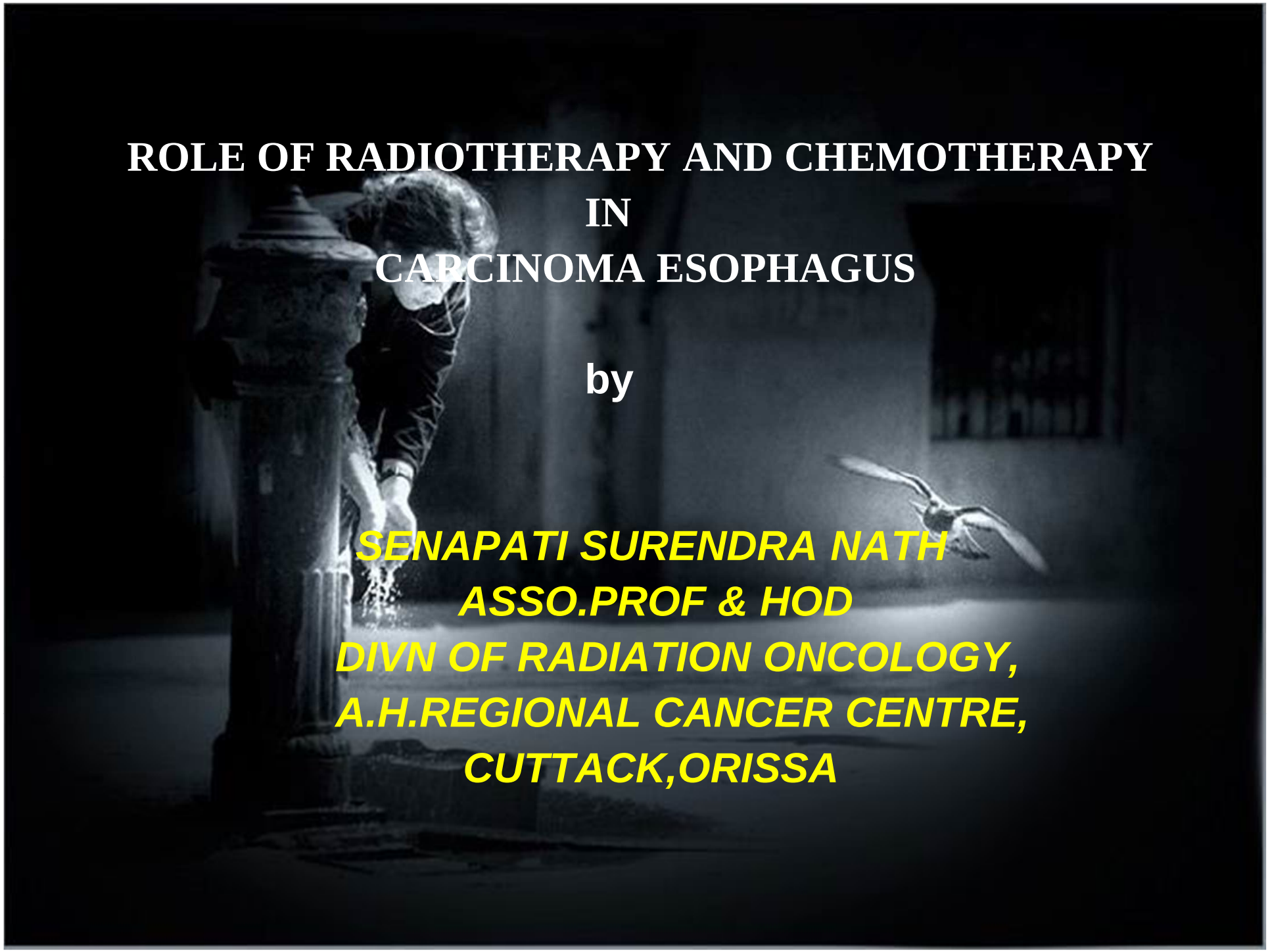

ROLE OF RADIOTHERAPY AND CHEMOTHERAPY IN CARCINOMA ESOPHAGUS

by

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A.H.REGIONAL CANCER CENTRE,
CUTTACK,ORISSA

INTRODUCTION

- Third most common gastrointestinal malignancy.
- 6th leading cause of death from cancer world wide.
- Ranks among ten most common cancers in the world.
- Incidence -10-50 per 100,000.(in India).
- Peak age:- 6th to 7th decade,M;F=6:1
- Surgery may be curative in early stages
- No consensus regarding best form of therapy.

INDIAN SCENARIO

TUMOR FACTORS

- Advanced stage of presentation

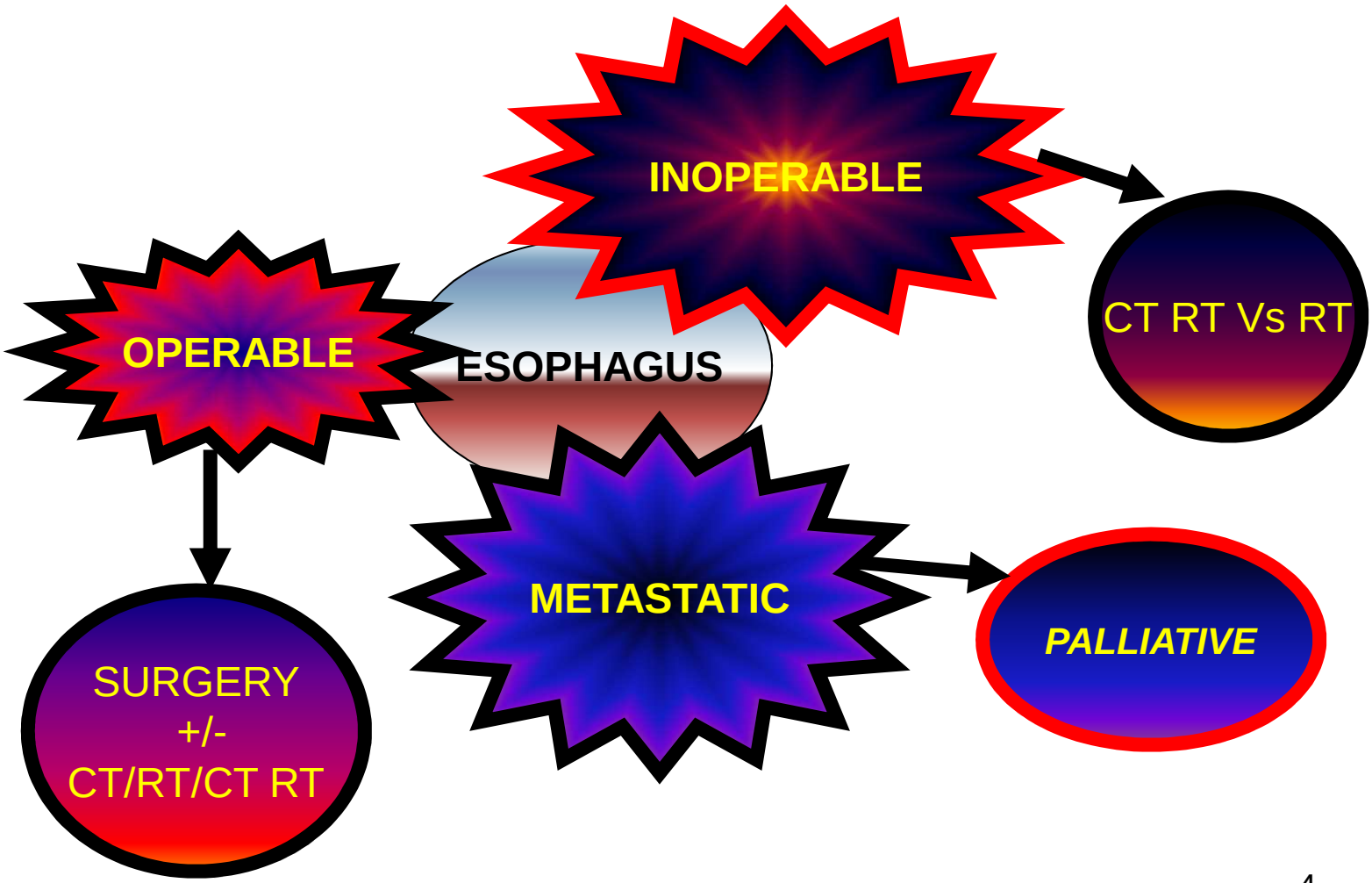
PATIENT FACTORS

- Mostly disease of the elderly
- Nutritionally deprived
- Poor performance status
- Marked degree of weight loss

SOCIAL FACTORS

- Poor economy to afford parenteral nutrition, antibiotics and growth factor
- Non availability of Expertise

TREATMENT STRATEGY



TREATMENT OF CA.ESOPHAGUS

Surgery

- Transhiatal esophagectomy
- Ivor Lewis Procedure
- Radical Esophagectomy

Radiation

- External beam Radiation
- Intraluminal Brachytherapy

Chemotherapy

- Single agent with RT
- Combination CT(CDDP+FU/ Taxane based,Topoisomerase inhibitors,EGFR receptor inhibitors)

a2

Slide 5

a2 Treatment of ca esophagus based on multidisciplinary approach.Surgert is the treatment of choice for invasive lesion.
acer, 06/09/2009

RADIOTHERAPY IN CA ESOPHAGUS

Pre Op Radiotherapy(INTENT)

Reducing tumor bulk

Sterilizing nodal areas

Reducing the risk of dissemination at surgery.

Post Op Radiotherapy(INDICATION)

Positive cut margins

Nodal positivity

Residual disease

RADIATION THERAPY TECHNIQUE

Simulation

Extent:-Assess from Barium study,Endosopy,CT Scan,PET

Positioning:- Supine/Prone Position

In CT SIM:- 5mm slices

Treatment Planning:-

Margin:-5 cm above and 5cm below the tumor and 2.5cm radial margin

Reduced Portal:-2 cm margin from gross disease.

Lesion above carina:- include supraclavicular lymph nodes.

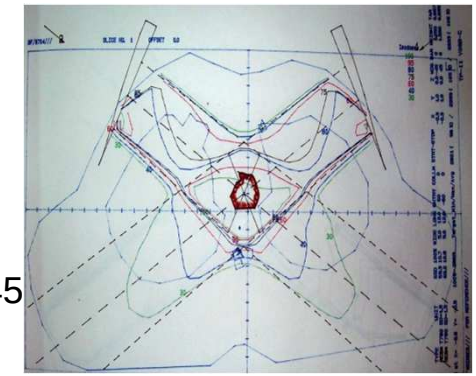
Lower Esophagus:-include Coeliacaxis (T12)and gastrohep.lig.

UPPER THIRD OESOPHAGUS

T shaped field dimensions

- Length- length of the lesion + Superior margin to include supraclavicular nodes + inferior margin of 5 cms.
- Width- cover medial two thirds of clavicle, 1 to 1.5 cm below it.
- Individual template is made for each patient to block lungs .

- **PHASE I (AP/PA PORTALS)**
- Upper third oesophagus: T – shaped field , blocks placed to shield lungs.



