Intraluminal Brachytherapy:

Oesophagus

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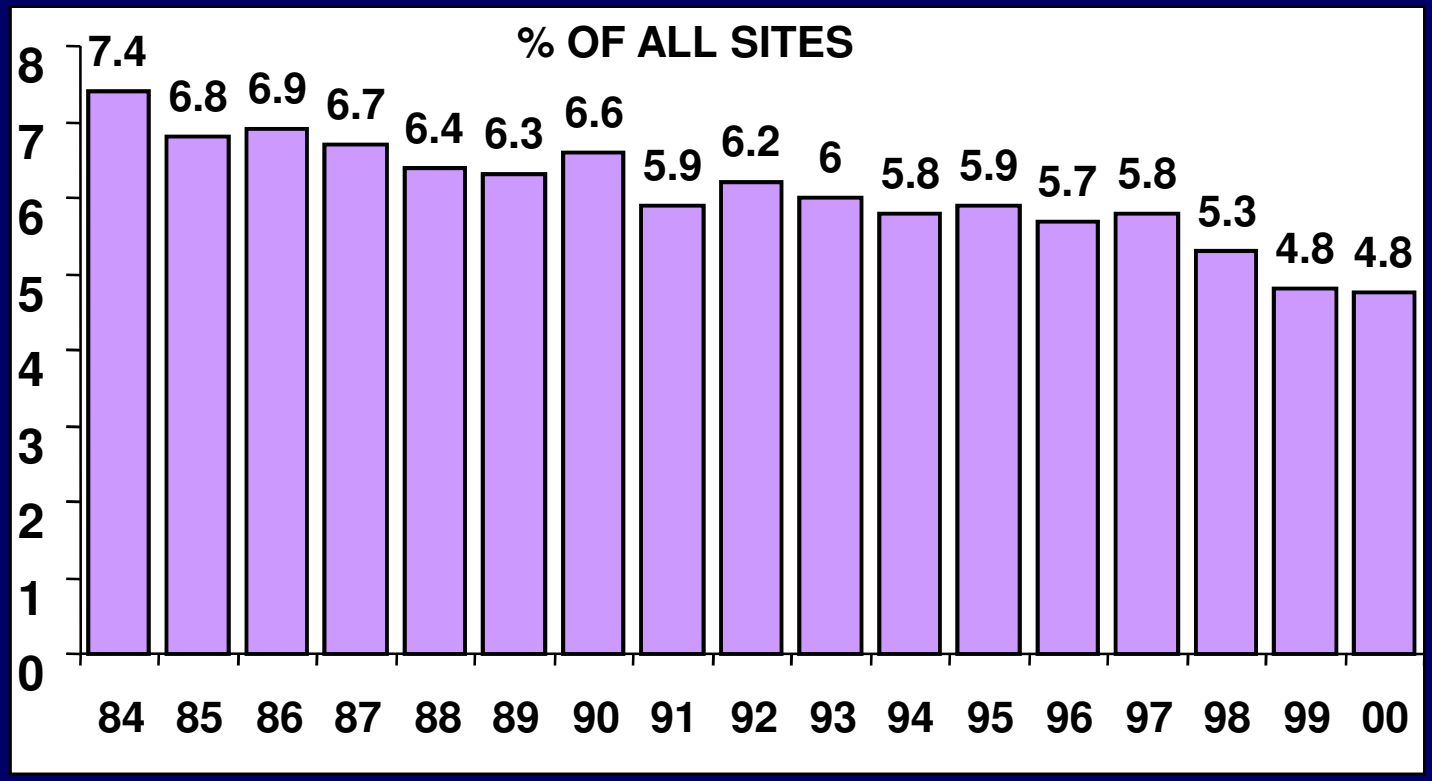
The Problem of Cancer Esophagus in India

Amongst the 5 most common cancers registered al TMH

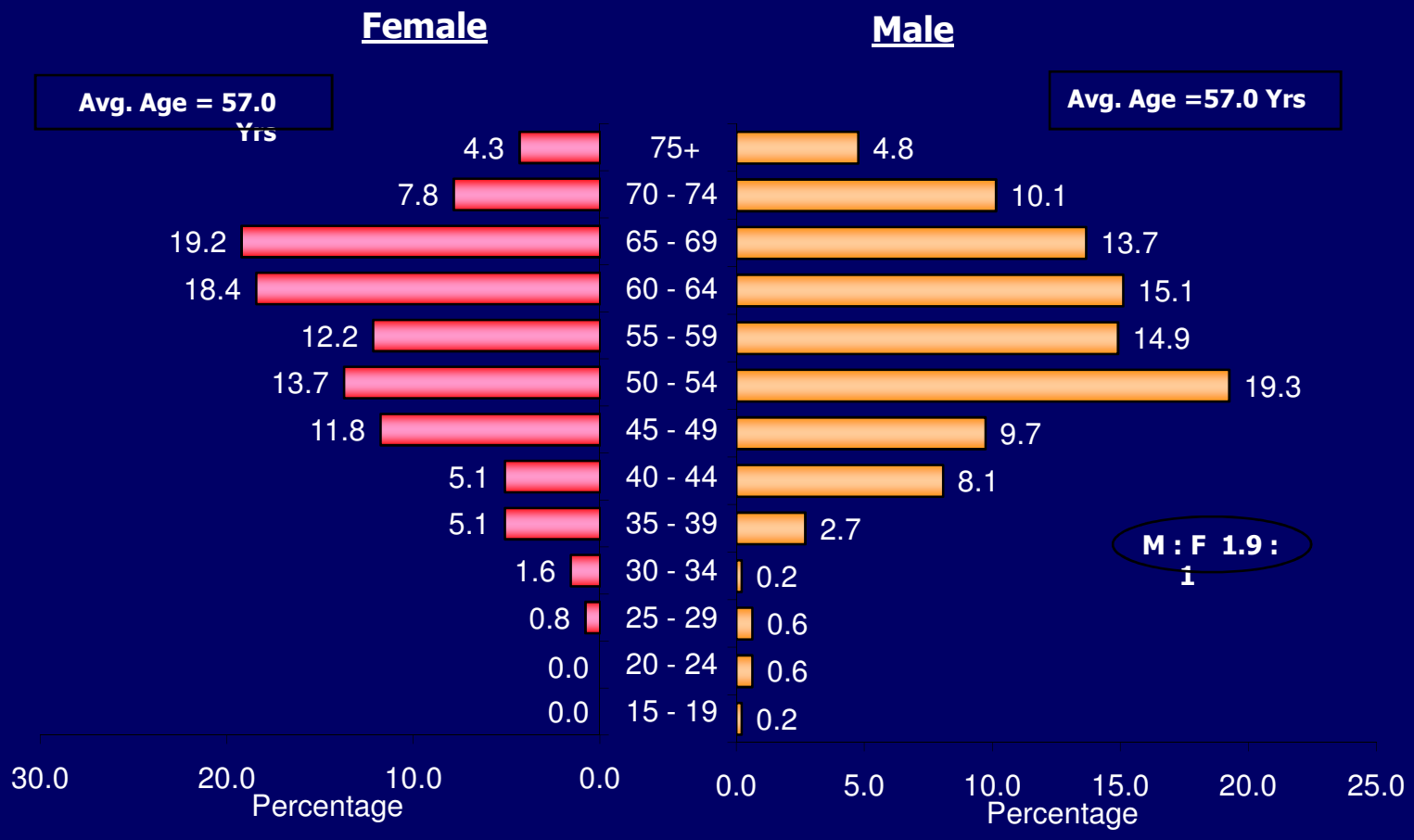


Total No of cases: 15591
Males: 8822
Females: 6769

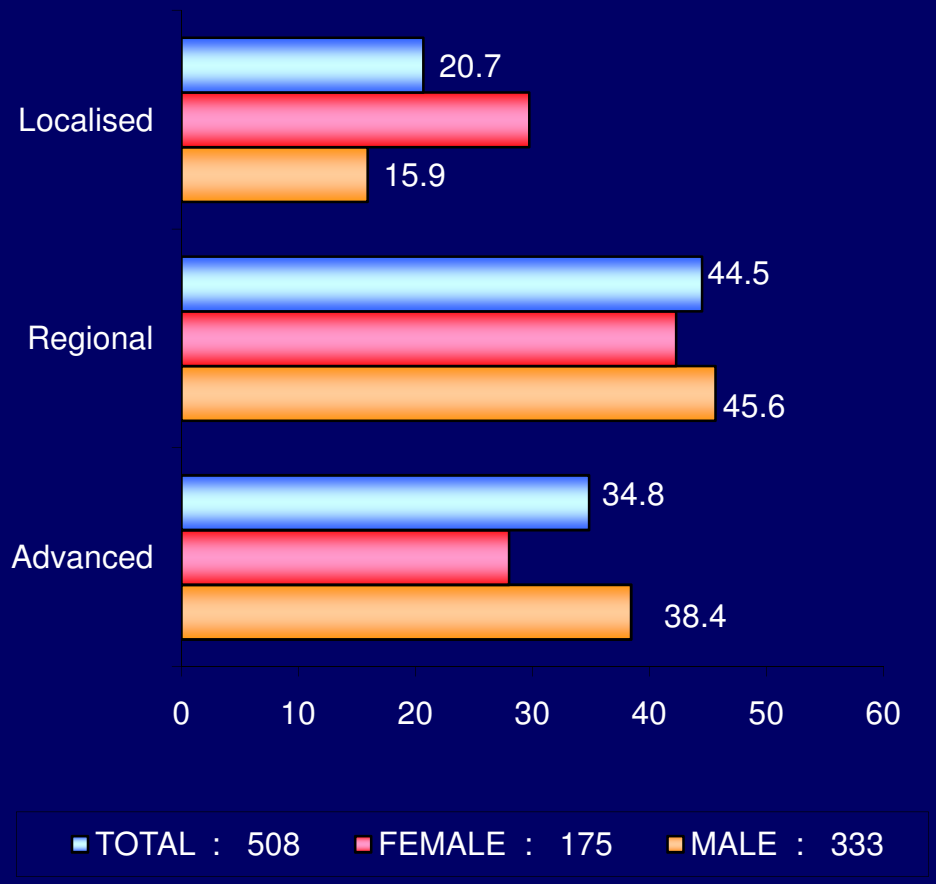
Cancer Esophagus: 741 (4.7%)
Males: 504
Females: 231

