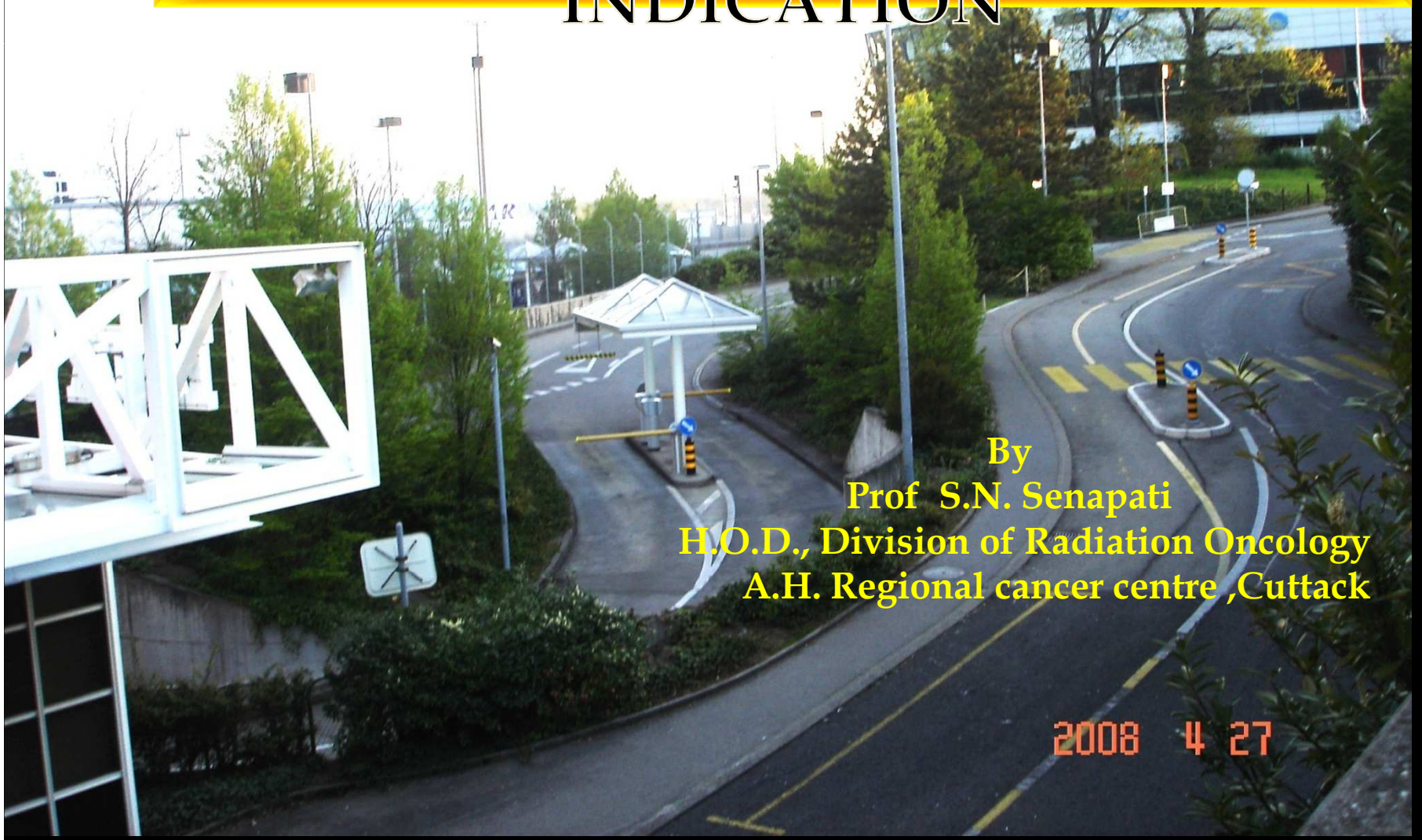
RADIATION & ITS INDICATION

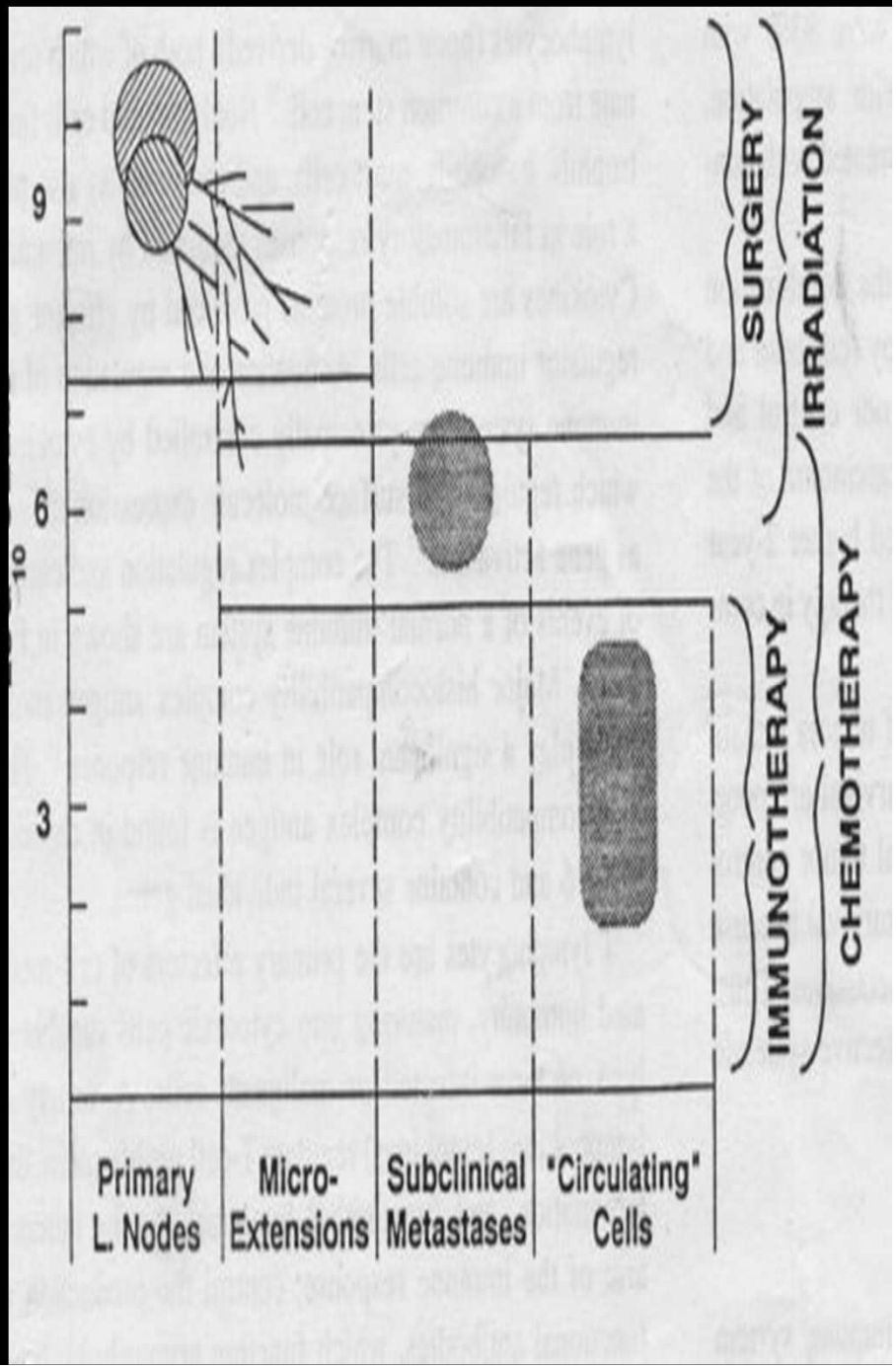


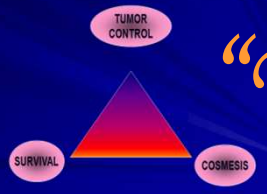
By
Prof S.N. Senapati
H.O.D., Division of Radiation Oncology
A.H. Regional cancer centre ,Cuttack


Surgery
Chemotherapy
Radiotherapy

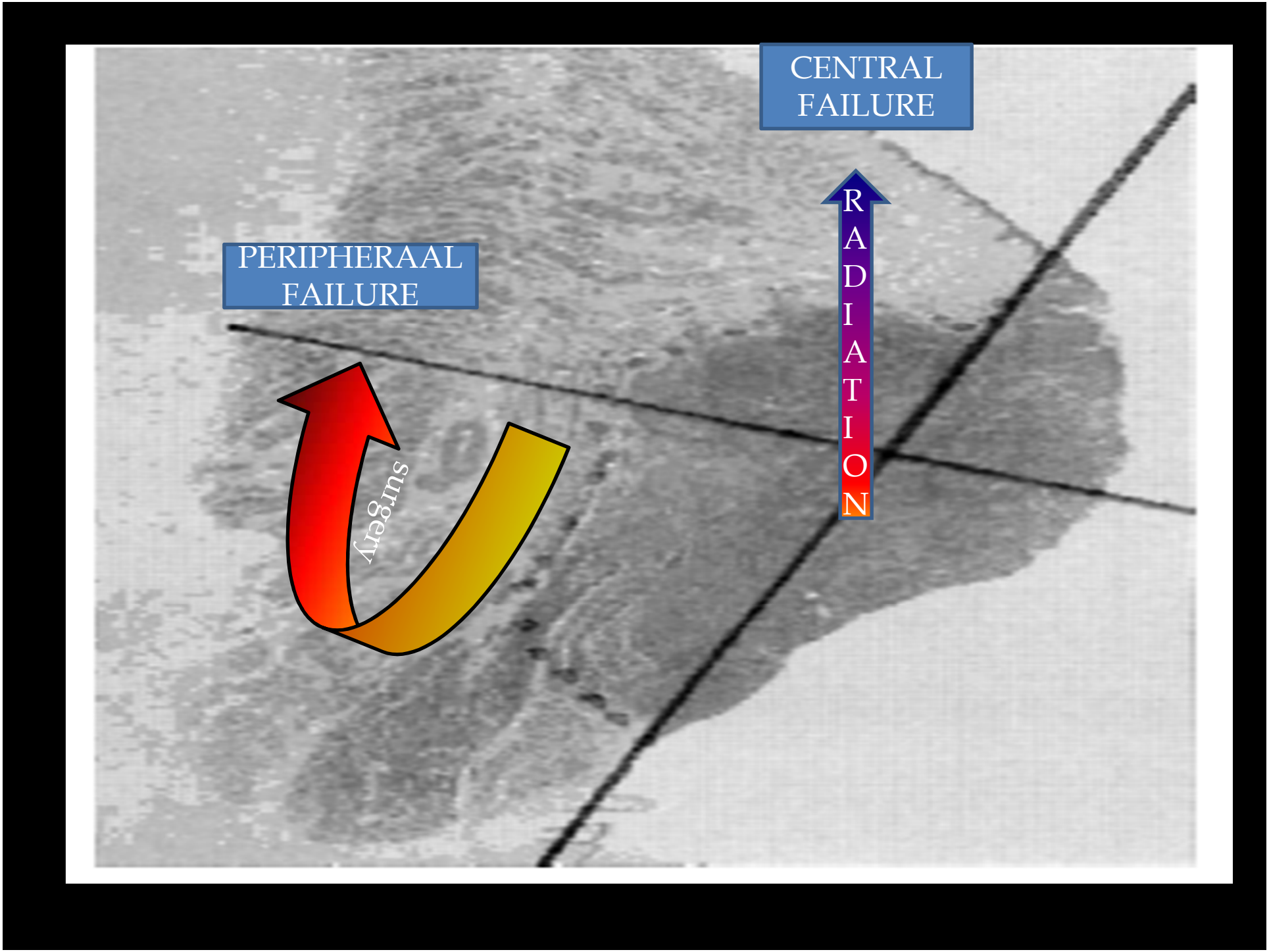
TREATMENT OF CANCER BASED ON MULTIDISCIPLINARY APPROACH

- SURGERY
- RADIATION
- CHEMOTHERAPY
- HORMONAL THERAPY
- IMMUNOTHERAPY

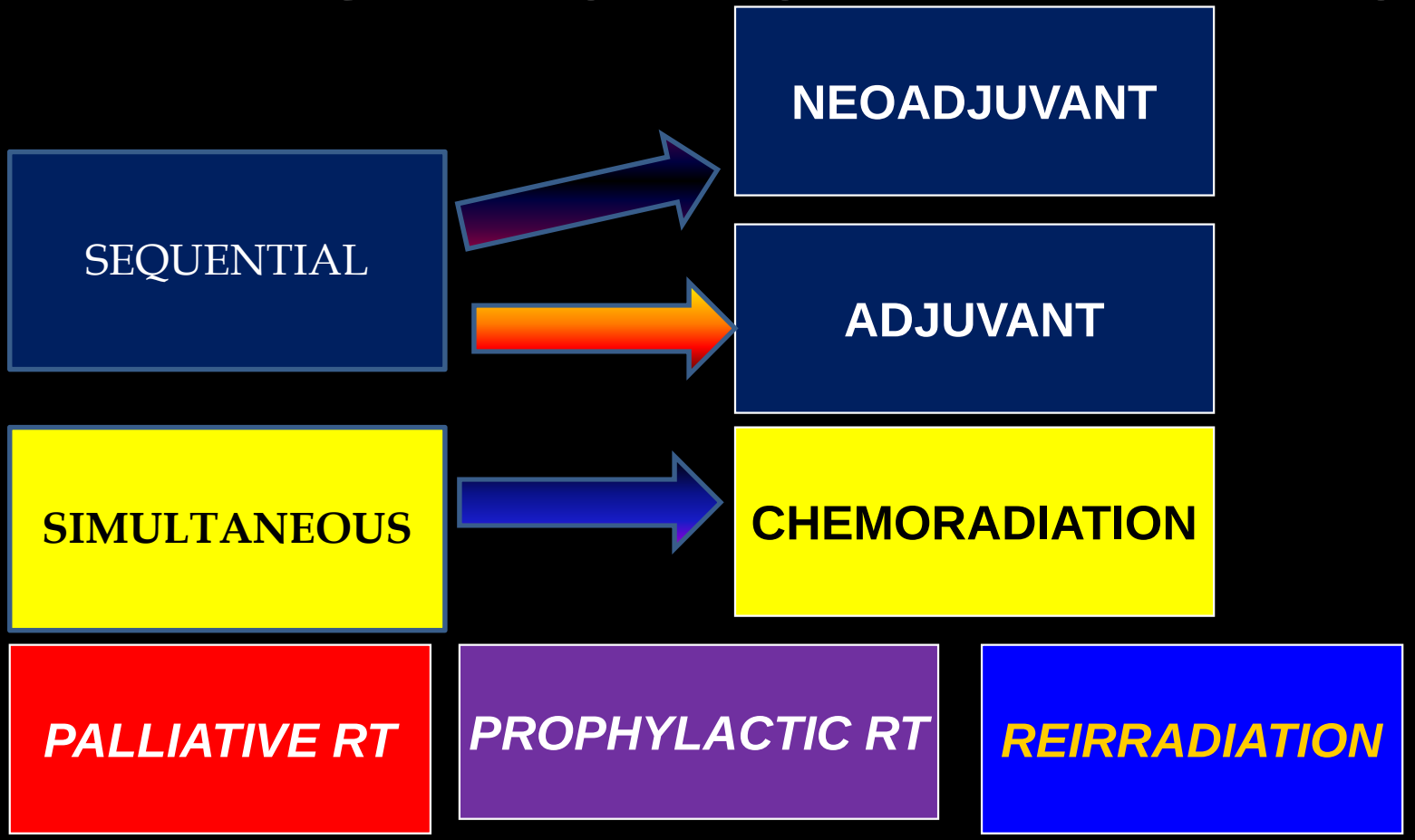




"There Is No 'I' In A Team"


CENTRAL FAILURE
RADIATION
PERIPHERAAL FAILURE
surgery

INDICATION OF RADIATION



Neoadjuvant Chemotherapy Prior to Radiation

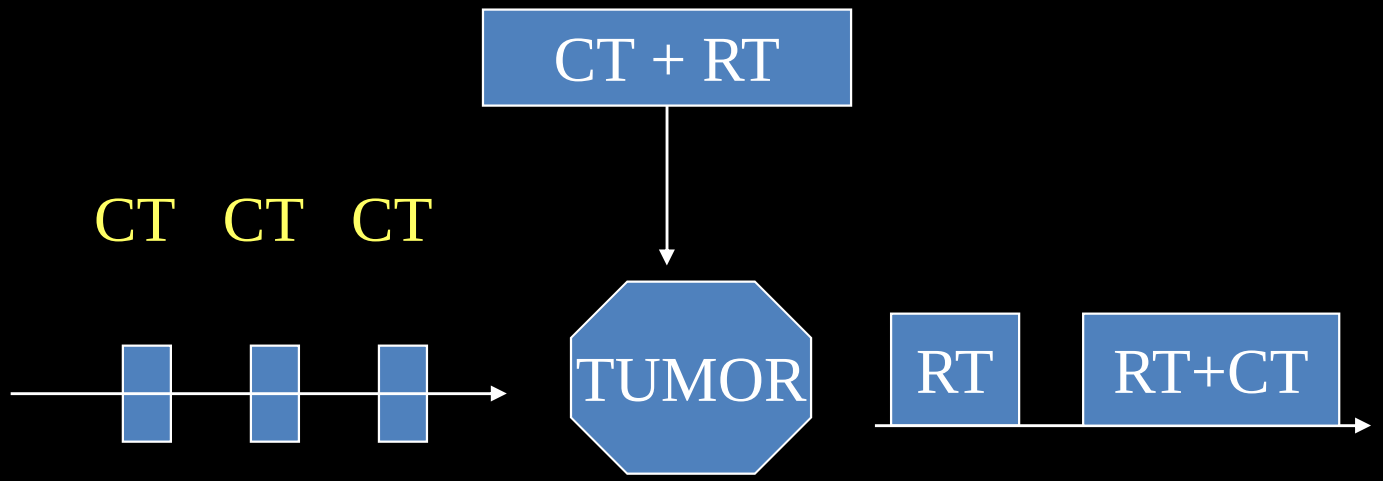
Pros

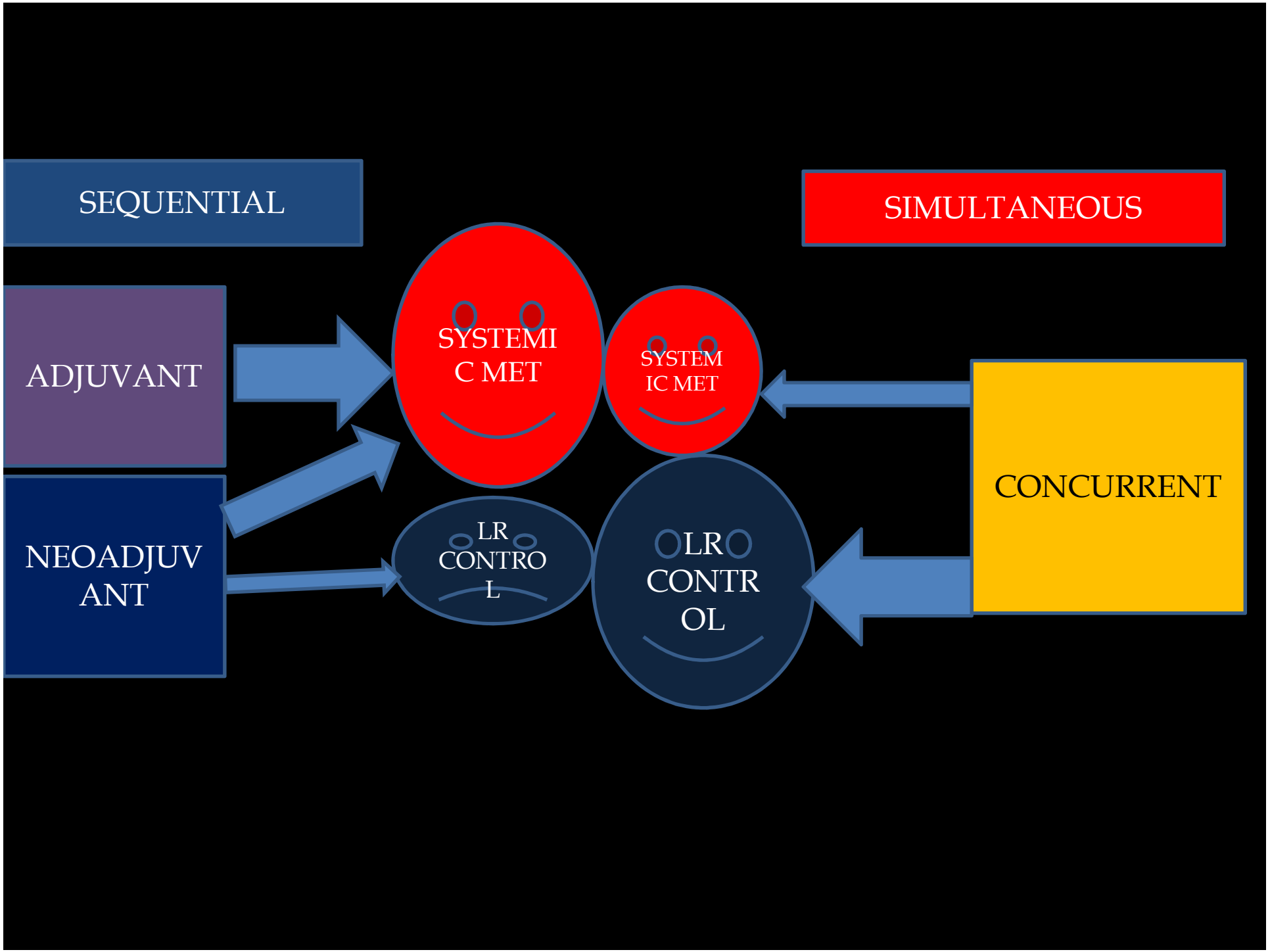
- **Tumor size reduction**
- **Effect on micrometastasis outside radiation field**
- **Theoretically less toxic concurrent Rx**