- **PHASE II**
- Two anterior oblique wedged fields.
- Gantry angle 45 to 60 (if >65 beam passes through the humerus) & wedge 30 to 45

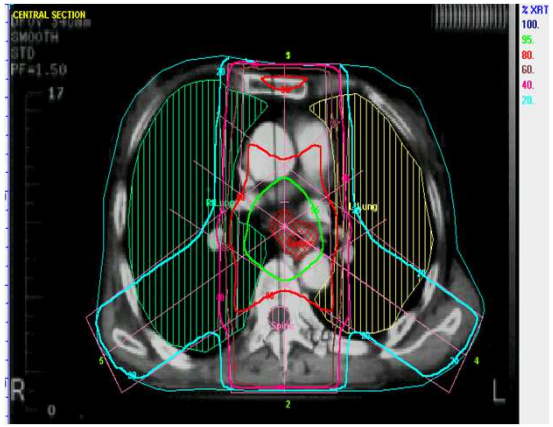
MIDDLE THIRD OESOPHAGUS

PATIENTS POSITIONING : Supine or prone(results in better coverage as esophagus shifts anteriorly by 1 to 2 cm) with arms above head to prevent obstruction of treatment beams by the arms.

- **TARGET VOLUME** :
- Length: Tumor as defined by OGD & Ba swallow + 5 cm superior & inferior margin (2-3cm for phase II)
- Lateral: Extraesophageal spread defined by CT scan & Ba swallow + 2-3 cm margin
- Tumors extending upto/ above carina, supraclavicular LN are included in the target volume

- **PHASE I (AP/PA PORTALS)**
- Middle third extending to carina: T – shaped field , blocks placed to shield lungs.
- Middle third not extending to carina – lesion length + 5 cm superior and inferior margins

- **PHASE II**
- LC above carina: anterior & two anterior oblique wedged fields.
- LC below carina: anterior & two posterior oblique fields



LOWER THIRD OESOPHAGUS

PHASE I

L shaped field dimensions:
Length- length of the lesion & need to cover celiac nodes
(L1 lower border)
Width- cover medial two thirds of the diaphragm on left, vertebral transverse process on right

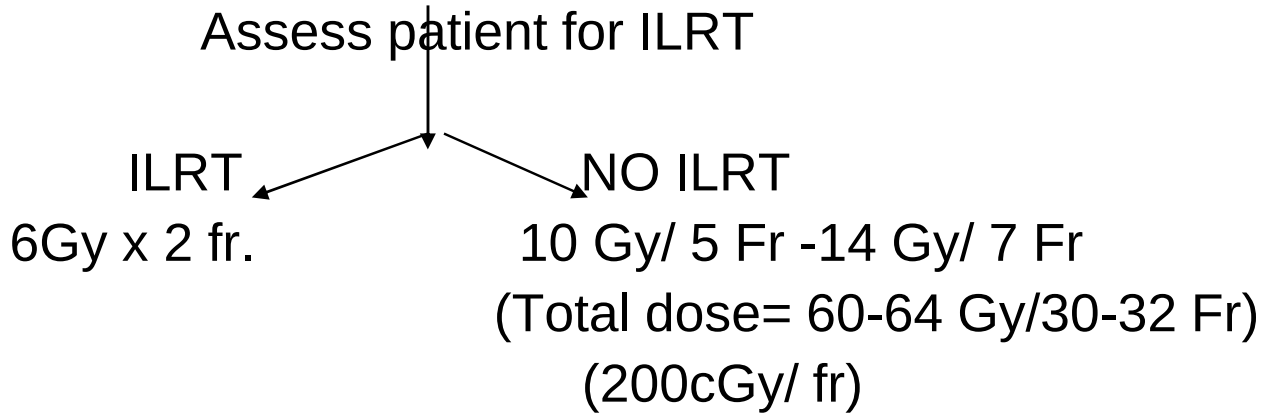
PHASE II

Anterior & two posterior oblique fields.
Gantry angle 115 to 120 & wedge 15 to 30

Dose prescription protocol

Definitive Radiotherapy:

- Only Radiotherapy- Phase I – 40 Gy/ 20 Fr
  Phase II – 10 Gy/ 5 Fr



PALLIATIVE RADIOTHERAPY

Ext RT 20 Gy/5 Fr or 30Gy/10Fr
Followed by ILRT 8 Gy x2 Fr
OR
ILRT 8 Gy x2 Fr Followed by
Ext RT 20 Gy/5 Fr or 30Gy/10Fr

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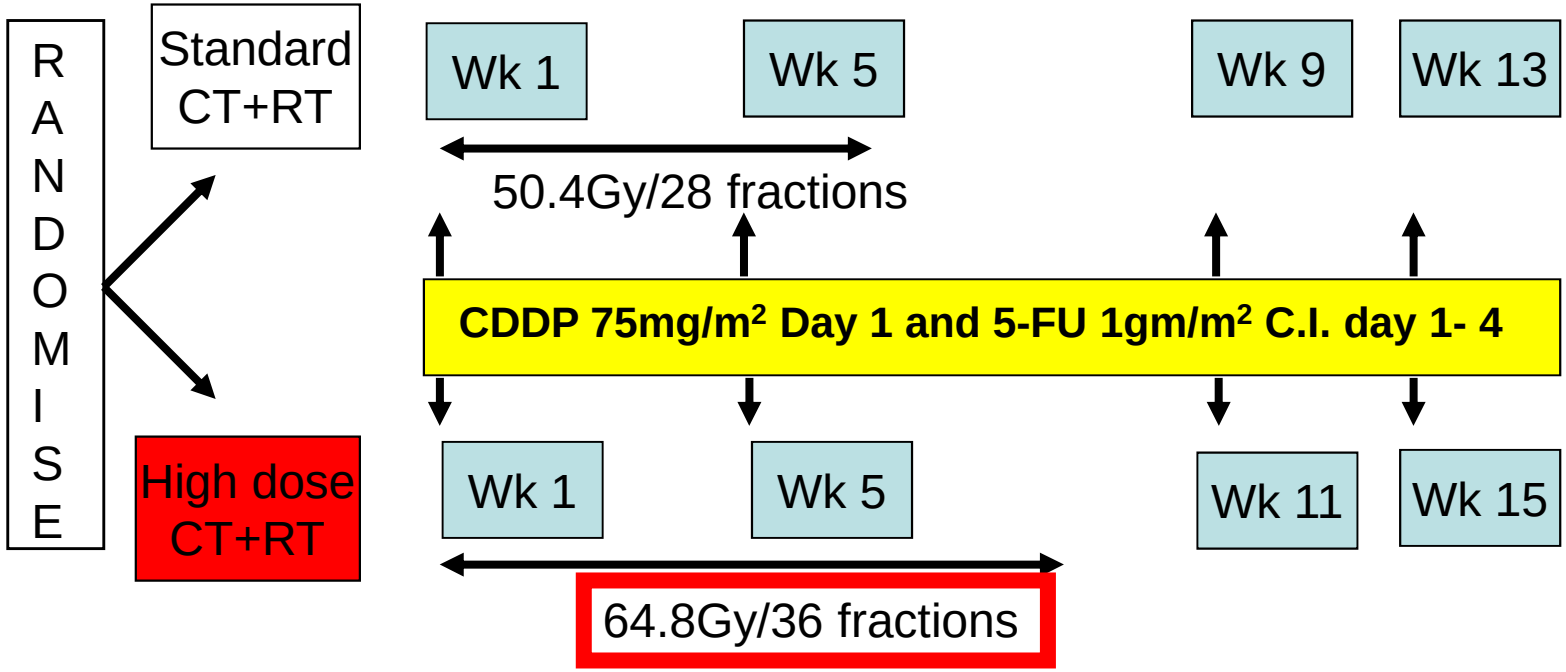
High dose vs standard dose concurrent chemo-RT Intergroup 0123 trial: (n=236)



High dose vs standard dose :

- **Treatment deaths 10% vs 2%**
  - **Median OS 13mo vs 18.1mo, p= NS**
- **2-year survival (31% *v* 40%).**
- **Cumulative inc. of local failure AT 2Yrs(High Vs Std) :-56%Vs52 %(.71)**

Minsky BD et al. JCO 2002;20:1167-1174

STANDARD RADIATION DOSE FOR PTS TREATED WITH CONC 5 FU+CDDP=50.4 Gy

a4

IT IS THE FOLLOW UP OF RTOG 85-01 TRIAL.
IT IS THE COMPARISION OF 50.4 VS 64.8 G(!.8 VS 2GY0,(5 CM MARGIN IN 50.4 vS 30GY WHOLE ESO FOLLOWED BY 5CM MARGIN UP TO 50GY)
CYCLE 3 STARTED 4 WKS AFTER
CYCLE 3 AND 4 AT 4 WKS INTERVAL THAN 3 WKS.

NO DIFFERENCE IN MEDIAN SURVIVAL ,2YRS SURVIVAL RATE BUT INCREASED TREATMENT RELATED DEATHS.

acer, 07/09/2009

BRACHY THERAPY

AMERICAN BRACHYTHERAPY SOCIETY RECOMMENDATION

- Should be limited to tumor less than 10cm
- Dose;- HDR-5Gy/# X 2,1#/Week
- LDR-20Gy single fraction
- For Palliation:-HDR-10-24 Gy in 2#
  -LDR -20-25Gy in single #
- Dose Prescription:- 1cm from midsource
- Recommended Active Length:-Visible mucosal tumor with 1-2 cm proximal and distal margin.
- Timing:- 2 to 3 weeks after completion of EBRT
- Concurrent Chemotherapy and Brachytherapy not recommended.
- Contraindication:-Tracheobronchial inv,Cervical esophagus location,stenosis that can not be bypassed.

