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THE ROLE OF BRACHYTHERAPY ALONE AND IN CONJUNCTION WITH TELETHERAPY OR CHEMOTHERAPY IN ADVANCED OESOPHAGEAL CARCINOMA

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A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Doctor of Philosophy (Medicine)

Johannesburg, February, 1998

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Declaration

I declare that this thesis is my own unaided work, except where otherwise acknowledged. This thesis is being submitted for the degree of Doctor of Philosophy (Medicine) at the University of the Witwatersrand, Johannesburg. This thesis has not been submitted before for any degree or examination at any other university.

Signed this 27th day of February, 1998



RANJAN K. SUR

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It is thus with pride that I present this work which was written up at a very demanding period of my life when I was given the reins to manage the department, plan its transfer and move to Johannesburg Hospital, as well as plan its day to day activities, including academia and research.

I would like to dedicate this work to my friend Vic Levin who brought me to this beautiful country, gave me the opportunity to carry on with my research on oesophageal brachytherapy, provided the support and encouragement that one looks for in a Head of department, and facilitated my professional life in this country.

Ranjan Sur
Johannesburg, South Africa

Preface

The following papers have been published/submitted for publication and are based directly or indirectly on the work presented in this thesis:

1. **Sur R.K.**, Donde B., Levin C.V., Mannell A.
   Brachytherapy and Chemosensitization in palliation of Advanced Oesophageal Cancer. *(submitted for publication)*

2. **Sur R.K.**, Donde B., Levin C.V., Mannell A.
   Fractionated High Dose Rate Intraluminal Brachytherapy in Palliation of Advanced Esophageal Cancer.
   International Journal of Radiation Oncology Biology Physics 1998: 40: 447 - 53

3. **Sur R.K.**, Levin C.V., Donde B.
   The Value of high dose rate microsource brachytherapy in treatment of oesophageal carcinoma.
   South African Medical Journal 1997; 87: 81 -2

4. Didcott C.C., **Sur R.K.**, Donde B., Cronje S.L.
   Palliative Treatment of Esophageal Cancer combining Brachytherapy and Recurrent Dilatation using the Didcott dilator.
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Endocurietherapy/ Hyperthermia Oncology 1994; 10 : 199- 202.

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Journal of Medical Physics 1994; 19: 104- 7.

15. **Sur R.K.**, Kochhar R., Negi P.S., Gupta B.D.
High Dose Rate Intraluminal Brachytherapy in Palliation of Esophageal Cancer.
Endocurietherapy/ Hyperthermia Oncology 1994; 10 : 25- 9.

The following conference presentations are done from work directly or indirectly based on the thesis presented:

1. *Brachytherapy in Practice - International Brachytherapy Congress*, Corsica, France, May, 1997

   Fractionated Brachytherapy in palliation of advanced esophageal cancer - poster .
   Received Best poster prize

2. *Biannual Congress of the South African Society of Radiation Oncology*, Durban, March, 1997

   a. Preliminary Results of chemosensitization with brachytherapy in palliation of advanced esophageal cancer - paper
   b. High dose rate intraluminal brachytherapy in palliation of advanced esophageal cancer - paper

3. *International Brachytherapy Congress*, Nice, France, September, 1995

   Intraluminal HDR for Esophageal Cancer : South African Experience - poster

4. *Biannual Congress of the South African Society of Radiation Oncology*, Th'banchu Sun, South Africa, September 1995.

   a. Fractionated High Dose Rate Intraluminal Brachytherapy Alone in Palliation of Advanced Esophageal Cancer : Preliminary Report of a Randomized Prospective Trial - paper
   b. Palliation of Carcinoma of the Oesophagus with brachytherapy and the Didcott dilator.

c. Adverse Effects of Teletherapy Dose Fractionation on Complications in Telebrachytherapy Treatment of Carcinoma Esophagus : Final Report.

The following papers have been published by the author previously on oesophageal brachytherapy

1. **Sur R.K.**
Sucralfate in Radiation induced mucositis.
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2. Sur M., Taylor L., Cooper K., **Sur R.K.**
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Carcinoma Esophagus treated with External Irradiation and Intraluminal Therapy : A Case Discussion.
Medical Physics Bulletin 1990; 15 : 127- 9.

