

Combined Modality Therapy with Surgery and Radiation Therapy in Locally Advanced Head & Neck Cancers



Dr. GK Rath

Prof. & Head

Department of Radiation Oncology,

Chief,

Dr BRAIRCH, AIIMS, New Delhi.

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1-3	N1	M0
Stage IV A	T4a	N0-N1	M0
	T1-4a	N2	M0
Stage IV B	Any T	N3	M0
	T4b	Any N	M0
Stage IV C	Any T	Any N	M1

Locally Advanced Disease

- Stage III and Stage IV disease except dist mets
- Divided into resectable and unresectable subgroups
- Recent sub-grouping by UICC

Definition of subgroups of HNSCC with different risk of treatment failure according to TNM-UICC AJCC classification [3]

Prognostic subgroup	TNM features	Stage classification
Low-risk subgroup	T1–T2 N0	I–II
Intermediate-risk subgroup	T3 N0 T1–3 N1	III
High-risk subgroup	T4a N0–N1 T1–T4 N2	IVA
Very high-risk subgroup	T4b any N Any T N3	IVB
Poor prognosis subgroup	Any T any N M1	IVC

Corvo R. Evidence based radiation oncology in HNSCC. Radiother Oncol 2007 (in press)

Treatment Modalities

- Three main modalities of treatment
 - Surgery
 - Radiation Therapy
 - Chemotherapy
- Optimal combination of above three modalities

Principles of Treatment

- Early Disease (Stage I, II) - Monotherapy
 - Surgery or Radio-therapy - Comparable results
 - 5 year survival stage I - 80 - 90%
 - 5 year survival stage II - 60 - 80%
- Choice depends –
 - Tumor factors – Site, Size, Type
 - Patient factors
 - Facilities available

Locally Advanced Disease

- Advanced disease (Stage III, IVA)
Combination therapy

Surgery + Post operative RT

Concurrent Chemotherapy + RT

- 5 year survival stage III - 40-50%
- 5 year survival stage IVA - 20-30%

**Pignon et al. Lancet 2000; 355: 949*

Why is combined treatment necessary?

- Advanced lesions (85% are stage III and IV cancers)
- Single modality of treatment gives unsatisfactory results
- Failure to control disease above clavicle (loco regional)

Historical evidence

- Strong (1969) observed failure rate of 70% in patients treated with surgery alone.
- Addition of post-operative RT resulted in improved NED status to about 50% (Vikram et al 1984)

Are two modalities of treatment competitive?

- The two modalities are complimentary
- Surgery to remove the gross tumour
- RT to eradicate the microscopic disease

Combined Modality Treatment: Possible regimes

- RT -----> Surgery (Pre-op RT)
- Surgery + RT (Intra-operative RT)
- **Surgery -----> RT (Post-op RT)**
- Radical RT -----> Salvage Surgery

RT -----→ Surgery (Pre-op RT)

- Not a common regime
- Borderline operable lesions
- Well oxygenated tumors
- Reduces the viability of tumor
- Improves resectability
- Delayed wound healing
- Have been used for RMT & PNS tumors

Pre-op RT

- Retrospective analysis : Preop RT vs Postop RT vs RT alone (10 vs 39 vs 15 pts)
- Pre-op RT : 30-55.2 Gy
- The 5-year DFS rates were 90% with preop RT, 63% with PORT, and 31% with RT alone
- Sample Size : small

Huang et al. Head Neck. 2001;23(9):758-63

Post-operative RT

- Takes care of microscopic disease after removal of gross disease.
- Considered when risk of loco regional failure $> 20\%$
- Optimal timing and dose major considerations (4-6wks, Dose 60-64 Gy/30-32#/6-6.5 wks)
- Commonly done in stage III, IV tumors and selectively in early stages.

Advantages:

- Better information about the tumor pathology
- Knowledge of tumor spread
- Tailoring of radiation dose and volume

Disadvantages:

- Potential delay in starting RT
- Tumor hypoxia
- Wound healing

Preop vs. Postop RT

Preop RT

- ↓ viability of tumor, wound implantation
- Improves resectability
- Postop RT superior to preop RT in H&N Cancer (RTOG, 73-03) trial, 1991)
- Timing of postop RT critical-Within 3-6 weeks of surgery, >6 weeks delay detrimental (*Peters, IJROBP 26;3-11, 1993*)

Postop RT

- Pathologic information to modify dose or treatment portals
- Allows proper wound healing
- Allows delivery of ↑ dose of radiation

Indications

Absolute Indications

- Microscopically involved mucosal margins of resection
- Extra capsular extension