ADDITION OF BRACHYTHERAPY IN CURATIVE APPROACH TO ESOPHAGEAL CANCER DOES NOT APPEAR TO SIGNIFICANTLY IMPROVE SURVIVLAL IN COMBINED EBRT/CT RT

Chemotherapeutic options

- 5FU-20%
- CDDP-21%
- Methotrexate-18%
- CDDP+5FU-35%
- CDDP+5FU +IFNa-50%
- Paclitaxel+CDDP-52%
- Irinotecan+CDDP-57%

a1

TREATMENT OUTCOME

- **Surgical resection is the standard treatment for operable esophageal cancer ie Stages I, II and most cases of III**
- ***Local failure after surgery:-12% to 67%(Mei et al,Gignoux et al)***
- **5 Yrs survival with surgery:- 12-20%**
- **Median survival is 15 to 18 months.**
- **Upper & middle third, SCC - LR > Distant.**
- **Lower third, AC – Distant recurrences.**

Table 2. Five-Year Survival Rates for Esophageal Carcinoma, According to the Tumor–Node–Metastasis Classification.*

Stage	Tumor	Node	Metastasis	5-Yr Survival
				%
0	Tis	N0	M0	>95
I	T1	N0	M0	50–80
IIA	T2-3	N0	M0	30–40
IIB	T1-2	N1	M0	10–30
III	T3 T4	N1 Any N	M0 M0	10–15
IVA	Any T	Any N	M1a	<5
IVB	Any T	Any N	M1b	<1

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a1 acer, 06/09/2009

IS SURGERY ENOUGH FOR OPERABLE CA ESOPHAGUS

- STAGE I-III :-SURGERY IS THE MAIN STAY OF TREATMENT
- LOCOREGIONAL FAILURE:-12 TO 67%

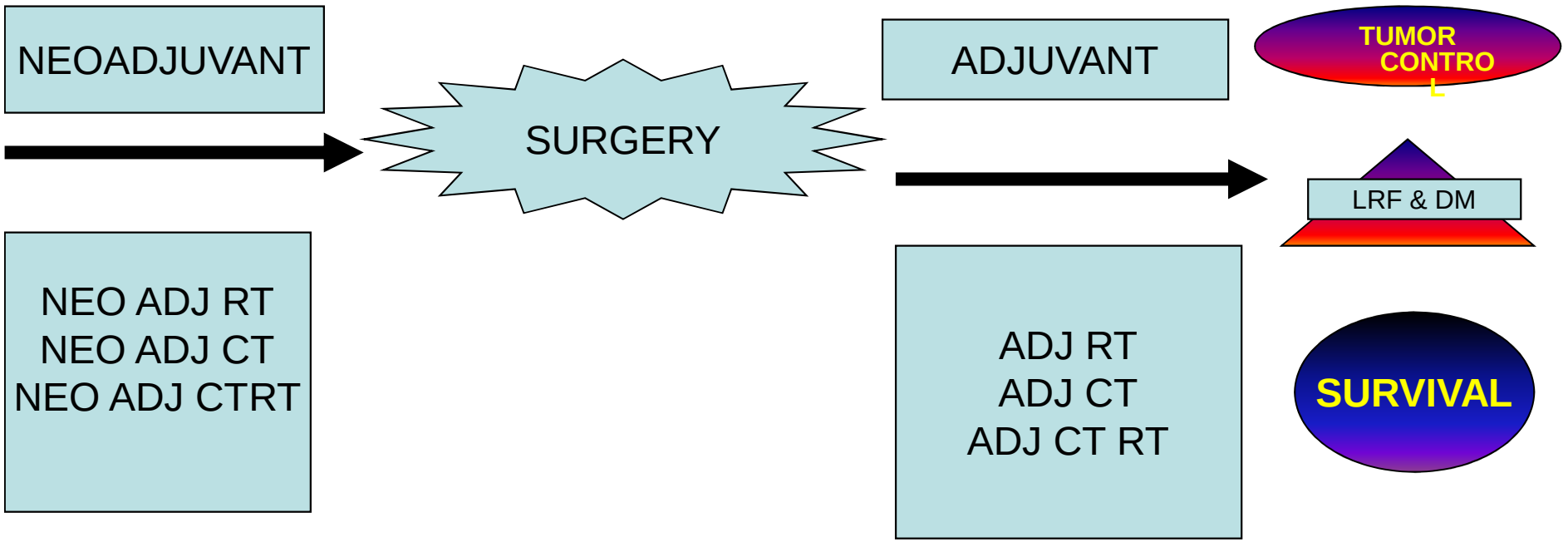
Authors	Patients	Patient (Surg)	Median Survival	2 Yrs Survival	3Yrs Survival
Walsh et al	110	55	11	26	6
Urba et al	100	50	18	NA	15
Bosset et al	282	139	19	40	35
Kelsen et al	440	227	16	37	23
MRC	802	402	13	34	NA

Cause of Failure and poor survival:-(RESECTABILITY,MICROMETASTASIS)

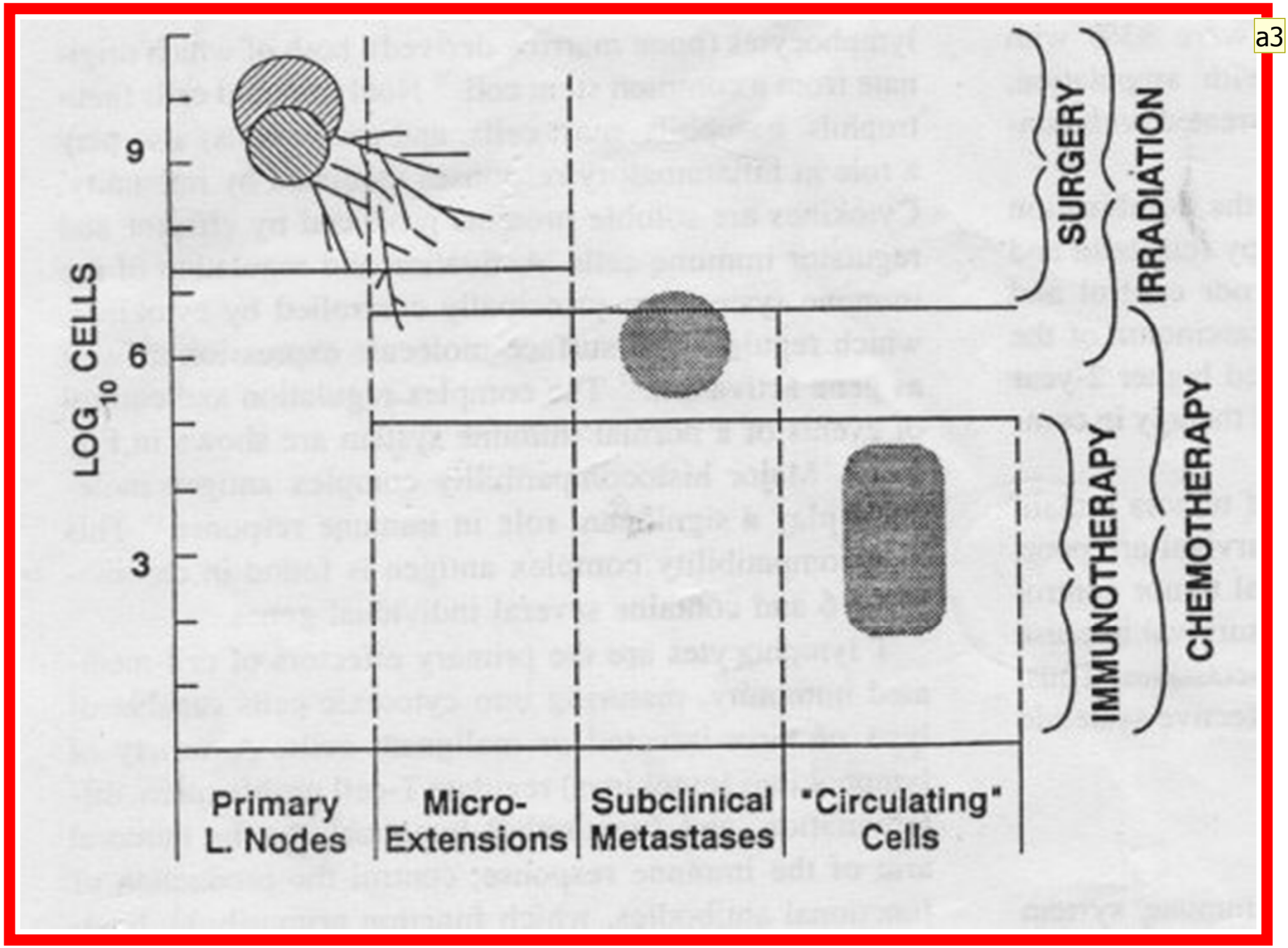
The proximity of vital mediastinal structures often compromises the resection.

Micrometastasis at the time of initial diagnosis

HOW TO IMPROVE THE LOCOREGIONAL CONTROL AND SURVIVAL IN OPERABLE CA.ESOPHAGUS



Radiotherapy :- For locoregional control
Chemotherapy :- For both local and systemic control


a3
LOG10 CELLS
9
6
3
SURGERY
IRRADIATION
IMMUNOTHERAPY
CHEMOTHERAPY
Primary L. Nodes
Micro-Extensions
Subclinical Metastases
"Circulating" Cells

a3

10(9):-1cm
10(10):-10gm
10(8):-1mm
10(12):-1Kg cross the body burden
Gross tumor surgry/rt
Surgery:-Peripheral failure,RT:-Periferal failure
acer, 07/09/2009

PREOPERATIVE RADIATION IN OPERABLE CA ESOPHAGUS

- **WHY Preoperative Radiation?**
  - Allows for tumor downstaging → R0 resection
  - Sterilizing nodal basin.
  - Decreases the possibility of intraoperative spillage.
  - Avoidance of surgery in rapidly progressive disease.

Neoadjuvant Radiotherapy Randomized Trials

Study	Patient	Dose of RT	Resectability	Local Failure	Median survival mo	5-year survival (%)	*p* Value
Launois (1981	RT + S 62 S 47	40 Gy	76 70	NR NR	10 12	9.5 11.5	NS
Gignoux (EORTC) (1988)	RT + S 115 S 114	33 Gy	47 58	46 67	48 45	10 8	NS
Wang (1989)	RT + S 104 S 102	40 Gy	93 85	13 12	NA NA	35 30	NS
Arnott (1992)	RT + S 90 S 86	20 Gy	NA NA	NR NR	8 8	9 17	NS
Huang	RT + S S 106	40 Gy	92 90	NR NR	11 22	46 25	Statistical analysis was not done

a5

5 RANDOMISED TRIAL REPORTED.
NO DIFFERENCE IN RESECTION RATE.
ONLY 2 SERIES REPORTED THE LOCAL FAILURE RATE.rEPORT OF gIGNOUX ET AL MENTIONED SIGNIFICANT LOWER LOCAL FAILURE RATE IN PT WHO RECIEVED PRE OP RT.
acer, 07/09/2009

a6

ONLY 2 STUDY REPORTED LOCAL FAILURE RATE.OUT OF WHICH ONE STUDY FAVOURS THE DECREASE IN LOCAL FAILURE(GIGNOUX) AND ANOTHER STUDY NO DIFFERENCE.
tHERE WAS NO DIFFERENCE IN MEDIAN SURVIVAL.
ONE STUDY FAVOURED INCREASE IN 5 YR SURVIVAL BUT THE STATISTICAL ANALYSIS WAS NOT MENTIONED.
tHE DOSE OF RADIATION USED ALSO NOT UNIFORM.aDEQUATE INTERVAL BETWEEN RT VS SURGERY WAS NOT ALLOWED(ATLEAST 4-7 WKS
acer, 07/09/2009

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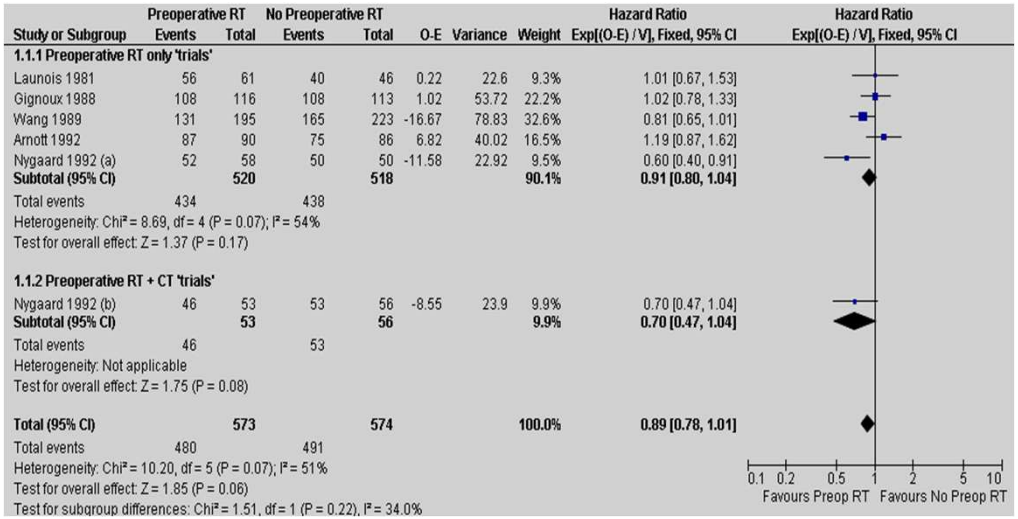
Preoperative RT in potentially resectable esophageal cancer- Metaanalysis(MRC+OCCG-1995-98)