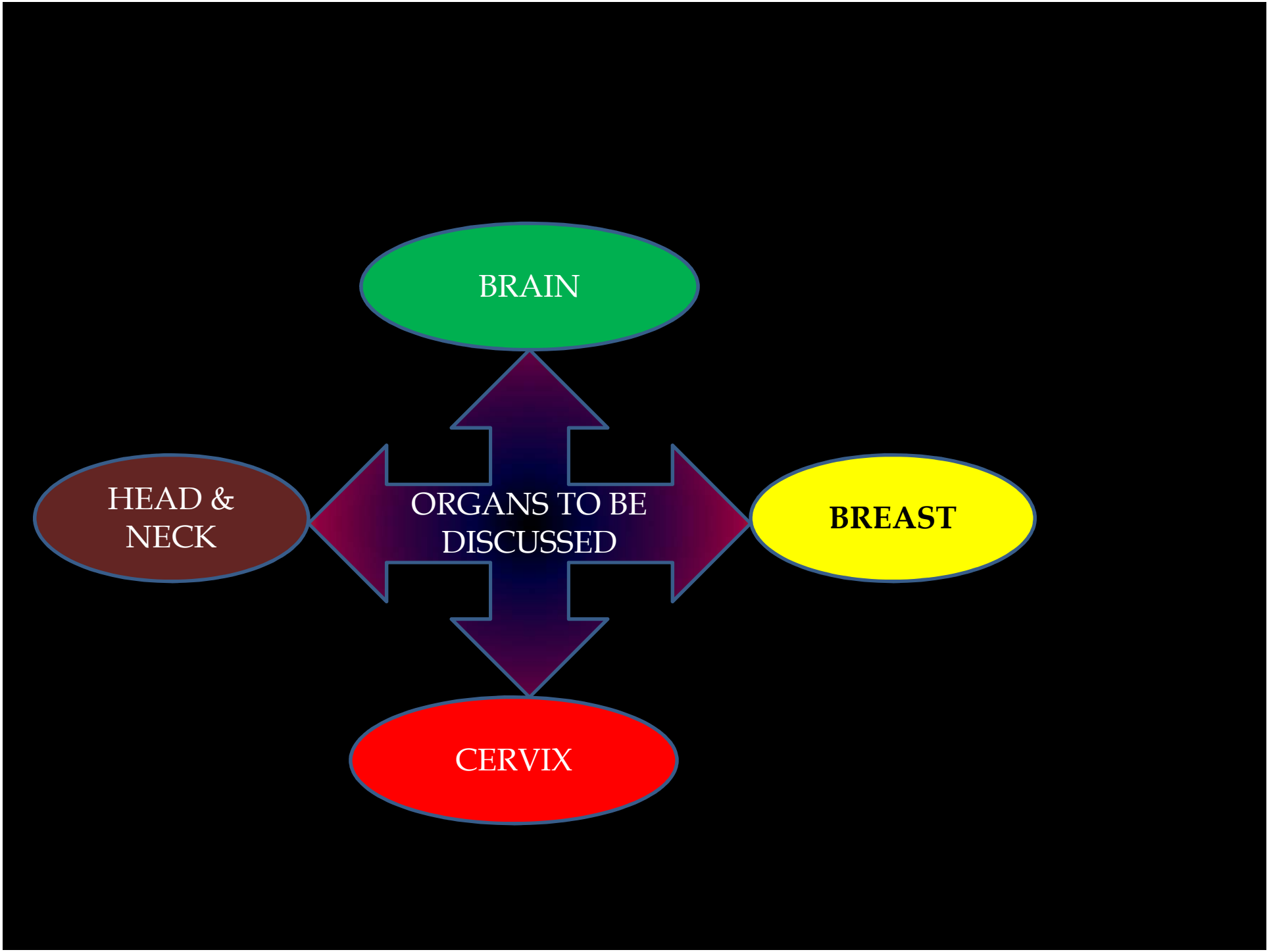
Cons

- **Delayed radiation as definite Rx**
- **Development of resistant clone-->Tumor regrowth**
- **Residual side effect from chemoRx--->dealyed radiation**

MODES OF ADMINISTRATION




SEQUENTIAL
SIMULTANEOUS
ADJUVANT
NEOADJUVANT
SYSTEMIC MET
SYSTEMIC MET
LR CONTROL
LR CONTROL
CONCURRENT


BRAIN
HEAD &
NECK
ORGANS TO BE
DISCUSSED
BREAST
CERVIX

LOW GRADE GLIOMA

LOW DOSE VS HIGH DOSE

EORTC 22844

LOW DOSE Vs HIGH DOSE
EORTC 22844

n = 379 (343 evaluated)

Study period – 1985-91

27 institution 10 countries

Low grade Glioma,supratentorial

Arm A – 45Gy in 5 wks

Vs

Arm B – 59.4Gy in 6.6 wks

RESULT :- Median follow up -74 mo

	45 Gy Vs 59.4Gy	
5 yrs O.S	59%	58%
D F S	50%	47%

No survival Advantages

LOW VS HIGH DOSE

NCCTC
RTOG
ECOG

n = 211 (203 eligible)

- Study period (1986-94)

Arm A – 50.4 Gy in 28#

(n = 101)

Arm B – 64.8Gy in 36#

(n = 102)

Result :-

	Arm A	Arm B
Over all 5 yr. survival	72%	65%
Neuro toxicity (Gr III to V)	2.5%	5%

No improvement in over all survival

Shaw E et al
JCO (2002)20: 2267-76

LOW GRADE GLIOMA
LOW Vs HIGH DOSE

- RTOG & EORTC HAVE ADOPTED 54Gy AS STANDARD DOSE FOR LOW GRADE GLIOMA.

Low grade gliomas : Role of RT

Main indications for adjuvant RT

- Subtotal surgical resection
- Substantial risk of residual disease
- Inoperable lesions
- Progressing lesions
- No feasibility of repeat surgical excision
- Follow up compliance : poor

Early post op RT /Deffered RT till Progression

EORTC - 22845

n = 311

Study period -1986-19Gy

24 institution across Europe

Early radiation – 154 pts

vrs

Deferred radiation till progression = 157 pts

RT Dose – 54Gy, 1.8Gy/#

RESULTS:-

Median follow up- 7.8 yrs

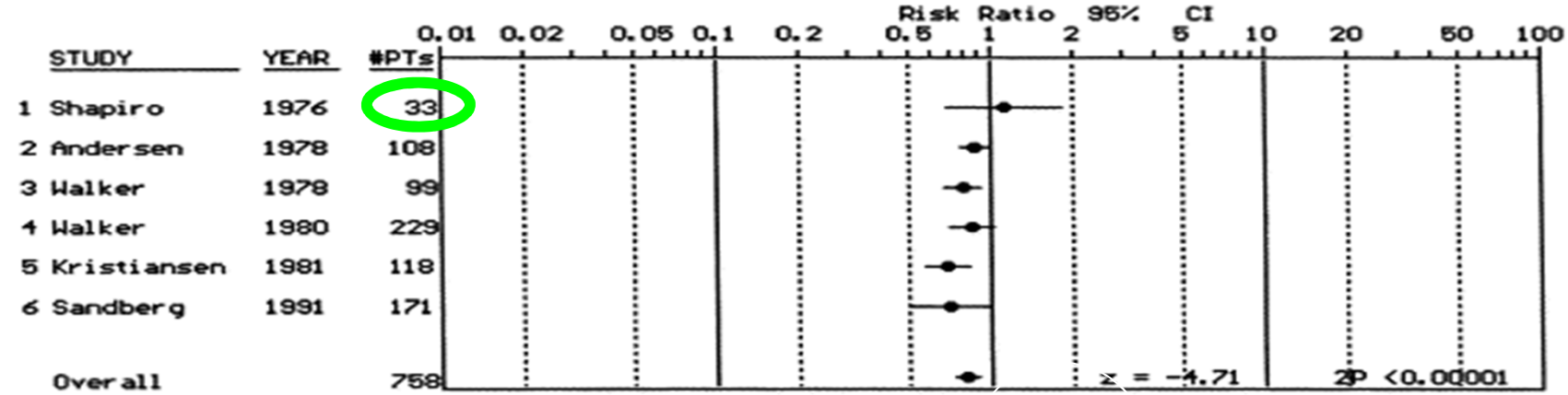
Median progression free survival	PORT	DIFF
	5.3 yrs	3.4 yrs
O.S	No difference	
Median Survival	7.4 yrs	7.2 yrs

Improvement of progression free survival but No change in survival (? Due to better effect of salvage RT)

RT in Malignant Glioma

Study	Post-operative Radiotherapy		No Post-operative		Risk Ratio for 1-year Mortality (Random Effects)	95% Confidence Interval	
	Deaths	Total	Deaths	Total		Low	High
Shapiro, 1976 (62)	12	17	10	16	1.13	0.69	1.84
Andersen, 1978 (1)	44	51	57	57	0.86	0.77	0.97
Walker, 1978* (78)	52	68	30	31	0.79	0.68	0.92
Walker, 1980 (79)	74	118	82	111	0.85	0.71	1.01
Kristiansen, 1981 (36)	51	80	35	38	0.69	0.57	0.84
Sandberg-Wollheim, 1991 (60)	34	84	50	87	0.70	0.51	0.97
TOTAL	267	418	264	340	0.81	0.74	0.88

* Only results for the evaluable patients were reported.



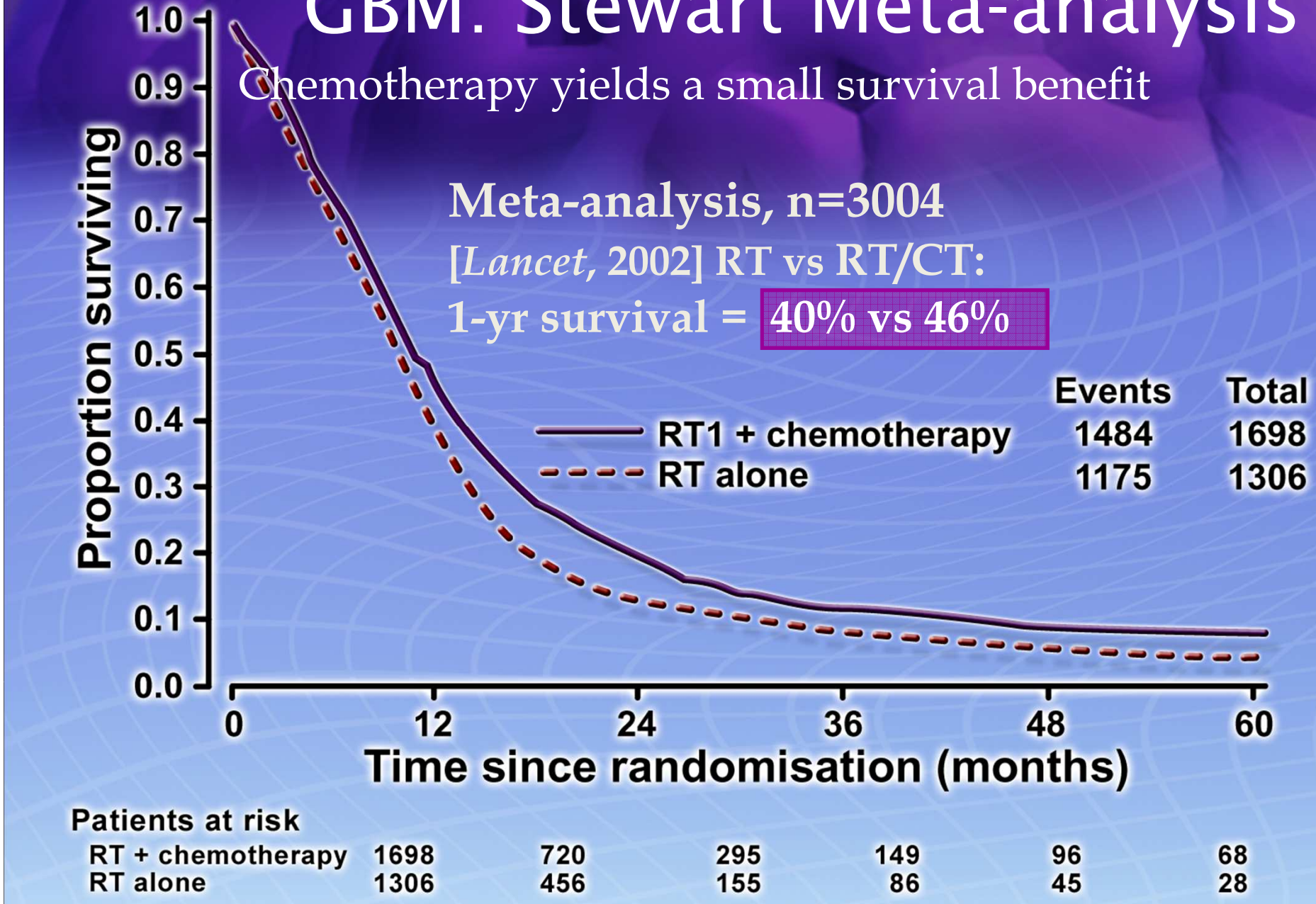
Favours Post-operative RT ≈ Favours No Post-operative RT

overall risk ratio = 0.81 (95% CI, 0.74 to 0.88; p<0.00001)

Laperriere N Radiother Oncol'02

GBM: Stewart Meta-analysis

Chemotherapy yields a small survival benefit



Chemotherapy in Adult High-Grade Glioma: Meta-Analysis

- Glioma Meta-analysis Trialists Group. *Lancet* 2002: 359: 1011-1018
  - Individual patient data
  - 3004 patients, 12 randomized controlled trials (RT + chemotherapy *versus* RT)
  - Hazard ratio: 0.85 (.78-.91, $p<0.001$)
    - 15% relative decrease in risk of death
    - 6% increase in 1-year survival (40% to 46%)
    - 5% increase in 2-year survival (15% to 20%)
    - 2 month increase in median survival

Radiation Dose with Conventionally# RT

Stenning SP, Br J Cancer'91

443 pts

RANDOMISE

- 45 Gy,20#
- 60 Gy,30#

3 mths increase in median surv in 60 Gy arm [p<0.007]

Nelson DF, RTOG 7401

626 pts

- 60 Gy WBRT
- 60Gy WBRT+10Gy boost
- 60 Gy+BCNU
- 60 Gy+semustine+DTIC

No stat sig difference
in surv in 4 arms
Med.Surv=9.3 mo in 60Gy
Vs 8.2 in 70 Gy

Lapaerriere N Radiother Oncol'02:64.259-73

RT Volume: RCTs

Shapiro etal,Arch Neurol'76

571 Pts

RANDOMISE

- 60.2 Gy, WBRT
- 43 Gy WBRT+17.2 Gy boost(pre-RT enhanced Tm vol+2cm margin)

No stat sig difference in survival in both arms

Kita etal,Gan No Rinsho'89

RANDOMISE

- 40 Gy/20# WBRT f/b 18 Gy/9# boost = 23 pts
- 56 Gy/28# Focal RT =26 pts

No stat sig difference in survival rate

Laperriere N Radiother Oncol'02:64,259-73

Concomitant & Adjuvant *TMZ*+RT :RCT

EORTC&NCIC Clinical Trials Groups

Stupp R 40th ASC Annual Meeting June'04

573 pts GBM

RANDOMISE

- RT=60 Gy,30#,2 Gy/#
- RT+TMZ
  - Concomitant-75mg/m2/d x 42 days
  - 6# adj TMZ=150-200mg/m2/d x 5daysq28d

	RT (n=286)	RT/TMZ (n=287)	p-value
Age, median (range) [years]	56.6 (23.1-70.8)	55.7 (19-70.5)	NS
Tumor resection	70%	68%	NS
WHO PS : 0 / 1 / 2	39% / 49% / 12%	39% / 48% / 13%	NS
Steroids at baseline	75%	67%	p=0.041
Progr.-free surv. (95% c.i.)	5.0 mo (4.2-5.5)	7.2 mo (5.8-8.3)	p< .0001
Median survival (95% c.i.)	12 mo (11.2-13.2)	15 mo (13.6-16.8)	p< .0001
2-year survival (95% c.i.)	8% (4-12%)	26% (20-32%)	p<.0001

CT + RT
TERMOZOLAMIDE
(EORTC)

n = 573

G.B.M.

85 Institution median age -65

Arm A – RT (n = 286)

Arm B – RT + Canc Tm_2 + adj Tm_2 (n=287)

CT-

Canc Tm_2- 75mg/m^2(maxm – 49 days)

Adj Tm_2- 200mg/m^2 6 cycles (at 28 days int)

RESULT –

Median follow up 28 mo

	RT	RT+TM^2	P
Median over all survival	12.1m0	14.6 mo	<.001
2 yr O.S	10.4%	26.5%	
Median time to progression	5.6 mo	6.9 mo	<0.001
Drug related toxicity	0%	16%	

SURVIVAL BENEFIT

HIGH GRADE GLIOMA
ISSUES

- DOES POST OP RADIATION IMPROVES THE SURVIVAL:-*YES.STANDARD OF CARE*
- WHAT SHOULD BE THE DOSE OF RADIATION:-*60GY*
- WHETHER WHOLE BRAIN OR FOCAL RADIATION:-*NO WHOLE BRAIN RT*
- WITH DOSE ESCALATION SURVIVAL IMPROVES:-*NO*
- POST OP RADIATION+CHEMOTHERAPY DOES IT IMPROVES THE SURVIVAL:-*YES*

TAKE HOME MESSAGE:-1

Head & Neck Cancer

Heterogeneous group of tumor.

Significance:

- Different anatomical site :-
  Different tumor kinetics,different biological behavior.
- Proliferation of cells not similar in all sites.
- Treatment outcome:- Differs.

General guidelines for selecting a treatment modality:

- Stage I / II disease- Single modality (Surgery or RT)

- Stage III & IV disease -- Combined modality
  Surgery + Radiotherapy (In most patients),
  Chemotherapy + radiotherapy (In selected patients)

When different modalities are available, the modality that gives *maximum chance of cure* should be used.
When different modalities have similar results, a modality that gives *better quality of life, with organ / voice preservation,Functional and cosmetic results is preferred*

SURGERY VS RADIOTHERAPY

Surgery is preferred over radiotherapy as a single modality in

1. Young patients -due to high incidence of second primary

2. Sub mucous fibrosis

3. Lesions involving or close to bone - to prevent radionecrosis.

4. Sites where surgery is not morbid (cosmetically and functionally)

RT is preferred over surgery as a single modality, where

1. Severe impairment of function / cosmesis with surgery.
2. Surgery has high morbidity and poor results e.g. nasopharyngeal carcinoma.
3. Patient refuses surgery / high risk of surgery

Radiotherapy

External beam radiotherapy and / or brachytherapy are used either as a single modality or as a part of multi-modality treatment.