Relative Indications

- Close margins (<5mm)
- Multiple positive neck nodes (2 or more)
- pT3-T4 with negative margins (except pT3 larynx)
- Perineural spread or microvascular emboli

**Corvo R. Evidence based radiation oncology in HNSCC.
Radiother Oncol 2007 (in press)*

Postop RT : Literature

Peters et al MDAH	1993 Int J Rad Onc Bio Phy	Pri Failure Rate is significantly high $p=0.02$, when dose <54 Gy vs >57.6 Gy	Minimum 57.6 Gy to operative bed with boost upto 63Gy and RT to be started asap
Ampil et al Louisiana State Univ	2003 J Oral Maxillofac Surgery	In close/positive margins LRFR 25% when dose <60 Gy vs 8% when its >60 Gy	
Muriel et al Univ Hosp Spain	2001 Radiotherapy Oncology		OTT significant prognostic factor and time b/w Sx & RT an independent predictor of failure

Postop RT : Literature

Ang et al M D Anderson Hospital	2001 IJROBP	In high risk pts, higher LRC and survival rates when PORT course reduced (5 vs 7wks) $p=0.03$	OTT had an impact
Ampil et al Louisiana State University	1993 J Oral Maxillofac Surgery	Local and regional recurrence rate 37% vs 20% when PORT delayed	Timely initiation of PORT important

Technique of EBRT

- Treatment Unit : Co-60 or Linac 4-6 MV photons
- Volume of irradiation

Primary tumor +/- neck nodes

- Total Dose : 60-64 Gy
- No. of Fractions : 30-32
- Dose/fraction : 180-200 cGy
- Duration : 6-6.5 weeks

Postoperative IMRT in head and neck cancer:

Rationale

- Despite high dose PORT in patients with locally advanced HNC with certain high risk factors, loco-regional recurrences rate is about 30%.
- IMRT has a potential to reduce the radiation accompaniments
- In Last 5 yrs, IMRT has been shown to be beneficial in head & neck cancer

Postoperative IMRT in head and neck cancer

- Studer* et al used Postop IMRT in HNC
- No of pts : 71
- Period of study : Jan 2002 - Aug 2006
- Sites: oral cavity, hypopharynx, larynx, PNS
- Mean Dose : 66.3 Gy (60–70), with 2–2.3 Gy/Fr
- Compared the results with historic series

*Studer et al. *Radiation Oncology* 2006, 1:40

Postoperative IMRT in head and neck cancer

- No grade IV toxicity
- All pts completed treatment without interruption
- Grade III xerostomia in 43 pts
- 2-year actuarial local control: 95%
- 2-year actuarial DFS: 90%
- Concluded that Postop IMRT resulted in high loco-regional tumor control rates compared with large prospective 3DCRT trials.

Postoperative IMRT in head and neck cancer: literature

Author, ref	(year)	n pIMRT (dIMRT)	HNC subsites	T3/4, rec, OCC	pIMRT dose	Chemotherapy	2-y L(R)C	median FU
Lee et al [15]	(2003)	43 (107)	all	53, 0, 2%	66 Gy	35% of pIMRT	83% LC	25 (6–78)
Chao et al [9]	(2004)	74 (52)	all	52, 0, 12%	~68 Gy (+/-4.7)	none of pIMRT	90% LRC	26 (12–55)
Feng et al [10]	(2005)	86 (72)	all but NPC/SNC	90 III/IV, 3, 23%	~70 Gy (66–76)	12% of all	~85% LRC	36 (6–127)
Yao et al [12]	(2005)	51 (100)	all	53, 0, 19%	64–66 Gy	none of pIMRT	~92% LC	18 (2–60)
own	(2006)	71 (230)	all SCC	25, 18, 31%	~66 Gy (60–70)	83% of pIMRT	95% LC 91% NC	17.6 (2–48)

Accelerated Post op RT

- Accelerated Treatment: 76 pts treated with 63 Gy in 5 wks
- Conventional Treatment: 75 pts treated with 63 Gy in 7 wks
- For high-risk patients, a trend toward higher LRC and survival rates was noted when PORT was given in 5 wks
- A 2-week reduction in the PORT duration did not increase the late treatment toxicity.

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

Accelerated Post op RT ...contd...