Chapter 6

ABSTRACT

BACKGROUND

Oesophageal cancer is the most common cancer amongst black South African men. More than 95% of the cases are diagnosed at a stage where treatment options are essentially palliative. Treatment options include bypass surgery, laser therapy, intubation, external beam radiotherapy, chemotherapy and a combination of these. The prognosis is dismal. The median survival regardless of the method is less than 5 months. Most methods are expensive, and utilise in-patient and hospital resources often for prolonged periods of time. These are also associated with morbidity and mortality of the procedure. Brachytherapy has been reported to be an effective means of palliating oesophageal cancer in patients who have not responded successfully to other means of therapy. It is relatively safe, cost effective and can be done on an out patient basis thus allowing for optimal utilisation of resources.

Unfortunately, there are no randomised prospective studies in the literature on the use of brachytherapy alone in oesophageal cancer. Further, there is no consensus on the "most effective" brachytherapy dose, as most studies are retrospectively reported, and are usually conducted on small numbers of patients. Often the results lack patient details, and are based on patients who have failed other methods of therapy.

This report looks at the results of brachytherapy when used alone in the palliation of advanced oesophageal cancer, and further examines :

1. The question of dose optimisation in a randomised prospective setting
2. The role of teletherapy and teletherapy combined with brachytherapy boost in the palliation of oesophageal cancer in a randomised prospective trial.

3. The role of high dose fraction teletherapy in opening an occluded oesophageal lumen in patients, in whom initial brachytherapy is not possible due to tight strictures, and/or long lesions.
4. The role of chemosensitisation with brachytherapy in palliation of advanced oesophageal cancer in a randomised prospective study.

PURPOSE

IA. BRACHYTHERAPY ALONE

To optimise the dose of brachytherapy when used alone in patients with advanced oesophageal cancer (staged as CT stage III &IV) with regard to -

a. Dysphagia free survival
b. Overall survival
c. Complication free survival
d. To identify prognostic variables that may have an impact on the treatment outcome
e. To evaluate the complications encountered in the various treatment groups. These include strictures, fistulae and procedural morbidity, and mortality following treatment

IB. TELEBRACHYTHERAPY IN PATIENTS IN WHOM INITIAL BRACHYTHERAPY IS NOT POSSIBLE:

In patients with long lesions and with locally advanced disease, causing total obstruction of the oesophageal lumen, to evaluate the role of tele-brachytherapy in palliation of patients. To evaluate -

a. Dysphagia free survival
b. Overall survival
c. Complication free survival

d. To identify prognostic variables that may have an impact on the treatment outcome

e. To evaluate the complications encountered, specifically, strictures, fistulae, procedural morbidity and mortality following treatment.

STUDY II

Following completion of the above study I (A), to conduct a prospective randomised study to determine the value of :

CHEMOTHERAPY AS A SENSITIZER TO BRACHYTHERAPY IN PALLIATION OF PATIENTS WITH LOCALLY ADVANCED (CT STAGE III) OESOPHAGEAL CANCER.

To compare :

a. Dysphagia free survival

b. Overall survival

c. Complications free survival

d. Identification of prognostic variables that may have an impact on the treatment outcome

e. Evaluation of the complications encountered, specifically strictures, fistulae, procedure related morbidity and mortality following treatment.

PATIENTS AND METHODS

STUDY I A

One hundred and seventy two patients with advanced oesophageal cancer were randomised to receive 12 Gy/2#/2 weeks (Group A); 16 Gy/2#/2weeks (Group B) and 18 Gy/3#/3 weeks (Group C) by High dose rate intraluminal

brachytherapy (HDRILBT). Treatment was given weekly, and the dose prescribed at 1cm from the source axis. Patients were followed up monthly and assessed for dysphagia relief, and for development of complications. (Sur et al., 1998)

Study IB

1. Postgraduate Institute of Medical Education and Research, India

A total of 50 patients with advanced squamous cell carcinoma of the esophagus were randomised into 2 treatment groups. Group A (n=25) received 35 Gy/15#/3 weeks of external beam radiotherapy (EBRT) followed 3 weeks later by 12 Gy/2#/2 weeks HDRILBT. Group B patients (n=25) received 35 Gy/15#/3 weeks EBRT alone. ILBT was prescribed at 1 cm from the center of the source axis. Patients were followed up every 3 months clinically, radiologically, and endoscopically, and were assessed for relief of dysphagia and development of any complications (Sur et al., 1994a).