TMH cancer registry 2000

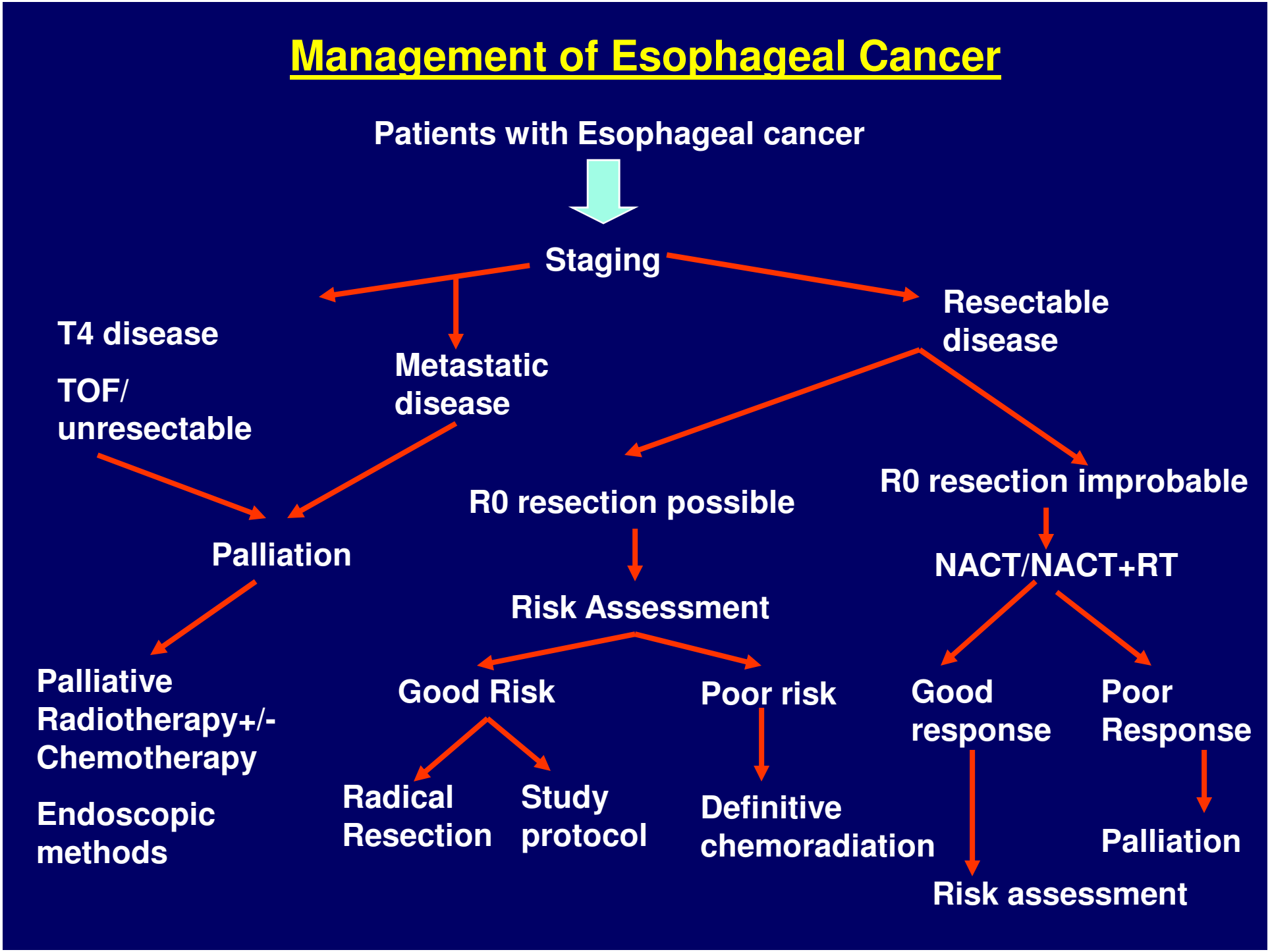
Age Distribution



Clinical Extent of Disease



Management of Esophageal Cancer



Role of Intraluminal Radiotherapy

- Definitive

Boost –consolidate response of external RT

- Limits dose to critical structures
- Dose escalation to primary
- Limited role in this setting with the use of CT/RT protocols

- Palliation

As a Sole Modality

With External RT

- Dysphagia relief-symptom free survival
- Relieves dysphagia and improves swallowing status.
- Short treatment
- Very rapid relief (vs. external RT)
- Relieves bleeding/ pain (better than external RT)
- Limits the dose to critical structures.
- Balance between potential benefits vs. potential risks

Selection Criteria For Brachytherapy in Esophagus

Good Candidates

1. Primary tumor <10 cm in length.
2. Tumor confined to esophageal wall.
3. Thoracic esophagus location.
4. No regional lymph node or systemic metastases.

Poor Candidates

1. Extraesophageal extension.
2. Tumor>10 cm in length.
3. Regional lymphadenopathy.
4. Tumors involving GE junction or cardia.

Contraindications

1. Tracheo-esophageal fistula/ deep ulcerative lesion.
2. Stenosis which cannot be bypassed.
3. Cervical esophagus involvement.

Is ILRT Required in Radical Setting After EBRT ?

50 untreated cases of squamous cell cancers of middle1/3rd Esophagus, KPS>70

All patients received 35Gy/15# EBRT

	Number	ARM	Relief of Dysphagia (1 year)	Local Control 1yr	Overall Survival 1yr	strictures
Group A	25	20Gy/10# EBRT	37.6%	25%	44%	4%
Group B	25	6GyX2# HDR	70% P=NS	70% P=NS	*78% P=sign.	8%

Sur et al IJROBP 1992

Is ILRT Required in Radical Setting After EBRT ?

186 untreated patients of squamous cell carcinoma, tumor length<7cm

All patients received 50Gy/25# of EBRT.

	Number	ARM	Local control	Overall Survival 5yrs	strictures
Group A	93	20Gy/10# EBRT	39%	10%	8%
Group B	93	19.6-26Gy 3-4#	*57% P=sign	*17% P=sign.	10%

Yin et al Brachytherapy 1991

Does Chemotherapy Add to The Benefit ?

A PHASE I/II STUDY OF EXTERNAL BEAM RADIATION, BRACHYTHERAPY AND CONCURRENT CHEMOTHERAPY IN LOCALIZED CANCER OF THE ESOPHAGUS (RTOG 92-07): PRELIMINARY TOXICITY REPORT

LAURIE E. GASPAR, M.D.,* CHUNLIN QIAN, PH.D.,† WALTER I. KOCHA, M.D.,‡ LAWRENCE R. COIA, M.D.,§ ARNOLD HERSKOVIC, M.D.‖ AND MARY GRAHAM¶

Total 50 patients with curative intent

Received 50Gy/25# EBRT with concurrent cisplatin +5FU

15Gy/3# HDR ILRT concurrently with 3rd cycle chemotherapy

Only 70% patients could complete EBRT, 3rd # of HDR abandoned in most pts.

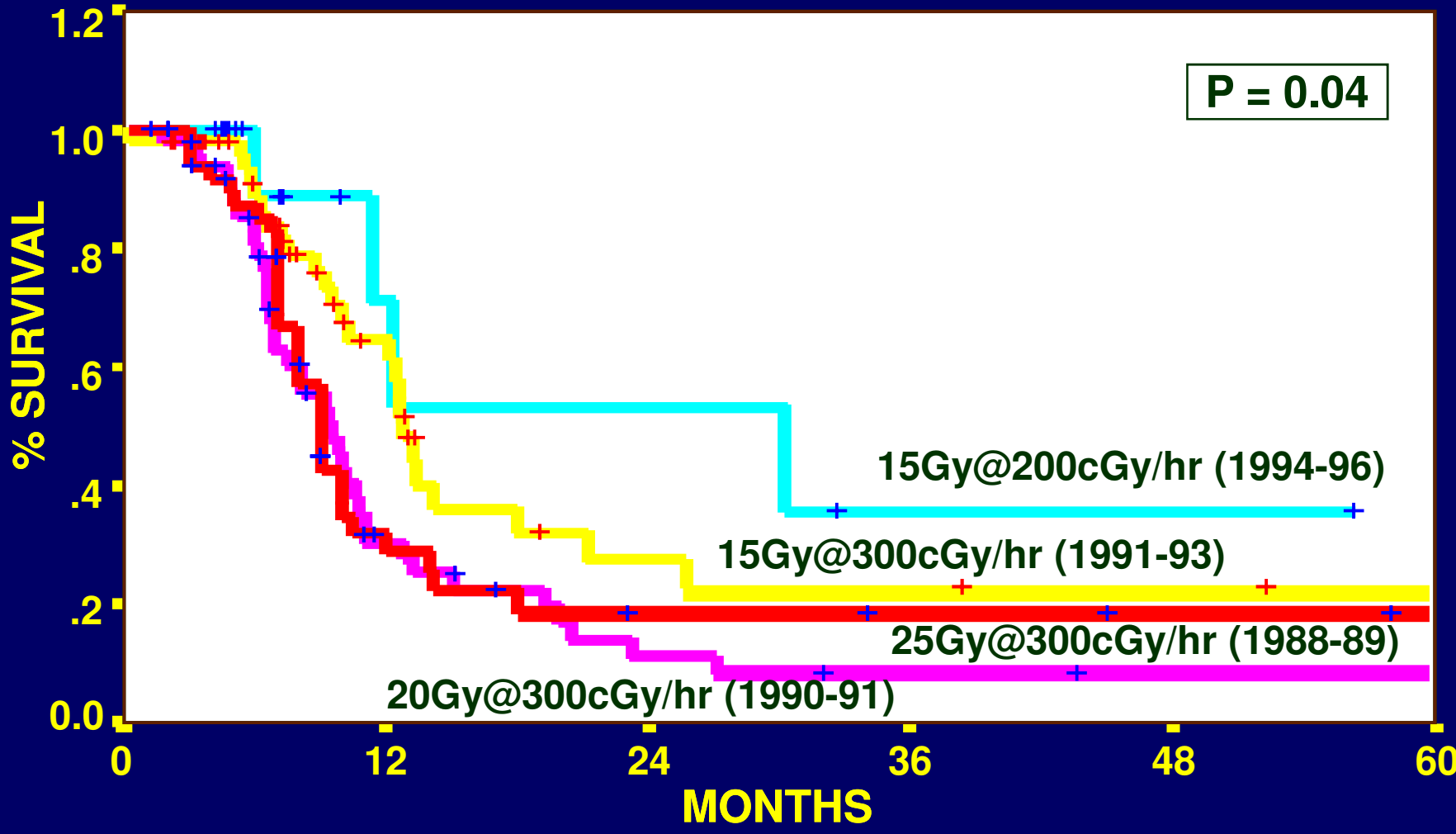
1yr survival rate- 48% not different from CT+RT data from RTOG 85-01

	Life-threatening	Fatal	All (%)
Upper aerodigestive tract excluding fistulas*	6	0	6 (12%)
Fistula	3	3	6 (12%)
Gastrointestinal tract†	1	0	1 (2%)
Hematologic‡	8	1	9 (18%)
Infection	2	0	2 (4%)
Skin§	0	1	1 (2%)
Renal	0	1	1 (2%)
Other	3	0	3 (6%)

34% Life Threatening toxicities

Gaspar et al Cancer 2000

CARCINOMA OESOPHAGUS
EXTERNAL RT +/- 5FU + ILRT (LDR)
DYSPHAGIA FREE SURVIVAL [1988 -1996]



Vinay Sharma et al Dis Oeso 2000

Treatment Complications

	STRICTURE	ULCERATIONS	T.O.F
ILRT - LDR			
• 25Gy@ 200cGy/hr +/- 5FU	30%	20%	10%
• 20Gy@ 300 cGy/hr + 5 FU	24%	30%	12%
• 15Gy@ 300 cGy/hr + 5FU	08%	28%	12%
• 15Gy@ 200 cGy/hr +/- 5FU	33%	22%	--

Vinay Sharma et al Dis Oeso 200

Schedule for Definitive Radiotherapy And Brachytherapy in Radical Setting

External beam radiation:

- 45–50 Gy in 1.8–2.0-Gy fractions, five fractions/week, weeks 1–5

Brachytherapy

- HDR—total dose of 10 Gy, 5 Gy/fraction, one fraction/week, starting 2–3 weeks following completion of external beam
- LDR—total dose of 20 Gy, single course, 0.4–1.0 Gy/hr, starting 2–3 weeks from completion of external beam

* All doses specified 1 cm from midsource or mid-dwell position.

ABS Recommendations

TMH- Post 50Gy of EBRT- 12Gy/2#HDR weekly (6GyX2)

Conclusion (ILRT in definitive setting)

1. ILRT has a definitive role as a boost after EBRT.

2. ILRT improves dysphagia relief, local control and overall survival with some additional toxicity.

3. Chemotherapy does not add to the benefit gained by the combination.

4. Chemotherapy significantly adds up to toxicity if given to patients receiving a combination of EBRT and ILRT.

5. Concurrent administration of chemotherapy with ILRT should be avoided.

Palliative Setting

Modalities available for palliative therapy

Surgery
Intubation (Self Expanding Metal Stents 'SEMS' and semi-rigid prosthetic tubes)
Thermal Ablation
- (a) Laser therapy (Nd-YAG or Diode)
- (b) BICAP probe
- (c) Argon Plasma Coagulation

Photodynamic Therapy
Radiotherapy (External beam radiation therapy and brachytherapy)
Chemotherapy
Dilatation
Chemical Injection therapy
Enteral feeding (nasogastric tube, PEG)

PEG: percutaneous endoscopic gastrostomy.