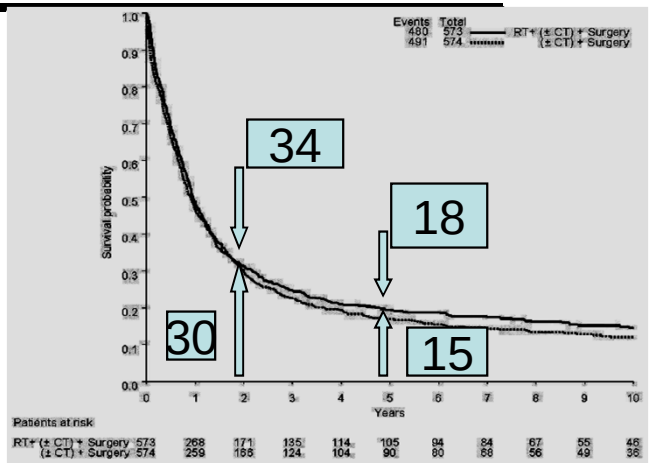


Study or Subgroup	Preoperative RT Events	Total	No Preoperative RT Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.1.1 Preoperative RT only 'trials'								
Launois 1981	56	61	40	46	0.22	22.6	9.3%	1.01 [0.67, 1.53]
Gignoux 1988	108	116	108	113	1.02	53.72	22.2%	1.02 [0.78, 1.33]
Wang 1989	131	195	165	223	-16.67	78.83	32.6%	0.81 [0.65, 1.01]
Arnott 1992	87	90	75	86	6.82	40.02	16.5%	1.19 [0.87, 1.62]
Nygaard 1992 (a)	52	58	50	50	-11.58	22.92	9.5%	0.60 [0.40, 0.91]
Subtotal (95% CI)		**520**		**518**			**90.1%**	**0.91 [0.80, 1.04]**
Total events	434		438					
Heterogeneity: Chi² = 8.69, df = 4 (P = 0.07); I² = 54%								
Test for overall effect: Z = 1.37 (P = 0.17)								
1.1.2 Preoperative RT + CT 'trials'								
Nygaard 1992 (b)	46	53	53	56	-8.55	23.9	9.9%	0.70 [0.47, 1.04]
Subtotal (95% CI)		**53**		**56**			**9.9%**	**0.70 [0.47, 1.04]**
Total events	46		53					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.75 (P = 0.08)								
Total (95% CI)		**573**		**574**			**100.0%**	**0.89 [0.78, 1.01]**
Total events	480		491					
Heterogeneity: Chi² = 10.20, df = 5 (P = 0.07); I² = 51%								
Test for overall effect: Z = 1.85 (P = 0.06)								
Test for subgroup differences: Chi² = 1.51, df = 1 (P = 0.22), I² = 34.0%								

Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI

0.1 0.2 0.5 1 2 5 10

Favours Preop RT Favours No Preop RT



1147 patients from 5 RCTS(Pre op RT+S Vs S)

Moderate benefit to the use of preoperative RT

- At a Median follow up 9Yrs the hazard ratio 0.89(p=0.06)
- 11% reduction in the risk of death
- At 2 years, absolute survival benefit of 4% and 5 yrs 3%

Statistically No Survival Advantages in preop RT+S Vs S alone in potentially resectable esophageal Cancer(**p = 0.06)**

Arnott JS et al., Int J Radiat Oncol Biol Phys 41:579, 1998

Slide 20

a7 acer, 07/09/2009

WHAT IS THE EVIDENCE-PRE OP RADIATION

- PREOPERATIVE RADIATION DOES NOT IMPROVE RESECTABILITY,DOES NOT SIGNIFICANTLY DECREASE LOCAL FAILURE RATE OR IMPROVE SURVIVAL

ESMO RECOMMENDATION:-Preoperative radiation does not add any survival benefit to surgery alone.This treatment is not recommended (II A)

/el Type of Evidence

/els of Evidence and Grade of Recommendations[13,14]

I		Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power).
II		Evidence obtained from at least one well-designed experimental study. Randomized trials with high false-positive and/or-negative errors (low power).
III		Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled, single group, pre-post, cohort, and time or matched case-control series.
IV		Evidence from well-designed, nonexperimental studies such as comparative and correlational descriptive and case studies.
V		Evidence from case reports.
Grade		Grade of Recommendation
A		There is evidence of type I or consistent findings from multiple studies of type II, III, or IV.
B		There is evidence of type II, III, or IV and findings are generally consistent.
C		There is evidence of type II, III, or IV but findings are inconsistent.
		There is little or no systematic empirical evidence.

PRE OP CT IN OPERABLE CA. ESOPHAGUS

Rationale

- Downstaging
- Eradication of micrometastasis
- Pathologic evaluation of treatment response with possible selection of adjuvant therapy

Disadvantages:

- Development of drug resistant clones.
- Delay in definitive therapy for nonresponders
- Delay in definitive treatment:- Poor nutrition.

(50% of patients do not respond to chemotherapy)

a8

Neo adjuvant Chemotherapy
Resection rate,Local Recurrence,Overall survival

STUDY	NO.OF PTS.	RESECTION RATE	LOCAL /DIST RECURRENCE	3 YR SURVIVAL
INT 0113	CT+S 213 S 227	62% 59%	32% 41% 31% 50%	23% 26%
MRCOCWG	CT+S 400 S 402	60% 54%		32% 25%
MAGIC	CT+S 250 S 253	66% 69%		5 yrs 36% 23%

a8 There is no difference in resection rate,local recurrence/distant failure and 3 yr survival.
3 randomised trial INTer group 0013 having 440 pts,
Medical research council oesophageal cancer working group 802 pts and Magic trial 503 pts.In MRCOWG,curative resection could reach statistically significant.There was survival advantages in MRCOCWG and MAGIC Trial.
acer, 07/09/2009

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Neoadjuvant chemotherapy
Randomized Trials

Study (year)	Patients	Chemotherapy	pCR (%)	Median Survival (mo)	5-year Survival (%)	*P* value
Roth (1988)	C + S 19	Neo: C,Vin,	NA	9	NA	NS
	S 20	Bleo Adjuvant: C, Vin		9	NA	
Nygaard (1992)	C + S 0	C, Bleo	NA	8	3-y 3	NS
	S 41			8	9	
Ancona (2001)	C + S 47	CF X 2 or 3	13%	25	34	NS
	S 47			24	22	
Schlag (1992)	C + S 22	CF X 3	NA	10	NA	NS
	S 24			10		
INT 0113 (1998)	C + S 213	Neo CF X 3	2.5%	14.9	3 y 26	NS
	S 227	Adj CF X 2		16.1	23	
MRC (2002)	C + S 400	CF X 2	4%	16.8	2 y 43	*P* =0.004
	S 402			13.3	34	

Slide 25

a9 In MRC trial though there was sttistically improved overall survival but the median duration of follow up was short.
acer, 07/09/2009

Neoadjuvant chemotherapy Meta-analysis

- There were eleven randomised trials involving 2019 patients. Eight trials (1729 patients) reported sufficient detail on survival to be included in a meta-analysis for the primary outcome.

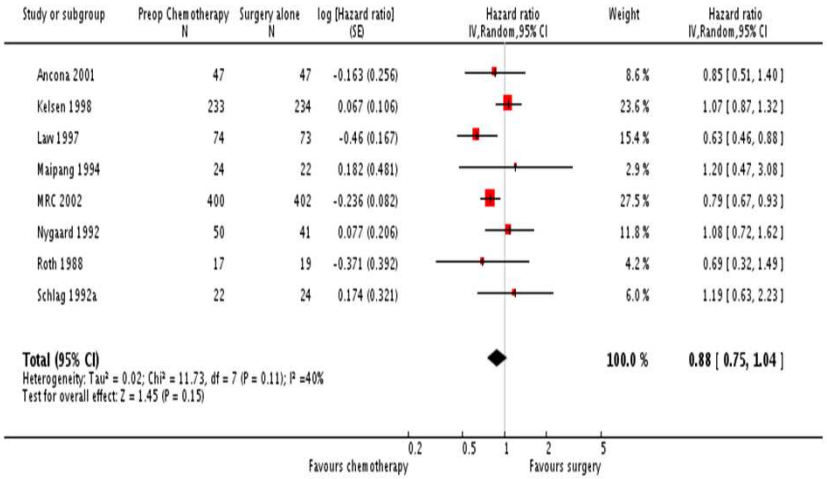
- There was some evidence to suggest that preoperative chemotherapy **improves survival, but this was inconclusive** (HR 0.88; 95% CI 0.75 to 1.04).

- **No difference between overall rate of resections** (RR 0.96, 95% CI 0.92 to 1.01) or the **rate of complete resections** (R0) (RR 1.05; 95% CI 0.97 to 1.15) between the preoperative chemotherapy arm and surgery alone. \

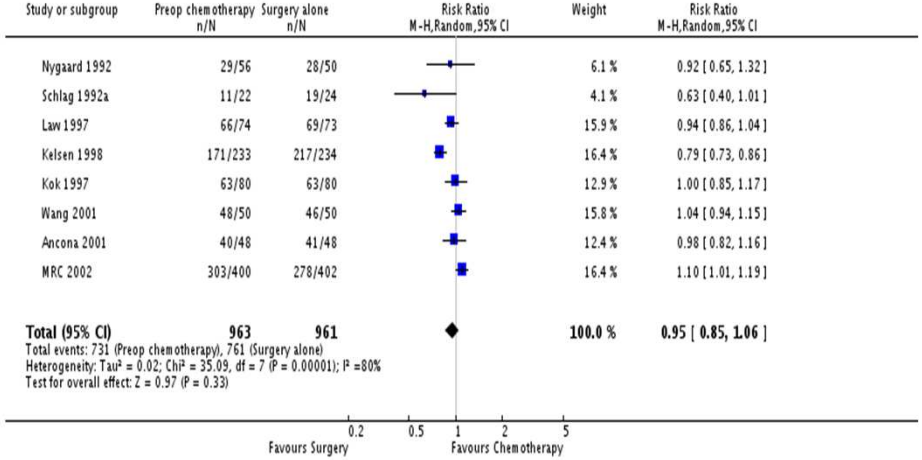
- No differenceof tumour recurrence (RR 0.81, 95% CI 0.54 to 1.22) or non-fatal complication rates (RR 0.90; 95% CI 0.76 to 1.06).