Radiotherapy is used in 3 different settings

- **Radical curative radiotherapy(Alone/combn.with C.T)**
- **Post-operative adjuvant radiotherapy**
- **Palliative radiotherapy**

Indications for Brachytherapy (BRT):

- Accessible lesions
- Small (preferably < 3cm) tumours
- Lesions away from bone
- N0 nodal status

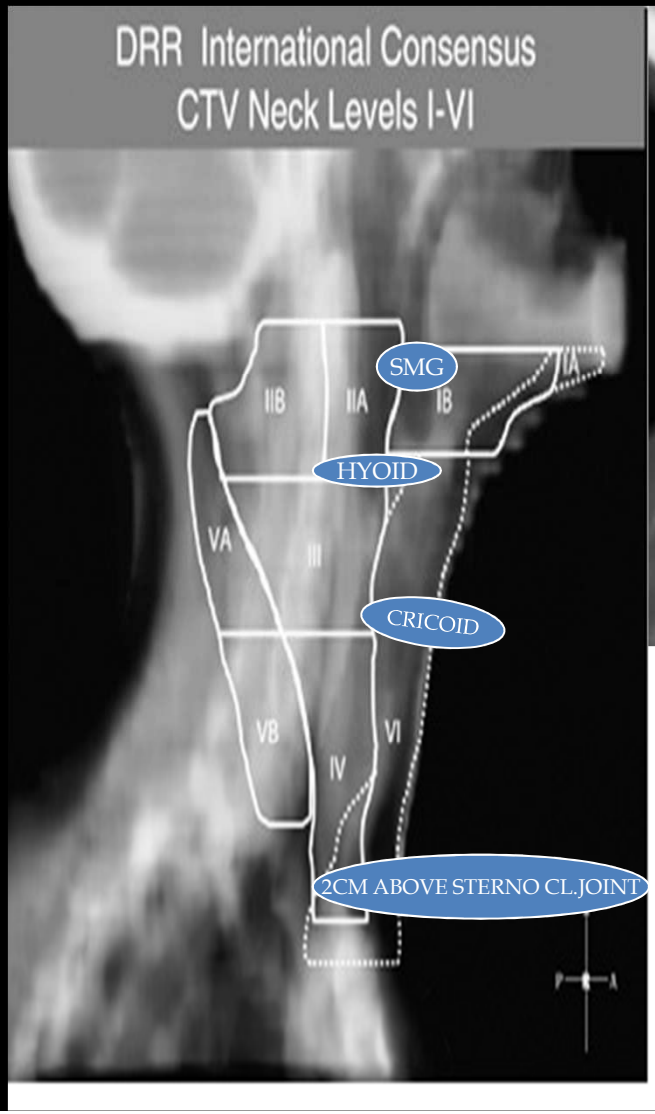
Tumour suitable for brachytherapy

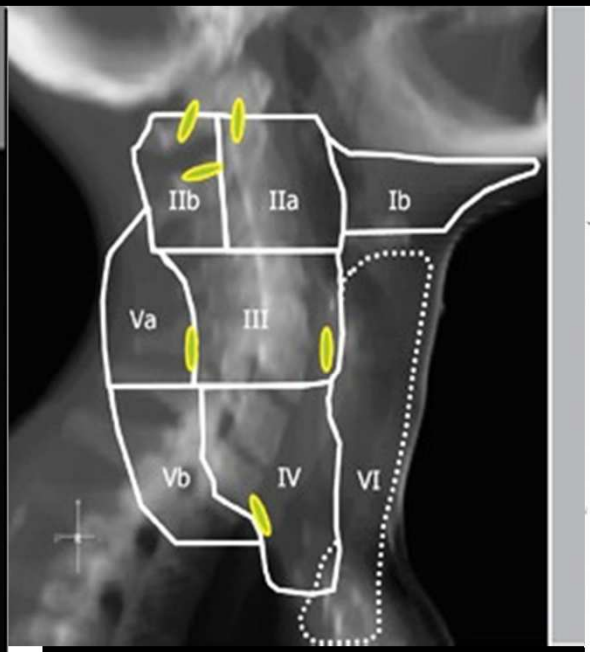
- **T1-2 N0: Radical BRT: 60-70Gy Low Dose Rate 192Iridium Or equivalent doses with fractionated high dose rate.**
- **T1-3 N0-1: External RT: 56-60Gy/ 28-30#/ 6 wks Boost BRT: Low dose rate 192Iridium: 15-20Gy or High Dose Rate: 14Gy in 4 fractions over 2 days (4-3-3-4 Gy)**

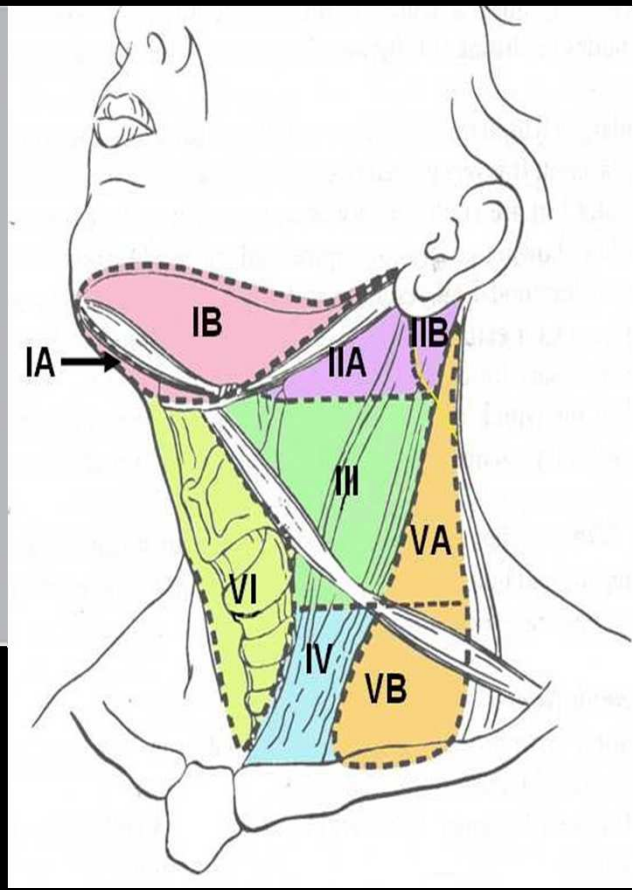
Tumours not suitable for brachytherapy:

- **T1-4 N0-2: Concomitant Chemoradiation: 66-70Gy/33-35# /6-7 wks + concomitant weekly Cisplatinum, 30mg/m2 for 6-7 wks Or**
- **External RT: 66-70Gy/33-35# /6-7 wks (reducing fields)**

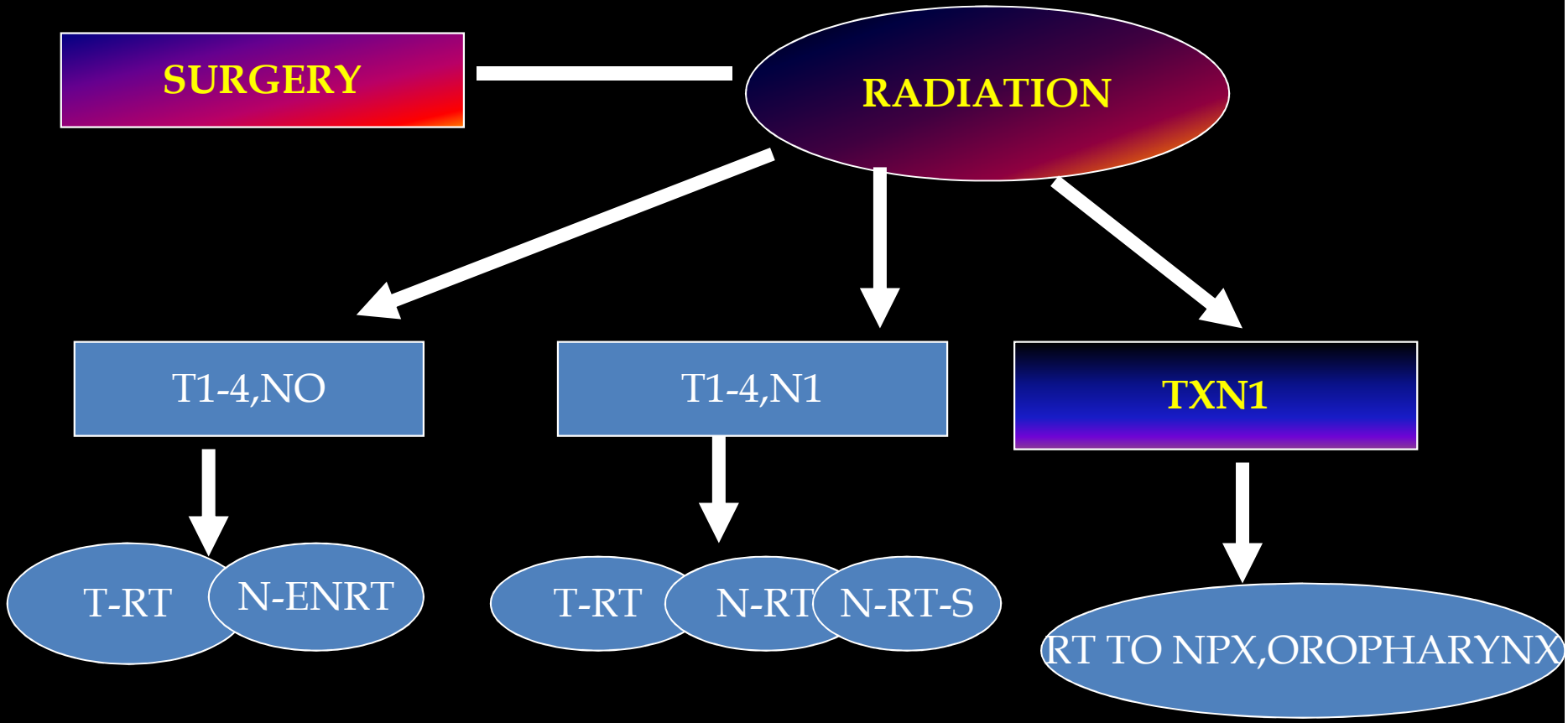
Digital reconstructed radiograph (DRR) levels I–VI. CTV, clinical target volume.







MANAGEMENT OF NECK NODE



PATIENT IN WHOM THE PRIMARY LESION TO BE TREATED BY RADIATION ,WHO HAVE CLINICALLY –VE NODES AND WHOM THE RISK OF SUBCLINICAL DISEASE IS 20% OR GREATER,USUALLY RECEIVE ELECTIVE NECK RT OF 45-50Gy

Table 46.2 DEFINITION OF RISK GROUPS

Group	Estimated Risk of Subclinical Neck Disease %	Stage	Site
I Low risk	<20	T1	Floor of mouth, retromolar trigone, gingiva, hard palate, buccal mucosa
II Intermediate risk	20–30	T1	Oral tongue, soft palate, pharyngeal wall, supraglottic larynx, tonsil
		T2	Floor of mouth, oral tongue, retromolar trigone, gingiva, hard palate, buccal mucosa
III High risk	>30	T1–4	Nasopharynx, pyriform sinus, base of tongue
		T2–4	Soft palate, pharyngeal wall, supraglottic larynx, tonsil
		T3–4	Floor of mouth, oral tongue, retromolar trigone, gingiva, hard palate, buccal mucosa

From Mendenhall WM, Million RR. Elective neck irradiation for squamous cell carcinoma of the head and neck: analysis of time–dose factors and causes of failure. *Int J Radiat Oncol Biol Phys* 1986;12:741–746, with permission.

- OROPHARYNX,NASOPHARYNX,SUPRAGLOTTIC LARYNX AND HYPOPHARYNX-LOWER NECK NODE WITH SINGLE ANT FIELD

IN +VE NECK NODE

- ADVANCED DISEASE HAS BETTER CHANCE OF CURE WITH ALTERED # /CONCOMITTANT RT
-

NODE SIZE AND DOSE OF RADIATION BEFORE SURGERY

NODE SIZE	DOSE OF RT
3-4 cm,MOBILE	50GY
5-6CM,FIXED	60GY
7-8 CM	70-75GY

TIME OF SURGERY:-4-6 WKS AFTER RT.INITIAL REGRESSION IS SLOW. MUCH REGRESSION AT 4-6 WKS

CERVICAL L.N METASTSIS WITH UNKNOWN PRIMARY

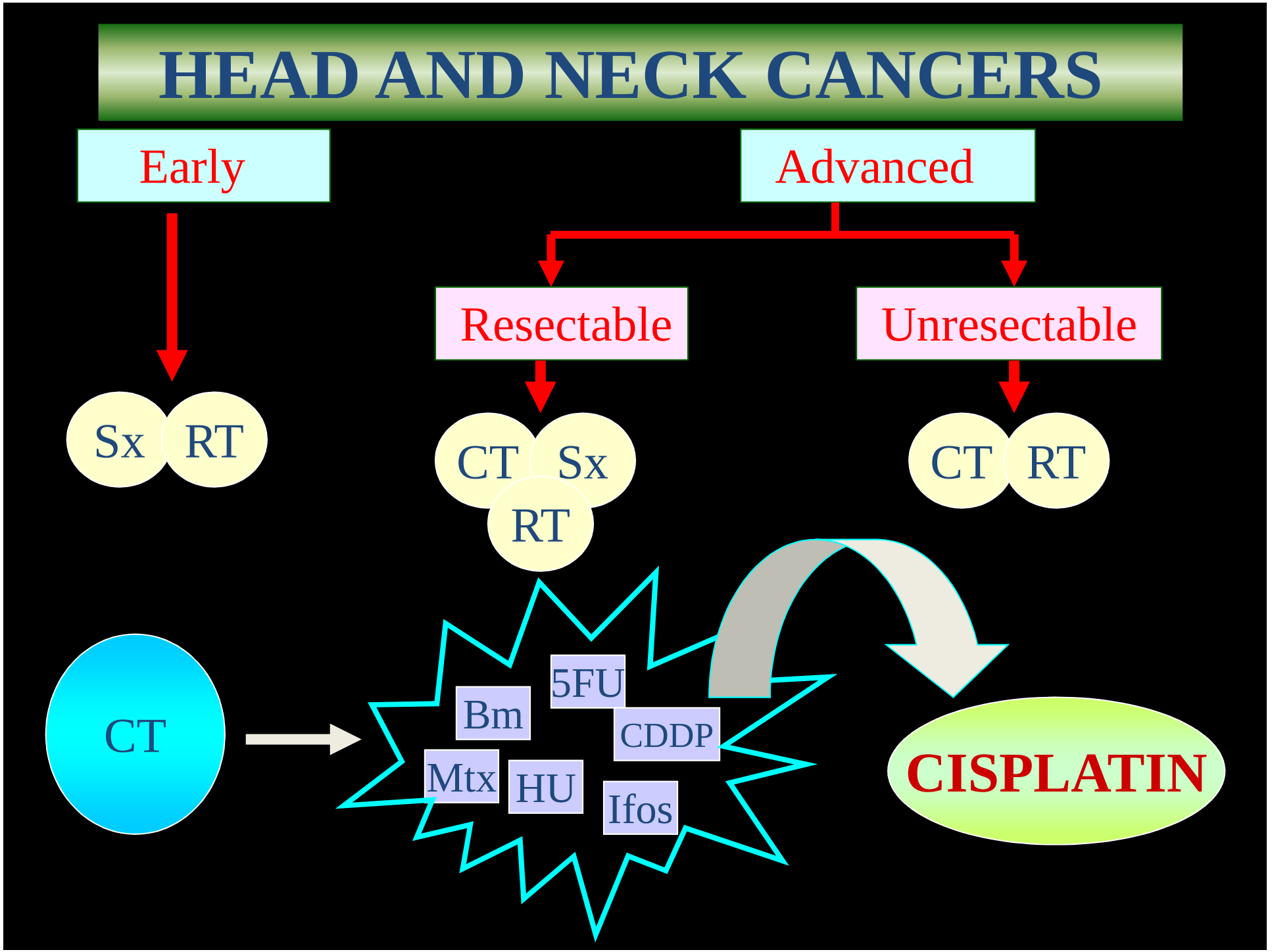
UPPER NECK NODE METASTASIS:-PROGNOSIS BETTER THAN LOWER NECK

ADENO CA.OF NECK NODE,PRIMARY:-BELOW THE CLAVICLE

IF UPPER NECK:-SALIVARY GLAND,PARATHYROID,THYROID

DIAGNOSIS:-CLINICAL EXAMINATION,DL BIOPSY,NEEDLE BIOPSY,CT,MRI,FDG PET

- TREAT INVOLVED AREA OF NECK
- RT TO NASOPHARYNX,OROPHARYNX,BOTH SIDE OF NECK
- ORAL CAVITY,LARYNX AND HYPOPHARYNX TO BE EXCLUDED


HEAD AND NECK CANCERS
Early
Advanced
Resectable
Unresectable
Sx
RT
CT
Sx
RT
CT
RT
CT
Bm
5FU
CDDP
Mtx
HU
Ifos
CISPLATIN

SURGERY Vs S+RT

Treatment	Ipsilat neck failure (No –N_3b)	Contralat neck failure (No –N_3b)
Surgery	51/199 (25.6%)	35/130(27%)
Radiation	54/292(18.5%)	7/172(4%)
Combined	8/105 (7.8%)	3/85(3%)

Barkley et al A.J.Surg 124 : 462-467,1972

(Post operative RT eleminated subclinical disease after surgery in both Ipsilat neck as well as Contralat neck)

But no comment on survival.