Best Method of Palliation

In Selected Patients

Method	Median survival (mo)	Series
EBRT	5	Rider et al
Bypass Sx	5	Mannell et al
Laser	4	Seagalin et al
Chemotherapy	4	Kelsen et al
Intubation	2.5	Mannell et al
Fractionated Brachytherapy	6-9	Sur et al

Single-dose Brachytherapy vs. Metal Stent For Palliation

Total no of patients 209
Stent placement (n=108)
Brachytherapy (n=101)

Brachytherapy dose –single dose 12Gy

Results

- Long-term Dysphagia relief better (115 vs. 82 days, P=0.015)
- Better Quality of life
- Lesser complications 21%vs 33% (p=0.02)
- No difference in median survival

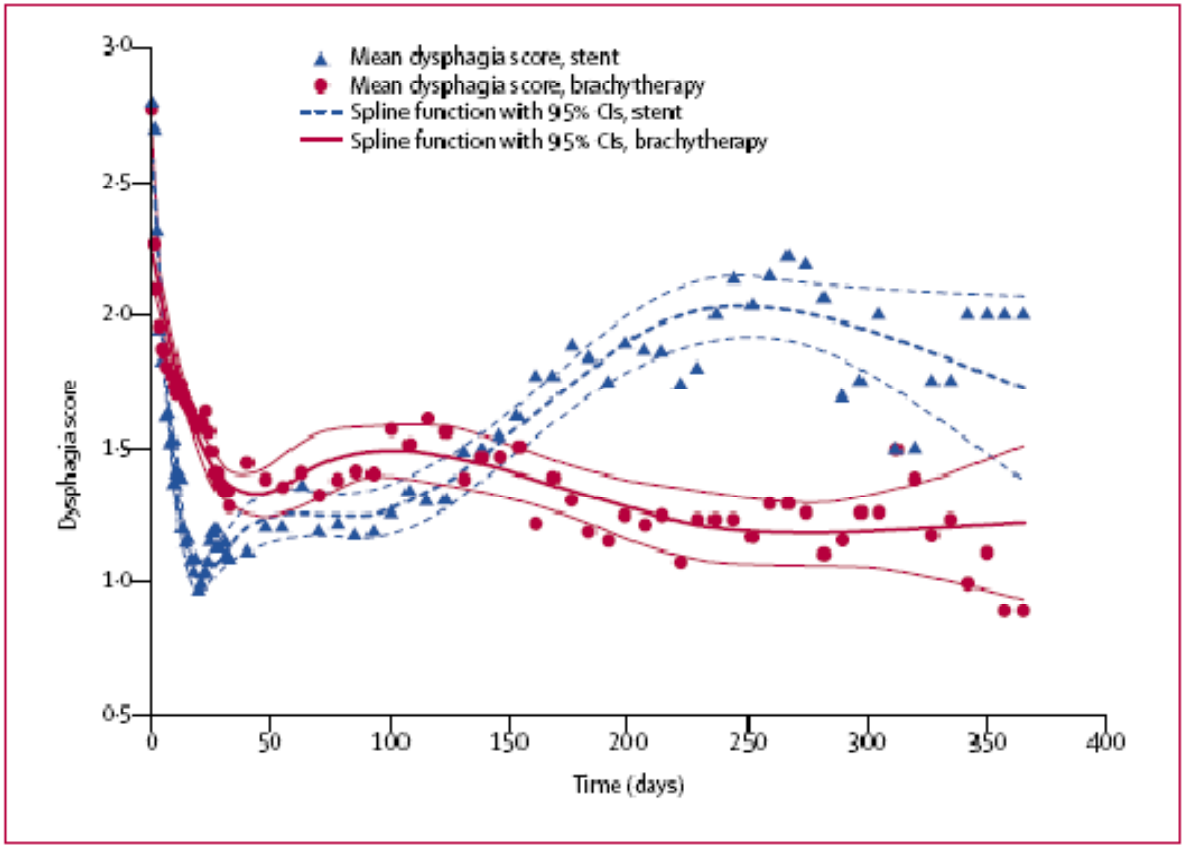


Figure 2: **Dysphagia scores**

Homs et al Lancet 2004

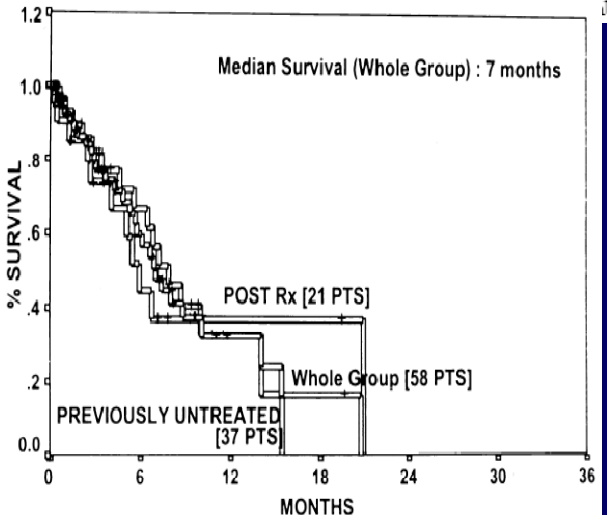
TMH Experience

PALLIATION OF ADVANCED/RECURRENT ESOPHAGEAL CARCINOMA WITH HIGH-DOSE-RATE BRACHYTHERAPY

VINAY SHARMA, M.D.,* UMESH MAHANTSHETTY, M.D., D.N.B. (R.T.),*
KETAYUN A. DINSHAW, D.M.R.T. (LOND.), F.R.C.R. (LOND.),* RAMAN DESHPANDE, M.S.,† AND SANJAY SHARMA, M.S.†

...bai, India

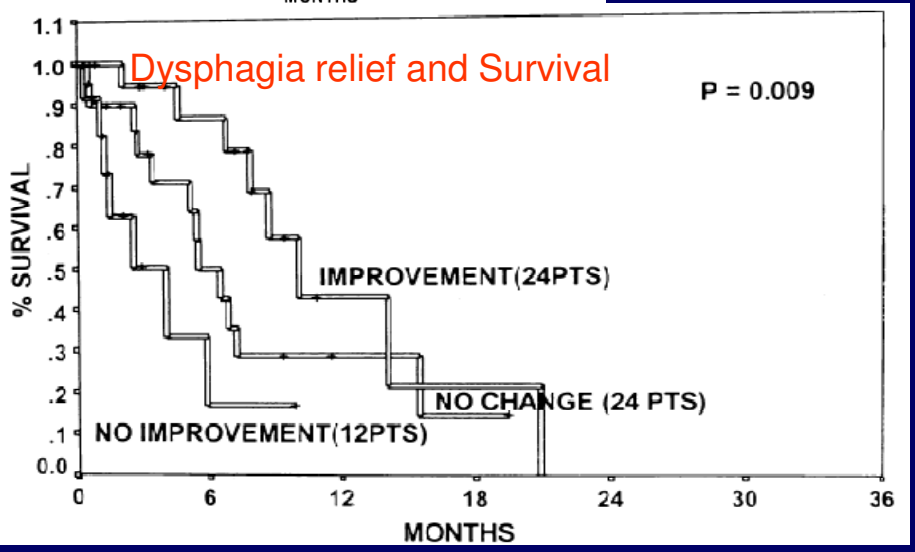
No. of patients	58
Male:female	37:21
Age group	32–88 years (mean 64 years)
Previously untreated cases	37
Old age and KPS <50%	29
Second primary tumors	4
Distant metastasis	4
Post-treatment recurrent cases	21
Post-RT recurrence	15
Post-surgery recurrence	5
Post-CT/prosthesis	1
Site of lesion	No (%)
Upper third	10 (17%)
Mid third	38 (66%)
Lower third ± c.o junc.	10 (17%)
Lesion length (cm)	
<5	14 (24%)
5–10	39 (67%)
>10	05 (9%)



Stricture-9

Ulcerations- 6

Fistula - 4



Protocol- HDR 6GyX2# 1 week apart

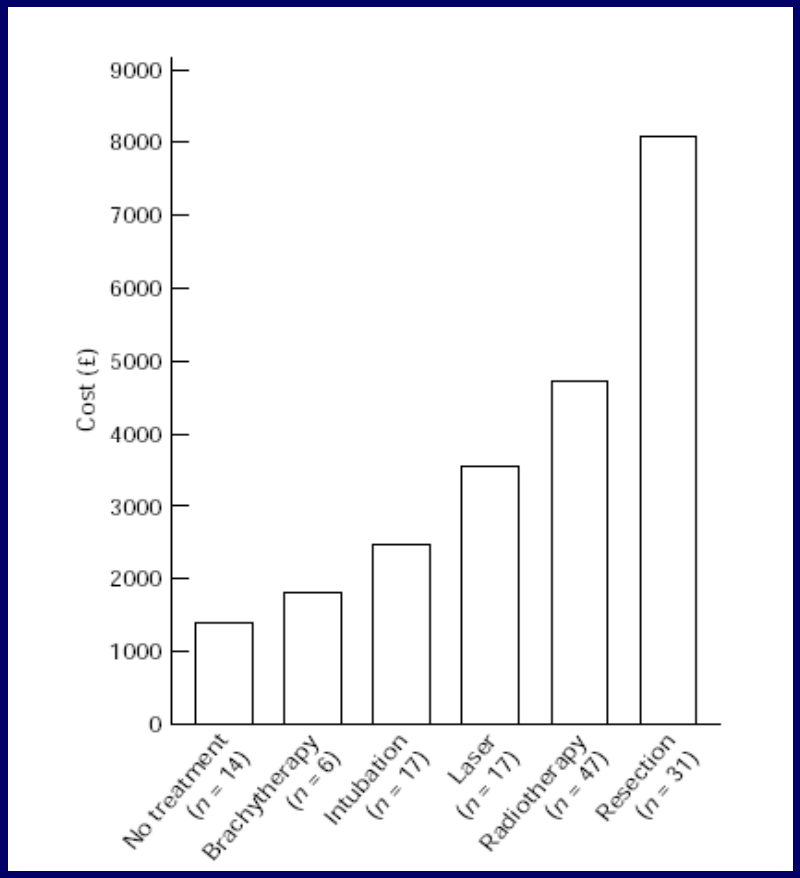
N=58

Sharma V et a IJROBP 2002

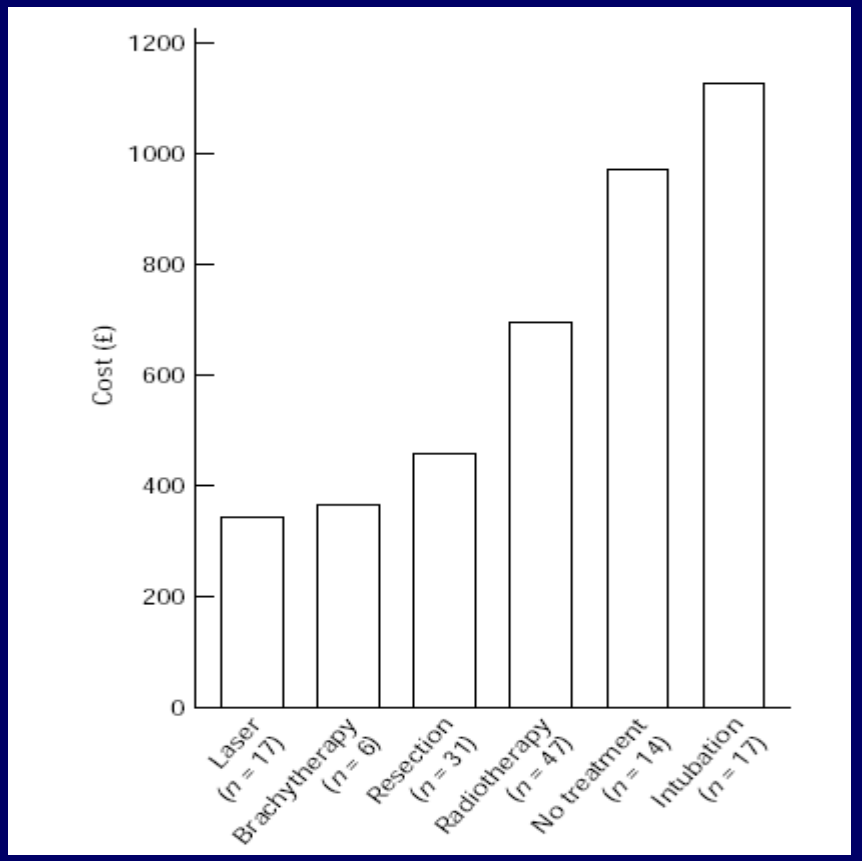
Palliation of Dysphagia by Radiotherapy+/- Chemotherapy

