Adjuvant Treatment For Head & Neck Cancers

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Head & Neck Cancers

Paradigm shifts in management

- Multidisciplinary approach
- Advances in understanding Biology
- Exciting advances in radiotherapy delivery
- Newer chemotherapeutic agents

Intensification of treatment

Improvement in survival

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Single Modality Treatment

Definitive Radiotherapy

- Historically - only treatment for advanced unresectable cancers.
- Response and dose dependent on tumor volume/number of tumor clonogenic cells

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Single Modality Treatment - Definitive Radiotherapy

Author (Institute)	No. of patients (Year)	T-stage	Dose	Local Control
Cellai.E (Univ. of Florence)	205 (1970-1985)	(Early Glottic Ca) T1a: 45 T1b: 110 T2 : 50	61-64Gy	 43(96%) 97(88%) 38(76%)
Chang (Univ. of Oregon)	74 (1971-1991)	(Pharyngeal Ca) T1:6 T2:27 T3:32 T4:9	 60-70Gy 59-72Gy 59-74Gy 60-70Gy	 100% 55% 31% 29%
Overgaard (Danish Cancer Soc.)	478 (1963-1985)	T1larynx Glottic:358 Supra: 117 Sub: 3		 81% 55%
Dinshaw (TMH)	568 (1990 - 1996)	All sites (except nasophx) All stages	60 - 70 Gy	53%

Surgery Vs Surgery + Post op RT

Author/Group	No. of pts.	Stage	Results
Kokal et al (Virginia1988) (Randomised)	46 Sx (27) Sx + PORT (24)	III, IV	Rate of relapse was 37% Vs 68 % (P value- NS). 3 yr OS rate 58.5% and 46.5 %
Huang et al (Virginia 1992)	125(High risk factors) Sx (71) Sx+ PORT (54)	LA	LRC - 59 Vs 31% (P value- S) OS- 50 Vs 30% (P value -S)
Fletcher (M.D Anderson1977)	169	IV	Rate of failure above the clavicles 24 Vs 13%
Badawi et al (1982)	328	III, IV	Rate of failure above the clavicles 48 Vs 16% and OS - 40 Vs 25%
Francheschi D MSKCC (1992)	297	Oral tongue ca III ,IV	LRR 43 Vs 29% Neck rec. 29 Vs 13%
Mishra et al India 1996	140 Sx- 52 PORT- 70	LA Ca BM	DFS 68 % Vs 38 %. OS 94% Vs 84%

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Single Modality Treatment

- **Radical radiotherapy & Surgery give consistent and reproducible results in early stage cancers**
- **Dismal results in advanced stage disease**
- **Complications & failures to RT related to :**

  Stage, Total dose, Dose/ fr, Overall time

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Adjuvant Radiotherapy

- **Why?- Rationale and evidence.**
- **Who? – Indications and evidence.**
- **What dose?- Rationale and evidence.**
- **When?- Rationale and evidence**

Why Adjuvant Radiotherapy ?

- Reduces local and locoregional recurrences.
- Scarce level I evidence but well studied in several retrospective studies

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Adjuvant Radiotherapy

AUTHOR (Institute)	NO. OF PTS.	TREATMENT	RESULTS (Local cont.)
Huang (Univ. of Virginia)	125 (1982-1988)	* 71(Surg alone) * 54(Surg+RT)	Perinod.---31%(p=0.03) +ve C/M-- 41%(p=0.001) Perinod.---66% +ve C/M---68%
Zelefsky (MSKCC)	51 (1973-1985)	* Surg+RT	T2:84-100% T3:86-100% T4:84-50% → 64%
Peters (M.D.Anderson)	240 (1983-1989)	* Surg+RT	74%
Dinshaw (TMH)	348 (1990-1996)	* Surg+RT	T2 - T4: 79%

Who should receive Adjuvant Radiotherapy?

- **High-risk features**
- Microscopically +ve surgical margins
- ECS
- LVI
- PNI
- 2 involved neck nodes
- > 1 positive nodal group,
- Nodal diameter>3 cm,
- 6 week interval between surgery and radiation and
- Oral cavity primary site.