2. University of the Witwatersrand, South Africa

Forty five previously untreated patients with advanced inoperable oesophageal cancer who failed initial brachytherapy due to tight stenosis or long lesions, received treatment with a combination of EBRT + HDRILBT. EBRT was given to a dose of 20 Gy/5#/1 week. 2 weeks later HDRILBT of 10 Gy was given in a single fraction at 1 cm, from the centre of the source axis. The patients were followed monthly and assessed for relief of dysphagia and development of any complications (Sur et al., 1996c).

Study II

Chemosensitisation with brachytherapy in palliation of advanced oesophageal cancer

Following completion and analysis of study I(A) above, 200 patients with inoperable, locally advanced oesophageal cancer were randomised into 4 treatment groups. Group A(n=50) received injection 5 FU 500 mg/m^2/daily for 5 days as a slow continuous infusion. HDRILBT of 16 Gy/2#/1 week was given 8 Gy per fraction on days 2 and 4 of chemotherapy. Group B (n=50) received brachytherapy as in Group A but without chemotherapy. Group C (n=50) received Inj 5 FU 500mg/m^2/daily for 5 days, as a slow continuous infusion. HDRILBT of 18 Gy/3#/1 week was given 6 Gy per fraction on day 1, 3 and 5 of chemotherapy. Group D (n=50) received brachytherapy as in Group C, but without chemotherapy. All patients were followed up monthly and assessed for relief of dysphagia and development of any complications.

RESULTS:

Study I A : Brachytherapy Alone

Twenty two patients died before completing treatment due to advanced disease and poor general condition. The overall survival was 19.4% at the end of 12 months for the whole group (A - 9.8 %, B - 22.46 %, C - 35.32 % ; p >0.05). The dysphagia free survival was 28.9% at 12 months for the whole group (A - 10.8 %, B - 25.43 %, C - 38.95 %, p>0.05). Forty three patients developed fibrotic strictures needing dilatation (A5/35, B15/60, C23/55, p=0.032). Twenty seven patients had persistent luminal disease (A11, B6, C10) 15 of which progressed to fistulae (A7, B2, C6, p=0.032). There was no effect of age, sex, race, histology, performance status, previous dilation, presenting dysphagia score, presenting weight, grade, tumour length, and stage of disease on overall

survival, dysphagia free and complication free survival (p>0.05). On a multivariate analysis, brachytherapy dose (p=0.002) and tumour length (p=0.0209) were found to have a significant effect on overall survival, and the brachytherapy dose was the only factor that had an impact on local tumour control (p=0.0005) while tumour length was the only factor that had an effect on dysphagia free survival (p=0.0475). When compared with other forms of palliation currently available (bypass surgery, laser, chemotherapy, intubation, external radiotherapy), fractionated brachytherapy gave the best results with a median survival of 6.2 months.

STUDY IB

1. POSTGRADUATE INSTITUTE OF MEDICAL EDUCATION AND RESEARCH, INDIA

Both groups were comparable in terms of patient characteristics. The 12 month actuarial survival was 69% in group A and 16% in group B (z=4.077). At 6 months, local control of the disease was 89.5% in group A and 16% in group B (p<0.01, chi square test), while the corresponding values for relief of dysphagia were 84.2% and 12.5% (p<0.01, chi squared test). Beyond 6 months, statistical comparison was not possible because of poor survival in group B. Four patients in group A developed oesophageal strictures, which were easily dilated. No other complications were encountered.