Resectable Head & Neck Cancer
Pre Vs Post op RT
RTOG 73 - 03

Estimated 4 yr Locoregional control percentage hy Rx & Region

Site	Pre op (%)	Post op (%)	Total (%)
Oral cavity	40	44	42
Oropharynx	47	61	54
Supraglottic Larynx	53	77	64
Hypopharynx	50	61	55
All Regions	48	65	57
For 194 pts who competed planned t/t	56	74	

POST OF RADIATION IS THE STANDARD OF CARE

Risk stratification in post op setting in H&N Cancer

HIGH RISK FACTORS :

Extracapsular Extension Of Nodal Disease

≥2 of the following factors

- Oral cavity site
- Microscopicaly positive mucosal margins
- Nerve invasion
- ≥ 2 involved neck nodes
- > 1 positive nodal group
- Node size>3 cm

INTERMEDIATE RISK FACTOR:

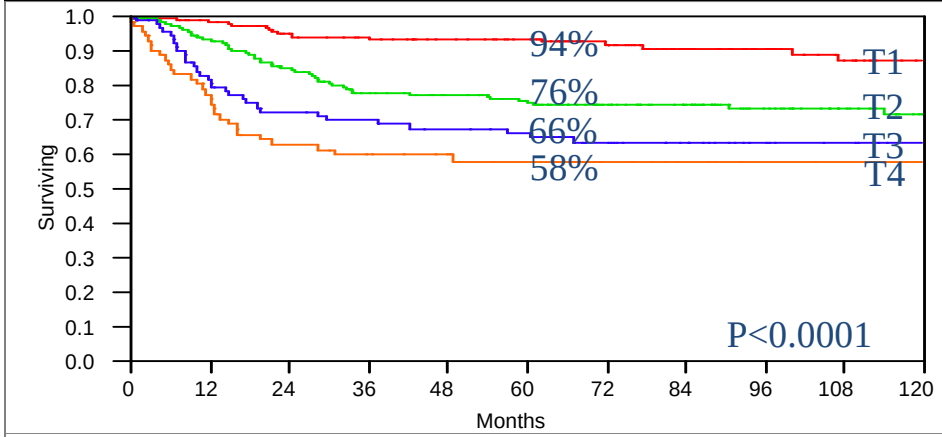
No ECE

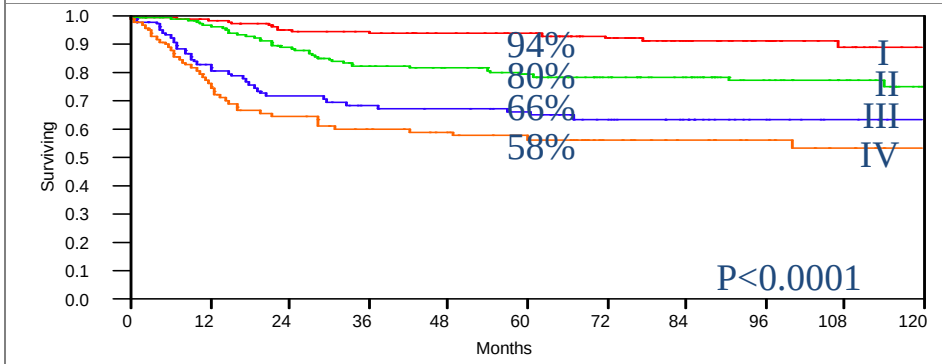
One of the above risk factor

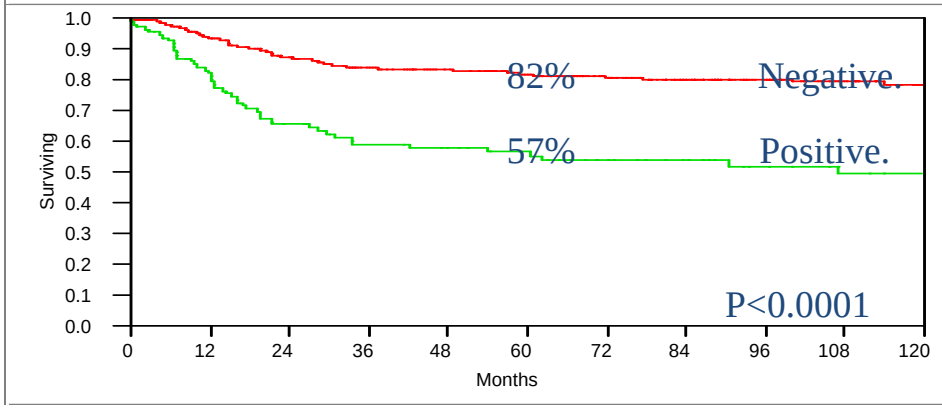
***LOW RISK FACTOR*:**

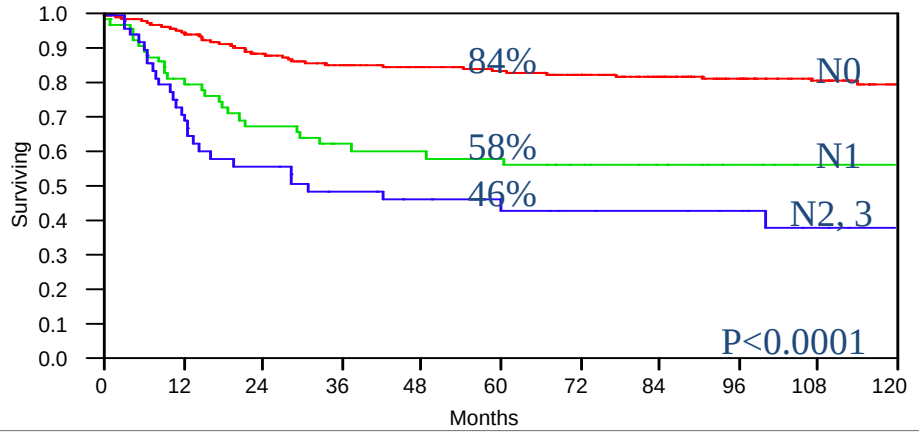
None of the above factor

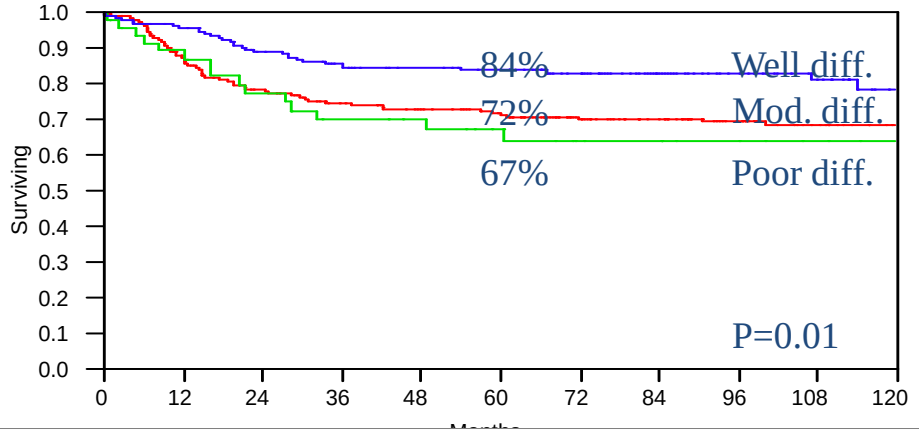
Disease-Specific Survival Vs Risk factors in Ca. Oral cavity

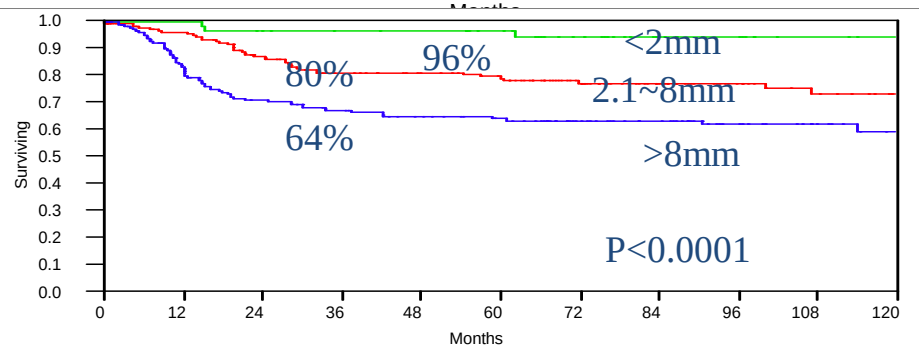






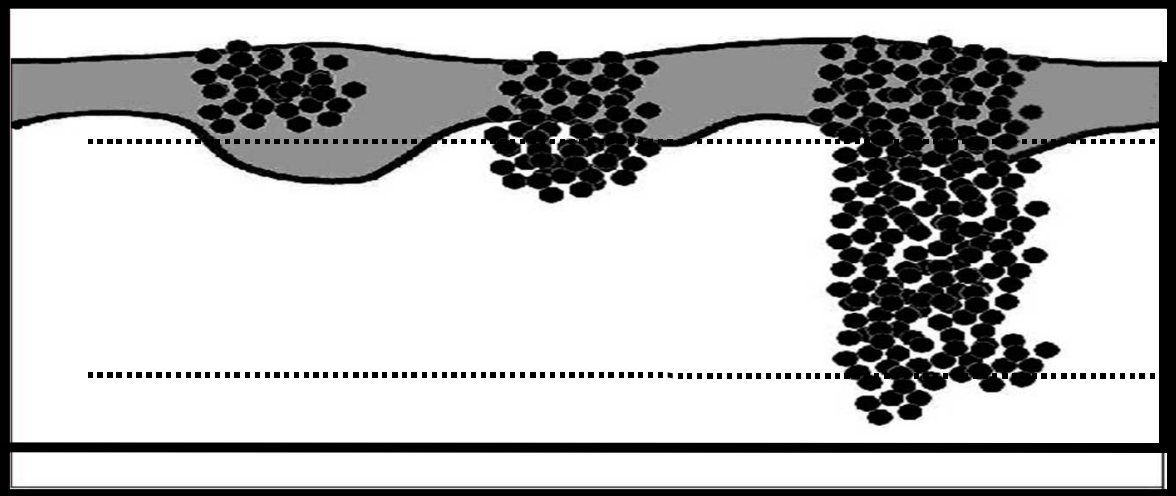






Depth of Invasion

	<2 mm n=60	2.1-8 mm n=190	>8 mm n=187
Risk of Occult Metastasis	2%	15%	19%
Overall pN+	5%	27%	45%



Fukano et al. 34 pts,

For tumor thickness

- <5mm, 1/17 : 5.8%,
- >5mm, 11/17 : 64.7%,
- <3mm, no cervical LN, p=0.0003

Shah et al: depends on relation of the thickness of primary tumor with cervical nodal mets

- 2 mm or less : 13%
- 2-9 mm : 46%
- >9mm : 65%

Bayers et al : SCC of tongue, T1 to T4 with clinical node-ve

- <4mm depth : 31%
- 4-8mm : 47%
- >8mm : 76% p= 0.0001

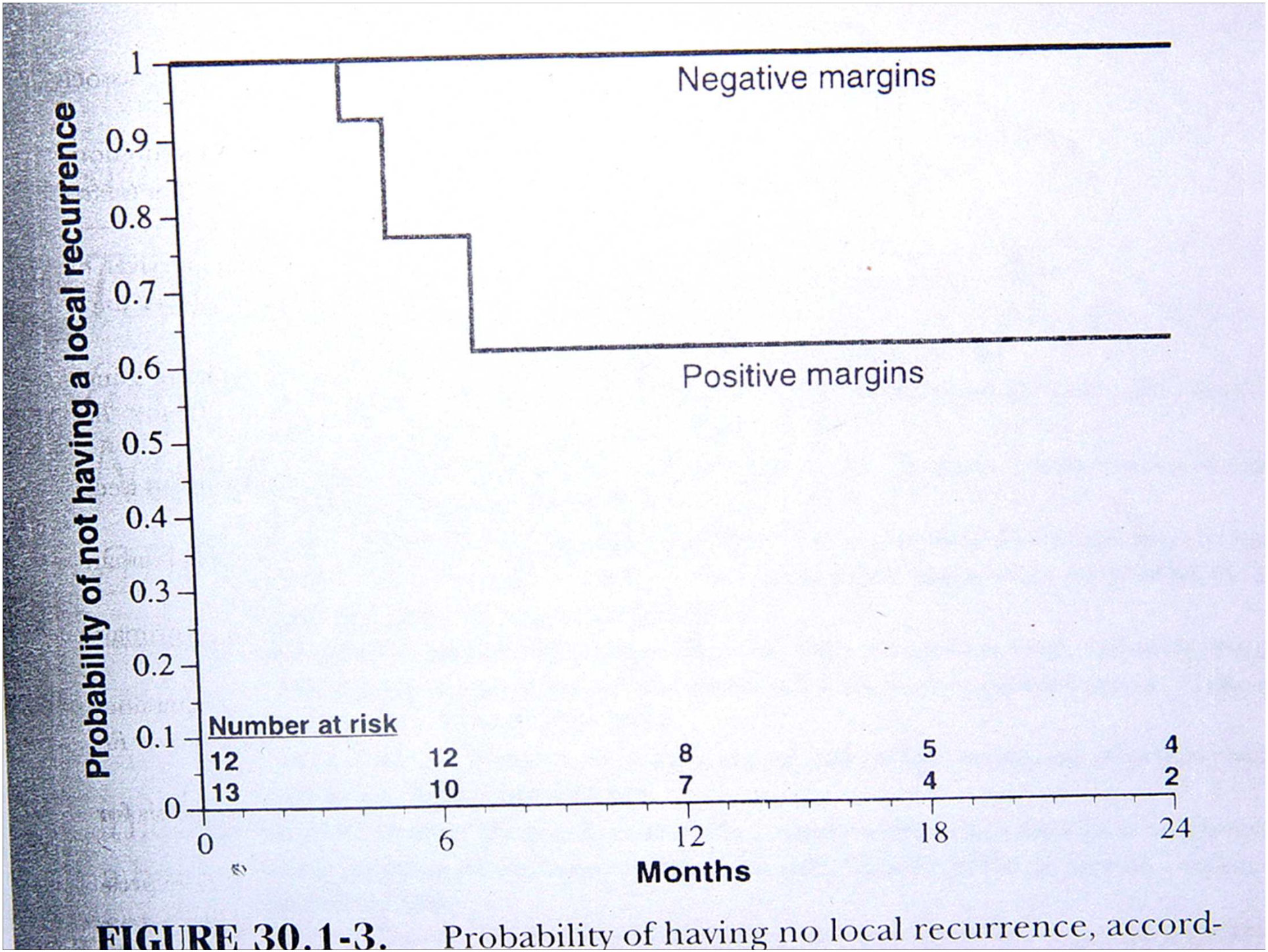


FIGURE 30.1-3. Probability of having no local recurrence, accord-

- **Early Disease (Stage I, II) - Monotherapy**

  Surgery or Radio-therapy

NOOOOOOOOOOOOOO

Risk factor & Radiation Dose

- ECE the single most independent variable
- 2/more risk factors are associated with higher risk of recurrence
- No adverse surgical- pathologic features:– No PORT .5yr LRC and survival 90% & 83% with surgery alone.
- One adverse feature & ECE – 57.6 Gy 5yr LRC- 94%

  INT. RISK
- Highrisk (ECE, 2/more adv. Features) – 63 Gy 5yr LRC – 68%

Peter L J et al I.J.R.O.B.P, 1993: 26(1):p 3-11

CONCURRENT CT RT IN HIGH RISK PATIENTS

	#pt	F/U	LC	LRC (CTRT Vs RT)	DFS (CTRT Vs RT)	Survival (CTRT Vs RT)
RTOG 9501 [31]	459	46 month median	Not reported	80% vs 68%	33% vs 25%	42% vs 36%
				P = 0.003	p =0.04	P = 0.19
EORTC 22931 [30]	334	60 month median	Not reported	82% vs 69%	47% vs 36%	53% vs 40%
				P = 0.007	P =0.04	P = 0.02
Bachaud (1996) [29]	83	5 year minimum	84% vs 59%	Not reported	68% vs 44%	72% vs 46%
			P=0.05		P<0.02	P <0.01

CDDP-100MG/M2 AT 3 WEEKS INTERVAL
EBRT:-66Gy

- The survival benefit seen in CT & RT arm are due to Improved loco regional control

- 10% IMPROVEMENT IN 2YR LOCOREGIONAL CONTROL IS PREDICTED TO LEAD TO 6.7% 5YRS INCREASE IN OVERALL SURVIVAL

  (Wadsley et al,IJROBP-2004)

- Cisplatinum based concurrent chemo-radiation should be considered for high risk pts that are medically able to tolerate concurrent CT

Time factor in PORT setting.

- Timing:– within 6wks of Post OP.
- Duration of Rx Vs 5yrs acturial LRC

< 11 wks – 5yrs LRC-76%

11-13 WKS –62%

> 13 WKS – 38%

Ang KK 51: 571-78,2001

Treatment strategy in post op Head & Neck Cancer

- Low Risk → No adv. Factor – Obs
- Int Risk → One risk factor
  No ECI – RT
- High Risk → 2 risk factor
  & ECI – CT+RT. Alt#

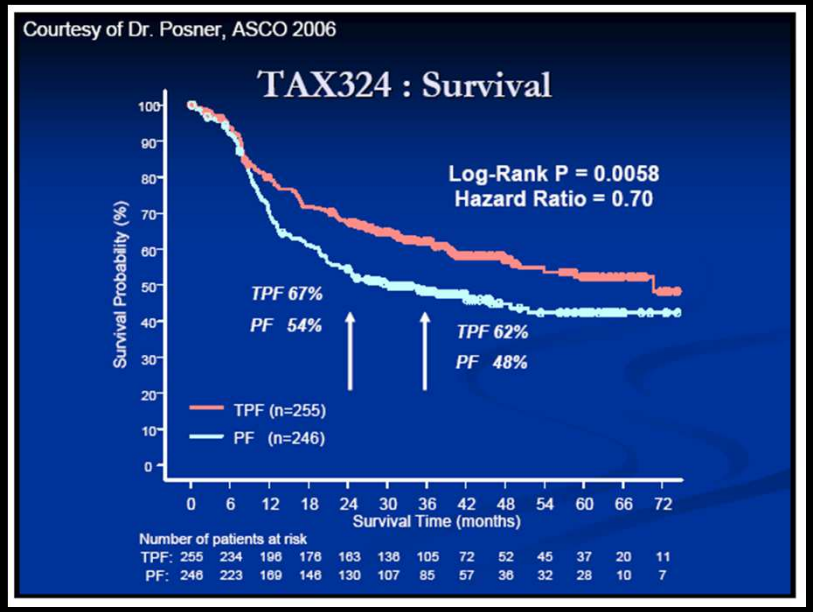
NEOADJUVANT CT

- DECREASES THE TUMOR BURDEN
- CONTROL MICROSCOPIC SYSTEMIC DISEASES
- RESPONDER TO NEOADJUVANT CT RESPONDS TO SUBSEQUENT RADIATION

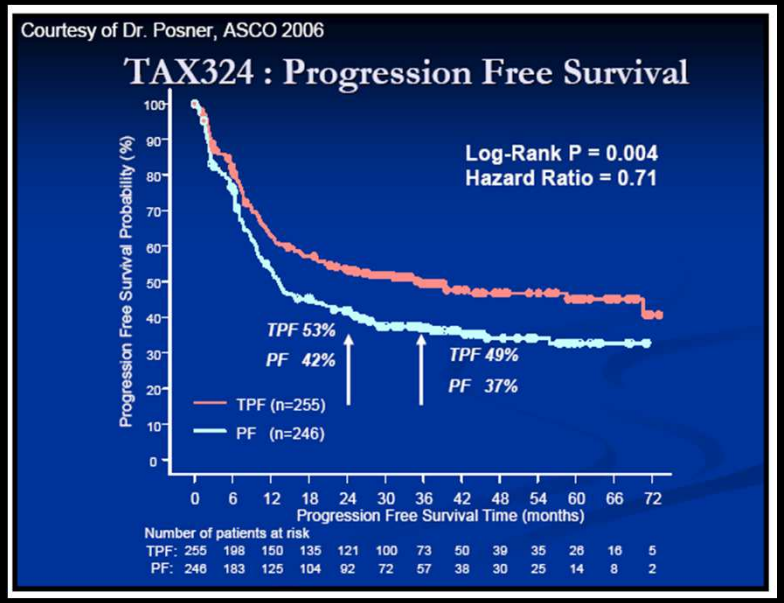
Recent Randomized Trials of Induction Chemotherapy followed by Locoregional Treatment versus Locoregional Treatment Alone

Author (Reference)	Year	No. of Patients	Chemotherapy	Overall Survival
Martin (234)	1990	75	FP	No difference
Jortay (235)	1990	187	VBM	No difference
Richard (236)	1991	222	VB(IA)	Advantage:
Mazeron (237)	1991	131	FPBM	No difference
Jaulerry (238)	1992	100	PBVdMi	No difference
Jaulerry (238)	1992	108	FPVd	No difference
Tejedor (239)	1992	42	CpFt	No difference
Depondt (240)	1993	324	FCp	No difference
Di Blasio (241)	1994	69	FP	Advantage: standard

Courtesy of Dr. Posner, ASCO 2006



Courtesy of Dr. Posner, ASCO 2006



Tax 324: Response

Chemotherapy	TPF (N=255)	PF (N=246)	
Overall RR [95%CI]	72% [65.8 – 77.2]	64% [57.9 – 70.2]	p= 0.07
Complete RR [95%CI]	17% [12.1 – 21.6]	15% [10.8 – 20.1]	p= 0.66

Chemotherapy and CRT	TPF (N=255)	PF (N=246)	
Overall RR [95%CI]	77% [70.8 – 81.5]	72% [65.5 – 77.1]	p= 0.21
Complete RR [95%CI]	35% [29.4 – 41.5]	28% [22.5 – 34.1]	p= 0.08

Courtesy of Dr. Posner, ASCO 2006

Tax 324 Survival: ITT Population

	TPF - 255	PF - 246
Median Survival (Mo) 95% CI	70.6 + 49 - NR	30.1 20.9 – 51.5
Died *	41%	53%
KM Survival 1 – Year 2 – Year 3 - Year	 80% [75.0 - 84.9] 67% [61.5 – 73.2] 62 % [55.9 – 68.2]	 69% [64.1 – 75.7] 54% [48.2 – 60.8] 48% [41.7 – 54.5]
Hazard Ratio TPF:PF [95% CI]	0.70 [0.54 - 0.90]	
Log-Rank p Value	0.0058	