		Palliation of Dysphagia	
Series	Total No. Patients	At the End of Treatment (%)	Duration
Radiation therapy alone			
Wara et al.	103	89	6-mo average
Petrovich et al.	133	87	34% ? 6 mo
			18% ? 3 mo
			35% ? 3 mo
Roussel et al.	69	70	—
Caspers et al	127	71	54% until death
Whittington et al	25	—	5% at 9 mo
Combined modality therapy (Radiation + chemotherapy)			
Coia et al.	102	88	67–100% until death
Seitz et al	35	100	—
Whittington et al	26	—	87% 3-y actuarial
Algan et al	8	100	—
Gill et al	71	60	—
Urba and Turris	27	—	59% until death
Izquierdo et al	25	64	Median, 5 mo

Cost Effectiveness of Palliative Modalities



Primary Cost of Treatment



Cost of survival per month after treatment

Farndon et al Brit Jour Surg,1998

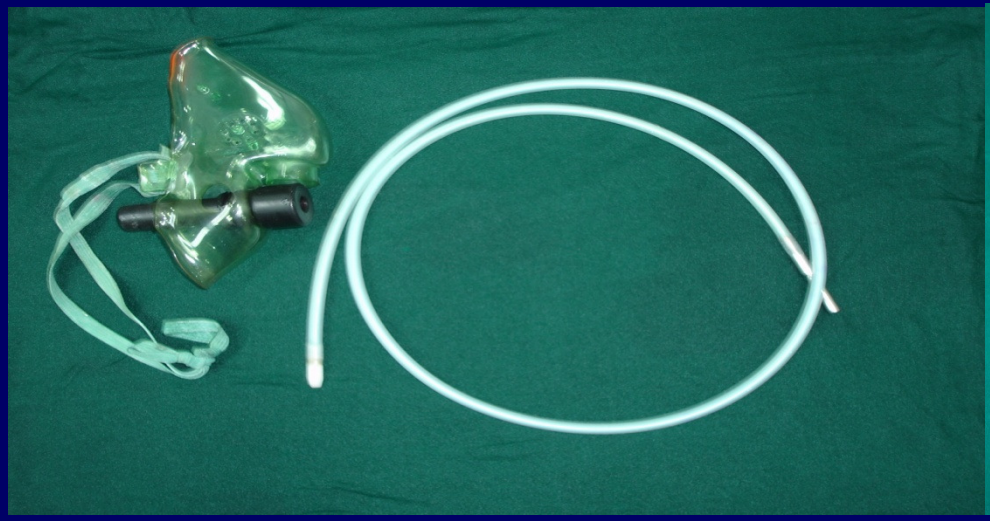
Technique

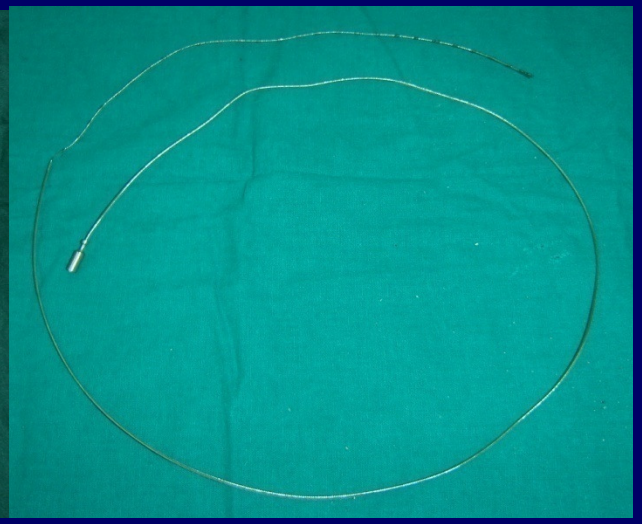
1. Blind insertion
2. Fluoroscopy assisted
3. Endoscopic insertion- most convenient, safe, assessment of disease/response.

Recommended external diameter of the applicator- 0.6-1cm.

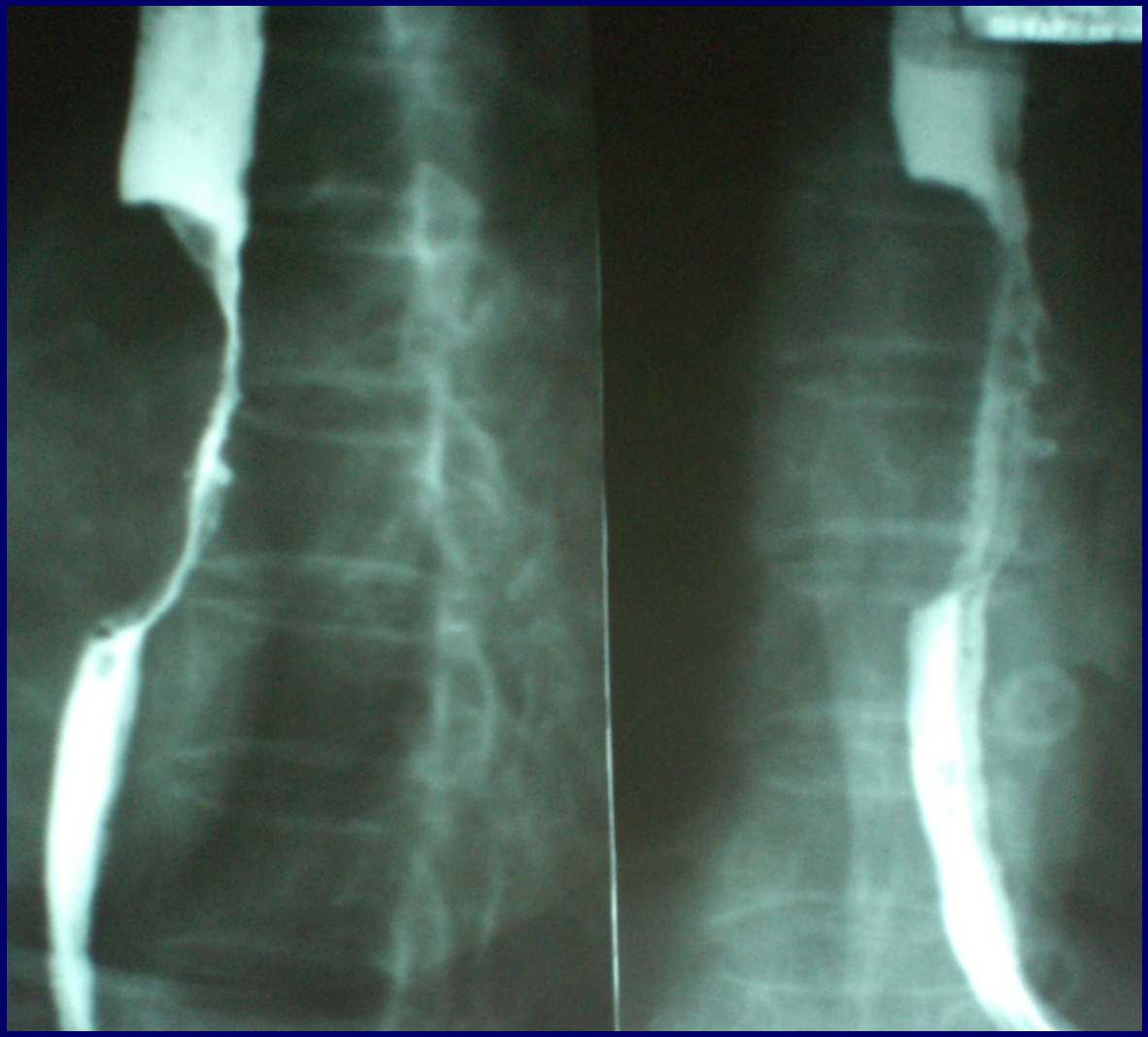
Narrower catheters deliver more to mucosa.

Large catheters – more risk of abrasions/perforations.