2. UNIVERSITY OF THE WITWATERSRAND, SOUTH AFRICA

A preliminary analysis of the first 20 patients treated was undertaken following four months of treatment. It was found that the incidence of strictures with this regime had increased. It was thought that the high dose per fraction when using EBRT was the probable cause. EBRT dose was therefore brought down to 15 Gy given in five fractions, 3 Gy per fractions over one week. A total of 45

patients were therefore entered. 34 received EBRT of 20 Gy/5#/1 week and 10 Gy HDRILBT while 11 received 15 Gy/5#/1 week and 10 Gy HDRILBT. The dysphagia free survival at one year was 34% for the whole group (20Gy-37%, 15 Gy-33%), and the overall survival was 31% for the whole group (20Gy- 34%, 15 Gy- 28%). Complication free survival was 55% for the 20 Gy group and 83% for the group that received 15 Gy EBRT ($p>0.05$). Age, sex, race, length of tumour, tumour grade, or dose of EBRT made no impact on dysphagia free, overall, and complication free survivals. In all patients the oesophageal lumen had opened up sufficiently in 2 weeks, making brachytherapy possible.

STUDY II : CHEMOSENSITISATION WITH BRACHYTHERAPY

Two hundred patients were randomised into the 4 treatment groups. Nine died before completing the treatment due to poor general condition and progressive disease. The patients were comparable to each other with regard to the prognostic variables. Both the groups that underwent brachytherapy alone (B & D) had a higher proportion of patients with poor Karnofsky's performance status (KPS), when compared to the chemobrachytherapy groups(A&C) and this was significant statistically ($p=0.007$). The dysphagia free survival for the patients who completed treatment was 18.88% at one year (Group A- 11.65%, Group B- 34.3%, Group C- 8.06%, Group D- 30.47% at 1 year). The overall survival for the whole group was 22.3&% at one year (Group A- 22.14%, median- 6.17 months; Group B- 31.09%, median - 7.07 months; Group C- 13.58%, median- 7.23, Group D- 22.39%, median- 6.63 at 1 year). Both the dysphagia free and overall survivals in both chemosenstisation groups were worse than the brachytherapy alone groups ($p>0.05$). This was attributed to the higher incidence and mean time of occurrence of fibrotic strictures in the chemosensitisation groups (Group A- 12/50, 125.9 days, Group B- 7/49, 151.6 days, Group C- 11/48, 147.2 days, Group D- 7/44, 153.3 days, $p>0.05$). Twenty one patients failed treatment due to persistent luminal disease causing

oesophageal lumen obstruction after brachytherapy. Failures were similar amongst all groups (p>0.05). Nine prognostic variables were analysed from this study. These included age, sex, race, presenting performance score, previous dilatation, presenting dysphagia score, presenting weight, grade of tumour, length above and below the mean tumour length, and protocol . All these factors were analysed for their effect on overall, dysphagia and stricture free survivals using univariate and multivariate analysis. On multivariate analysis race had an impact on dysphagia free survival (p=0.0208), possibly due to small numbers in the other group while grade was the only factor that had an impact on overall survival (p=0.0232) and stricture free survivals (0.0372) on univariate analysis. Prior dilatation had an impact on stricture free survival, with patients who had undergone previous dilatation having better survival than those undilated (p=0.0003). Again, this result could also be influenced by the smaller number of patients in the undilated group. There was no effect of any other variable on any of the outcomes on multivariate and univariate analysis. Addition of chemotherapy had no impact on stricture free survival (p=0.2514). Similarly brachytherapy dose had no impact on the incidence of strictures (p=0.6020)

There were no morbidity or mortality associated with any brachytherapy treatments. No cases of perforation were observed.

CONCLUSIONS

Fractionated brachytherapy is the best modality for palliation of advanced oesophageal cancer. It offers the best palliation to patient when compared with all other modalities currently available. The optimal brachytherapy dose ranges between 16 Gy in 2 fractions and 18 Gy in 3 fractions given a week apart.

EBRT + ILBT boost is better than EBRT alone in palliation of advanced oesophageal cancer. It provides the patient with lasting relief of dysphagia which

is associated with improved overall survival due to maintenance of the nutritional status of the patient. There is no significant morbidity associated with telebrachytherapy treatment.

High dose per fraction EBRT has a role in opening a constricted oesophageal lumen so as to make brachytherapy possible in patients who failed initial HDRILBT for advanced oesophageal cancer. Patients have prolonged dysphagia free and overall survival with acceptable morbidity rates.

There is no role of chemosensitisation with brachytherapy in advanced oesophageal cancer. Chemosensitisation is associated with increased stricture formation and earlier onset of strictures than brachytherapy alone of the same dose alone. The best results are obtained if brachytherapy is completed within one week of treatment. Results are similar with HDRILBT doses of 16 Gy/2#/1 week and 18 Gy/3#/1 week.

