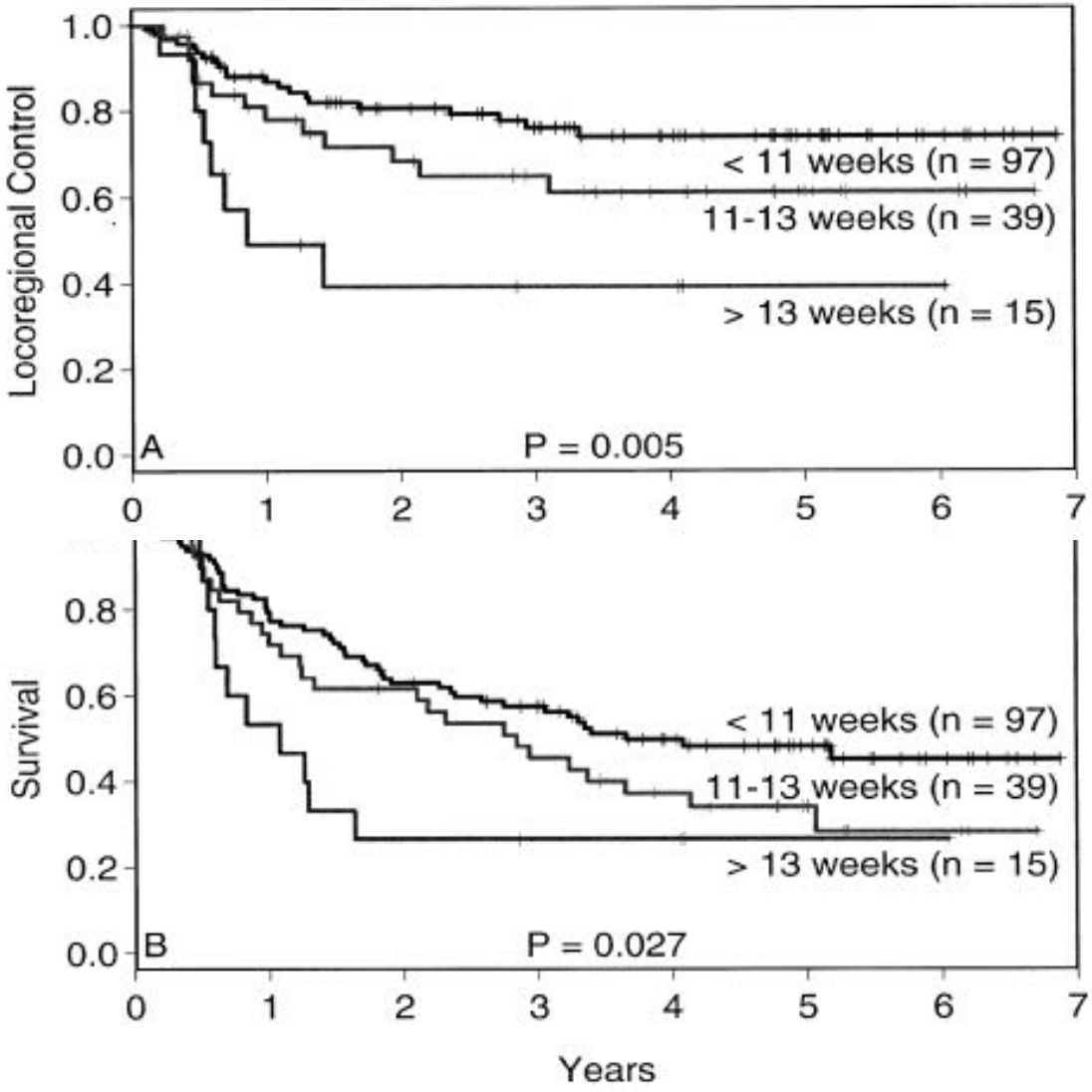
Total treatment package (TTP)

HR patients



Ang 2001

Dose

Close margin <3mm

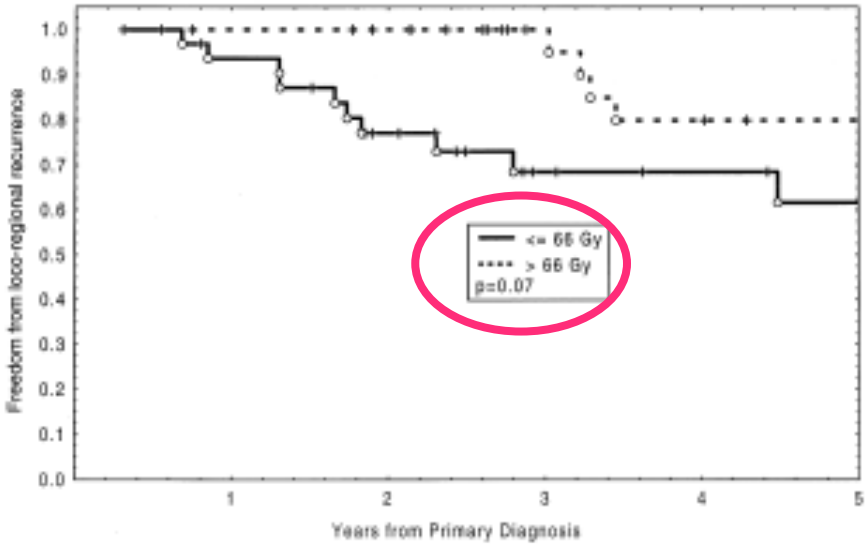


Fig. 3. Freedom from locoregional recurrence according to the applied dose of irradiation in patients resected with close surgical margins (< 3-mm distance from tumor). Total dose ≤ 66 Gy (n = 35) vs. > 66 Gy (n = 31) p = 0.07.