- Trials reported risks of toxicity with chemotherapy that ranged from 11% to 90%.

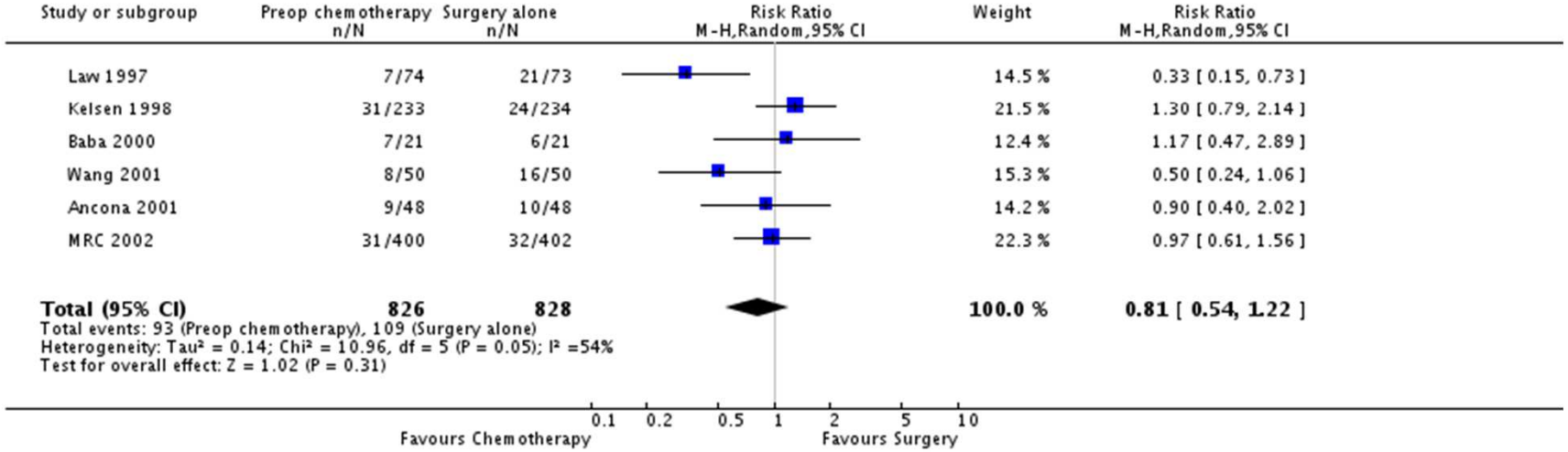
Review: Preoperative chemotherapy for resectable thoracic esophageal cancer
Comparison: 1 Survival
Outcome: 1 Hazard ratio



Review: Preoperative chemotherapy for resectable thoracic esophageal cancer
Comparison: 2 Rate of resection
Outcome: 1 All resections



Review: Preoperative chemotherapy for resectable thoracic esophageal cancer
Comparison: 3 Tumour recurrence
Outcome: 1 Local-regional recurrence



WHAT IS THE EVIDENCE:-PRE OP CHEMOTHERAPY

- No improvement in curative resection rate
- No Difference in Local Recurrence rate
- No difference in Overall survival

ESMO RECOMMENDATION:-Evidence for clinical benefit from preoperative chemotherapy exists for adenocarcinoma. Patients with adenocarcinomas of the lower esophagus/GE junction may be managed with pre- and postop. Chemotherapy. (I B)

Preoperative chemoradiation - rationale

- **Combination of CT + RT**
  - Downstage the disease:- Enhances resectability
  - Drugs enhances radiosensitivity
  - Reduced dissemination of tumor cells during surgery :- Hence reduces distant metastasis
  - Remove microscopic persistant disease after CT RT
- **Used as a planned approach in clinically resectable tumors**
  - Agents
    - 5-FU, CDDP
    - more recently, paclitaxel& docetaxel
  - Radiation
    - conventionally (30 – 50Gy @ 1.8 Gy to 2 Gy / #)
    - hyperfractionated or accelerated – 1.5Gy BID (45Gy)
- **Pathological CR rates** ~ 25% (16 –56%)
- **Survival** – median: 12 – 25 months; 5 year: 16 – 55%

a10

Pre op.CT+RT+S Vs S

AUTHOR	MEDIAN FOLLOW UP	REGIMEN	NO OF PTS	Ro resection/ Dist Met		PATH CR	LOCOREG FAILURE	3-Yr Survival	SURVIVAL DIFF
Urba et al	8.2	5fu+cddp+Vbl+RT+S S	50 50	90 90	60% 65%	28 -	19% 42% P=0.02	30 16	p=0.15
Boset et al	4.6	Cddp+RT+S S	143 138	81 69		26 ---		34 36	NS
Walsh et al	1.5	5fu+cddp+RT+S S	58 58	NR NR		25		32 6	P+0.01
Burmeister et al	5.4	5fu+cddp+RT+S S	128 128	80 59		16 ---		35 30	NS
Tepper et al	6.0	5fu+cddp+RT+S S	30 26	NR NR		33	13 15	39 16	P=0.008

Slide 30

a10 5 randomised trial compared ctrts vs s.Path Complete response was seen in 25 to 28%.3 yr survival in treatment arm was 30-40% .Study by Urba et al revealed stastistically better local control in CTRTS arm.3 yrs Survival advantages were seen in study by Walsh and Tepper et al.The criticism for low survival in surgery arm may be due to advanced disease.The above 2 trials have small no of patients,There was no difference in resection rate except Boset study.No difference in dist failure rate.

acer, 08/09/2009

Preoperative chemo-radiation Metaanalysis - 1

- Preoperative chemo-radiation improved **2-year survival** by **6.4%** (nonsignificant; 95% CI, -1.2% to 14%)
- **Treatment related mortality increased by 3.4%** (95% CI, -0.1% to 7.3%)
- Recommendation is to use in the context of a clinical trial.

Kaklamanos IG et al. Ann Surg Oncol. 2003;10:754-61

WHAT IS THE EVIDENCE -Pre op CT RT +S Vs S

- Complete pathological response:-25-28%.
- 2/3rd patients disease down staged.
- No survival advantages except study done by walsh et al and Tepper et al. (But the number is small)
- Nonsignificant trend towards increased treatment related mortality was seen in neoadj.arm.

BECAUSE OF TOXICITY AND ONGOING UNCERTAINITY ABOUT BENEFIT ASSOCIATED WITH PRE OP COMBINED CTRT,IT SHOULD BE USED CAUTIOUSLY AND PRIORITY SHOULD BE GIVEN TO ENROLLING THE PATIENT IN CLINICAL TRIAL

ESMO RECOMMENDATION:-Although meta-analyses and one recent phase III trial suggested that preoperative chemoradiation confers a survival benefit,, it is not clear which patients (stage, tumor location, histology) will most benefit from this preoperative treatment [I, B]

POST OP RT

Rationale

Detail pathological Report available

Can treat areas of risk, sparing normal radiosensitive structure.

Pathological T1N0 or Metastatic lesion can be spared for Radiation.

Bulky Disease,Gross Residual disease,Proved microscopic residual/+ve Margin

Disadvantages

Limited tolerance following gastric pull up and irradiation of a devascularised tumor bed

Indications for Post-operative RT

- Standard Indications
  - Positive Margins
  - Gross Residual Disease
- Less Clear
  - + LN
  - + ECE on adenopathy

a13

Post operative RT after curative resection

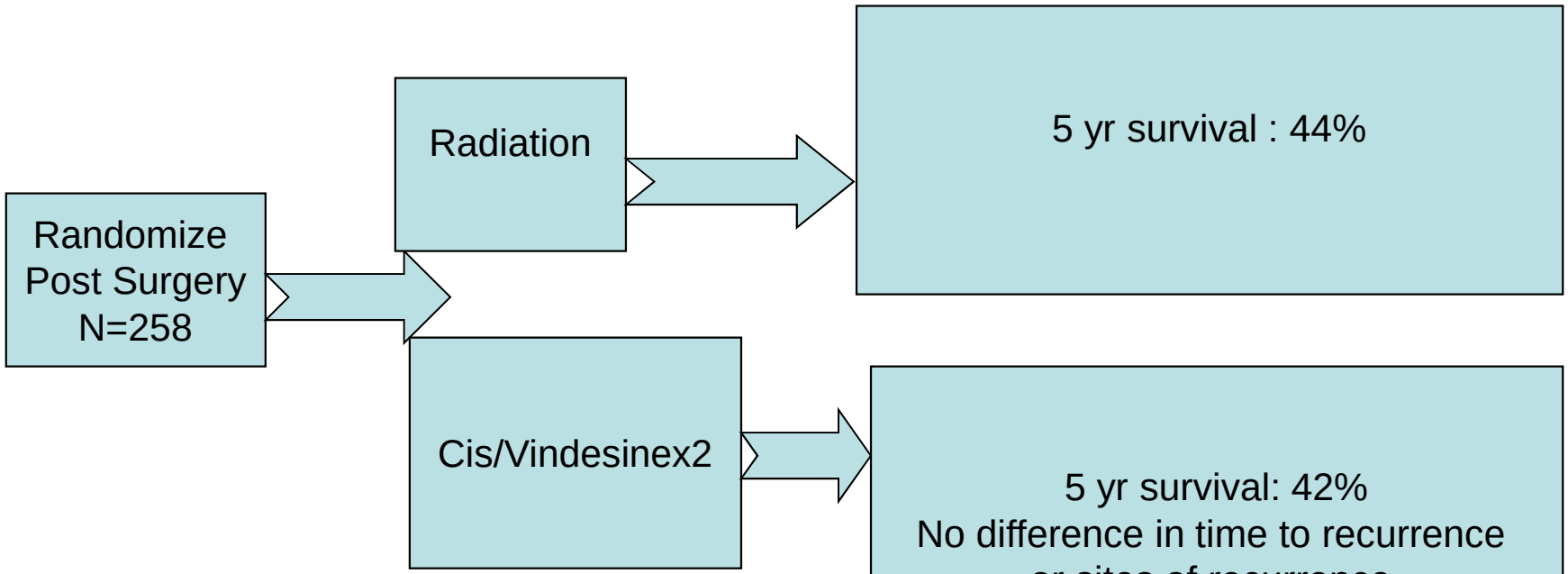
Trial	*No*	*RT dose/#*	*Local recc % PORT vs SX*	*Median Surv PORT VS Sx*	*Overall Surv. PORT vs Sx*
Teniere '91 (French)	**221**	45-55Gy/ 25-30#	15% vs 30% overall **10% vs 35% for pN0, p<0.02**	18 vs 18 mo	21% vs 19% at 5 years p=NS
Zieren '95 (German)	**68**	55.8Gy/31 #	48.5% vs 65%	14 vs 13 mo	22% vs 20% at 3 years
Xiao ZF '03 (Chinese)	**495**	50-60Gy/ 25-30#	16.2% vs 25.9% (P<0.05)	-	**34.1 vs 17.6 for N+ (p=0.06)**
Fok '91 (Hong Kong)	**60 (C)** **60 (P)**	49-52.5Gy/ 14-15#	15% vs 36% (scc) (p=0.02)	8.7 Vs 15.2 mo (p=0.02)	**10% vs 13%, p=N.S**

Slide 35

a13 In the study by F0k the dose per fraction was 3.5 Gy.Study by Tenier,Xiao etal,Fok et al there was decrease local recurrence in PORT.There was no change in overall survival.

acer, 08/09/2009

Adjuvant Radiation Vs chemotherapy



Radiotherapy (50 Gy)
2 courses of chemotherapy consisting of cisplatin (50 mg/m2) and vindesine (3 mg/m2) following curative resection

Chest 1993 Jul;104(1):203-7

WHAT IS THE EVIDENCE Post operative RT

- PORT after **curative resections decreases local recurrence**
- Do not improve over all survival
- Therefore PORT may be offered for **positive surgical margins, N+ disease** or perhaps after **non-curative resections**

What about post-op chemotherapy alone?