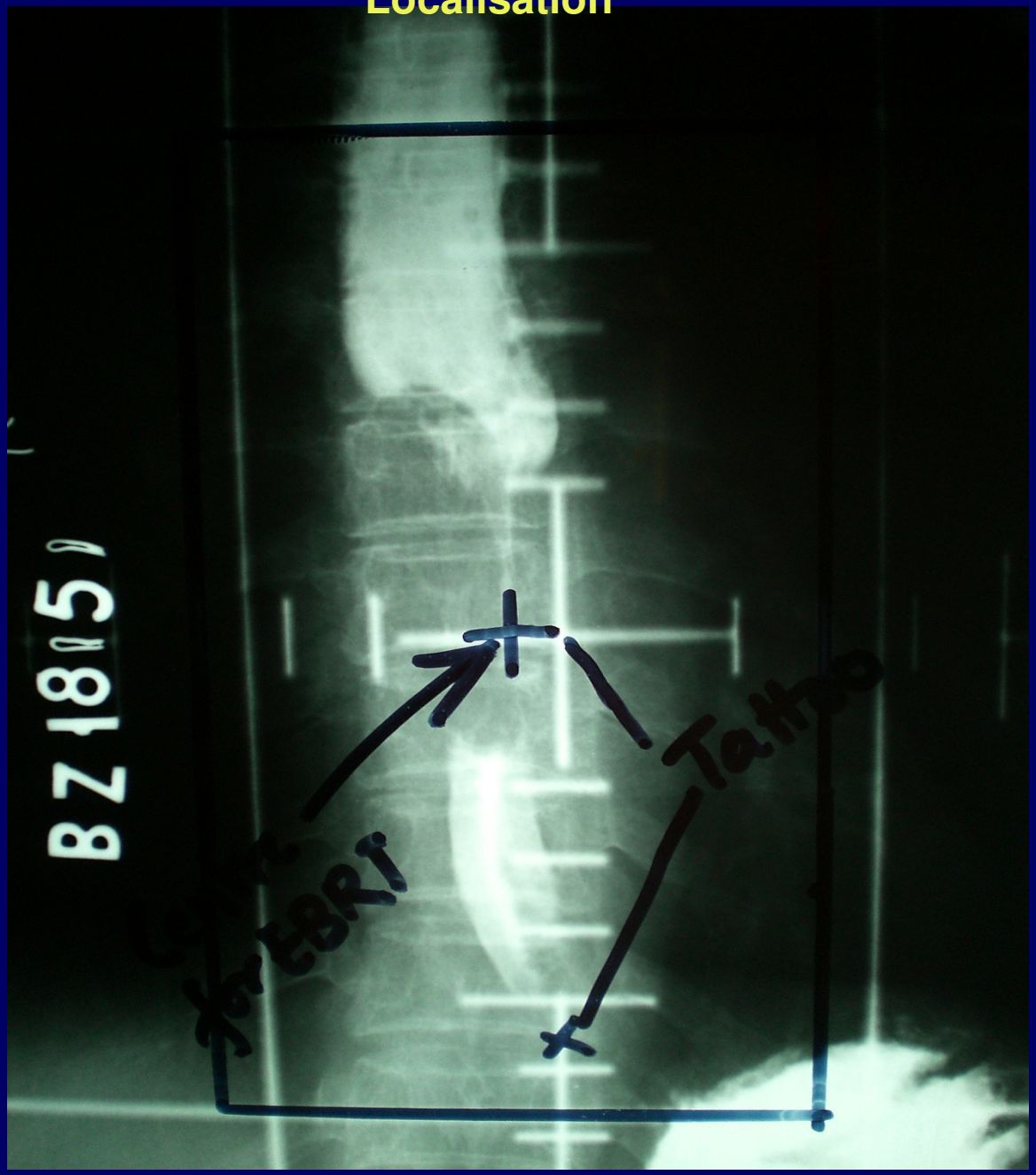




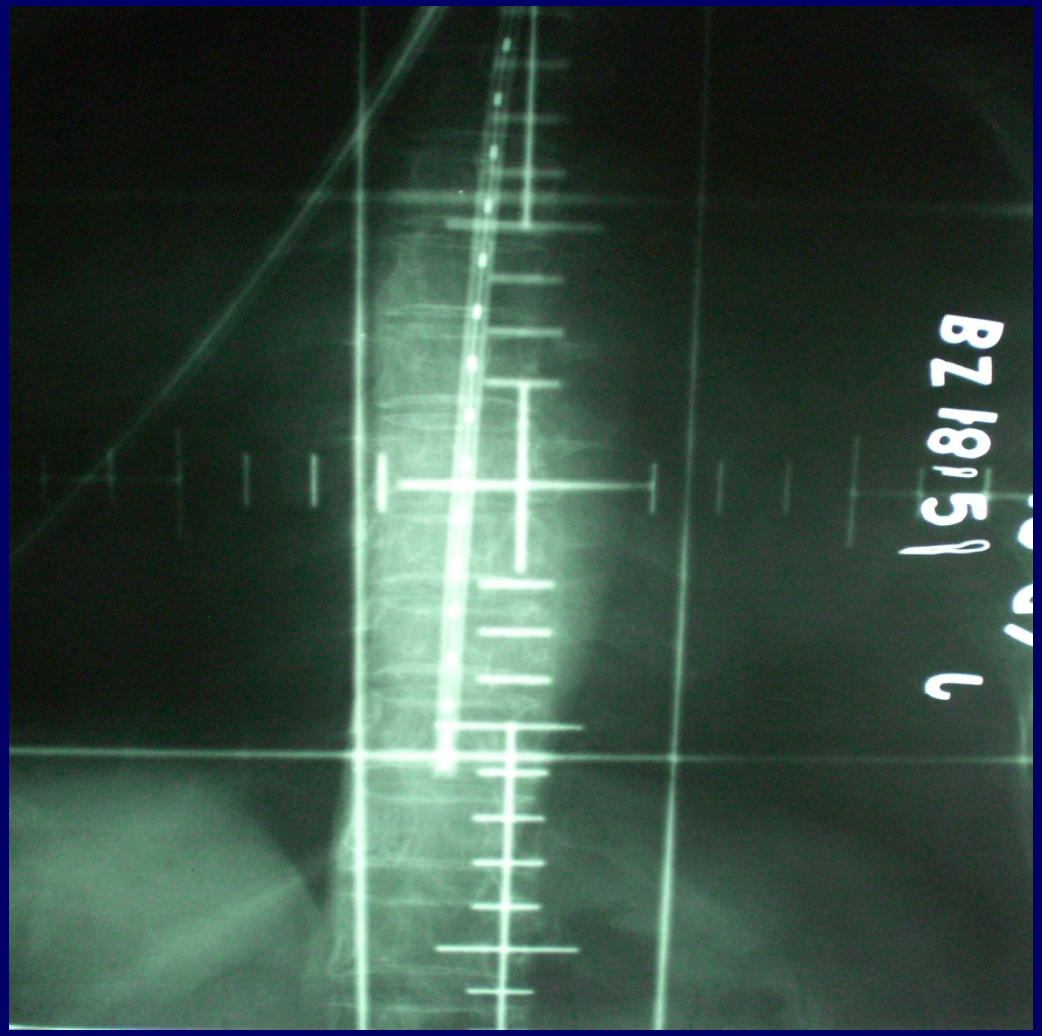
Pre Treatment



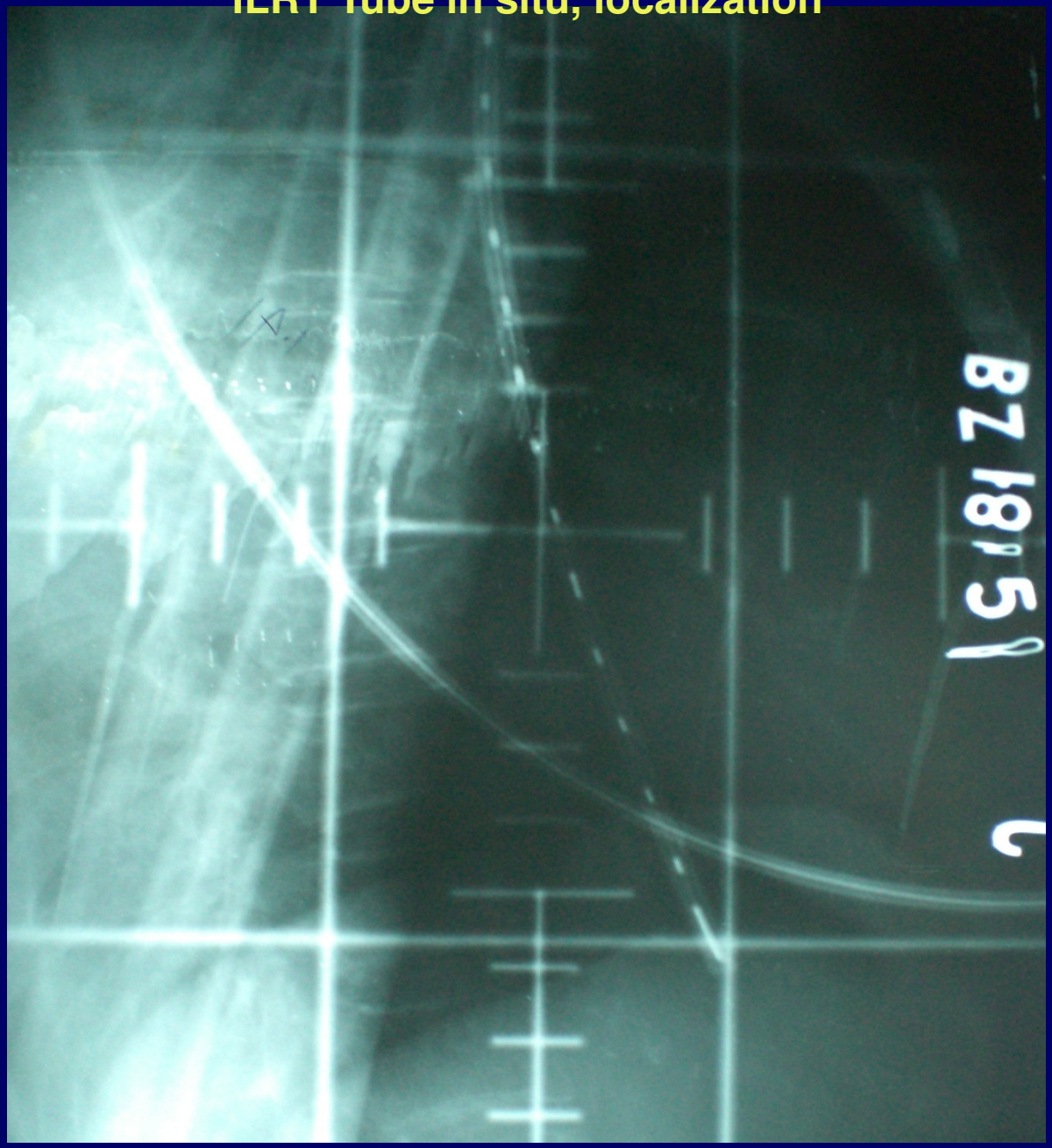
Localisation



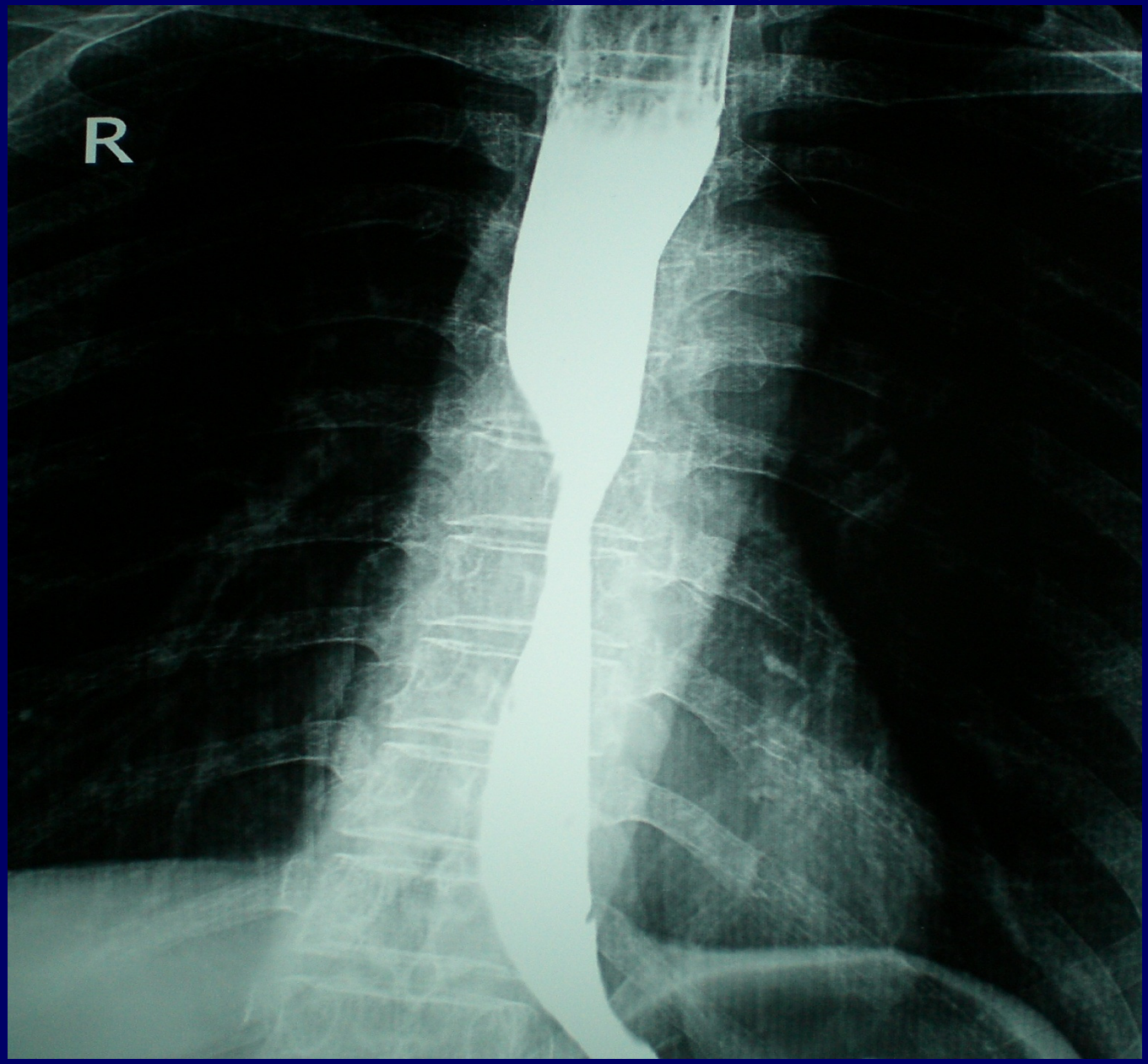
ILRT Tube in situ, localization



ILRT Tube in situ, localization



Post-Treatment



Brachytherapy Dose Fractionation

Target Volume – Visible Mucosal tumor with 2cm craniocaudal margin.

Dose Prescription – 1 cm from mid-source or mid dwell position without optimization.

Several doses and fractionations have been used and ideal not known.

HDR/MDR/LDR

Single dose/Fractionated radiotherapy.

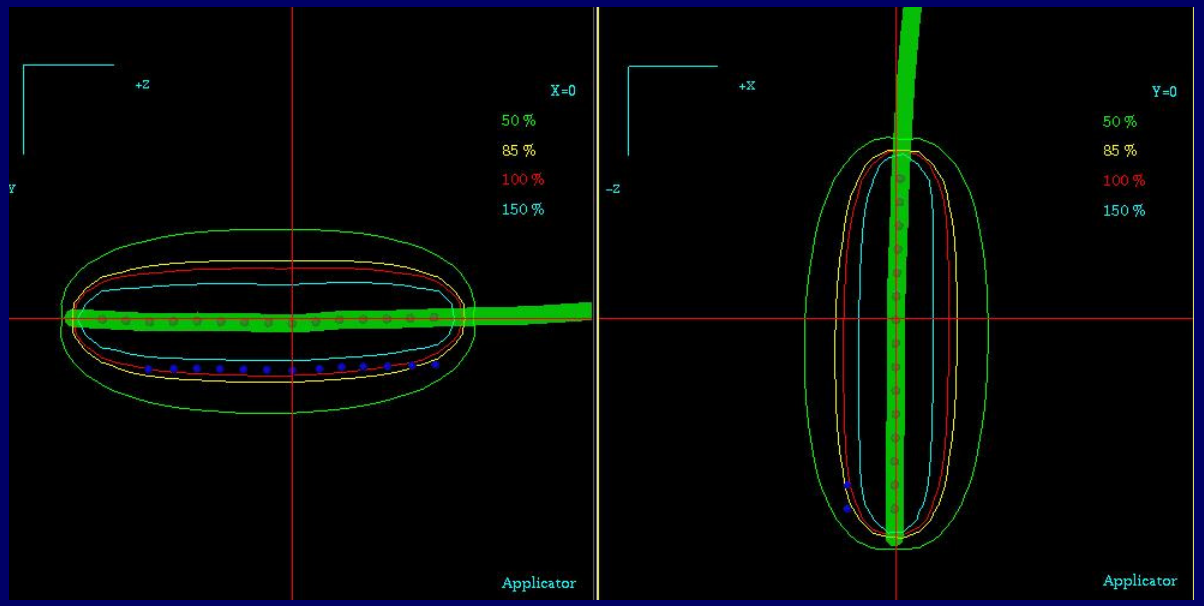
10Gy/15Gy-single dose as per previous external RT/ tolerance/life expectancy.