*Cut-off: December 3, 2005; The Median Follow-Up is 42 Months

Courtesy of Dr. Posner, ASCO 2006

Current Data for Induction Chemotherapy

- Pignon, et al. Meta-analyses: 63 randomized trials
- Results:
  - Significant benefit to chemotherapy (10% reduction in hazard ratio of death, 4% absolute advantage in survival at 2 and 5 years)
  - CCR: clear benefit
  - ICT: no statistically significant benefit in survival and locoregional control (LRC)
    - Exception: patients receiving cisplatin and 5FU
    - Significantly different from other regimens

Pignon, J. et al. Lancet. 2000

Conclusion: Induction Chemotherapy

- CCRT with platinum agents is standard of care
  - Meta-analysis favors either high dose cisplatin q 3 weeks or 2 agents in a weekly regimen.
- Sequential IC followed by CCRT vs. CCRT must be examined since a definitive survival advantage has not been demonstrated.
- If IC is used, TPF is better than PF; however, other regimens should be examined which may be less toxic, easier to administer and potentially more effective

Efficacy of radiation therapy and concurrent chemotherapy in Head & Neck cancer

	French Trial (n = 226)	P	German Trial (n = 270)	P	Nasopharynx Intergroup Trial (n = 193)	P	Duke University Trial (= 116)	P
Local control rate %	66 v 42	--	35 v 17	<.004	NR	-	70 v 44	.006
Disease-free survival rate,%	42 v 19	.002	NR	-	69 v 24	<.001	60 v 40	.07
Survival rate %	51 v 31	.003	49 v 24	<.0003	78 v 47	.005	42 v 28	.05
Mucositis rate%	67 v 36	-	38 v 16	<.001	NR	-	77 v 75	-

Randomized Trials of Concurrent Multiagent Chemotherapy and Radiotherapy versus Radiotherapy in Stage III and IV Disease

Author (Reference)	No. of Patients	Study Population	Chemotherapy	Radiotherapy	Local Regional Control (P)	Survival (P)
Keane, 1993 (299)	212	Larynx and hypopharynx	MMC, 5-FU	50 Gy, split	40% vs. 40%	40% vs. 40%
Zakotnik, 1998 (300)	64	Unresectable	MMC, Bleo	66-70 Gy	75% vs. 29% (.007)	38% vs. 10% (.019)
Adelstein, 1999 (301,302)	100	Resectable	Cisplatin, 5-FU	60 Gy, split	7% vs. 45% (<.001)	42% vs. 34% (<.01)
Calais, 1999 (303)	226	Oropharynx	Carbo, 5-FU	70 Gy	66% vs. 42% (.03)	51% vs. 31% (.02) (3-y)
Merlano, 1996 (304)	157	Unresectable	Cisplatin, 5-FU (alternating)	60-70 Gy	64% vs. 32% (.038)	24% vs. 10% (.01) (5-y)
Adelstein, 2000 (305)	295	Unresectable	Cisplatin	70 Gy		37% vs. 20% (.016) (3-y)
			Cisplatin, 5-FU	60-70 Gy, split		29% vs. 20% (.13) (3-y)
Wendt, 1998 (306)	270	Unresectable	Cisplatin, 5-FU, L	70 Gy, b.i.d., split	36% vs. 17% (<.004)	48% vs. 24% (<.0003) (3-y)
Brizel, 1998 (307)	116	Resectable and unresectable	Cisplatin, 5-FU	70-75, Gy b.i.d.	70% vs. 44% (.01)	55% vs. 37% (.07) (3-y)

Status of Con. CT &RT

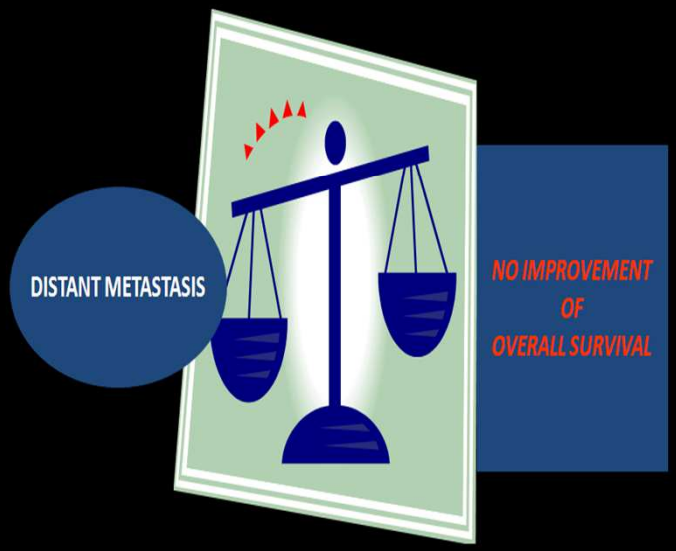
Metaanalysis

- Absolute Survival benefit at 5 yrs 8%
- CDDP alone is as good as Poly chemotherapy
- Effect of Chemotherapy decreases with Age
- Significant toxicity .

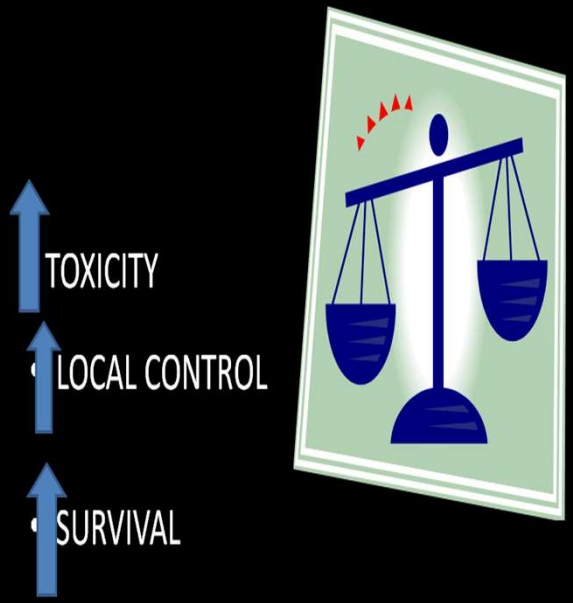
CONCLUSION-
Concurrent CTRT

- RT+CT(concurrent) :- LRC, DFS, OS
- MONOCHEMOTHERAPY using Cisplatinum seems give better overall result
- No consensus regarding optimal radiation –dose fractionation
- Acute toxicities with use of concurrent CT & RT is high,so can considered IMRT
- Recommended as standard of care in Locally advanced H&N cancer.

NEOADJUVANT CT



OUTCOME VERSUS TOXICITY(CONCURRENT CTRT)



Meta-Analysis of Chemotherapy in H&N Cancer (MACH-NC)

- Analyzed 63 randomized trials, 1965 - 1993
- Locoregional Rx +/- chemotherapy
- Updated individual patient data
- Total of 10,741 patients

Lancet 355:949-955, 2000

CHEMOTHERAPY IN ADVANCED HEAD & NECK CANCER-OVERALL SURVIVAL

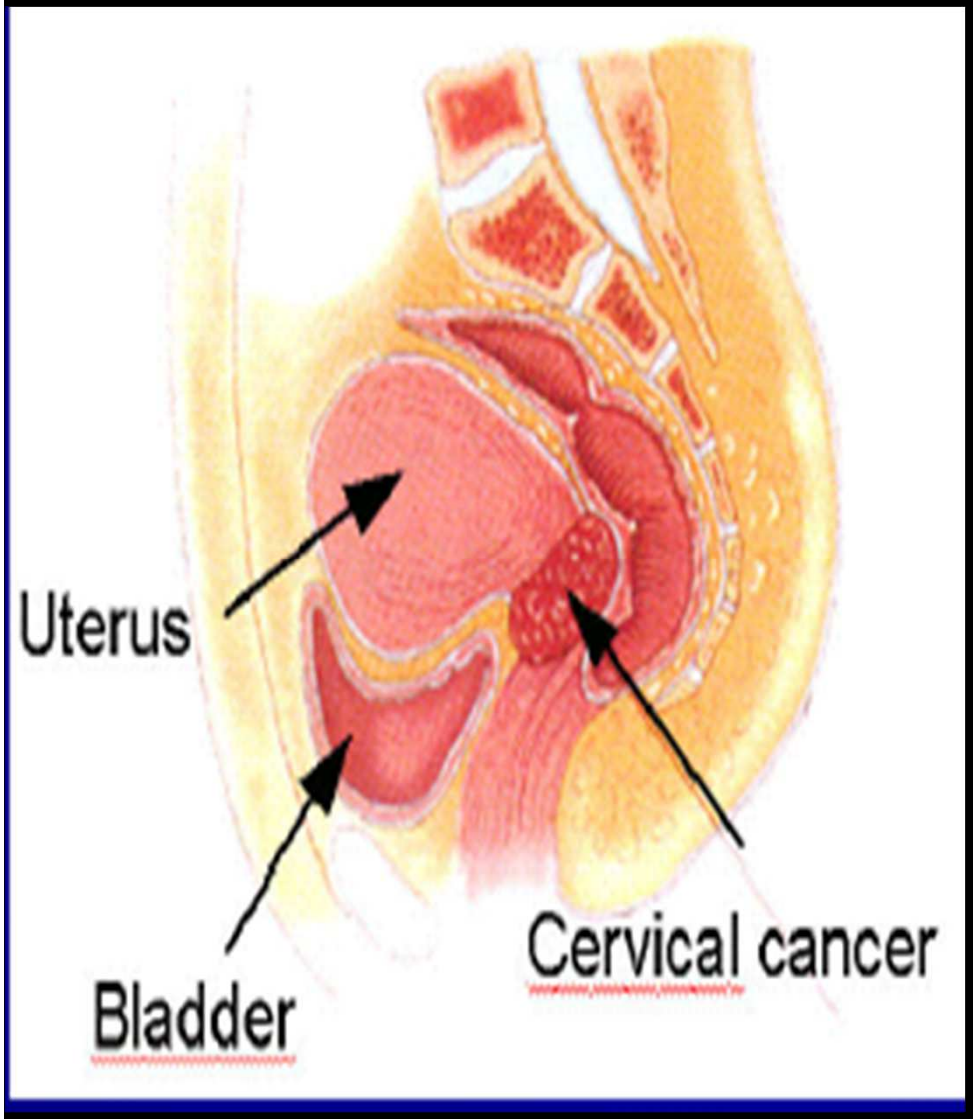
REGIMEN	ABSOLUTE BENEFIT-5YRS	RISK REDN	p
ADJUVANT	1%	2+/-7%	NS
NEO ADJUVANT.	2%	5+/-3%	NS
CONCOMITANT	8%	19+/-3%	<.0001
TOTAL	4%	11+/-2%	<.0001

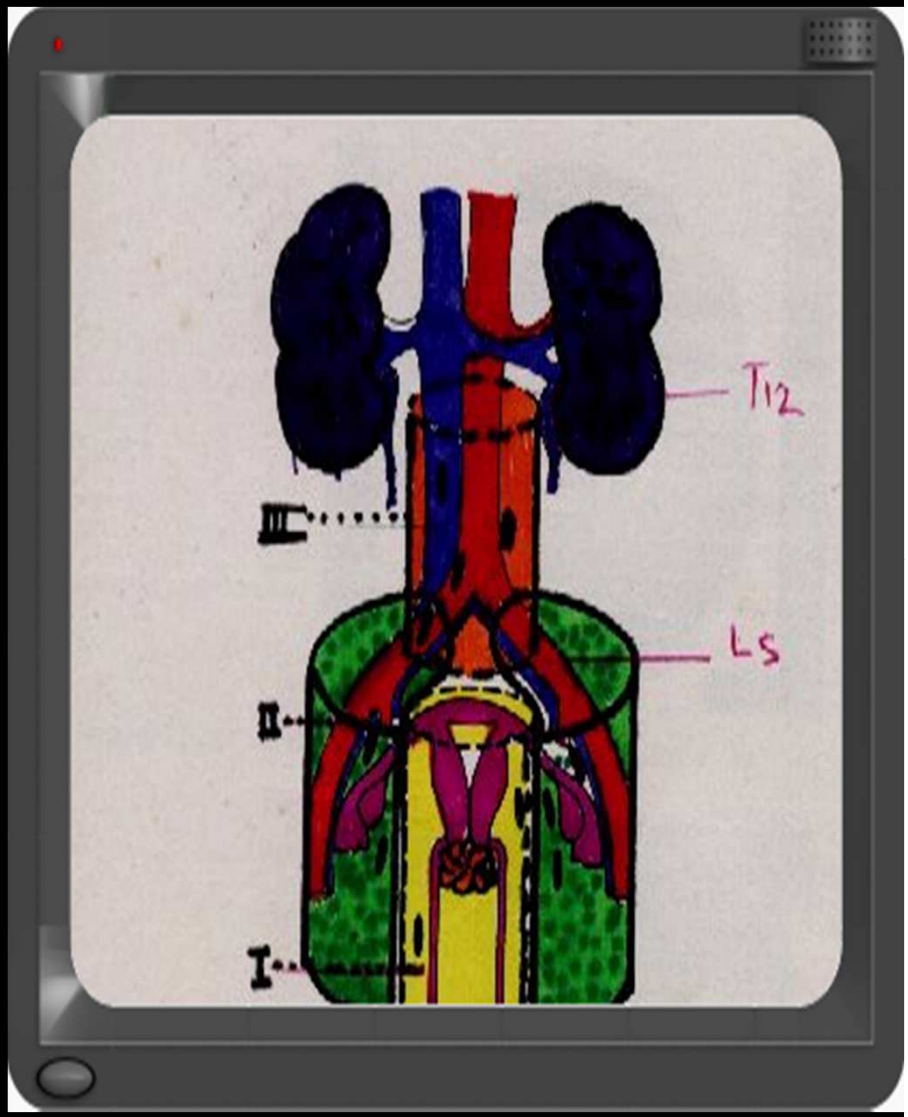
TAKE HOME MESSAGE

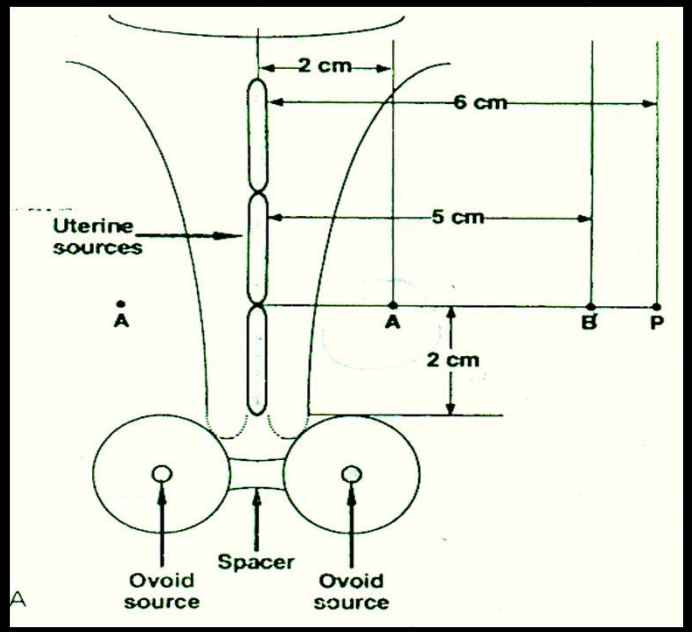
- S+RT IS THE ACCEPTED MODALITIES OF TREATMENT IN ADVANCED HEAD & NECK CANCER
- ORGAN PRESERVATION :-CT + RT CAN BE TRIED
- CONCOMITTANT CT+ RT IS BETTER IN TERMS OF SURVIVAL THAN NEOADJUVANT CT.
- MULTI AGENT CT CAN BE TRIED IN CONCOMITTANT SETTING
- HIGH RISK POST OP SETTING CAN CONSIDER CT + RT FOR BETTER LOCOREGIONAL CONTROL
- RECURRENT CA CAN TRY REIRRADIATION + CT

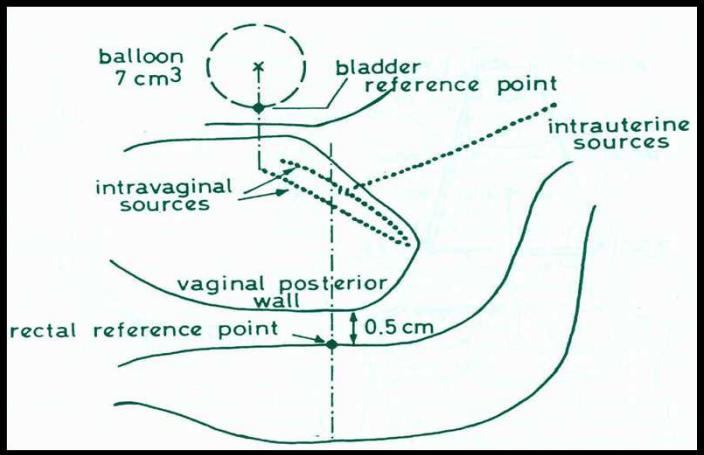
TAKE HOME MESSAGE:-2

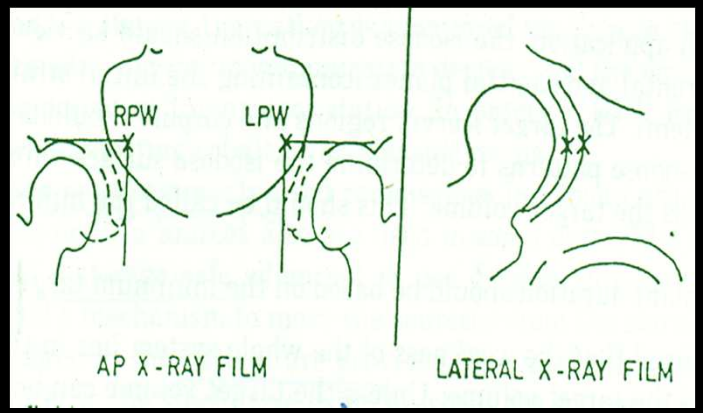
CARCINOMA CERVIX

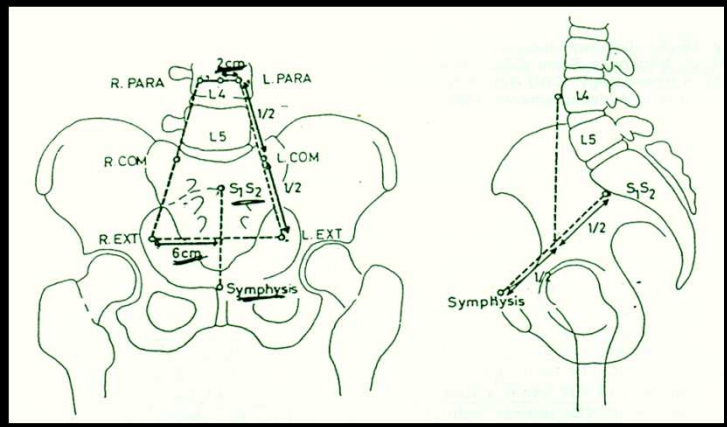





2 cm
6 cm
5 cm
Uterine sources
A
A
B
P
2 cm
Ovoid source
Spacer
Ovoid source
A


balloon 7 cm3
bladder reference point
intrauterine sources
intravaginal sources
vaginal posterior wall
rectal reference point
0.5 cm


RPW
LPW
AP X-RAY FILM
LATERAL X-RAY FILM


R. PARA
2cm
L. PARA
L4
1/2
L5
R. COM
L. COM
S1S2
1/2
R. EXT
L. EXT
6cm
Symphysis
L4
L5
S1S2
1/2
1/2
SympHysis

FIGO Staging System (clinical)

- Stage I: confined to the cervix
  - IA microscopic only (IA1 <3mm/IA2 <5mm)
  - IB visible lesion or microscopic > IA
  - IB1 < 4cm diameter
  - IB2 >4cm diameter
- Stage II: beyond cervix but not to pelvic sidewall.
  - IIA extension to upper 2/3 vagina (no parametrial involvement)
  - IIB extension into parametria
- Stage III : IIIA lower 1/3 vagina
  - IIIB extension to pelvic sidewall, hydronephrosis
- Stage IV: IVA invades bladder or rectal mucosa
  - IVB distant metastases

Lymph node involvement ↑ with Stage.
Nodal involvement is not part of staging system

STAGE Ib & IIa TREATMENT

Wertheim's Hysterectomy

Or

Radical radiation therapy

(Ext + Brachy)

Choice of treatment determined by age, menopausal status, ovarian preservation, co-morbid conditions, patient's wish & availability of expertise in surgery & RT

(NIH Guidelines 1997)

Risk Stratification (GOG Guidelines)

Deep stromal invasion
Large tumor diameter(>4cm)
LVSI

Intermediate risk (Any two)

Positive nodes
Positive surgical margins
Positive parametria

High risk (Any one)

Stage Ib/IIa
Impact of Lymph node Metastases

	Survival(%)	Relapse(%)
L.N –Ve	95.8 %	
L.N +Ve		
Pelvis	63.5%	32%
P.A	40.8%	57%
Pelvis+PA	18.4%	73.7%

Early Stage Carcinoma Cervix
Intermediate Risk : Role of Adjuvant therapy

GOG 92 : RCT (*Gynae Oncol 73 ;177-183: 1999)*

Outcome	No Adj RT N = 140	Adj RT N = 137	p value
2 yr RFS	79%	88%	.008
2 yr OAS	79%	87%	.008
Pelvic rec	21%	13%	
Dist mets	7%	2%	

Risk of Recurrence reduced by 44% (RR 0.56.p=0.01)

Mortality reduced by 36%(p=.005).

