

**EVALUATION OF TRIMODALITY
TREATMENT IN
POST-OPERATIVE HIGH RISK HEAD
AND NECK CANCER**

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AIMS OF STUDY

1. Compare an accelerated hyperfractionation radiotherapy regimen given over 12 days with a concomitant boost regimen given over 4.5 weeks in the postoperative treatment of high risk head and neck cancer patients.
2. Study of the possibility of improving the results of the concomitant boost regimen by adding concomitant cisplatin.
3. To test whether the DNA-adduct levels detected in the oral mucosa can predict the outcome of concomitant cisplatin

**The policy of giving Post-operative
Radiotherapy in “High Risk HNC” is:**

still based on careful clinical observations (level IV
evidence)

(No randomized studies, Level I or II)

High risk factors after radical surgery of HNC

(Ang, 2001)

*Primary tumour

- Site of the primary tumour (hypopharynx and oral cavity)
- T-stage
- Positive surgical margin

*Cervical nodes

- >one nodal group
- 2 positive nodes
- > 3 cm node
- Extracapsular infiltration
- Perineural extension

Muti-institutional Concomitant Boost Trial (Ang 2001)

Low risk: No risk factors

Intermediate risk: 1 risk factor - High risk:>1 risk factor

		5-year actuarial results	
Risk group	Schedule	LRC	Survival
Low risk	Surgery alone	90%	83%
Intermediate risk	57.6 Gy/65 wk	94%	66%
High risk		p	p
Conventional F	63 Gy/7 wk	60%	32%
Concomitant boost	63 Gy/5 wk	73%	45%
		0.11	0.08

Local control rates in the conventional and accelerated hyperfractionation groups

Accelerated hyperfractionation NCI Postoperative RT in high risk patients

Awwad & Lotayif et al. , 2002

Conventional (CF)

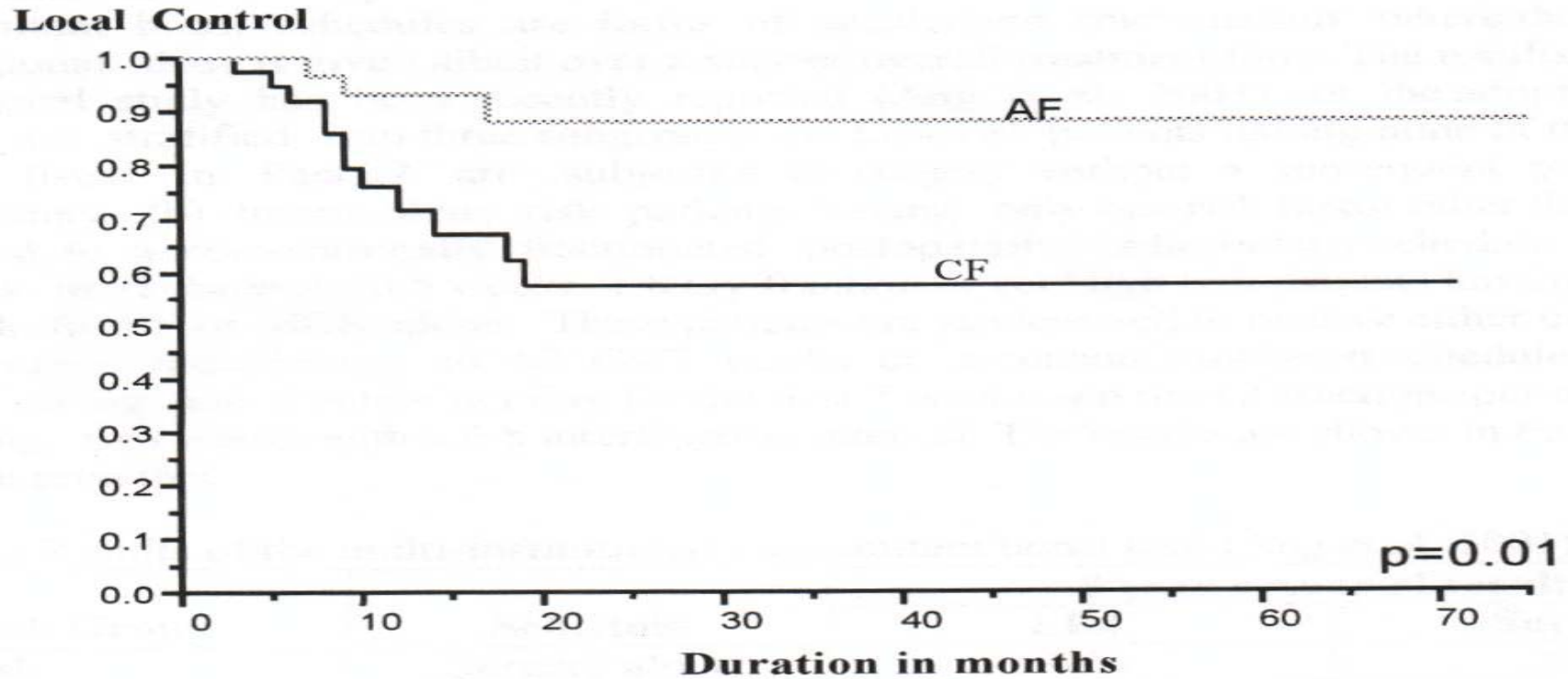
60 Gy/6 weeks (30 fractions, 2 Gy each, 5 f/wk)