- **Other important factors are advanced**
- T stage
- Recurrent disease
- Tumor spillage
- Multicentricity,
- Invasion of bone, cartilage, skin or soft tissue of the neck.
- Depth of tumor invasion

Risk Level	RTOG 85-03[4]	M.D. Anderson Cancer Center[5]	University of Pennsylvania[6]	UZ Amsterdam[7]	EORTC/RTOG[3]
Highest risk	Margins	ECS; 2+ factors	ECS; margins; 2+ LNs	ECS in 2+ LNs; T3 (with margins); pN3	ECS; margins
Intermediate or high risk	2+ LNs; ECS	1 risk factor	1 risk factor	ECS in 1 LN; T1-2,T4; with margins	Perineural invasion; LN+ at levels 4-5 in oropharynx and oral cavity cancer patients; vascular embolisms; and stage III-IV

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Adjuvant Radiotherapy: What dose?

- Several retrospective studies: 60-65Gy in 6-7 wks
- No definite dose response relationship beyond 57.6Gy except for patients with extranodal extension (dose response till 63 Gy)
- Hence, for patients with high risk features higher doses >60 Gy recommended.

[Peters.L.J.et al]. Int J Radiat Oncol Biol Phys. 26(1):3-11(1993)].

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Adjuvant Radiotherapy: Timing

- **Not been studied sufficiently.**

  Bhadrasain et al. (1979) n=22

  LRC - 70% (PORT within 7 weeks)

  - 27%(PORT more than 7 weeks)

- **Limited evidence and clinical experience suggests- within 6-8 wks post surgery or as soon as the wound heals.**

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Adjuvant Radiotherapy: Timing/ OTT

- Parsons et al showed that Irradiation should begin within about 6 weeks after surgery.*
- Local control was better whose overall treatment time from date of Sx to RT completion was less than 100 days.*
- Significant loss of local control was observed with prolongation**.
- Short OTT of radiation was found to be associated with higher rates for LRC, DFS, and OS.***
- LRC worsened by 9% with every week's prolongation of OTT.***

* Parsons et al IJROBP Vol 39; 1;137-148;1997

**Fowler et al IJROBP 1992, Ang KK et al:

***Langendijk et al IJROBP., Vol. 57, No.3 693–700,2003

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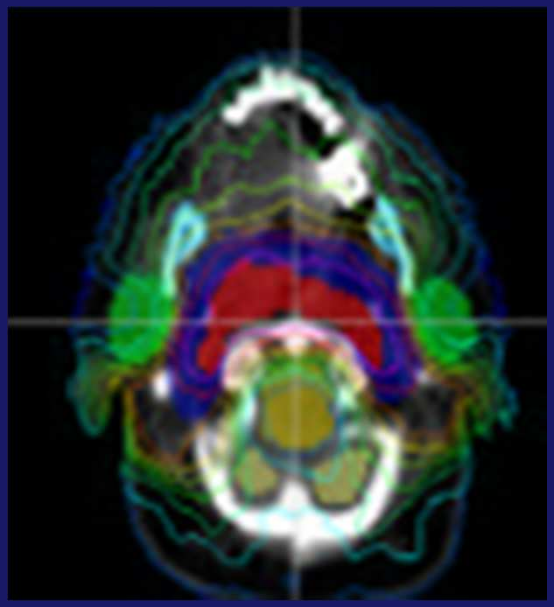
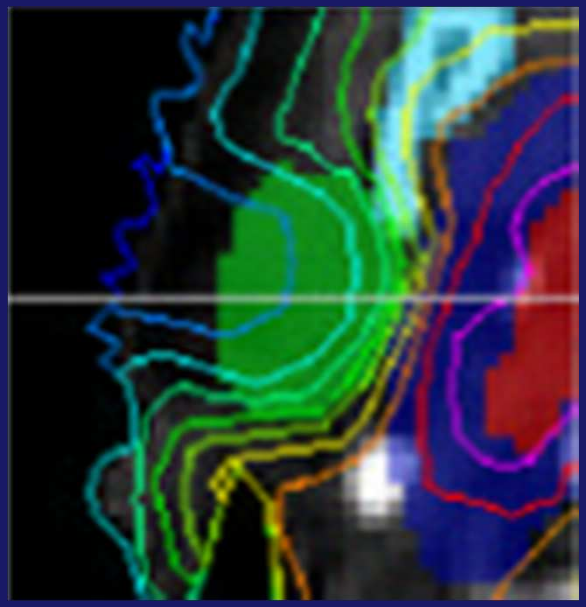
RT: The changing paradigm