"Grade A"

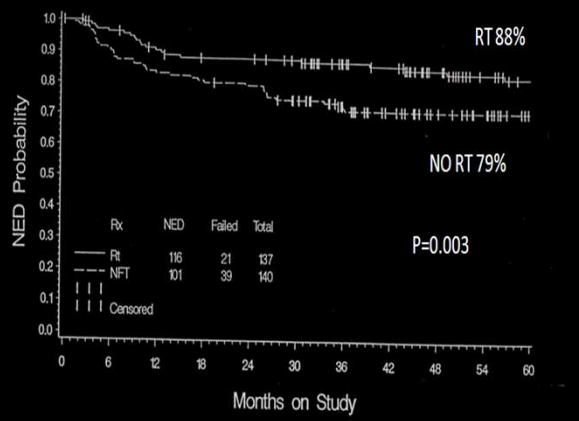
ADJUVANT PELVIC RT IS BENEFICIAL

Early Stage Carcinoma Cervix
High Risk : Role of Adjuvant Therapy

Intergroup 0107 RCT Trial (*Gynae Oncol 73 ;177-183: 1999)*

Outcome	PORT N = 116	POSTOPCT+RT N = 127	p value
4yr RFS	63%	80%	0.01
4yr OAS	71%	81%	0.01
Pelvic rec	17%	6%	
Distant mets	11%	7%	
Pelvic+ distant	4%	3%	

High Risk* Node Negative Stage IB Ca Cx: RH + PLND vs. RH + PLND + RT
(Sedlis et al, Gyn Onc 73, '99)



Defined a specific subgroup of patients with intermediate risk factors who are benefited from pelvic RT though at cost of increased toxicity

CHEMO-RADIATION SHOULD BE STANDARD OF CARE

"Grade A"

Latest news from SGO, 2004 (1)

A re-analysis of SWOG 8797

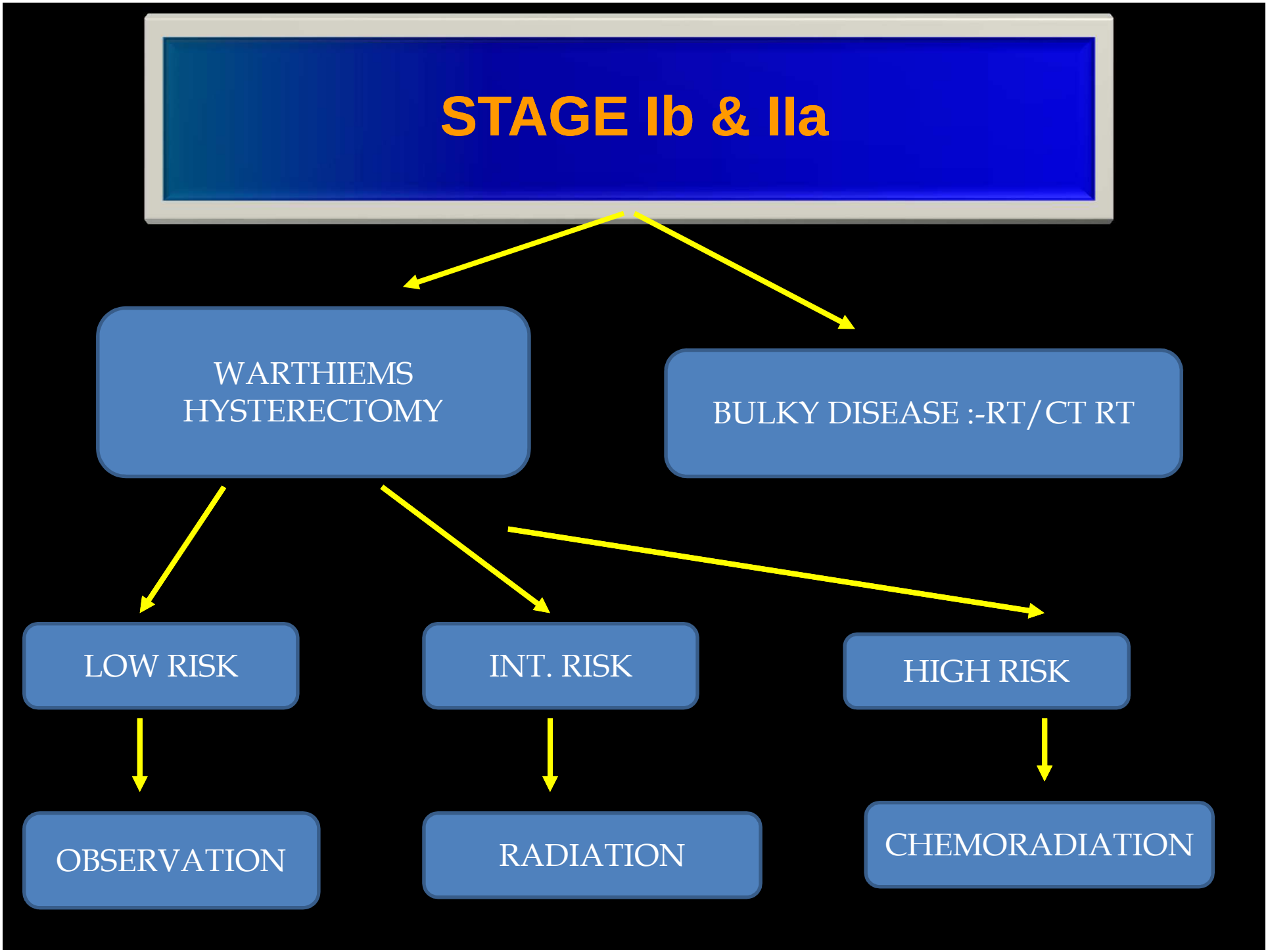
benefit of PO concurrent CRT

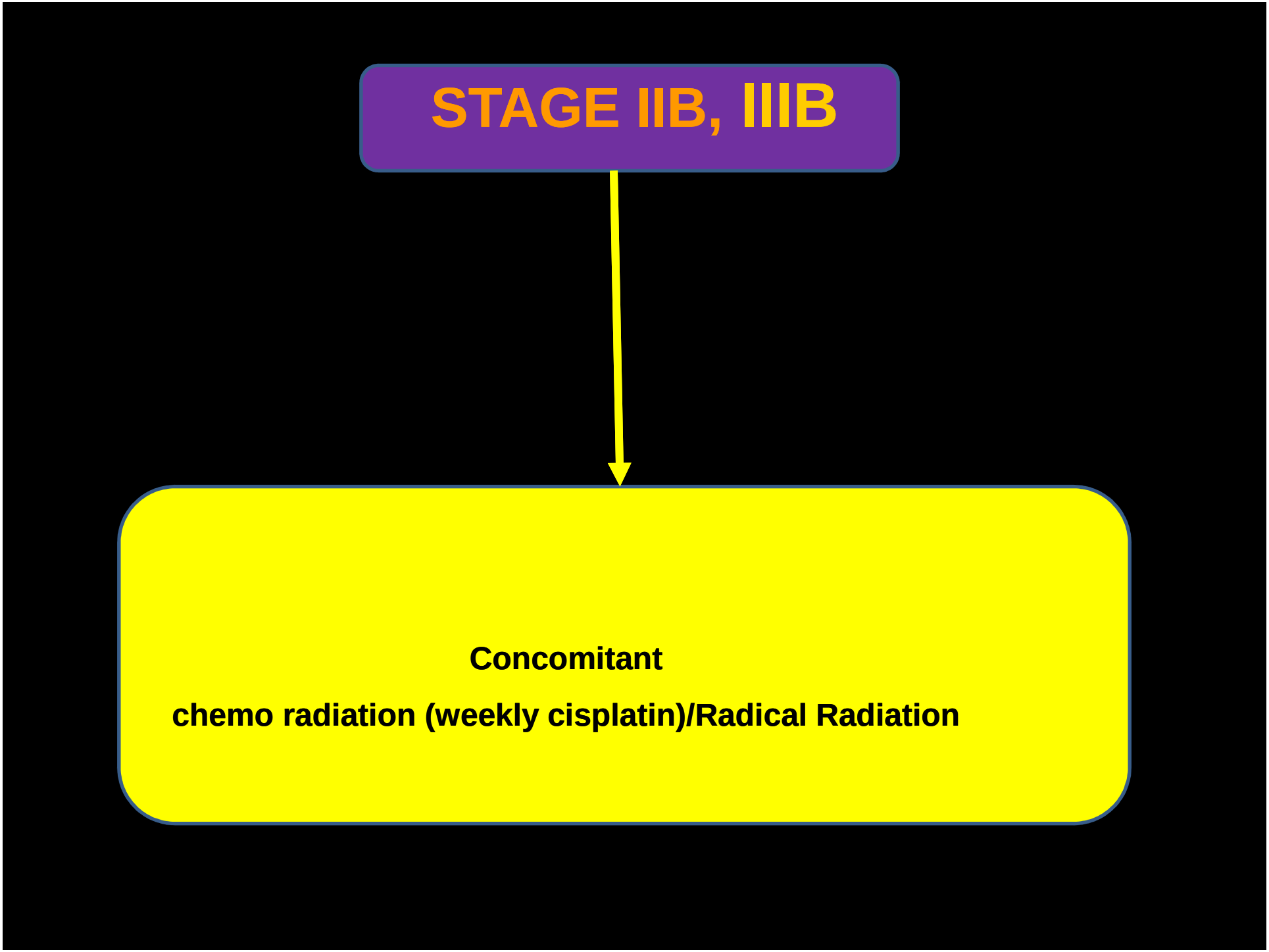
limited to those with

- Tumors > 2 cm,
- > 2 positive LN,
- Parametrial extension

Im et al. Abstract 8. Proc. to 35th annual meeting Society of Gynecologic Oncologists 2004.

Peters J. Clin. Oncol. 2000;18:1606–1613


STAGE Ib & IIa
WARTHIEMS HYSTERECTOMY
BULKY DISEASE :-RT/CT RT
LOW RISK
INT. RISK
HIGH RISK
OBSERVATION
RADIATION
CHEMORADIATION


STAGE IIB, IIIB
Concomitant
chemo radiation (weekly cisplatin)/Radical Radiation

NATIONAL CANCER INSTITUTE CLINICAL ANNOUNCEMENT

'CONCURRENT CHEMORADIATION FOR CERVICAL CANCER'

in February 1999

"Five major randomized phase III trials show that platinum based chemo when given concurrently with RT prolongs survival in women with locally advanced cervical cancer stages Ib2 - IVa as well as in women with stage I / IIa found to have metastatic pelvic lymph nodes, positive parametrial disease and positive surgical margins at the time of primary surgery

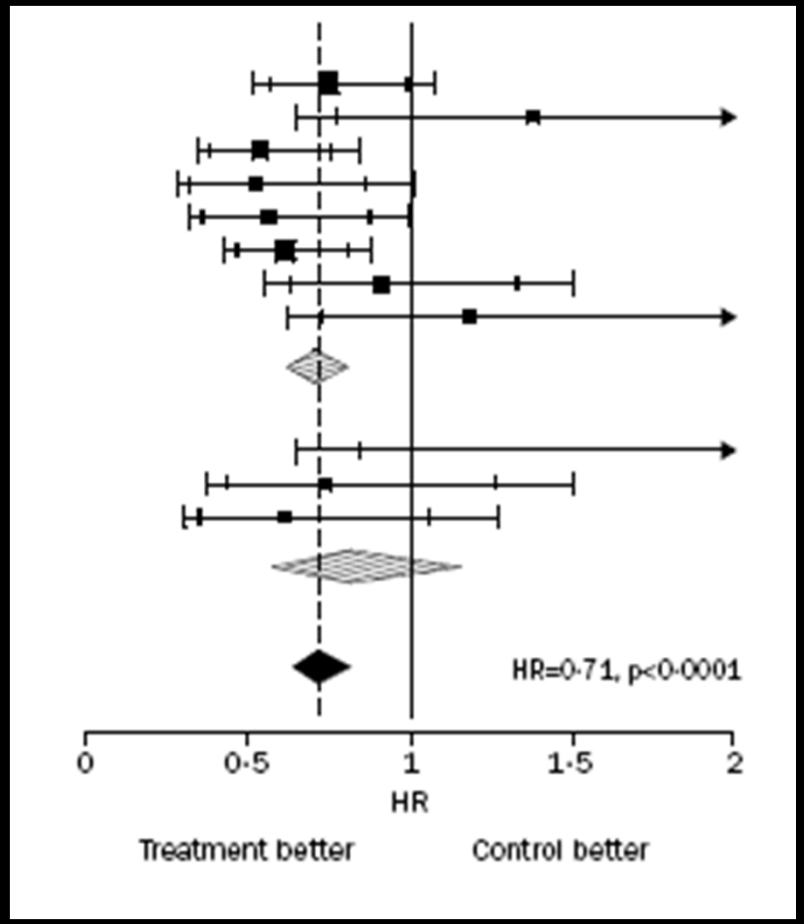
Concurrent Chemoradiation Results of Meta-analyses

"Grade A"

Cochrane Collaborative Group (19 Trials) (4580 patients)

Green JA et al Lancet 358;781 (Sept. 2001)

- 19 RCTs between 1981 and 2000 : 4580 randomized patients
- Increase in OAS by 12% & RFS by 16% (absolute benefit) (p=0.0001)
- Greater benefit in patients in stages IB2 and IIB
- Decrease in local and systemic recurrence (p=0.0001)



Update in July 2005: 21 trials and 4921 pts

- **Similar findings (absolute benefit: 10%)**
- **Test for Heterogeneity : Positive**
- **No data on late toxicities**

Cochrane Database Syst Rev. 2005 Jul 20;(3):CD002225.

Green et al meta-analysis on concurrent chemoradiation: *update*

Review strongly suggests that concomitant chemoradiation improves OS and DFS whether or not platinum was used with absolute benefits of 10% and 13% respectively.

Cochrane Database Syst Rev, 2005;Jul 20: (3)

Chemoradiation in Advanced Carcinoma Cx
Results of Meta-analyses

Canadian Group(9 Trials) - 4 year survival data

Lukka et al, Clinical Oncology 14;203(June 2002)

- **Cisplatin based Concomitant Chemo-radiation**
- **Significant improvement in Overall Survival**
  - Advanced Stages (Only 30% tumors)
  - Bulky IB tumors (prior to surgery)
  - High risk early disease (post-surgery)
- **Toxicites** Acute Grade 3/4 Hematological and G.I significantly higher : all short lived
  - 2 deaths due to the toxicities
  - No significant late toxicities seen

"Grade A"

CANADIAN STUDY

A CLINICAL Trial comparing Concurrent Cisplatinum & Radiation Vs Radiation alone for locally advanced Squamous Cell carcinoma of The cervix carried out by the National Cancer Institute of Canada Clinical trials Group

Pearcy R,etal.Proc.ASCO 2000;19:378

N=259

Stage III-Iva;32%

Cisplatinum

RT+CT Vs RT 0.90(0.63-1.29)

No benifit

Long term follow up of Potentiation of Radiotherapy by Cisplatinum in Advanced Cervical Cancer

Wong LC,et al,Gynaecol.Oncol 1989;35.159-163

N=64

Stage IIIA_IIB:30%

Cisplatinum

RT+CT Vs RT;-1.04(0.58-1.87)

No benifit

TAKE HOME MESSAGE

Early stages

Post op RT – Inermediate risk group

Post op CT+RT :- High risk group

Concurrent chemoradiation – Bulky stage Ib/Iia

Neoadjuvant CT+ Surgery + RT- Still investigational

Locally Advanced

Concurrent chemoradiation

Radiation Therapy in Breast Cancer

TNM Grouping and Staging

EBC

- ***Stage I***
  T1*, N0, M0
- ***Stage IIA***
  T0, N1, M0
  T1*, N1, M0
  T2, N0, M0
- ***Stage IIB***
  T2, N1, M0
  T3, N0, M0

LABC

- ***Stage IIIA***
  T0, N2, M0
  T1*, N2, M0
  T2, N2, M0
  T3, N1, M0
  T3, N2, M0
- ***Stage IIIB***
  T4, N0, M0
  T4, N1, M0
  T4, N2, M0
- ***Stage IIIC*****
  Any T, N3, M0

MBC

Stage IV
Any T, Any N, M1

INDICATIONS

- RADIATION TO INTACT BREAST- BCT
- POST MASTECTOMY
- PALLIATIVE RADIATION

Common Treatment Protocols

- Early breast cancer
- (Stage & II) :

Locally advanced Breast cancer
(Stage IIIA & IIIB)

BCT

NON BCT

III A

III B

IV

Surgery >
WBRT > Chemotherapy> Hormn Th

Surgery > RT >Chemotherapy>Hormn.Th
Surgery>Chemotherapy> RT >Hormn.Th

MRM > Chemotherapy>
LRRT >Hormn. Th

Operable

Inoperable

PALLIATION

CT > MRM> CT> LRRT >Horm.Th
MRM >CT> LRRT > Hormn.Th

CT>Surgery CT> LRRT >Hormn.Th
CT> RT > CT > Hormonal Th

INDICATION OF RADIATION IN BREAST CANCER

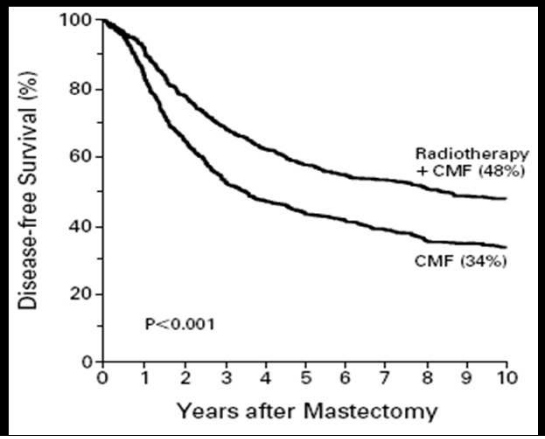
- Indications of Radiotherapy in EBC
- BCT - Radiotherapy forms an integral part of BCT
- Post Mastectomy Radiotherapy
- Chest wall irradiation - 1. Positive margins
  2. T3 tumors
  3. 4 or more + LN in axilla
  4. Unknown status
- Axillary irradiation - 1. 4 or more + LN in axilla
  2. Extranodal disease
  3. Inadequate axillary dissection
  4. Unknown axillary status

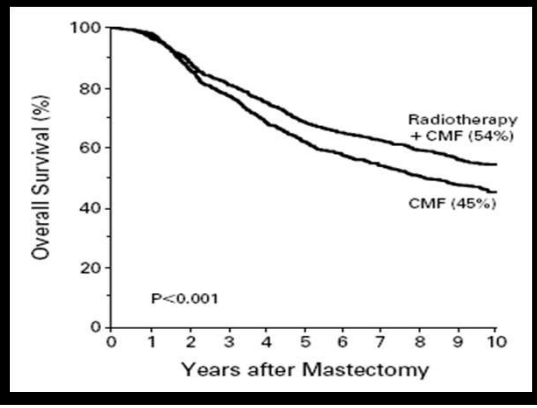
The NEW ENGLAND JOURNAL of MEDICINE

Overgaard et al. NEJM 1997 337:949

Volume 337:949-955 October 2, 1997 Number 14

PORT in High-Risk Premenopausal Women with Breast Cancer Who Receive Adjuvant Chemotherapy





1789 patients, 1982 – 1989, premenopausal, node + or Tumor > 5cm, M0

Total mastectomy, level I + II (partly) + CMF +/- 50Gy/25fx (electrons + photons)

Sx in 79 departments, RT in mainly 6 centres

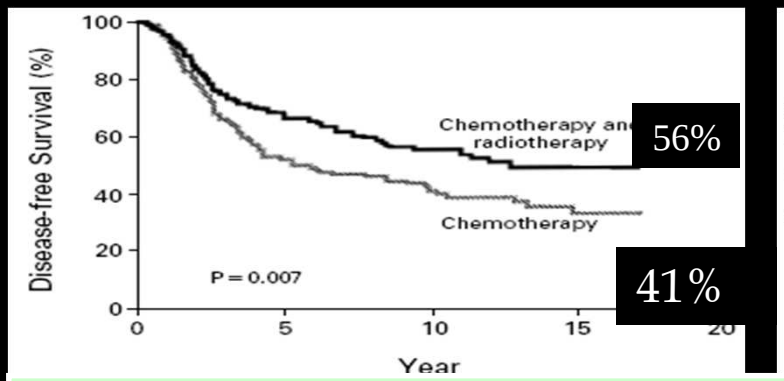
Conclusions: The addition of postoperative irradiation to mastectomy and adjuvant chemotherapy reduces locoregional recurrences and prolongs survival in high-risk premenopausal women with breast cancer.