Accelerated hyperfractionation (AHF)

46.2 Gy/12 days (36 f, 1.4 Gy/f, 3 f/day, treating 6 days/wk)

	3-year Results		
	CF	AHF	p
Local control	57±9%	88±4%	0.01
Survival	60±10%	46±%	0.29

Conventional and accelerated hyperfractionation groups and their 3 year results



Number at risk	0	12m	24 m	36m	60m
CF	39	24	11	8	3
AHF	31	27	16	10	5

Figure 1 Locoregional control in the accelerated hyperfractionation (AHF) and conventional fractionation (CF) groups using the Kaplan-Meier (product limit) estimate (Awwad and Lotayef et al, 2002)

TRIMODALITY TREATMENT FOR LOCALLY HIGH RISK HNC

Based on previous studies:

Trimodality Treatment needs to be tested in patients with high risk factors to:

- * Further augment local control**
- * Improve survival**

Al-Sarraf, 1997 and Bachaud, 1991 proposed the addition of **Cisplatin concomitantly with postoperative radiotherapy:**

- (a) Active against squamous cell carcinoma.**
- b) Radiosensitization (formation of DNA adducts and suppression of glutathione).**
- c) Deep extravascular penetration into hypoxic zones (beyond the oxygen penetration range)**

**EORTC concomitant postoperative
chemoradiotherapy Trial 22931
(334 patients) (Bernier et al 2001)**

Conventional fractionation 66 Gy/33 F

versus

Same plus Cisplatin (100 mg/m²) D1, D22, D43

	CF	Trimodal	p
Disease free Survival	41%	59%	0.0095
Overall survival	49%	65%	0.0057
G3-4 functional mucositis	21.3%	44.5%	0.0004
G 3-4 haemat toxicity	1.9%	11.9%	

TUMOUR SELECTION CRITERIA

- **Group I:**

I.1 Positive resection margin

I.2 Extracapsular nodal extension.

- **Group II:**

II.1 Primary tumour site: oral cavity and hypopharynx

II.2 Multicentric primary tumour

II.3 Close surgical margin < 5mm.

II.4 Invasion of soft tissue

II.5 Perineural invasion

II.6 Two or more involved cervical nodes

II.7 More than one involved cervical nodal group

II.8 Involved node more than 3 cm in diameter

The following groups of patients are considered as high risk patients and are selected for postoperative radiotherapy:

- a. Patients having either I.1 or I.2**
- b Patients having two or more of the factors in Group II.**

Patients judged to have a low risk of surgical failure are excluded from the study.

General Eligibility Criteria (1)

1. Primary squamous cell carcinoma of
 - * Oropharynx.
 - * Hypopharynx.
 - * Larynx.
 - * Maxillary antrum
- No distant metastases **beyond cervical nodes.**
 - Absence of uncontrolled medical diseases
 - Performance status 0, 1, 2 (**WHO scale**)
 - No previous malignant disease (**apart from rodent ulcer**)

General Eligibility Criteria (2)

5. Normal liver, kidney and hematological functions
6. **Hemoglobin level should ≥ 12 g/dl**
7. Applicability of the the proposed radiotherapy techniques
8. **Patient available and willing for long-term follow-up.**
9. Patient written consent

THERAPEUTIC GROUPS

- **Arm (1)** Accelerated hyperfractionation (AHF). 3F/day, 1.4 Gy each (4.2Gy/day), interfraction interval of ≥ 6 h (50.4 Gy/12 days)
- **Arm (2)** Concomitant boost schedule, 60.2 Gy/5 weeks, giving 1.8 Gy/F on days 1-5, 8-13, 15-19 and 22-23 and 2 fractions/D 1.85 Gy each on days 24-26 and 29-33.
- **Arm (3)** The same as in arm 2 while giving platinol 100 mg/m² on day 1. 80 mg./m² on days 22 and 43 with proper hydration.