Wide field radiation



Conformal radiation



Clinical motivation for high-precision techniques

More conformality = Better sparing

But, What are the exact Target Volumes in Different Subsites and Stages?

There is no consensus worldwide on

- The ideal high risk CTV volumes in each subsite.
- Prophylactic treatment areas in the soft-tissue and ipsilateral neck.
- Treatment of the contralateral neck
- Dose prescriptions – conventional vs. integrated boost.

Post-Op CTV

- The entire operative bed should be covered, especially in case of ECE.
- If level II (IIa or IIb) pN+, include the retrostyloid space up to the base of skull.
- If level V pN+, include the SCF.
- When a pathological lymph node abuts or invades a muscle – include the muscle at least in the entire invaded level.
- In selected LN dissection with one or few (pN1) marginal nodes affected – include the adjacent level.
- In pharyngeal tumors with pN+, include the lateral retropharyngeal nodes.

Gregoire et al. Proposal for the delineation of the nodal CTV in the node-positive and the post-operative neck. Radiotherapy and Oncology 79 (2006) 15–20.

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Adjuvant Radiotherapy

- **Local failures-30-50%**
- **Distal failures- 25%**
- **5 yr survival rate-30-35%**
- **Inspite of adjuvant radiation results are poor, esp. in patients with high risk features**
  - **Multiple nodal involvement.**
  - **Extranodal extension.**
  - **Perineural invasion.**
  - **Positive margins of resection.**
  - **Tumor thickness**
- **Hence, the need for Adjuvant chemoradiation**

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Adjuvant Chemoradiotherapy

- Evaluated in patients with high risk features
- Initiated by Bachaud et al, later confirmed by 2 major trials(EORTC and RTOG trials)

Prospective Trials on Adjuvant Chemoradiotherapy after Surgery

Author /Group	Year	No. of pts	Standard arm	Experimental arm	P Value	
					LRC	Survival
Bachaud	1991	88	RT	RT +Cisplatin	<.01	NS
Weissberg	1989	120	RT	RT+ Mitomycin	<.01	NS
Haffty	1993	120	RT	RT +Mitomycin	<.01	NS
Weissler	1992	26	RT	RT+ Cisplat + 5 FU	NS	NS
Smid	2003	114	RT	RT+ Mito + Bleo	P<0.037	*p* <0.036
Bernier	2004	334	RT	RT+ Cisplatin	<0.007	<0.02
Cooper	2004	459	RT	RT + Cisplatin	<0.01	<0.19

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer

Jacques Bernier, M.D., Ph.D., Christian Domenge, M.D., Mahmut Ozsahin, M.D., Ph.D., Katarzyna Matuszewska, M.D., Jean-Louis Lefèbvre, M.D., Richard H. Greiner, M.D., Jordi Giralt, M.D., Philippe Maingon, M.D., Frédéric Rolland, M.D., Michel Bolla, M.D., Francesco Cognetti, M.D., Jean Bourhis, M.D., Anne Kirkpatrick, M.Sc., and Martine van Glabbeke, Ir., M.Sc., for the European Organization for Research and Treatment of Cancer Trial 22931

The NEW ENGLAND JOURNAL of MEDICINE

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Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamous-Cell Carcinoma of the Head and Neck

Jay S. Cooper, M.D., Thomas F. Pajak, Ph.D., Arlene A. Forastiere, M.D., John Jacobs, M.D., Bruce H. Campbell, M.D., Scott B. Saxman, M.D., Julie A. Kish, M.D., Harold E. Kim, M.D., Anthony J. Cmelak, M.D., Marvin Rotman, M.D., Mitchell Machtay, M.D., John F. Ensley, M.D., K.S. Clifford Chao, M.D., Christopher J. Schultz, M.D., Nancy Lee, M.D., and Karen K. Fu, M.D., for the Radiation Therapy Oncology Group 9501/Intergroup

Adjuvant Chemoradiotherapy Meta-Analysis

Table 2. Efficacy data: randomized trials of chemoradiotherapy versus radiotherapy alone.