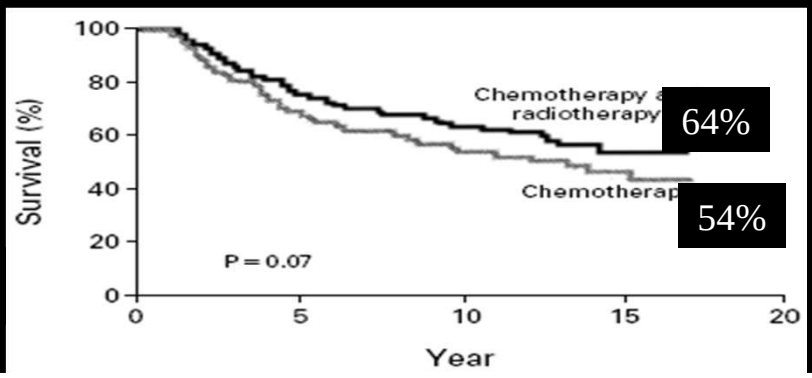
Ragaz et al. NEJM 1997 337:956

The NEW ENGLAND JOURNAL of MEDICINE

Volume 337:956-962 October 2, 1997 Number 14

Adjuvant Radiotherapy and Chemotherapy in Node-Positive Premenopausal Women with Breast Cancer





318 patients, 1979 – 1986, premenopausal, node +, any T, M0

MRM + CMF +/- 37.5Gy/16fx RT (photons) Sx by 'specialists', CT & RT in one centre

Conclusions: Radiotherapy combined with chemotherapy after modified radical mastectomy decreases rates of locoregional and systemic relapse and reduces mortality from breast cancer.

Post Operative RT

- Fletcher showed the benefits of postoperative LRRT in reducing the nodal recurrence from 20% to <5%, and the chest wall recurrence from 30% to <10%.

.

Early Breast Cancer
All RCTs confirmed equivalence of BCT to Mastectomy

Trial	No. of Patients (Median FU)	Survival		Local Recurr.	
		MRM	BCT +RT	MRM	BCT + RT
NCI Milan *1973-80*	701 (13 yrs)	69%	71%	2%	4%
NSABP-06 *1976-84*	1444 (12 yrs)	62%	62%	6%	10%
EORTC *1980-86*	903 (7 yrs)	75%	75%	9%	13%
Danish *1983-87*	905 (6 yrs)	82%	79%	7%	3%

Selected Randomized Trials of Breast-conserving Surgery with or without Radiation

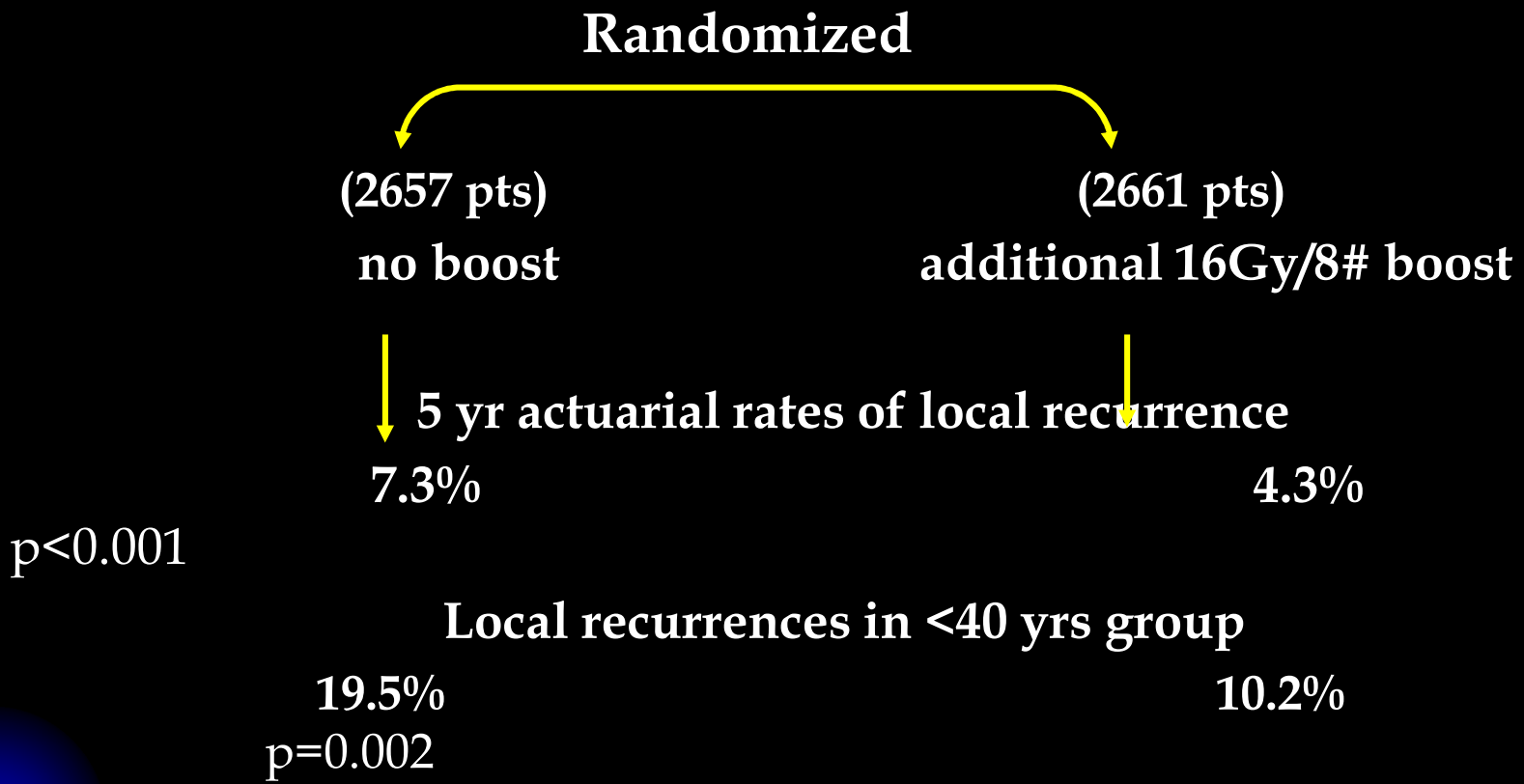
				LR		
Study	**T, N**	**No. of Patients**	**Follow-Up (yrs)**	**With RT(%)**	**Without RT (%)**	***p* Value**
Fisher et al.	<4 cm node positive/negative	930	10	12.4	40.9	<.001
Liljegren et al.	<2 cm node negative	381	10	8.5	24.0	.0001
Veronesi et al.	<2.5 cm	579	10	5.8	23.5	<.001
Clark et al.	<2 cm node negative	837	3	5.5	25.7	<.001
Fisher et al.	<2 cm node negative	1,009	8	2.8	16.5	<.001
Winzer et al.	<2 cm node negative	347	5.9	3.2	27.8	<.001

BCS Vs BCS+RT

STUDIES	LOCAL REC	LOCAL REC.	5 YRS.SURV	5YRS.SURV	FOLLOW UP
	S	S+RT	S	S+RT	
MILAN	19	2	65	65	18
NSABP	10	8	63	59	12
SWEDISH	18	2	90	91	08
ONTARIO	29	7	85	87	15
SCOTLAND	16	6	77	75	10

Tumor Bed Boost
EORTC data

- BCT for stage I and II breast cancer
- RT to whole breast 50Gy/25#/5wks



NEJM 2001 vol 345, no 19,1378-1387

Boost to the tumor bed
Comparison of electron vs implant

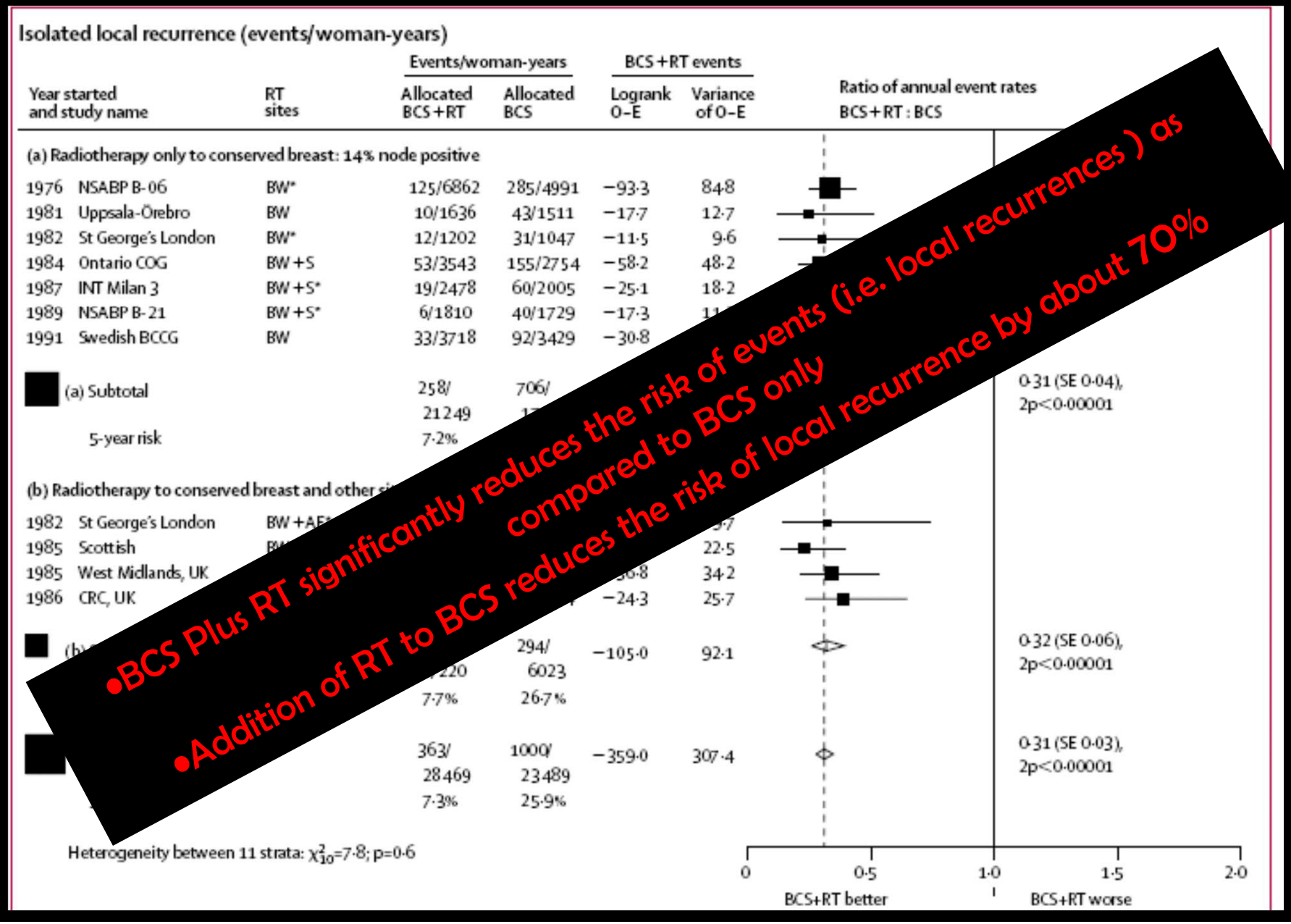
	Electrons			Implant		
Study	No of pts	10 yr DFS	Br. Relapse	No of patients	10yr DFS	Br. relapse
Fourquet et al	129	68%	39%	126	78%	24%
Mansfield et al	416	78%	18%	654	76%	12%
Perez et al	490	79%	6%	119	80%	7%
Recht et al	79	-	8%	685	-	9%
Touboul et al	160	85%	15%	169	86%	8%

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials

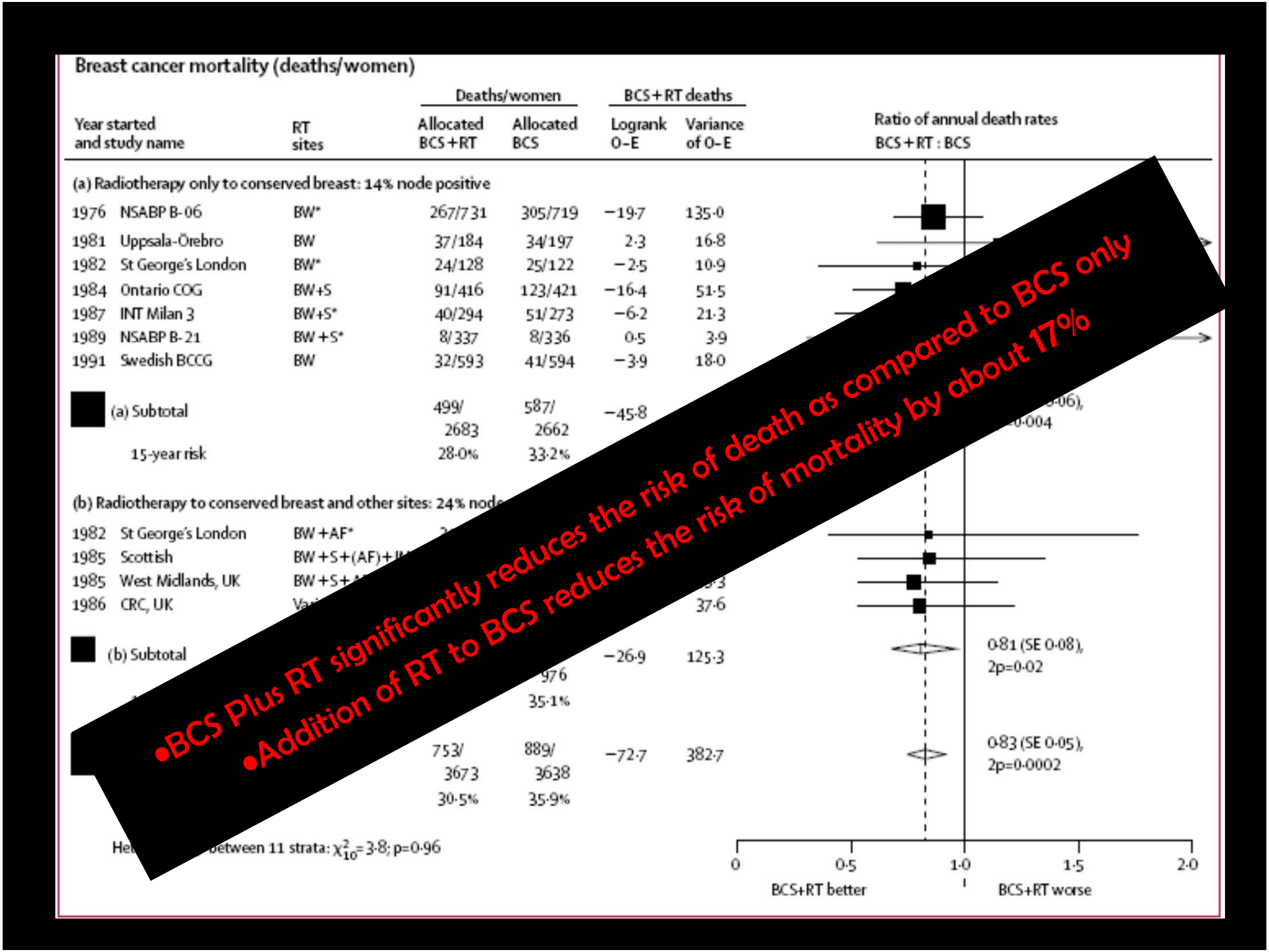
EBCTCG Lancet 2005; 366: 2087-2106

EBCTCG RESULTS



•BCS Plus RT significantly reduces the risk of events (i.e. local recurrences) as compared to BCS only

•Addition of RT to BCS reduces the risk of local recurrence by about 70%


Breast cancer mortality (deaths/women)
Deaths/women
BCS+RT deaths
Year started and study name
RT sites
Allocated BCS+RT
Allocated BCS
Logrank O–E
Variance of O–E
Ratio of annual death rates BCS+RT : BCS
(a) Radiotherapy only to conserved breast: 14% node positive
1976 NSABP B-06 BW* 267/731 305/719 −19·7 135·0
1981 Uppsala-Örebro BW 37/184 34/197 2·3 16·8
1982 St George's London BW* 24/128 25/122 −2·5 10·9
1984 Ontario COG BW+S 91/416 123/421 −16·4 51·5
1987 INT Milan 3 BW+S* 40/294 51/273 −6·2 21·3
1989 NSABP B-21 BW+S* 8/337 8/336 0·5 3·9
1991 Swedish BCCG BW 32/593 41/594 −3·9 18·0
(a) Subtotal 499/2683 587/2662 −45·8
15-year risk 28·0% 33·2%
(b) Radiotherapy to conserved breast and other sites: 24% node
1982 St George's London BW+AF*
1985 Scottish BW+S+(AF)+
1985 West Midlands, UK BW+S+
1986 CRC, UK
(b) Subtotal −26·9 125·3
976
35·1%
753/3673 889/3638 −72·7 382·7
30·5% 35·9%
0·81 (SE 0·08), 2p=0·02
0·83 (SE 0·05), 2p=0·0002
Het between 11 strata: χ^2_{10}=3·8; p=0·96
0 0·5 1·0 1·5 2·0
BCS+RT better
BCS+RT worse
•BCS Plus RT significantly reduces the risk of death as compared to BCS only
•Addition of RT to BCS reduces the risk of mortality by about 17%

Accelerated Partial Breast Irradiation (APBI)

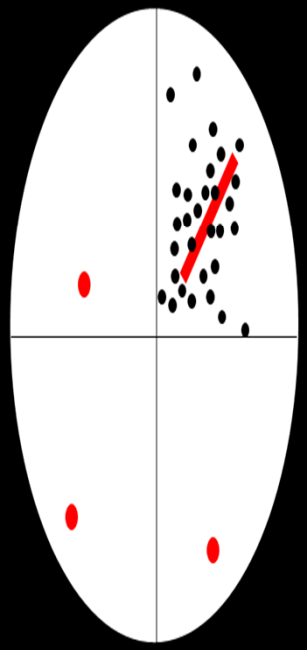
After Wide Excision of Lump & appropriate axillary surgery, irradiation of the tumour bed with 1-2 cm margins using a regime of accelerated RT