Schematic Presentation For Arm 3

Sat	Sun	Mon	Tues	Wed	Thurs	Fri
D1	D2	D3	D4	D5	D6	D7
I + Pt	I	I	I	I	-	-
D8	D9	D10	D11	D12	D13	D14
I	I	I	I	I	-	-
D15	D16	D17	D18	D19	D20	D21
I	I	I	I	I	-	-
D22	D23	D24	D25	D26	D27	D28
I + pt	I	I I	I I	I I	-	-
D29	D30	D31	D32	D33	D34	D35
I I	I I	I I	I I	I I	-	-
D36	D37	D38	D39	D40	D41	D42
-	-	-	-	-	-	-
D43						
Pt						

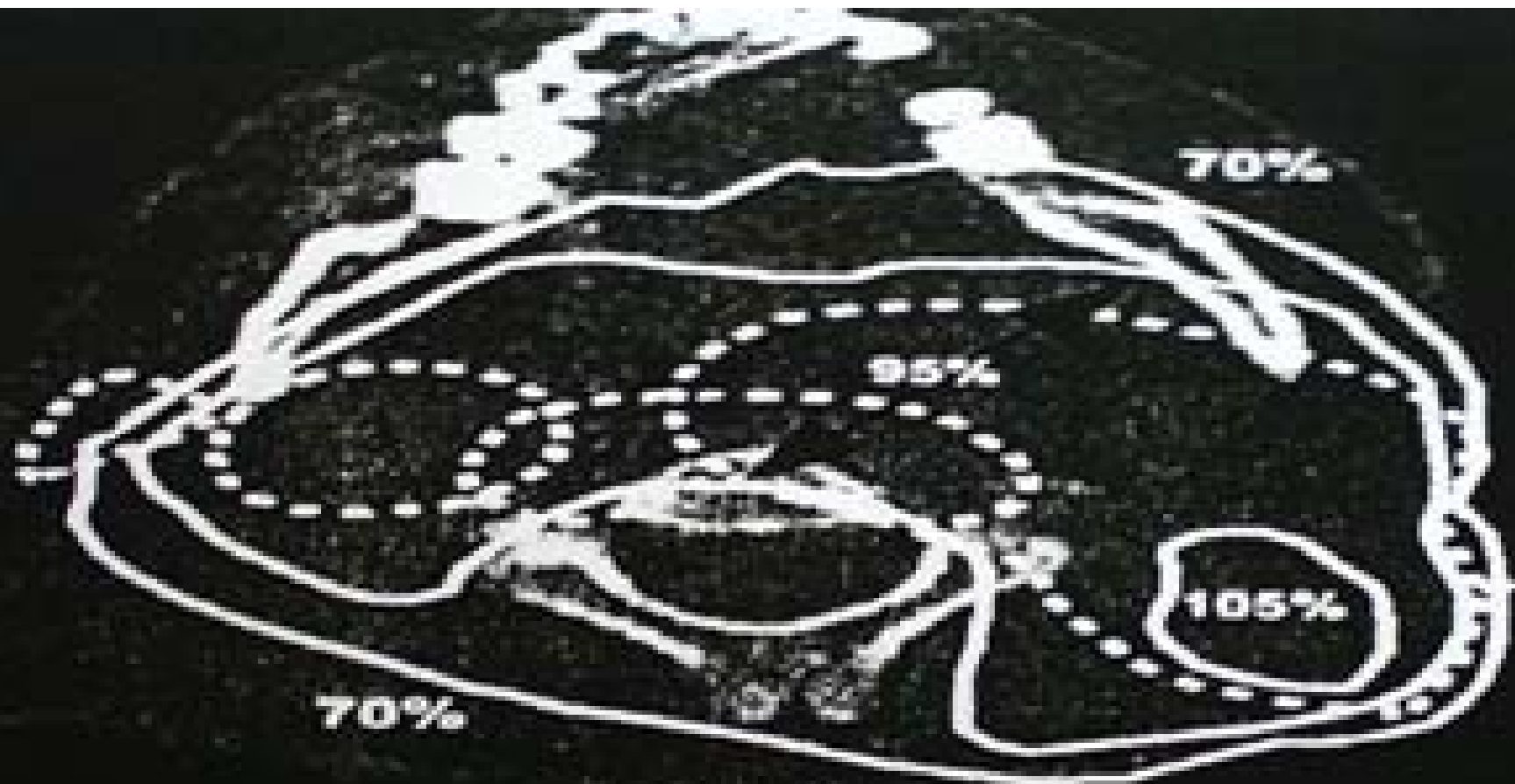
I = 1.8 Gy F on D 1-5,8-13, 15-19 and 22-23