- 2 randomized Japanese trials
  - **Ando N** et al. J of Thoracic and Cardiovascular Surgery. *1997; 114;204-205*
    - Randomized study; 205 patients
    - S + C vs. S 2 cycles alone
    - Chemo – of Cisplatin (70 mg+ Vindesine ./m2)
    - **5 y OS S + C 48.1 % vs. S 44.9% (p = NS)**

  - **Ando N** et al. JCO. *Dec 2003; 21(24): 4592-4596*
    - Randomized study; 242 patients
    - Thoracic SCCA
    - S+C vs. S alone
    - Chemo – 2 cycles of Cisplatin (80 mg/m2) + 5 FU (800mg/m2/5 day infusion)
    - 5 y OS S+ CT 61 vs. 51 % (p=0.3

      a11
      a12

      - **5 y DFS 55% vs. 45% (p=0.04);**
      - 5 Yrs DFS in N –VE patients (S Vs S+CT) 77% vs. 82% (p=0.3)
      - 5 Yrs DFS in N + patients 35% vs. 53% (p=0.06)

    - Adjuvant CT may benefit in node +ve Pts

Slide 38

a11 acer, 08/09/2009

a12 2 randomied study by japanese group by same author Ando N et al.In all the study post op 2 cycles were given.In 1st study cdddp+vindesin and in 2nd study cddp+5 fu was tried.In both the study there was no difference in OS.But in cddp+5fu group,there is improved 5 yrs DFS in post op CT group.The 5 yr DFS was better in node +ve group not node _ve pts.
acer, 08/09/2009

(WHAT IS THE EVIDENCE S Vs S+ POST OP CT in operable Ca Esophagus)

POST OP CT DOES NOT IMPROVE OVERALL SURVIVAL EXCEPT DFS IN RO & N1 PT.

a14

Post operative CT+RT Vs S alone

Trial	*No*	*RT dose/# CT PROT*	*Loco reg recc % POCTRT vs SX*	*Median Surv PORT CT VS Sx*	*Overall Surv. POCTRT vs Sx*
Mc Donalad Trial	**556 20% GE JN. Adeno**	45Gy/25# 5 FU+LV	**19 Vs 29%**	36 vs 27 mo	50% vs 41% at 3 years **p=0.005**
Taiwan Study	**60 Th.Eso S.C.C**	40Gy+15 to 20Gy boost Conc Cddp- 4 Cycle Cddp+5 FU	40% vs 60%		70% vs 33.7% at 3 years
Canadian Study	**n=70 N1 Adeno/SCC**	50(36+14) Gy CT-ConcCT RT Cddp+5 FU	13% vs 35.%	DFS10.2 Vs 10.6 mo O.S 47.5 vs 14.1 mo	**48% Vs 0% at 5 Yrs**

Incidence of Gr IV toxicity(41 % Vs 32%).in Mc Donald Trial.

Slide 40

a14 3 randomised trial has evaluated the role of poct rt vs s alone.The goal of Mc Donald study was to evaluate the effect of post op rt ct in Ca esophagus.How ever 20% of patients had Ca lower end of Esophagus.There was decrease in local recurrence,increased median survival and overall survival.In Mc Donald study there was increased Gr IV toxicity.

acer, 08/09/2009

Macdonald Trial – Overall Survival

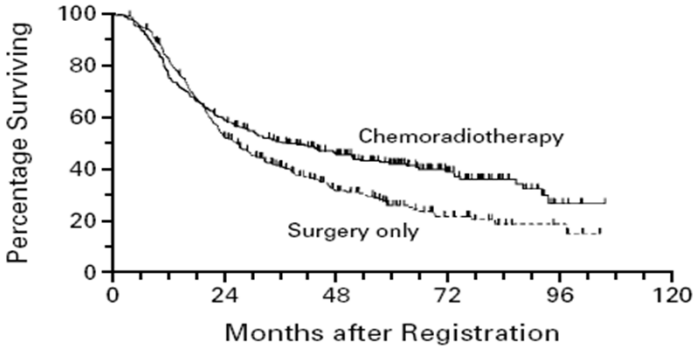


Figure 1. Overall Survival among All Eligible Patients, According to Treatment-Group Assignment.

Macdonald Trial – Relapse Free Survival

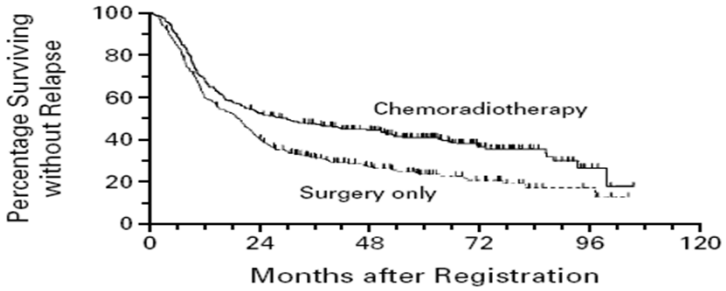
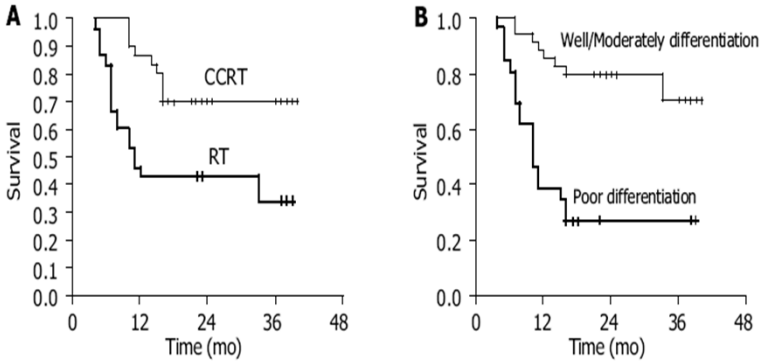


Figure 2. Relapse-free Survival among All Eligible Patients, According to Treatment-Group Assignments.

Taiwan Study - Results



Canadian Study – Overall Survival

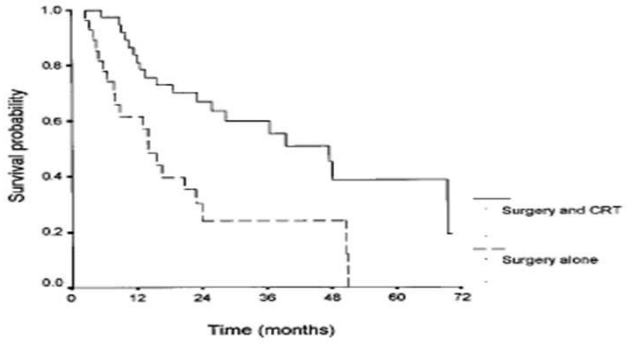


FIGURE 1. Overall survival Kaplan–Meier plot stratified by treatment received. CRT: adjuvant chemoradiation therapy.

Post operative CT+RT Vs S alone

Macdonald Trial - Conclusions

- **Add chemoRT for GE junction adenoCA**
  - **T3 or higher**
  - **+ LN**
  - **+ margins, + residual disease**
  - **? Selected T2 cases**

Taiwan Study - Conclusions

- **ChemoRT showed improved OS compared to RT alone in T3 or higher patients**

Canadian Trial - Conclusion

- **Benefit of ChemoRT in node + patients**

	No of Randomised Trial	Metaanalysis	Local Control	Survival
Pre op RT	5	1	No	No
Pre op CT	6	1	No	No except MRC Trial(G.E.Junction)
Preop CT RT	7	2	YES	Modest Improve in survival
Post op RT	4	0	YES	No
Post op CT	2	0	No	No
Post op CT RT	3	0	Yes	YES

INOPERABLE NON METASTATIC CA ESOPHAGUS

Radiation alone

Combination chemoradiation

RADIATION ALONE

AUTHOR	NO OF PTS	DOSE	2 YRS SURVIVAL	5 YRS SURVIVAL
Pearson	208	50Gy/4Wks	NA	17%
Beatty et al	344	>40Gy to > 50Gy	21%	0%
Schuchmann et al	127	<45Gy >45 Gy		0% 0%
Newaishy et al	444	50-55Gy/4 Wks	19%	9%
Okawa et al	96		NR	9%(I-20%,II-10%,III-3%,IV-0%)
Lederman et al	263		11%(yrs)	7%

Radiation Therapy Alone Inoperable Ca Esophagus

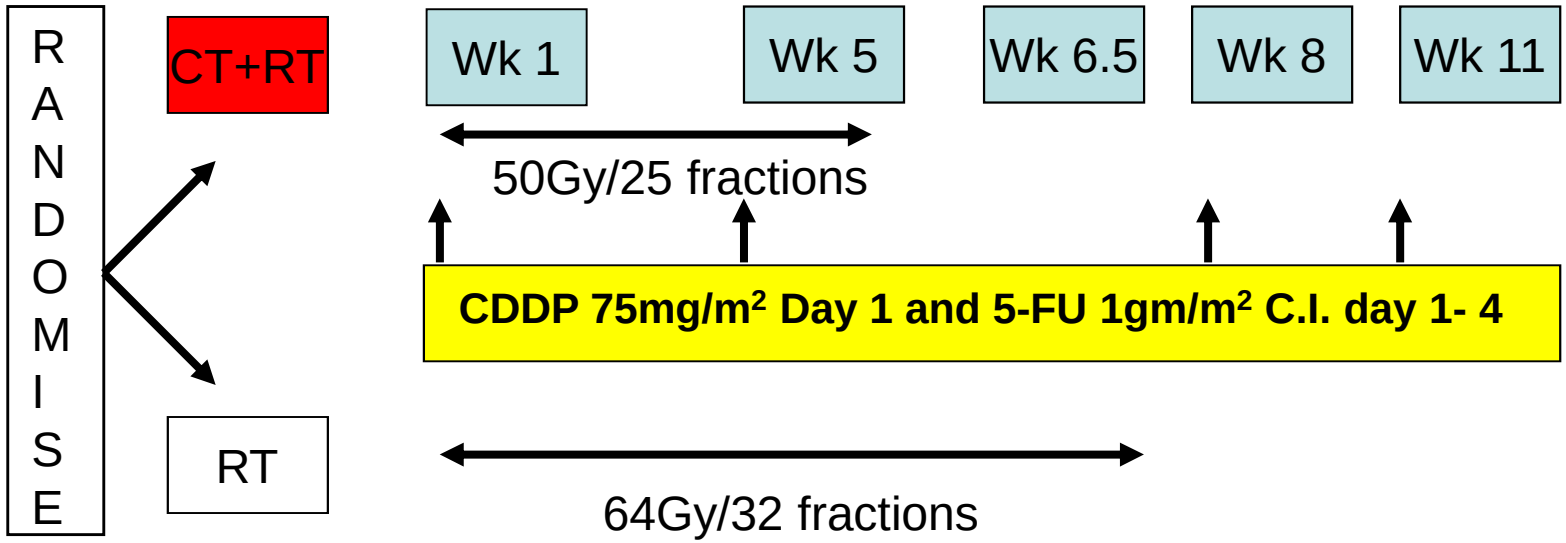
- Patients receiving radiation alone for inoperable esophageal cancer is palliative in vast majority of the cases having