Positive margin

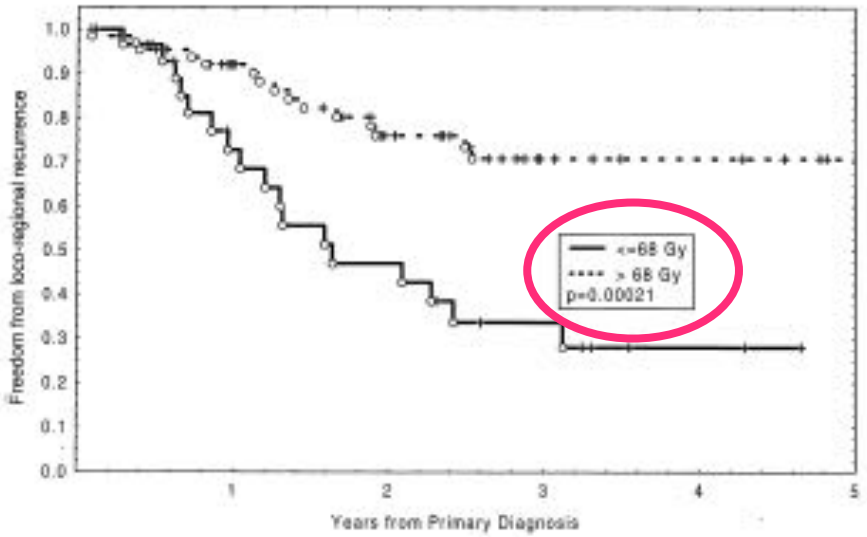


Fig. 4. Freedom from locoregional recurrence according to the applied dose of irradiation in patients resected with invasive tumor at the margin of resection. Total dose ≤ 68 Gy (n = 33) vs. > 68 Gy (n = 68) p = 0.00021.

Pfreundner, 2000

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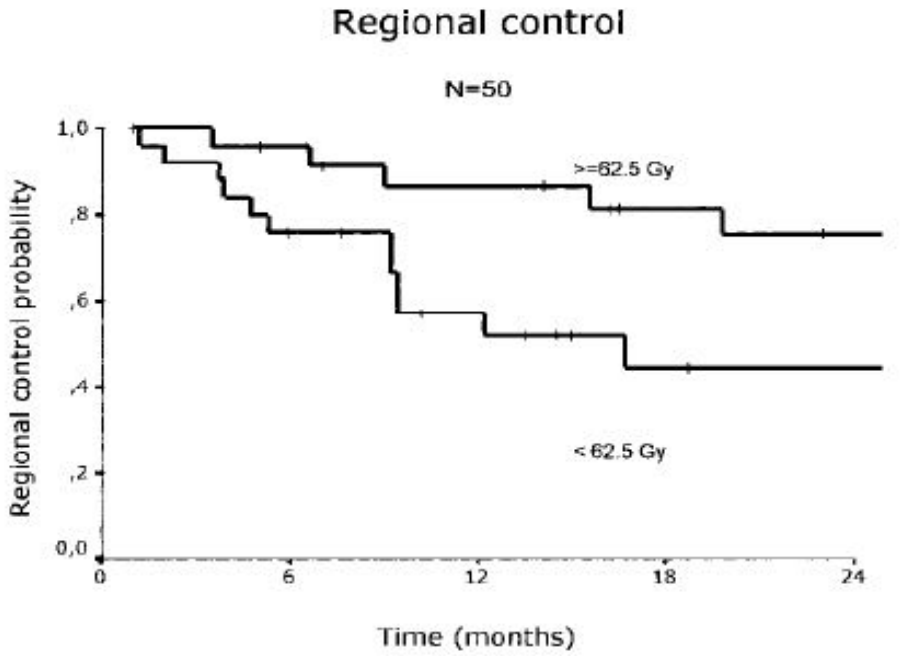
Dose

ECE +



At risk:					
>=62.5Gy	25	22	18	14	12
<62.5 Gy	25	17	11	6	5

FIGURE 4. Regional control rates in 50 necks after dissection with positive margins and postoperative radiotherapy with curative intention, stratified <62.5 Gy and ≥62.5 Gy; $p < .036$ (Kaplan-Meier analysis).

Smeele 2000

Conclusions

- Different prognostic groups pts with regard to locoregional control (LRC) and (OS) can be defined according to pathological features.

- Unfortunately, not all histological findings have a well established prognostic role.

- Optimal time factors and dose have been defined in adjuvant setting.

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