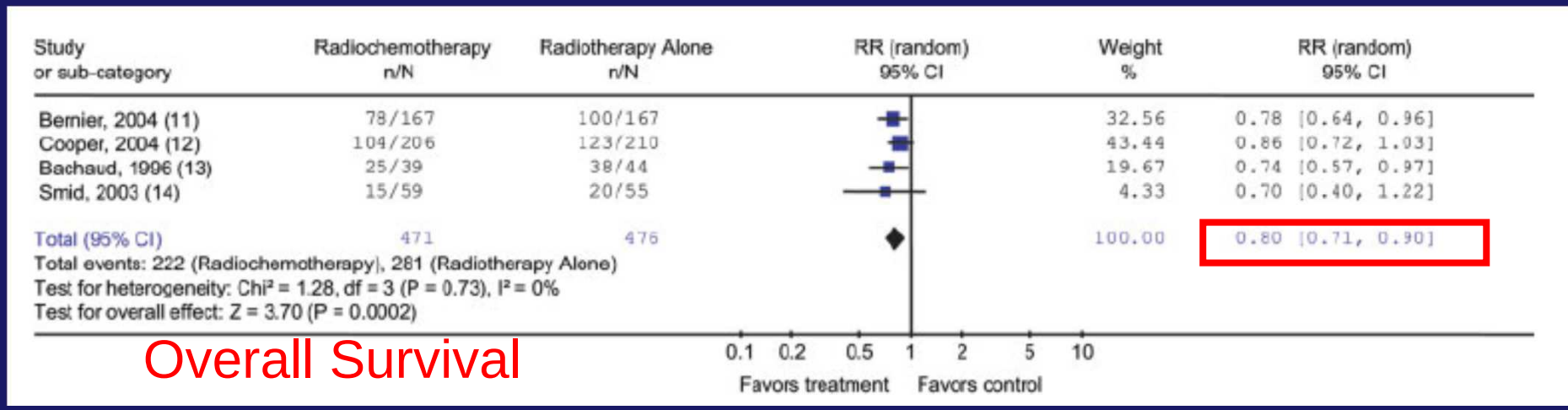
Author/year, ref.	No. of pts.	Treatment arms	Point in time*	Locoregional recurrence	Progression-free survival	Disease-free survival	Overall survival	Median survival, mo
Bernier et al, 2004[11]	167	CT/RT	5 y	18%	47%	NR	53%	72
	167	RT		31%	36%	NR	40%	32
				$p = .007$	$p =$ NR		$p =$ NR	$p =$ NR
			Overall	NR	HR = 0.75, $p = .04$	NR	HR = 0.70, $p = .02$	
				NR	95% CI = 0.56–0.99	NR	95% CI = 0.52–0.95	
Cooper et al, 2004[12]	206	CT/RT	3.8 y	19%	NR	40%	50%	45
	210	RT		30%	NR	30%	41%	32
				$p =$ NR		$p =$ NR	$p =$ NR	$p =$ NS
			Overall	HR = 0.61, $p = .01$	NR	HR = 0.78, $p = .04$	HR = 0.84, $p = .19$	
				95% CI = 0.41–0.91	NR	95% CI = 0.61–0.99	95% CI = 0.65–1.09	
Bachaud et al, 1996[13]	39	CT/RT	5 y	23%	NR	45%	36%†	40
	44	RT		41%	NR	23%	13%	22
				$p = .08$		$p < .02$	$p < .01$	$p =$ NR
			Overall	NR	NR	NR	NR	
				NR	NR	NR	NR	
Šmid et al, 2003[14]	59	CT/RT	2 y	14%	NR	78%‡	74%	> 48‡
	55	RT		31%	NR	60%	64%	32
				$p = .037$		$p = .099$	$p = .036$	$p =$ NR
			Overall	NR	NR	NR	NR	
				NR	NR	NR	NR	