Fractionated 6GyX2#, 6GyX3#, 8GyX2#,etc. ------- HDR. [10-14Gyin 1-2#-ABS]

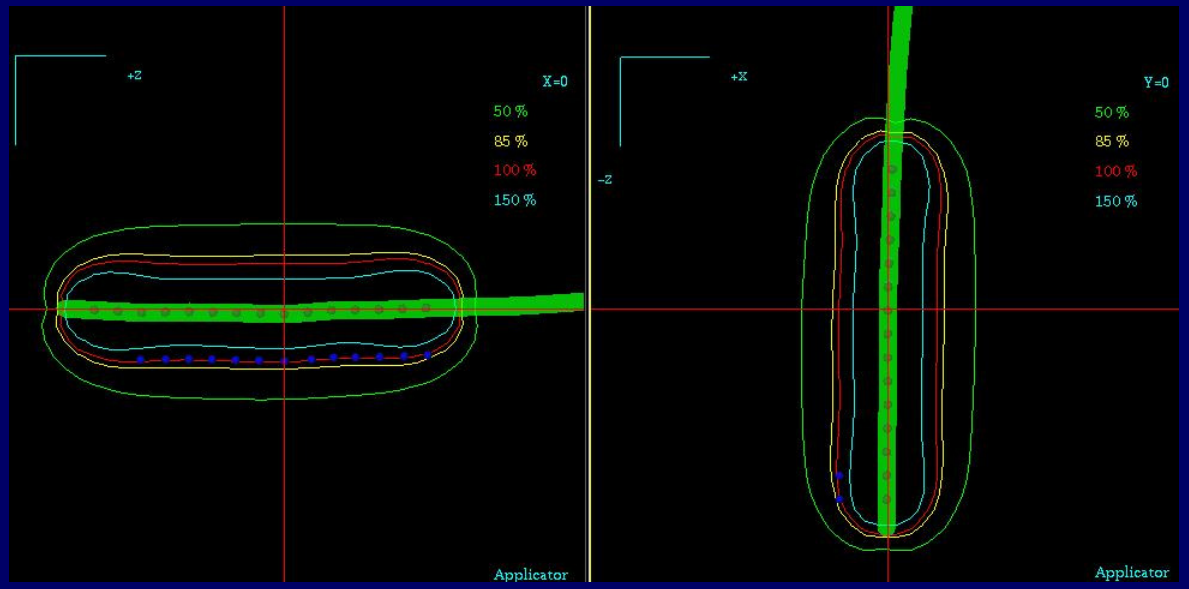
20Gy single course at 0.4-1Gy/1h------ LDR. [ABS]

Prescription

UNOPT



OPT



Dose/Fractionation (Palliation)

Review of Literature

Author (Ref.)	No. of Pts.	Dose	HDR	Dysphagia relief	Survival	Complications
						4 Stricture
Sur *et al.* (28)	9	12 Gy/2 fr	HDR	3/9 pts: 9 months	9 months	2 Failure
	10	20 Gy/3 fr	MDR	5.1 months mean	4 months	3 Esophagitis
Harvey *et al.* (13)	12	12.5 Gy/1 fr	HDR	4.5 months mean	5.8 months	9 Esophagitis
	51	15 Gy/1 fr	MDR	67%, 5 mths	5.5 month mean	5 Fistulas
Jager *et al.* (26)	37	15 Gy/1 fr	HDR	median	20%, 12 months	1 Hematesis
						2 Ulceration
	14	15 Gy/1 fr		6 months	NR	1 Stricture
Kulhavy *et al.* (15)	11	18 Gy/1 fr	HDR	8 months		3 Stricture
						1 Fistulas
TMH	35	12 Gy/2 fr		10.8%, 12 months	9.8%, 12 months	5 Stricture, 7 fistulas
Sur *et al.* (24)	60	16 Gy/2 fr	HDR	25.4%	22.4%, 12 months	15 Stricture, 2 fistulas
	55	18 Gy/3 fr		38.9%	35.3%, 12 months	23 Stricture, 6 fistulas
Present Series						
Previously untreated	37	12 Gy/2 fr/ 1 wk apart	HDR	31/37 (80%) Median 7.8 months	7.8 months (median)	4 Stricture 3 Ulceration 3 Fistulas
Post Rx recurrence	21			15/21 (70%) Median 10 months	5.9 months (median)	5 Stricture (post-RT:4) 3 Ulceration (post-RT)

Dose/Fractionation (Palliation)

FRACTIONATED HIGH DOSE RATE INTRALUMINAL BRACHYTHERAPY IN PALLIATION OF ADVANCED ESOPHAGEAL CANCER

RANJAN K. SUR, M.D., D.N.B.,* BERNARD DONDE, M.MED,* VICTOR C. LEVIN, B.SC, F.F.RAD,* AND AYLWYN MANNELL, M.S., F.R.C.S., F.R.A.C.S.†

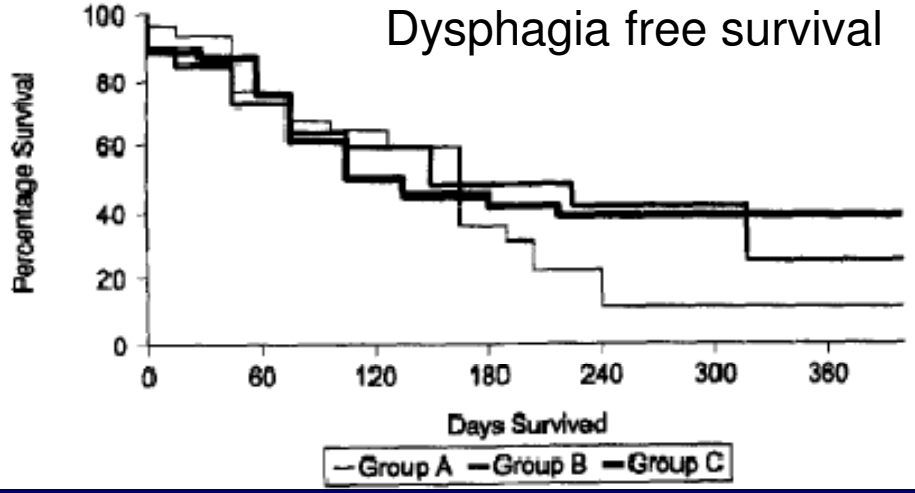
Group	Protocol	Stage III	Stage IV	Total
A	12 Gy/2 fractions; 6 Gy/fraction	30	6	36
B	16 Gy/2 fractions; 8 Gy/fraction	56	12	68
C	18 Gy/3 fractions; 6 Gy/fraction	66	2	68
		152	30	172

N= 182 patients

Advanced esophageal cancer

Preliminary analysis (6 mo) showed – Arm A fared worst- so discontinued

Dysphagia free survival



Complications

Group	Strictures	Total patients
A	5	35
B	15	60
C	23	55

$p = 0.014$; A vs. B = 0.217; A vs. C = 0.006; B vs. C = 0.055.

IJROBP 1998: 40(2);447-453

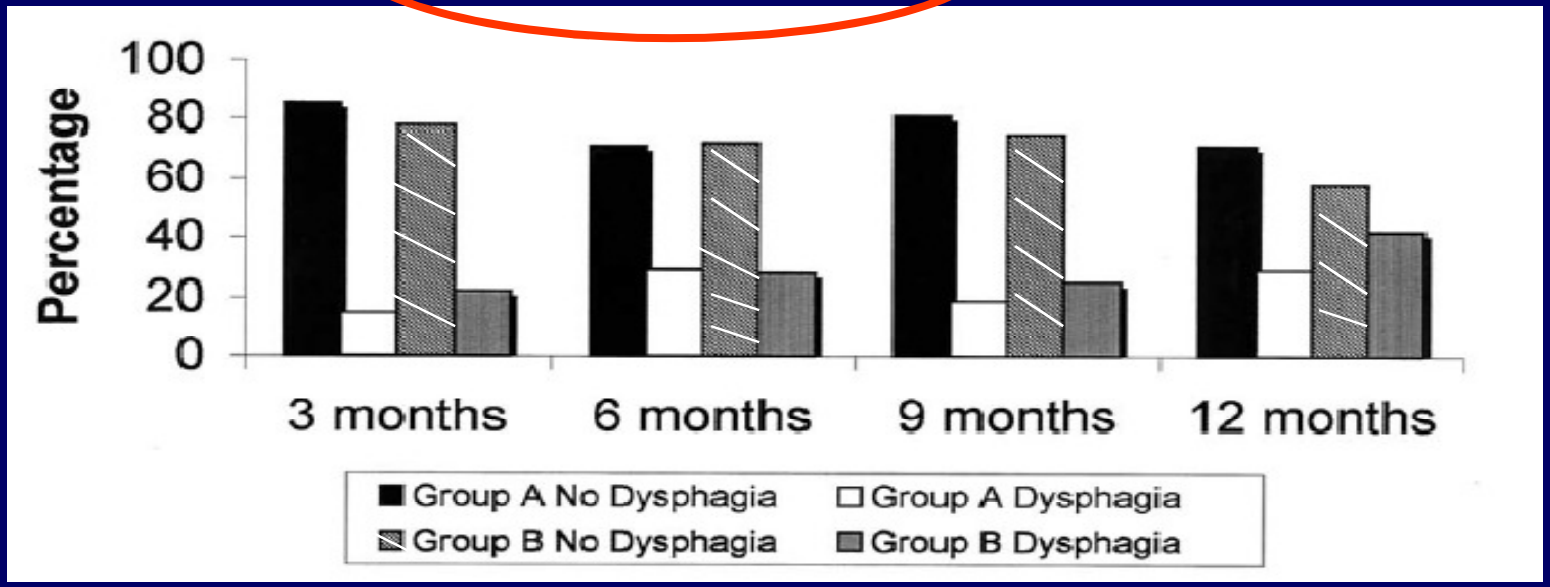
PROSPECTIVE RANDOMIZED TRIAL OF HDR BRACHYTHERAPY AS A SOLE MODALITY IN PALLIATION OF ADVANCED ESOPHAGEAL CARCINOMA—AN INTERNATIONAL ATOMIC ENERGY AGENCY STUDY

RANJAN K. SUR, M.D., D.N.B., PH.D.,* C. VICTOR LEVIN, F.F.RAD. (T.) S.A.,† BERNARD DONDE, M.MED.,* VINAY SHARMA, M.D., D.N.B.,‡ LESZEK MISZCZYK, M.D.,§ AND SUBIR NAG, M.D.||

N=232 patients, multi-institutional study

Advanced esophageal cancer.

Randomized between 6GyX3 and 8GyX2



IJROBP 2002: 53(1);127-133

Complication	Whole group (n = 222)	Group A (n = 118)	Group B (n = 104)
Fibrous strictures	25 (11.3)	12 (10.2)	13 (12.5)
Persistent disease	28 (12.6)	14 (11.9)	14 (13.5)
Tracheoesophageal fistula	23 (10.4)	11 (9.3)	12 (11.5)
Mean time to onset of strictures (d)	171	170	172
Mean time to onset of fistula (d)	138	140	136

Conclusions

1. Brachytherapy alone – excellent method of palliation.
2. Results better than other available modalities- overall survival- 7.9 months.
3. Brachytherapy schedules equivalent in terms of outcomes and toxicities.

Does addition of Ext. RT increase the benefit ?