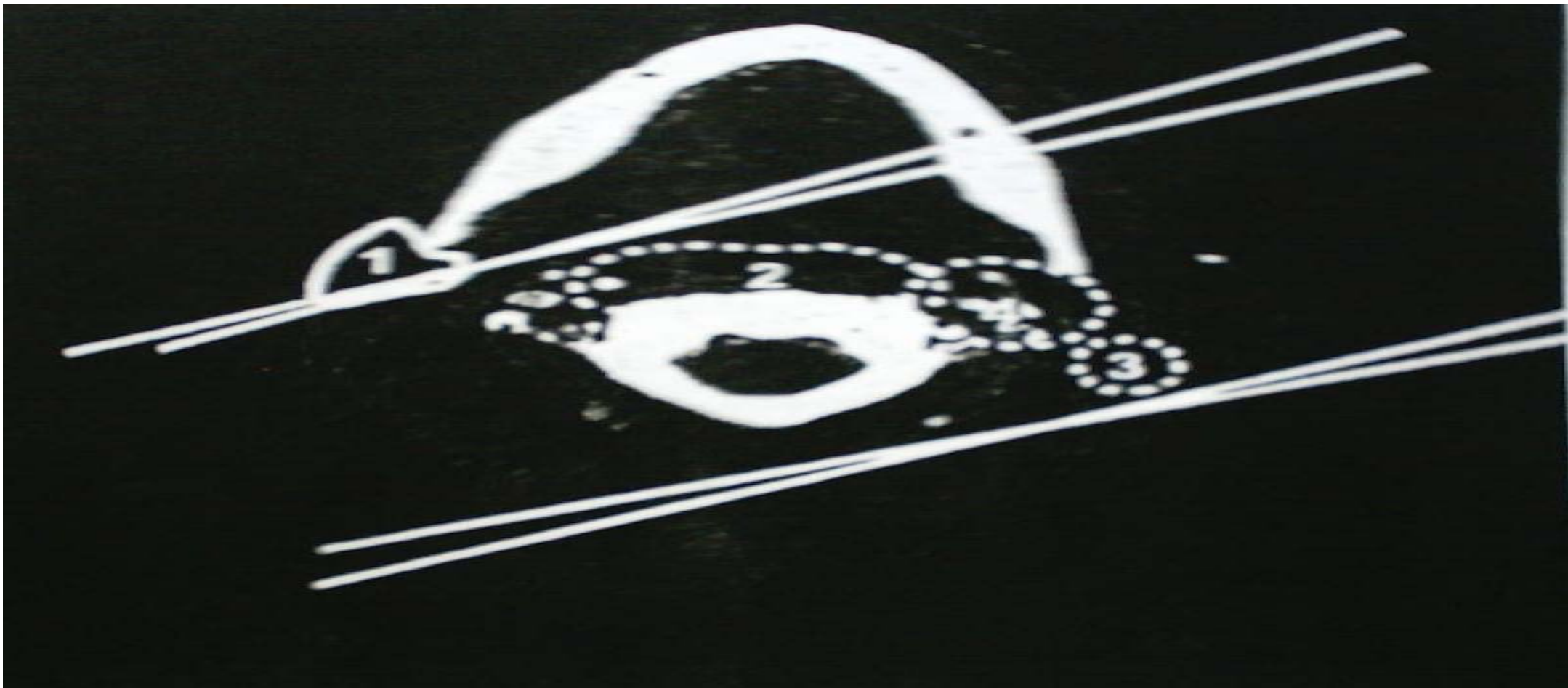
I I = 2 fractions per day 1.85 each on days D24-D26 and D29-D33.

Platinol is given on day 1 (100mg/m²) and days 22 and 43 (80 mg/m²).

POSTOPERATIVE RADIOTHERAPY TECHNIQUES

- **Tools:** 6 MV linear accelerator, CT, Simulator & 3D computer treatment planning system.
- Custom-made plastic shells for immobilization.
- Delineation of the gross target volume, the clinical target volume and planned target volume on serial CT cuts.
- A scheme for such volumes is adopted according to primary site (a) oral cavity, (b) larynx and hypopharynx, and (c) maxilla.
- Another scheme is adopted for cervical nodal areas





- Beam arrangement for the initial treatment of the patient.
- Broken lines: planning target volumes of nodes at risk for distant metastasis. 1: Rt. Parotid gland. 2: Retropharyngeal LNs, 3: Lt. Post neck nodes, 4: Lt. Jugular nodes

Determination of DNA-Platinol Adduct Levels

- 1. Collection of the buccal epithelial cells from the inner cheek with a cotton swab before starting cisplatin treatment, 24 hours after first dose and 24 hours after second dose.**
- 2. Cells will be collected at Phosphate Buffer Saline (PBS).**
- 3. Centrifugation will be done for 10 minutes at 200 gram and washed twice with PBS.**
- 4. Cells are put onto a microscope slide using a cytopsin followed by immunohistochemical procedure.**

ASSESSMENT

- 1. The tumor status will be assessed 3 months for 2 years to detect local recurrence and/or distant metastasis.**
- 2. Chest X-ray and blood picture should be routinely performed every 6 months.**
- 3. If recurrence is suspected a biopsy or FNAC should be taken**

Thank You