- 226 pts with one or more high-risk features (pT4, positive resection margins, pN >1, perineural invasion, ECE) treated with accelerated PORT
- Two arms : 60Gy in 6 wks vs 64Gy in 5 wks
- 2-year locoregional control were 80% +/- 4% for CF and 78% +/- 5% for AF (p = 0.52)
- improved locoregional control with Accelerated RT for the pts who had a delay in starting RT

Sanguineti et al. IJROBP 2005; 61(3):762-71

POSTOP CHEMORADIATION

Cooper et al. NEJM 2004; 350 : 1937-44.

n=459; surgery

	<i>RT alone (60-66Gy)</i>	<i>RT+ CDDP (100mg/m² IV D1,22,43)</i>
Recurrence (FU 45.9 mo)	30%	19% (p=0.01)
2 year LC, RC	72%	82%
OS (Mo)	31.9	44.9 (p=0.19)
Gd 3,4 toxicity	34%	77% (p<0.001)

POSTOP CHEMORADIATION

Bernier et al. NEJM 2004; 350 : 1945-52.

n=167; surgery

	<i>RT alone (66Gy)</i>	<i>RT+ CDDP (100mg/m² IV D1,22,43)</i>
Locoregional failure (5 yr)	31%	18% (p=0.007)
5 year OS	40%	53% (p=0.02)
5 year PFS	36%	47% (p=0.04)
Gd 3,4 toxicity	21%	41% (p=0.001)

Intra-operative RT

- Practiced in very few centers
- Mainly for advanced/recurrent disease
- May be used in primary management of PNS/skull base tumors
- Mainly two methods : IOERT and IOHDR*

**Limited experience at AIIMS*

IORT in Head and Neck Cancer

IORT-Electron

- Accessible lesion
- More homogenous and penetrating dose distribution

IORT-HDR

- Less accessible
- Heterogeneous dose (200% of prescribed dose at surface) & limited penetration

Results of IOERT

Institution	No. of pts	LR control	2yr survival	Complications
<hr/>				
<u>Mayoclinic(1994)</u>				
S+IOERT	17	41%	25%	3%
S+IOERT+EBRT	14	64%	39%	
<u>UCSF(1994)</u>				
Primary	5	100%	70%	16%
Recurrence	25	60%	(overall)	
<u>Ohio State Univ(1997)</u>				
IOERT+EBRT	28	79%	88%	15%
IOERT	12	50%	33%	
<u>Univ of Ryukyus (1992)</u>				
Gross residual	7	0%	0%	33%
Microscopic	12	55%	33%	
Close margins	11	82%	30%	

IOERT: Technique & Results Gunderson, Humana Press 1999

IOHDR for PNS Tumors

- Period of study : 1992 and 1998
- No. of patients : 34
- Dose of IOHDR : 10-12.5 Gy
- Dose of EBRT : 45-50 Gy
- 5-yr and 6-yr survival : 62%, and 44%

Nag et al. IJROBP 2004; 58(1):155-60.

Definitive RT with salvage surgery v/s combined surgery and RT AIIMS Data

- 119 pts of ca larynx T3N0M0
- Retrospective analysis
- Two arms Sx+RT and RT alone followed by Sx for salvage
- Non randomized, joint decision by Sx, RT team
- Actuarial 4-year DFS rates were significantly better with combined treatment (79.3 %) than with radical radiotherapy and surgical salvage (65.3 %) p value < 0.024

Thakar et al J Laryngol Otol. 2000;114(2):108-12

Definitive RT with salvage surgery v/s combined surgery and RT AIIMS Data

- 195 pts of Ca Hypopharynx T3N0M0
- Retrospective analysis
- Two arms Sx+RT and RT alone followed by Sx for salvage
- Actuarial 2-yr DFS rates were better with Sx+RT than with RT with surgical salvage ($p = 0.0021$).

Bahadur et al. J Laryngol Otol. 2002;116(1):29-32

Combined therapy in advanced head and neck cancers: AIIMS Study

- 252 cases with stage III and IV resectable cancers of the head & neck
- treated by combined regime of pre- or post-operative RT and radical surgery
- 193 patients completed the treatment protocol
- 58 cases (33.5 per cent) who failed either at primary or regional sites or both
- Nine cases (five per cent) developed distant metastasis

Bahadur et al. J Laryngol Otol 1992;106(5):412-5

Combined therapy in advanced head and neck cancers: AIIMS Studycontd..

- Absolute and determinate four year disease-free survival was 55 per cent and 61 per cent respectively.
- Authors concluded that reduction in primary and regional failures correlates well with a combined therapy

Bahadur et al. J Laryngol Otol 1992;106(5):412-5

Conclusions

- Locally advanced Head and neck cancer requires multimodal approach
- For operable lesions, most institutes practice surgery followed by PORT
- Addition of chemotherapy to PORT in pts with high risk factors: emerging role
- Newer techniques of RT like IMRT have shown encouraging results

Conclusions ...contd...

- Accelerated PORT for those where there is delay in starting RT
- Preop RT practiced in limited centers for selected sites
- Few institutes have studied role of Intra-operative RT in advanced head and neck cancer

Thank You