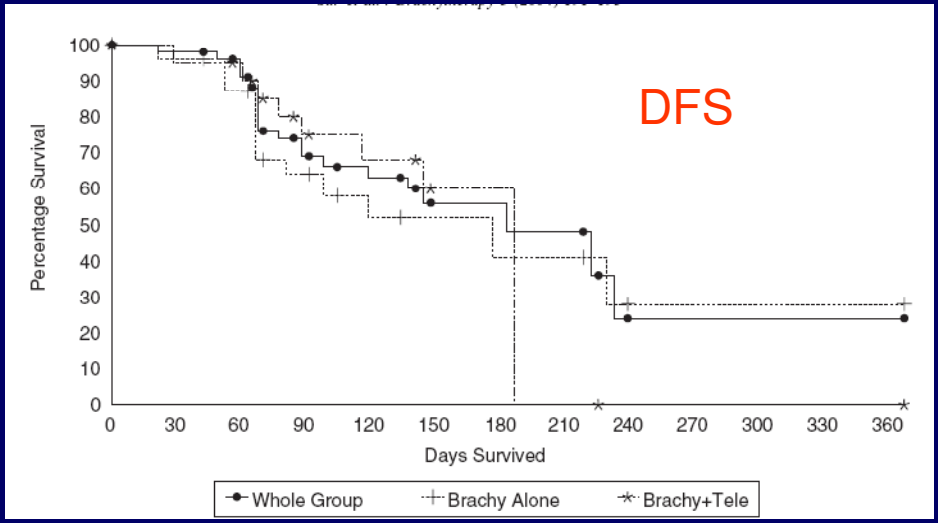
IJROBP 2002: 53(1);127-133

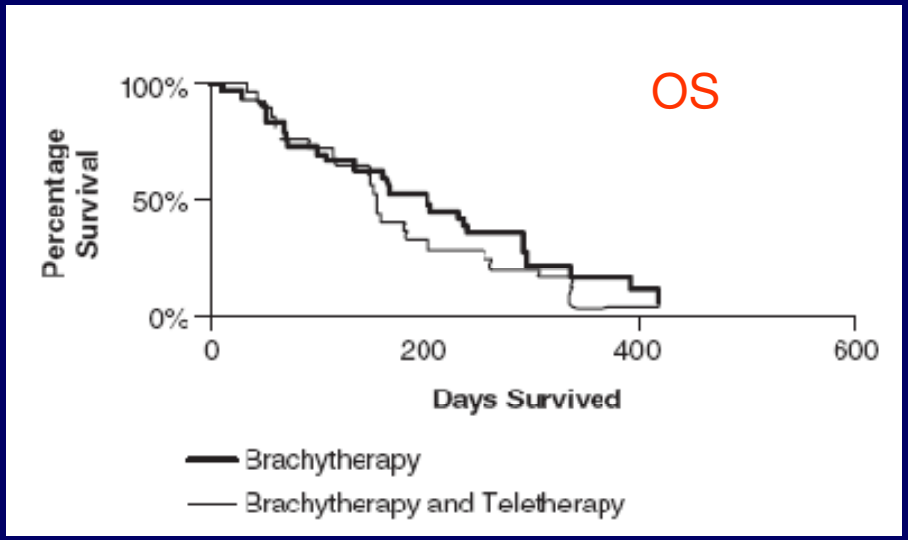
Randomized prospective study comparing high-dose-rate intraluminal brachytherapy (HDRILBT) alone with HDRILBT and external beam radiotherapy in the palliation of advanced esophageal cancer

Ranjan Sur[1,2,*], Bernard Donde[2], Conrad Falkson[1], Sheikh Nisar Ahmed[2], Victor Levin[3], Subir Nag[4], Raimond Wong[1], Glenn Jones[1]

60 patients

16Gy/2# HDR- randomized to observation vs. 30Gy/10# EBRT





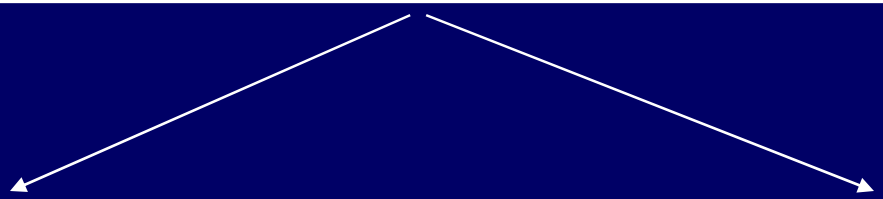
Addition of EBRT does not led to significant improvement in DFS, OS

Rates of complications were comparable

R Sur et al Brachytherapy 2004

Does addition of Ext. RT increase the benefit ? (Palliative Setting)

Palliation Of Advanced Esophageal Carcinoma



Intraluminal Brachytherapy

Intraluminal Brachytherapy with External Radiotherapy

IAEA Multi-institutional Phase III Randomized trial.

Study End-Points

Primary Objective:

Determine if addition of EBRT to HDR improves Freedom from dysphagia
Survival

Secondary Objective:

- Determine if addition of EBRT to HDR improves **D**ysphagia,
  Odynophagia
  Regurgitation
  Pain

- Determine if addition of EBRT to HDR improves Overall quality of life.

Study Design

Suitable Patient

RANDOMIZE

ILRT alone | **ILRT + EBRT**

ILRT: 8Gy x 2 fr, 1 week apart

ILRT + EBRT: ILRT same as above
EBRT 30Gy/10fr, within 2 weeks of 1st ILRT

Total patients- 219

IAEA CRP No:E33021

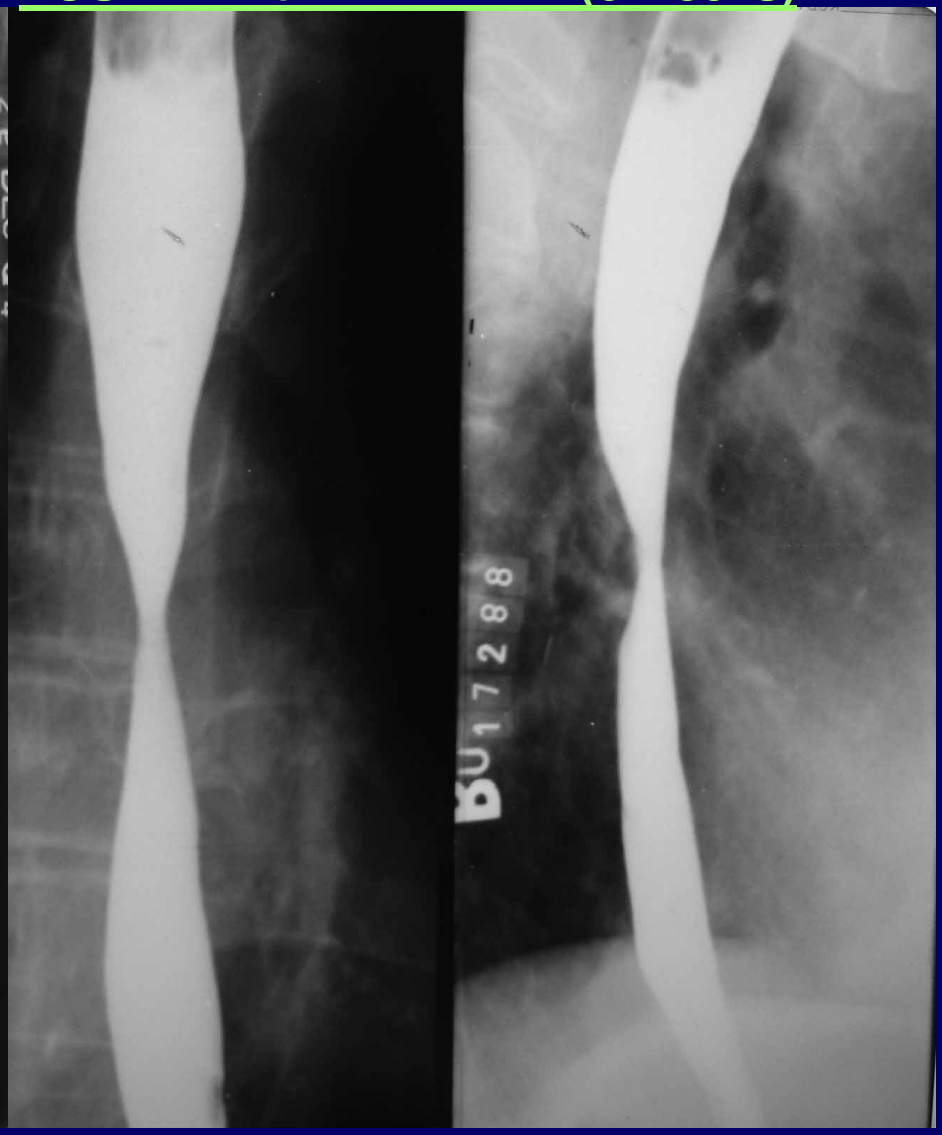
Patients treated at TMH- 29

PRE-TREATMENT STATUS

Response

POST ILRT RESPONSE

POST ILRT+ EBRT FILM (6 weeks)



Radiotherapy and Oncology 97 (2010) 488–494

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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

Adding external beam to intra-luminal brachytherapy improves palliation in obstructive squamous cell oesophageal cancer: A prospective multi-centre randomized trial of the International Atomic Energy Agency

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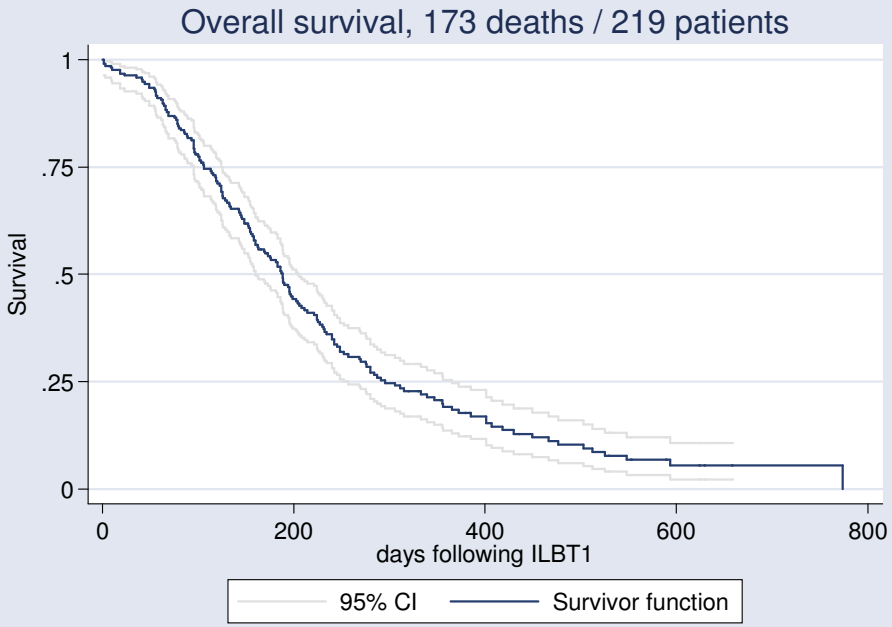
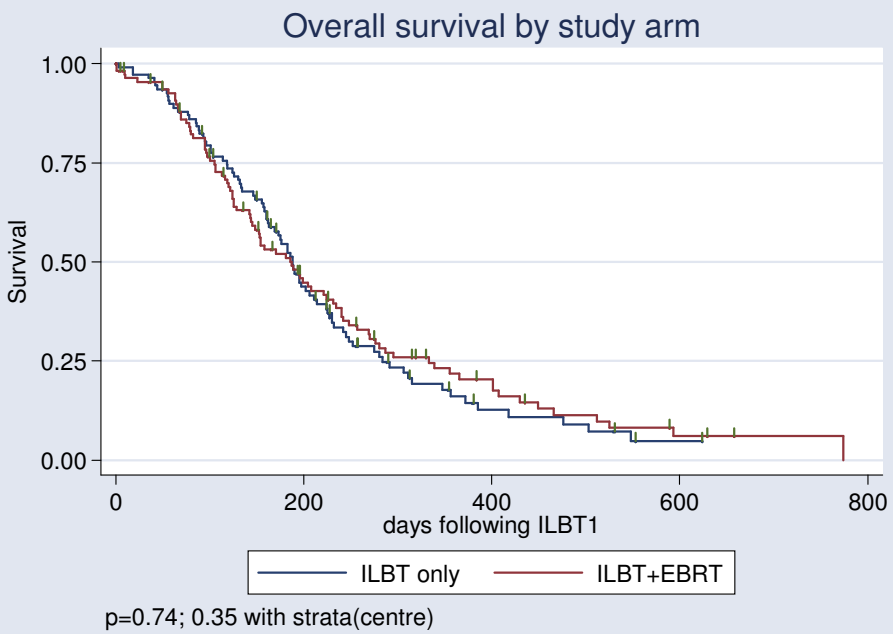
Results: Median follow-up was 197 days, with a median OS of 188 days and an 18% survival rate at 1 year. DRE was significantly improved with combined therapy, for an absolute benefit of +18% at 200 days from randomization ($p = 0.019$). In longitudinal regression analyses, scores for dysphagia ($p = 0.00005$), odynophagia ($p = 0.006$), regurgitation ($p = 0.00005$), chest pain ($p = 0.0038$) and performance status ($p = 0.0015$) were all significantly improved. In contrast, weight, toxicities and overall survival were not different between study arms.