MEDIAN SURVIVAL:-6 to 12 Months

&

5 YRS SURVIVAL RATE < 10%

Concurrent chemoradiation – Intergroup trial (RTOG 85-01) : n = 121 Landmark trial



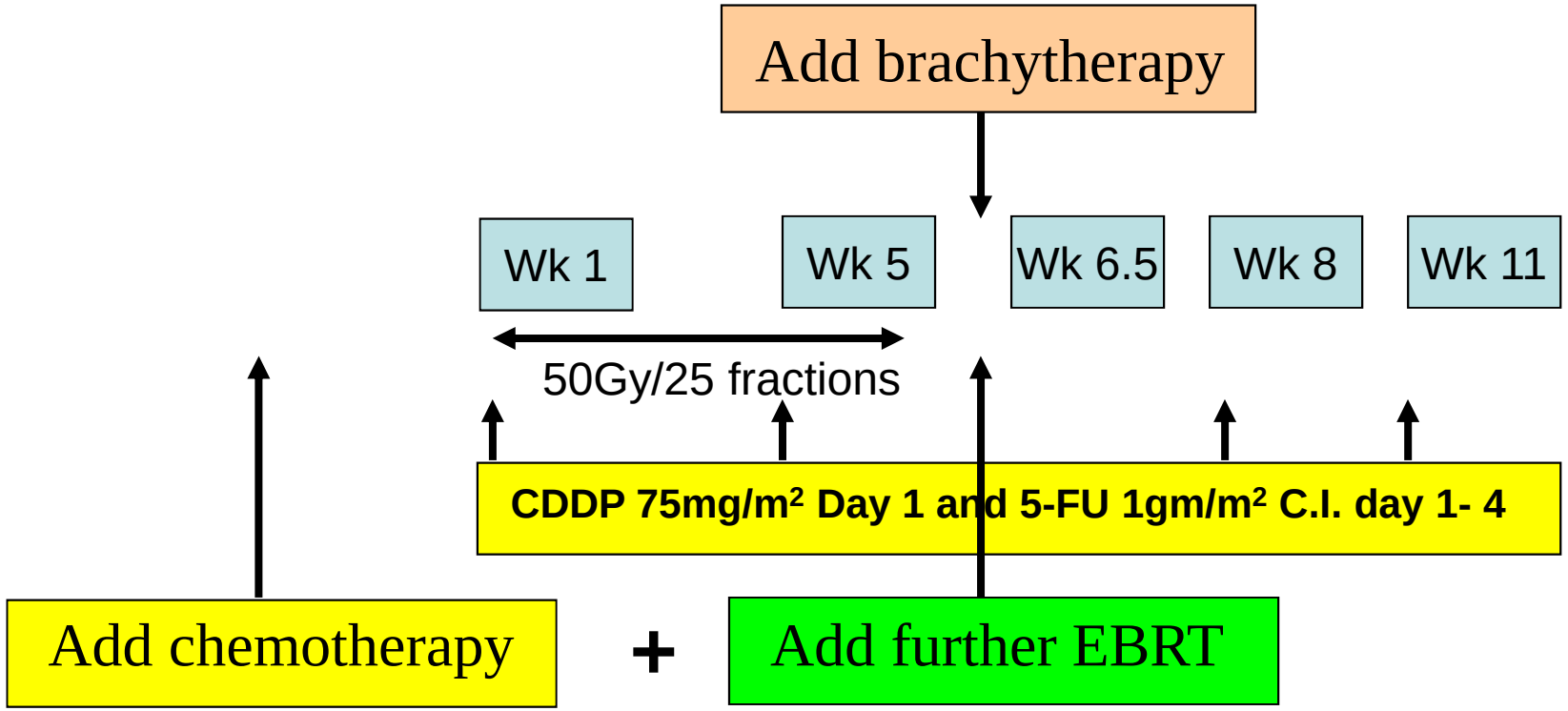
Herskovic A et al. NEJM 1992;326:1593-1598

	Comp-liance	*Gr III tox*	*Gr IV*	*Gr V*	*Local fail*	*Dist fail*	*Median and 5yr survival*
CT+RT (n=61)	**54%**	**44%**	**20%**	**3%**	**43%**	**22%**	**12.5 mo, 27%** p=.0001
RT (n=60)	**83%**	**25%**	**3%**	**0**	**64%**	**38%**	**8.9 mo, 0%**
P-value	**Sig**	**Sig**	**Sig**		**Sig**	**Sig**	**Sig**

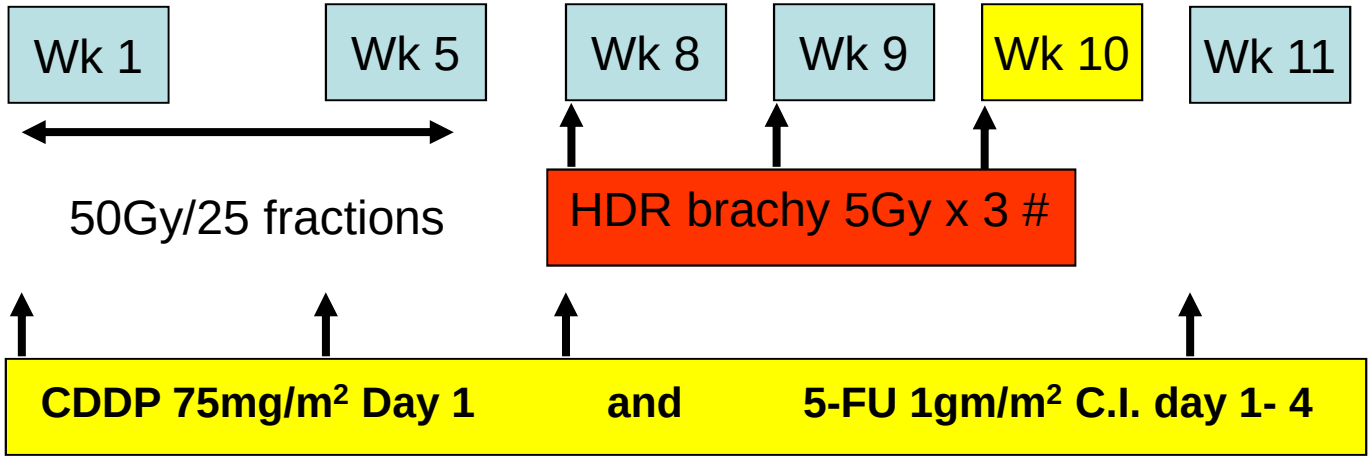
RTOG 8501 provided a convincing evidence of the superiority of chemoradiation.
Established chemoradiation as the conventional nonsurgical treatment for esophageal cancer.

a15 This is the RTOG 85-01 study ,which is a landmark trial where pts were treated with concurrent ct rt followed by ct vs rt alone.in this studIn this study there was improvement in local failure rate,median survival as well as 5 yrs survival.y

Concurrent chemoradiation – further intensification



External beam RT, concurrent CT and brachytherapy (RTOG 92-07) n=75(RTOG 85-01+Brachy)

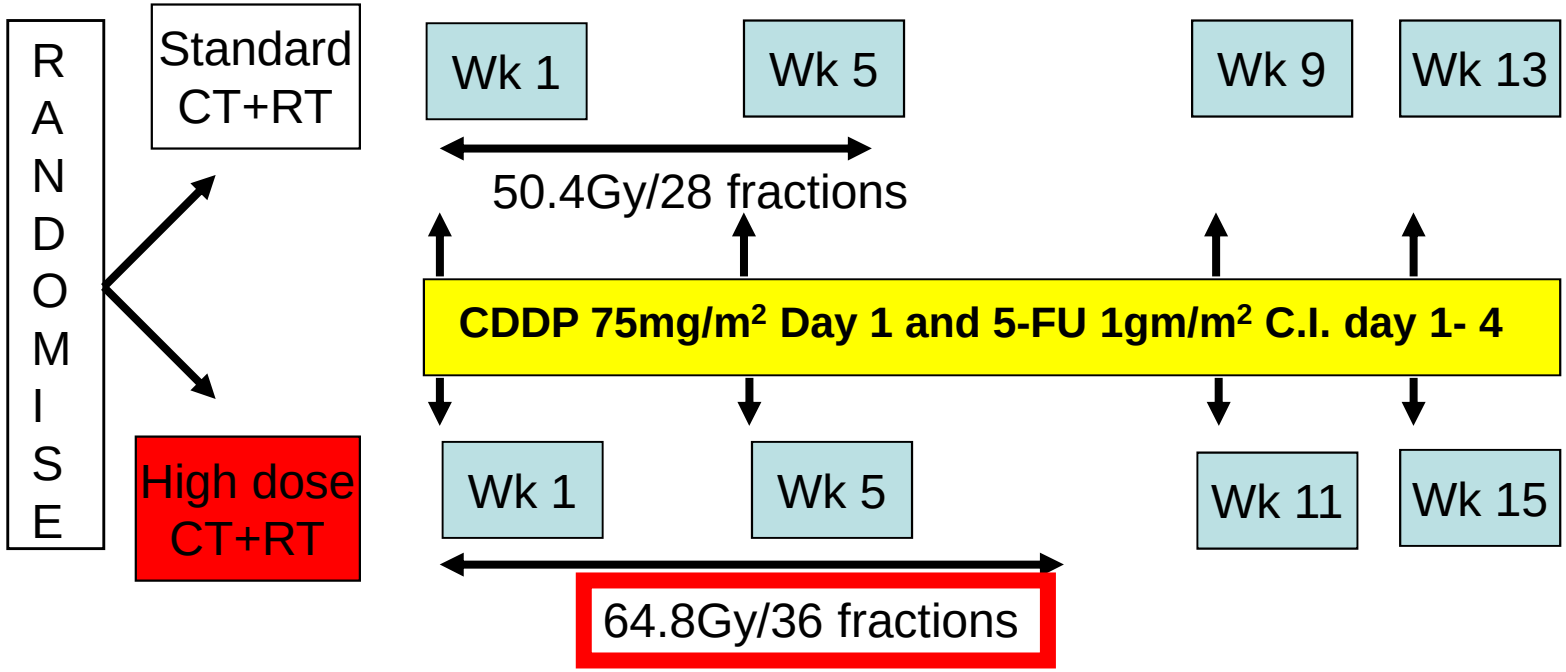


Toxicity and survival				
Grade III	***Grade IV***	***Grade V***	***Fistula***	***comp.resp***
58%	26%	8%	18%per Yr	73%