(shortened course & with larger dose per fraction)

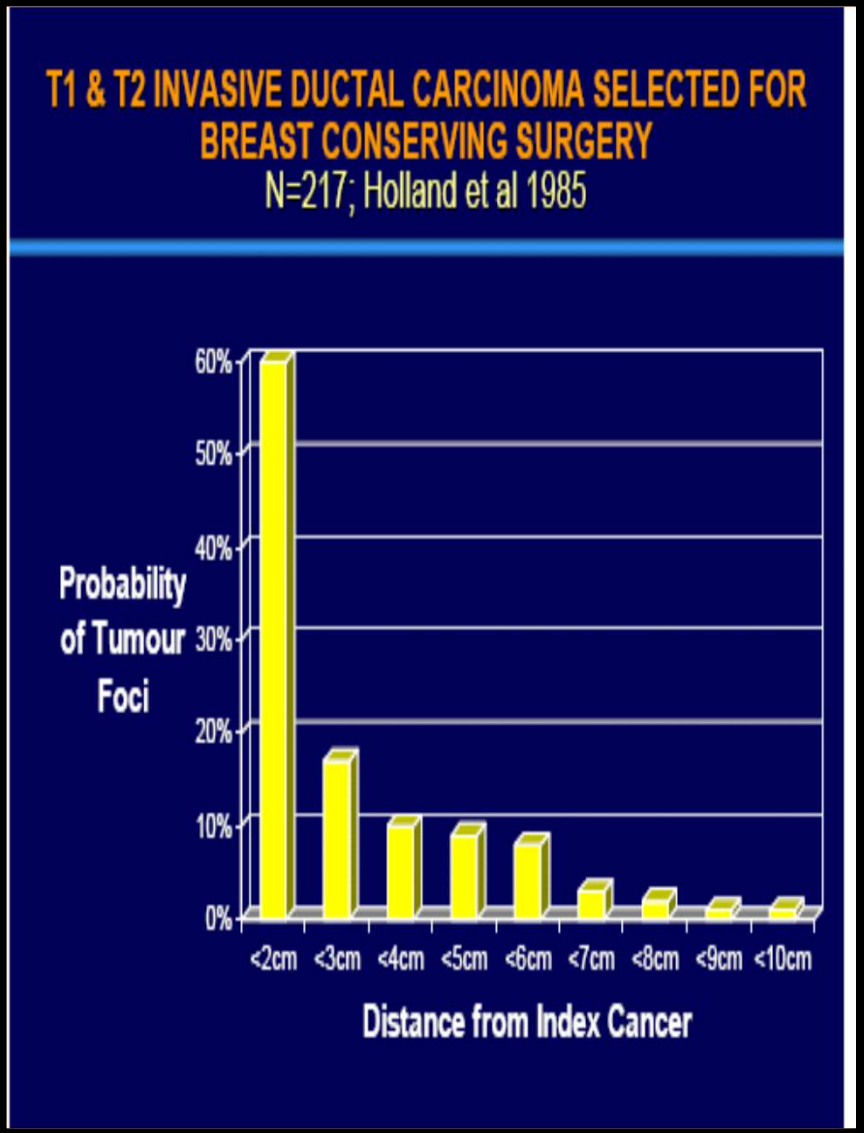
Why partial breast irradiation?

The vast majority of the recurrence (up to 90%) occurs in the index quadrant
Only 1% to 3% recurrence occurs in other quadrant

-- U. Veronesi (Milan III)



Treatment is focused to area of highest risk of residual occult disease/ recurrence



Patient Selection Criteria

	ABS [1]	ASBS[2]	William Beaumont Hospital [3]
Age (years)	≥45	≥50	≥45
Histology	Unifocal, IDC	IDC or DCIS	IDC
Tumor size	≤ 3cm	≤ 2cm	≤ 2cm
Surgical margins	Negative	Negative ≥ 2mm	Negative
Nodal status (Axillary/ sentinel)	N0	N0	N0
Cavity to skin distance	Not stated	Not stated	>5 mm

1 Arthur D, et al. Brachytherapy. 2003
2 ASBS Consensus statement for APBI. April 30, 2003.
3 Edmundson GK, el al. Int J Radiat Oncol Biol Phys. 2002

Accelerate Dose

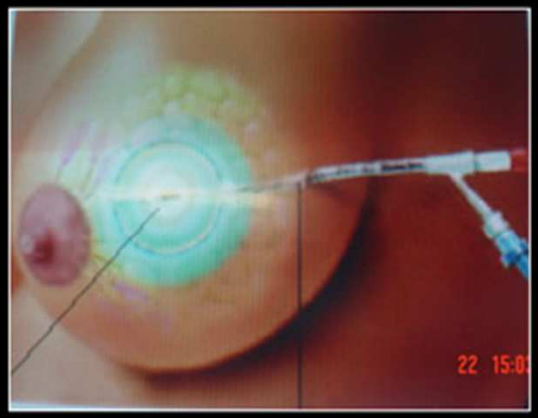
- The smaller tissue volume allows larger fraction sizes and thereby shorter overall treatment time
- Hypo-fractionation schedule decrease the time period
- Radiobiological modeling predicted safety of various dose fractionation schedule

  34Gy/10 fr/5 days BD equivalent to 50 Gy

  20Gy to 22 Gy Single fraction = 55Gy to 60 Gy

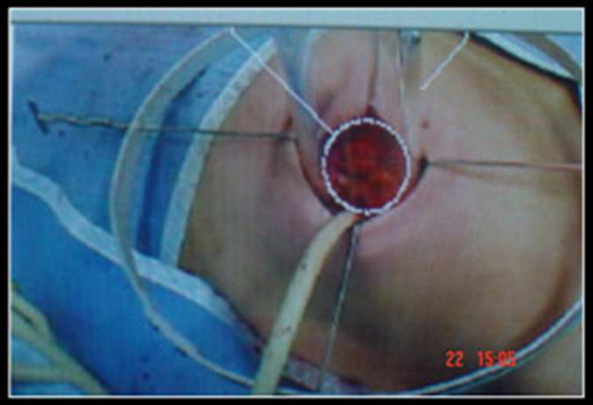
The Options for APBI

Interstitial Implant



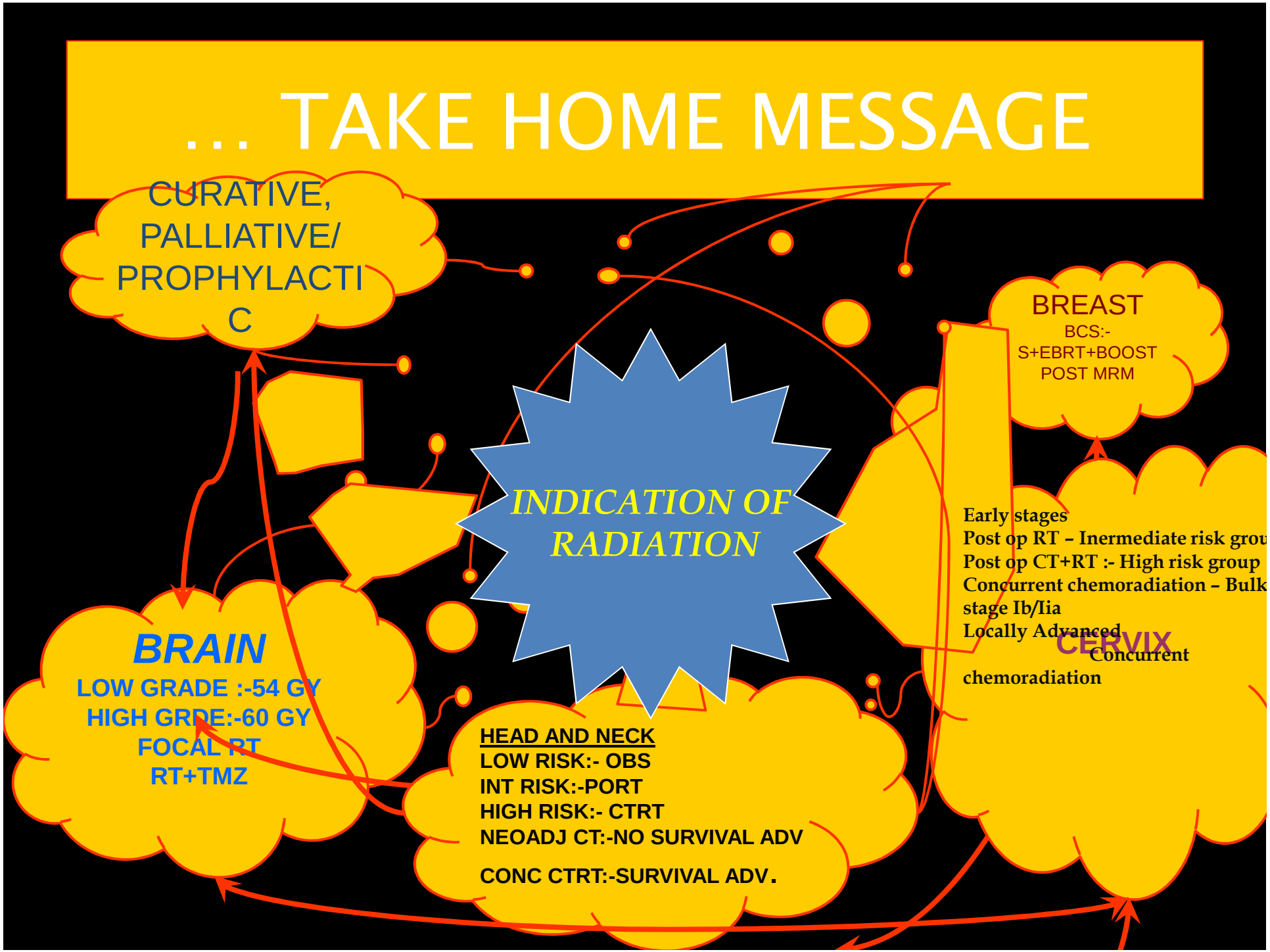
Mammosite

TARGIT



Intra op electrons [ELIOT]

3DCRT / IMRT


… TAKE HOME MESSAGE
CURATIVE, PALLIATIVE/ PROPHYLACTIC
INDICATION OF RADIATION
BREAST
BCS:-
S+EBRT+BOOST
POST MRM
Early stages
Post op RT – Inermediate risk grou
Post op CT+RT :- High risk group
Concurrent chemoradiation – Bulk
stage Ib/Iia
Locally Advanced
CERVIX
Concurrent
chemoradiation
BRAIN
LOW GRADE :-54 GY
HIGH GRDE:-60 GY
FOCAL RT
RT+TMZ
HEAD AND NECK
LOW RISK:- OBS
INT RISK:-PORT
HIGH RISK:- CTRT
NEOADJ CT:-NO SURVIVAL ADV
CONC CTRT:-SURVIVAL ADV.

THANK YOU


ADJUVANT CT


CONCURRENT CT WITH
ALTERED FRACTION RADIATION


NASOPHARYNX


RADIATION PLANNING FOR HEAD AND NECK
2007 3 18


Table 40:5
PAROTID GLAND
31 5:20PM


PARANASAL SINUSES
31 5:22PM


OROPHARYNX
OROPHARYNX
31 5:22PM


LARYNX


NASOPHARYNX

INDICATIONS FOR POST-OP RADIOTHERAPY

Primary:

- Large primary - T4 or T3 with soft tissue infiltration
- Close or positive margins of excision
- Deep infiltrative tumour
- High grade tumour
- Lympho-vascular and perineural invasion

Lymph nodes:

- Bulky nodal disease N2 / N3
- Extra nodal extension
- Multiple level involvement

Post-operative radiotherapy:

- Primary and nodal disease: 50 - 60 Gy/25-30 fr/5-6 weeks, using reducing fields.
- Site of residual disease, positive cut margins: 4-10 Gy Boost

MAXILLARY ANTRUM

- Post-operative Radiation
- T4 tumors
- High grade T3 tumors
- Adenoid cystic carcinoma
- Microscopically positive margins
- Presence of perineural invasion
- Multiple positive nodes or extra- capsular spread
- Multiple levels of node involvement

Larynx

Postoperative Radiation (indication)

-close / +ve Margin

- soft tissue extn of the primary to neck

- endothelial lined space invasion

-cartilage and perineural invasion

- multiple +ve nodes

- extranodal extension

- subclinical disease at opposite neck

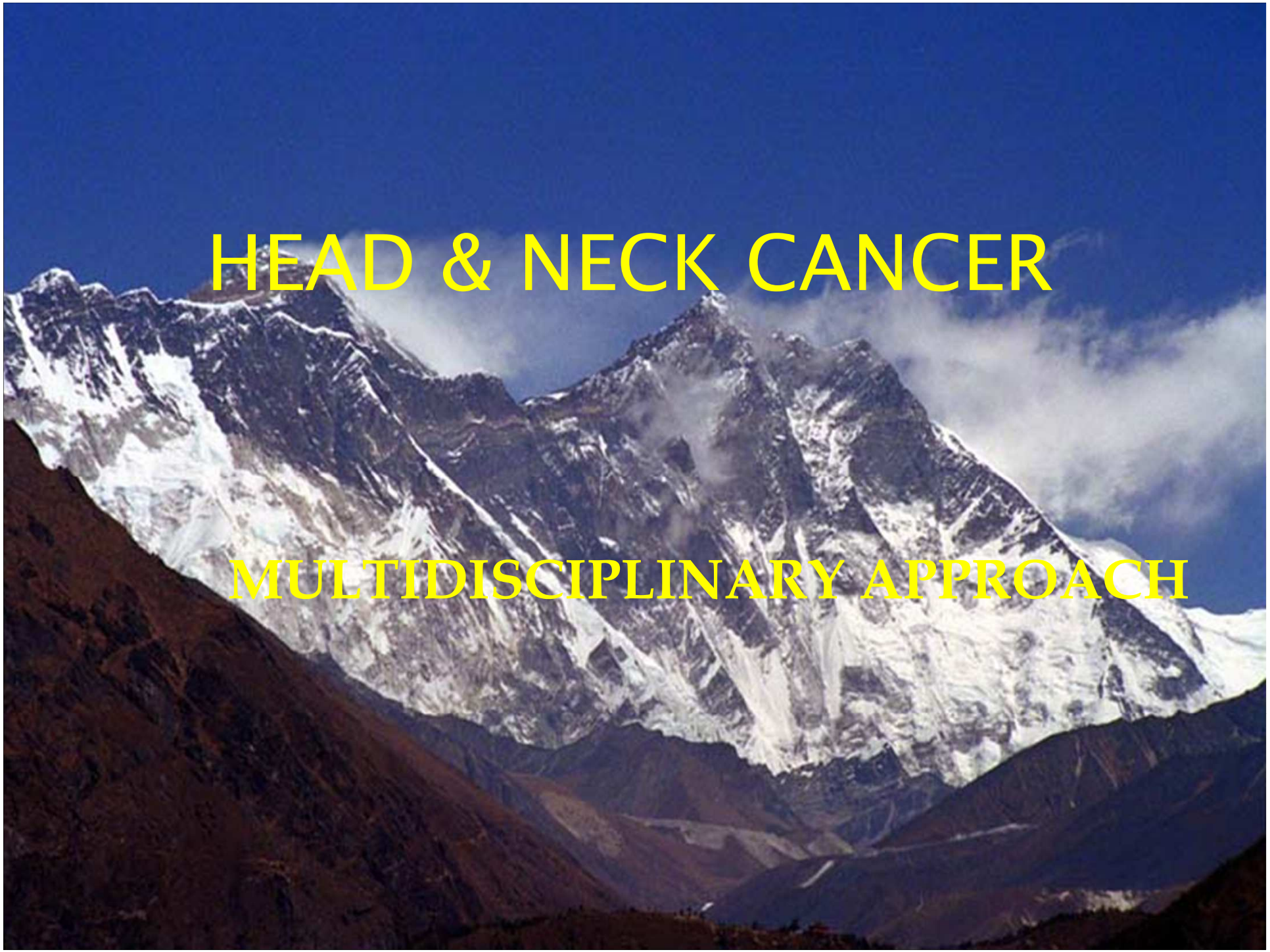
TREATMENT STRATEGY NPX

- STAGE I,II:- RADIATION
- STAGE III,IVB:- CHEMORADIATION

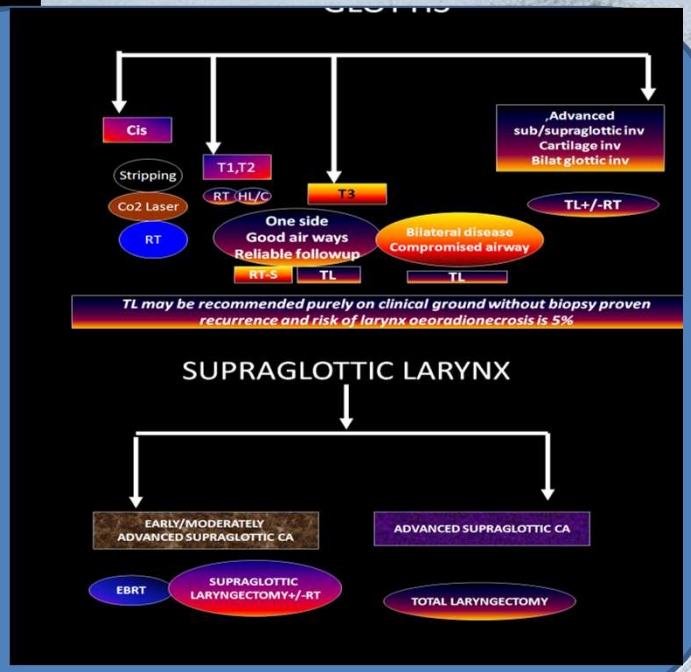
Concurrent Primary Chemoradiation

(Multi drug)

Auther	N	Study Population	CT	Local% Control	Survival %
Zakotnik'98	64	unresectable	MMC,Bleo	75vs29	38 vs10
Adelstein'99	100	resectable	Cisplat,5FU	77vs45	42vs34
Calais'99	226	oropharynx	Carbo,5FU	66vs42	51vs31
Merlano'96	157	unresectable	Cisplat,5FU	64vs32	24vs10
Adelstein'00	295	unresectable	Cisplat,5FU		29vs20
Wendt'98	270	unresecable	Cisplat,5FU	36vs17	48vs24
Brizel'98	116	Resectable & unresectable	Cisplat,5FU	70vs44	55vs37


HEAD & NECK CANCER
MULTIDISCIPLINARY APPROACH


TREATMENT PROTOCOL
IN
HEAD & NECK CANCER



- Close or positive margins
- Lymph node metastasis
- Adenoid cystic carcinoma
- High or intermediate grade tumours
- Deep lobe tumours
- Preop facial nerve paralysis
- Lymphatic or vascular invasion or perineural involvement
- Recurrent tumours

T1 / Selected T2 N0:

- Radiotherapy alone with or without Intraluminal Brachytherapy

Bulky T2 & T3-4 N0 / Any T N+

- Neo Adjuvant CT 2 cycles + Concurrent CT + RT

Table 43.5 GENERAL TREATMENT RECOMMENDATIONS BASED ON HYPOPHARYNX TUMOR STAGE

Stage I	Radiation alone or voice preservation surgery if feasible
Stage II	Radiation alone
Stage III and IV with functional laryngopharynx	Concurrent chemoradiation followed by selective neck dissection
Stage III and IV with dysfunctional laryngopharynx[a]	Laryngopharyngectomy with adjuvant RT or CRT

CRT, chemoradiation therapy; RT, radiation therapy
[a]Patients with bulky, destructive tumors that severely compromise the airway, destroy cartilage, bone, and deep soft tissue are often best served with immediate laryngopharyngectomy and postoperative radiation or chemoradiation.

Margin directed boost..

- N =509; Stage I & II Ca breast.
- Post-lumpectomy, re-excision when margin< 2 mm.
- WBRT -50Gy, followed by e- boost.
- Median f/u – 121 mths.
- No boost when no residual on re-excision (LR-6%).

Final margin status	+ve	0-2 mm	2-5 mm	> 5 mm
Boost dose	20 Gy	20 Gy	14 Gy	10 Gy
LR (12 yrs)	17%	9%	5%	0

***Neuschatz** et al.* **Cancer** 2003;97:30–9.