Abbreviations: pts., patients; CT/RT, chemotherapy plus radiotherapy; RT, radiotherapy; NR, not reported; HR, hazard ratio; CI, confidence interval; NS, not statistically significant; Y, years.
**Percentiles reflect the point in time that outcomes were measured; overall data reflect hazard ratios from Kaplan–Meier curves.*
†Survival corrected by deaths of intercurrent disease was 47% with chemoradiotherapy and 23% for radiotherapy alone.
‡Data extracted from survival curves by reviewer.

HEAD & NECK—DOI 10.1002/hed January 2007

Head & Neck Cancer

Adjuvant Chemoradiotherapy Meta-Analysis



Overall Survival

12.5% absolute improvement in OS (NNT=8)

Grade III/IV mucositis- 70% vs. 34%

Treatment related deaths-1-2%

HEAD & NECK—DOI 10.1002/hed January 2007

Adjuvant Chemoradiotherapy Meta-Analysis

Conclusions:

- Chemoradiotherapy beneficial for high risk factors :
  - Extranodal extension
  - Positive Cut margins
- Beneficial < 70 years of age
- Significant toxicity
- Need for intense supportive care

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Adjuvant Chemoradiotherapy: TMH EXPERIENCE

Oral Cavity Adjuvant Therapy - HN / 04/008/R

(Initiated in June 2005, Ongoing
498 pts accrued so far)

- **Phase III Study, 3 arms**

- **For High Risk, Locally Advanced, Stage III & IVA, Resectable Squamous Cell Carcinoma of Oral Cavity**

- **Target Accrual: 750 patients over 3 years**

SURGERY

↓

RANDOMIZATION

Adjuvant Conventional External Radiotherapy
v/s
Adjuvant Accelerated Radiotherapy (6 fr/ week)
v/s
Adjuvant Concurrent Chemoradiotherapy

Adjuvant Chemoradiotherapy

- **Postoperative chemoradiation - intensify treatment for resectable tumors to improve upon existing control rates.**
- **Existing evidence - adjuvant chemoradiation in patients with high risk features (Intergroup 0034 trial).**
- **High incidence of treatment related toxicity –need for intense supportive measures**

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Optimization of Radiotherapy Response

Biological optimization

- **Altered fractionation**
- **Biological response modifiers**
- **Targeted therapies**

CLINICAL INVESTIGATION Head and Neck

ACCELERATED VERSUS CONVENTIONAL FRACTIONATED POSTOPERATIVE RADIOTHERAPY FOR ADVANCED HEAD AND NECK CANCER: RESULTS OF A MULTICENTER PHASE III STUDY

- 226 patients.
- Median follow-up 30.6 mths
- Two arms CF RT 60Gy/30#/6wk or AF(biphasic concomitant boost with boost delivered during first and last weeks of treatment, to deliver 64 Gy in 5 week
- 2-yr LRC- CF 80% and AF 78% (p=0.52)
- 2-yr OS - CF 67% and AF 64% (p=0.84)
- Patients who had a delay in starting RT showed improved LRC with AF compared with those with a similar delay but who were treated with CF

Sanguineti et al IJROBP Vol. 61No 3;762–77;2005

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Optimization of Radiotherapy Response

Biological optimization: Targeted therapy

Agents being tested in various clinical trials are

- Cetuximab (RTOG0234, RTOG0522)
- Lapatinib
- Nimotuzumab

Toxicity to Multimodality Treatment

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

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

Oral Pain- 69%

Opioid Use-53%

Overall Incidence of- Hospitalization: 16%

Feeding Tube Insertion: 19%

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

Dysphagia: 56%

Affecting their overall QOL

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Conclusions

- **Appropriate Institution of Multidisciplinary approach**
- **Adjuvant radiotherapy is an essential component**
- **Adjuvant chemoradiotherapy is still investigational and reserved for high risk cases**
- **IMRT and other conformal techniques improve the therapeutic gain**
- **Targeted therapies are still investigational**
- **Intensive supportive care is essential for success**