Due to toxicity it should be used with caution,BENEFIT IS UNCERTAIN

Gaspar LE et al. Int J Radiat Oncol Biol Phys 1997;37:593-599

High dose vs standard dose concurrent chemo-RT Intergroup 0123 trial: (n=218)

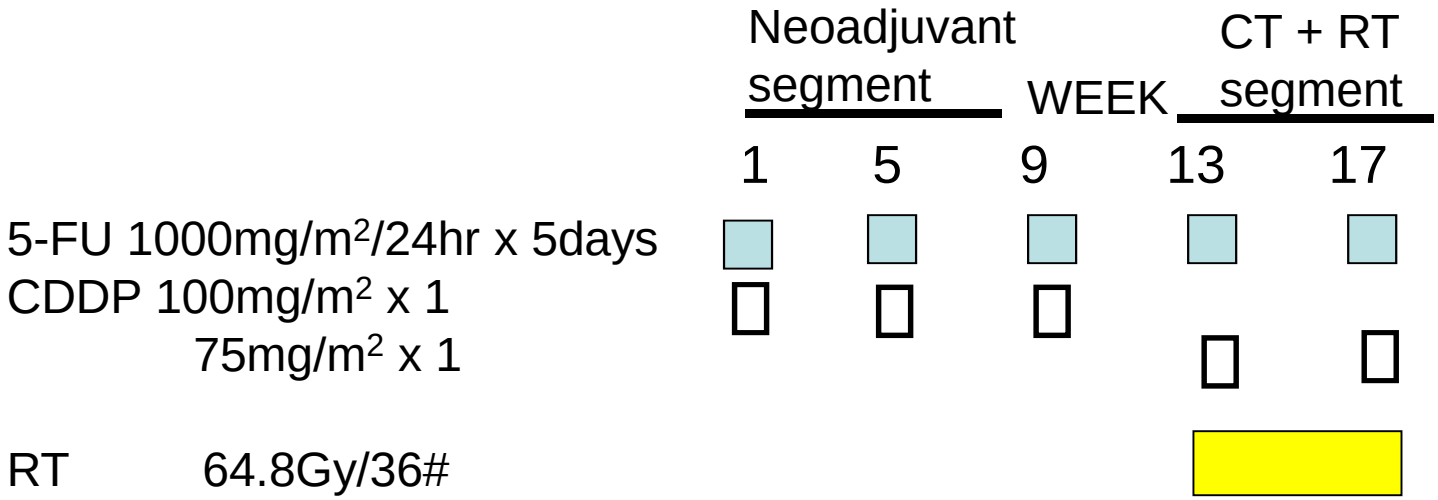


High dose vs standard dose :

- Treatment deaths 10% vs 2%
  - Median OS 13mo vs 18.1mo, p= NS
- **2-year survival (31% *v* 40%).**
- **Cumulative incidence of local failure(High Vs Std) :-56%Vs52 %**

Minsky BD et al. JCO 2002;20:1167-1174

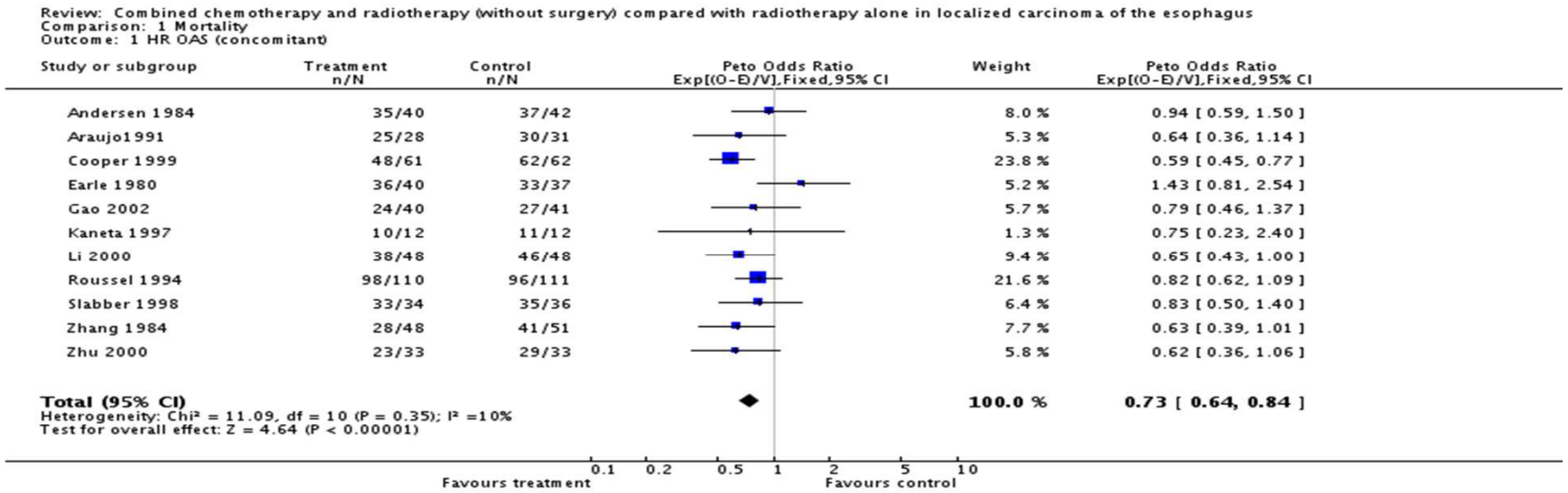
Neoadjuvant + concurrent chemo-RT Intergroup 0122 trial: (n=45)



Toxicity and survival				
Grade III	***Grade IV***	***Grade V***	***compliance***	***median OS***
39%	23%	13%	66%	20 months

Minsky BD et al. Int J Radiat Oncol Biol Phys 1999;43:517-523

Concurrent CT+RT- meta analysis - 11RCT



- With eleven concomitant RTCT studies.
- Concomitant RTCT provided significant reduction in mortality with a harms ratio (HR) of 0.73 (95% confidence interval (CI) 0.64 to 0.84).
- The absolute survival benefit for RTCT at 1yr and 2 yr was 9% (95% CI 5 to 12%) and 4% (95% CI 3 to 6%]) respectively.
- There was an absolute reduction of local recurrence rate of 12% (95% CI 3 to 22%)
- This was associated with a significant risk of severe and life-threatening toxicities

Cochrane Database of Systematic Reviews, Issue 3, 2009

Chemoradiation VS RADIATION

Based on the available data, when a non-operative approach is selected then concomitant RTCT is superior to RT alone for patients with localized esophageal cancer but with significant toxicities. In patients who are in good general condition, and the risk benefit has been thoroughly discussed with the patient, concomitant RTCT should be considered for the management of esophageal cancer compared with radiotherapy alone.

ESMO RECOMMENDATION:-For patients unable or unwilling to undergo surgery, combined chemoradiation is superior to radiotherapy alone [I, A].

LOCAL FAILURE & SURVIVAL APPEAR SIMILAR IN CHEMORADIATION VS SURGERY ARM IN INOPERABLE CA ESOPHAGUS

	RTOG 8501	MRC
LOCAL FAILURE	39-45%	31%
MEDIAN SURVIVAL	14-20 MO	13-16 MO
5 YR SURVIVAL	20-30%	20%

PREDICTOR OF RESPONSE TO CHEMORADIATION

- Radiation dose,5 FU/CDDP based regimen (Geh etal)
- Patient who achieved a pCR had improved survival(Borger et al)
- % decrease SVU in 18-FDG-PET-better response and survival(Blackstock etal)
- Absence of p53 and week bcl-X1- Higher response to Chemotherapy (Sarbia M et al)
- Pt with HIGH MVD(Micro vascular density had better survival(Kishi et al)
- Lymphocyte infiltration around the tumor –better survival(Morita et al).

Newer regimens

Table 4 — Trials of preoperative chemoradiation using paclitaxel-containing regimen

Reference	Number of patients	Radiotherapy dose	Induction chemotherapy	Chemotherapy with radiation	Resection rate	Complete response rate	Pathological complete remission ± minimal residual disease	Survival
Wright *et al.* [16]	40	58.5 Gy (tumour), 45 Gy to mediastinum	None	Cisplatin, 5-FU, paclitaxel	90%	39%		61% at 2 years
Adelstein *et al.* [17]	40	45 Gy (preoperative) + 24 Gy (post-op) if T3–4 or N1	None	Cisplatin, paclitaxel	95%	23%		30% at 3 years (projected)
Schnirer *et al.* [18]	10	45–50.4 Gy	N0	5-FU, paclitaxel	50%	20%	60% of patients undergoing surgery	–
Ajani *et al.* [19]	38	45 Gy	TCF	5-FU, cisplatin	92%	30%	71%	DFS and OS 72% and 63% at 3 years, 51% and 39% at 5 years
Safran *et al.* [20]	41	39.6 Gy	None	Cisplatin, paclitaxel weekly		29%		DFS and OS 40% and 42% at 2 years
Bains *et al.* [21]	41	50.4 Gy	Cisplatin, paclitaxel	Cisplatin, paclitaxel	R0 resection in 92%	22% of resected specimen (26% of patients with R0 resection)	36%	Not stated
Meluch *et al.* [22]	129	45 Gy	None	5-FU, carboplatin, paclitaxel	74%	38%	62%	2 year 47%, 3 year 41%, Median survival 22 months
Goldberg *et al.* [23]	29	60 Gy	Cisplatin, paclitaxel	5-FU, cisplatin, paclitaxel	75%	18%		DFS and OS 56% and 59% at 2 years, 45% and 45% at 4 years
Current 2004	16	45 Gy	TCF	TCF	75%	18.6% (25% of patients undergoing resection)	37.5%	OS at 1, 2, 3 and 4 years are 75%, 56%, 50%, 50%, respectively, median survival 40 months

DFS, disease-free survival; 5-FU, 5-fluorouracil; OS, overall survival; TCF, paclitaxel, cisplatin and 5-fluorouracil.

TAKE HOME MESSAGE

OPERABLE NON METASTATIC

- SURGERY:- Mainstay of treatment for operable Ca.Esophagus
- NEOADJUVANT RT :- Does not improve local control or survival
- NEOADJUVANT CT:- No improve resection rate,local control andsurvival
- NEOADJUVANT CHEMORADIATION:- Improves local control and modest improvement in survival.

NACT RT may be restricted to patients achieving significant response or pCR and non-responders may have worse outcome compared with patients treated with surgery only

- POST OP ADJUVANT CT:- Currently undefined.No improvement in locoregional control or overall survival(except R0,N1)
- POST OP ADJUVANT RT:- Improves local control,but not survival.
- POST OP ADJUVANT CT RT:- Improves local control and survival

TAKE HOME MESSAGE

INOPERABLE NON METASTATIC

- In inoperable non metastatic Ca.Esophagus Role of Radiation is only palliatve having median survival 6-12 mos.and 5 yrs survival rate is less than 10%.

- Definitive chemoradiation improves local control and overall survival in comparision to radiation alone.(If patient medically unfit for surgery,lack of facility(experienced surgeon),cervical disease.)

THANK YOU