Conclusion: Symptom improvement occurs with the addition of EBRT to standard HDRBT. The combination is well tolerated and relatively safe.





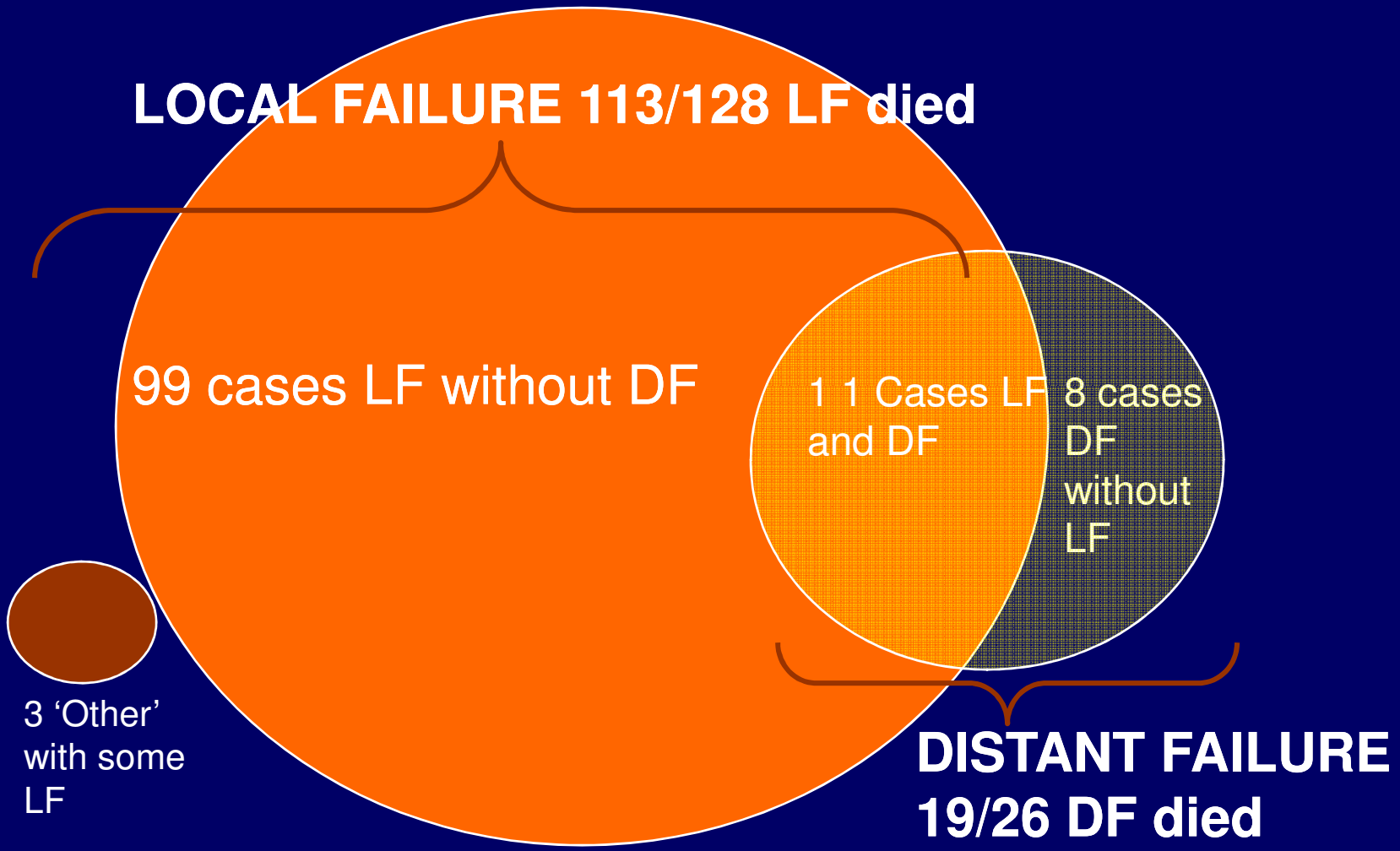
Occurrence of significant events. The numbers in the table represent events. Some patients had more than one type of event.

Event	Whole group *N* = 219	HDBT group *N* = 109	HDBT + EBRT group *N* = 110	2-Tailed *p*-value for difference
Perforation	4	1	3	0.62
Stricture	6	1	5	0.21
Stent	11	3	8	0.22
Dilatation	28	13	15	0.84
Fistulae	19	7	12	0.34
Second-line EBRT	21	21	0	n/a
Chemotherapy	2	1	1	1.00

HDBT: High dose-rate brachytherapy.

EBRT: External Beam Radiation Therapy.

Causes of death



Optimal EBRT dose/fractionation is unknown specially in limited resource settings and future trials are expected to answer those questions.

IAEA CRP No:E33021

Purpose

To determine if a shorter regime of EBRT (20Gy/ 5#) is not inferior in the palliation of dysphagia than a more protracted course of EBRT (30Gy/ 10#), both in combination with ILRT (8Gy/ 2#)

Study Design

Suitable Patient
1st Insertion of ILRT completed successfully
Stratified by Centre, M0/M+
RANDOMIZE

1# ILRT + 30Gy/ 10#

1# ILRT + 20Gy/ 5#

ILRT: 8Gy x 2 fr, 2-7 days apart

EBRT: within 3 – 14 days of 1st ILRT

Sample Size: 266
Time Period of Study: 3.5 years

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Study end-points

Primary Objective:

•Determine that 20Gy/ 5# is not inferior to 30Gy/ 10# for the outcome of dysphagia score, following 2 insertions of ILRT

Secondary Objective:

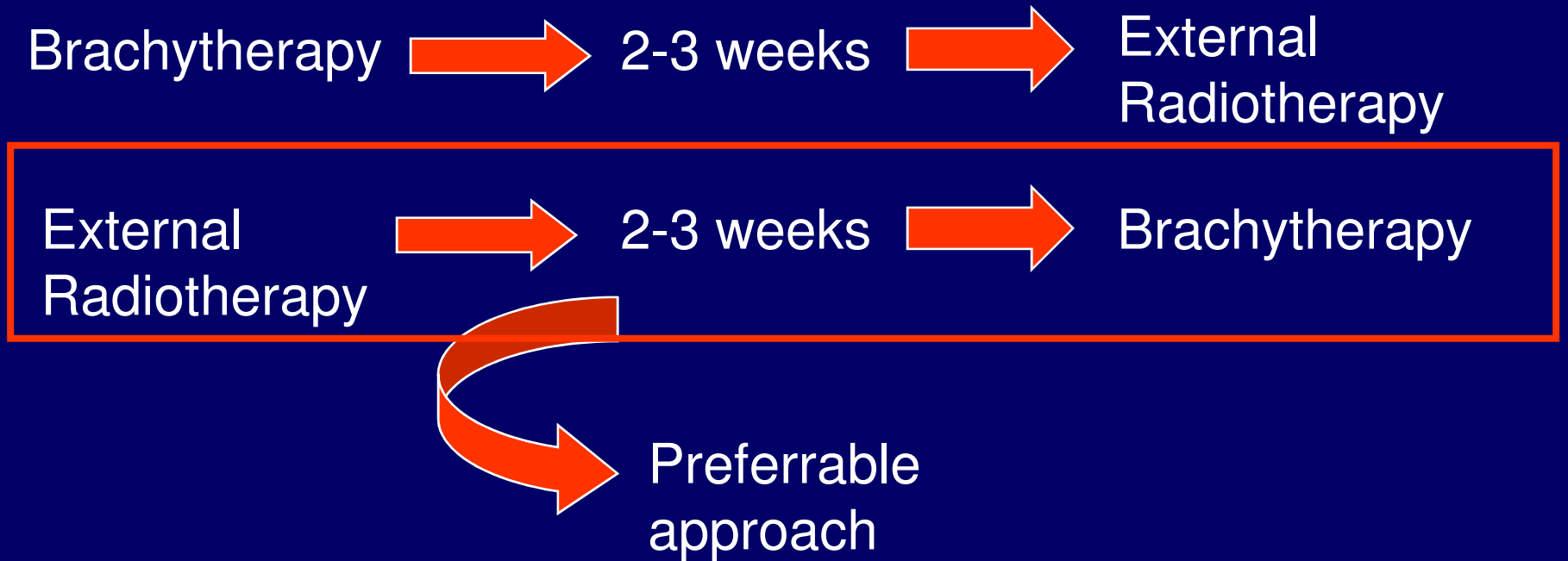
•Determine any difference in odynophagia, regurgitation, weight and performance status

•Determine any difference in overall toxicity, chest pain and Survival

•Validate the TMH – QOL questionnaire by comparing to EORTC QLQ-C30, KPS and PPSv2

Timing of Brachytherapy

Whenever given in combination with external radiotherapy- sequencing important.



Keyes* et al-

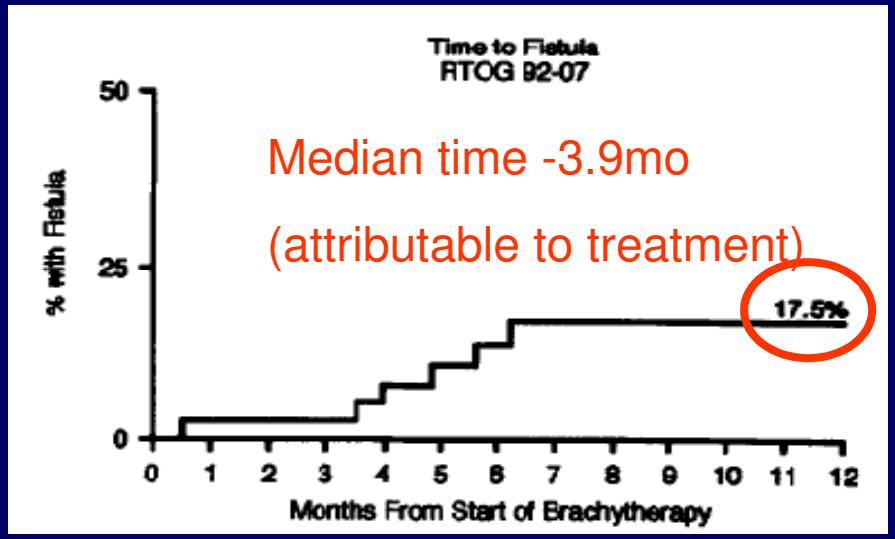
• Brachytherapy after EBRT yielded a higher rate of pathologically negative specimens compared to vice versa. (51% vs. 38%)

*Clin.Invest.Med.17(4):B115;1994

Complications

Depends on

1. Length of lesion treated
2. The type of initial lesion
3. Radiotherapy dose if given
4. Chemotherapy, type and timing if given
5. Type of applicator



Type	Stricture	Fistula
ILRT	4-10%	4%
ILRT+EBRT	10-15%	6-8%
ILRT+EBRT +CHEMO	20-50% (depending on timing of chemo)	8-18%%

Supportive Care

- IV hydration
- Gastrostomy/ Jejunostomy feeding encouraged.
- Nutritional support if caloric intake is poor.
- Antifungals/ gargles as and when required.
- Sucralfate/ local anesthetics
- Dilatations if required.

THANK YOU