Chapter 7

Introduction

THE PROBLEM

Seventy years ago, squamous carcinoma of the oesophagus was a rare disease in black South Africans (Rose, 1978). The incidence has risen since then and currently it is the most common cancer amongst black men in South Africa, and the second most common cancer amongst black women (Sitas et al., 1997). In the 1950s, a large number of cases were diagnosed in the former Transkei and Ciskei, and in predominantly rural areas of South Africa. The prevalence in urban population was considerably less (McGlashen, 1988). Cancer of the oesophagus remains the most frequently reported cancer in the Transkei, representing 45.8% of malignant disease (Sitas et al., 1997). The incidence of oesophageal cancer in Soweto, South Africa's largest urban black community, has risen and is estimated to be from four to five fold greater than that in the Transkei. In 1985, the age standardised incidence of oesophageal cancer in Soweto was 125/100,000 in men, and 37/100,000 in women (Kneebone & Mannell, 1985).

In South Africa, it is a common perception that squamous cancer of the oesophagus in black Africans is more advanced by the time of diagnoses, and that the patients more debilitated when compared with those suffering from the disease in Western countries (Hunt, 1978). In 1989, the national study group for oesophageal cancer in South Africa collected and centralized data on 1926 new cases of squamous carcinoma of the oesophagus seen in the Ciskei, and in major

provincial centers of South Africa from 1985 to 1988 (Mannell & Murray, 1989). There were 1438 men and 488 women (M: F-3: 1) of whom 55% were between 50 and 69 years of age (mean age, 56 years). 22% of the patients were in the fifth decade, 14.2% were 70 years of age or older, and 8.8% were younger than forty years of age. 62% of patients, complained of dysphagia to solid food , 12% had difficulty swallowing liquids and 24% suffered from total dysphagia. Although 2% of the patients had no dysphagia, they did have evidence of metastatic disease.

The South African Institute of Medical Research, recently reported the incidence of oesophageal cancer in South Africa (Sitas et al., 1997). Cancer of the oesophagus is a second most common cancer in all males (8.1% of all cancers). It is the most common cancer in black men (17.9%) (L. R. = 1 in 39). Among white males, by contrast, oesophageal cancer ranked eighth (1.5%) (L. R. 1 in 119), with a risk factor three times lower. Among coloured and Asian males, oesophageal cancer ranked fourth and seventh respectively.

When the South African incidence is compared with the rest of Africa, the age standardised rates amongst black males are comparable to rates from Zimbabwe but are high when compared to West African countries like Mali or Gambia. It has been estimated that in Mali, for example, 95% of the patients have advanced stage disease (Sitas et al., 1997).

In an attempt to palliate patients with advanced disease, various treatment options have become available. Mannell and Murray (1989) reported their series of 1926 cases seen in the department of Surgery, University of the Witwatersrand, Johannesburg. Palliative surgery, in the form of resection or bypass was conducted in 17% of the patients, external radiotherapy in 35%, Chemotherapy in 22%, intubation 37%, and no treatment in 6% of the patients. Studies from the department of Radiation Oncology, University of the Witwatersrand, have previously shown that the mean tumour length ranges from 7-14 cm (Sur et al., 1994b,c; 1996a,c).

It has been shown that length of the primary tumour is inversely related to its curability, and is directly related to its stage of advancement. For tumors smaller than 5 cm in length, 40% are localized, 25% are locally advanced, and 35% have distant metastasis or are unresectable for cure. For tumors larger than by 5 cm, only 10% are localized, 15% are locally advanced, and 75% have distant metastasis or are unresectable for cure (Clayton, 1928, Fleming, 1943, Merendiono & Maerk, 1952).

In South Africa, most patients with oesophageal cancer present at a stage where no curative options can be offered, and treatment is palliative in most cases. The main aim of treatment is to provide the patient with dysphagia free survival until death occurs due to aspiration, and/or progressive disseminated disease.

The median survival of untreated oesophageal cancer is 4 months (Rider & Mendoza, 1969). Conventional External Beam Radiotherapy (EBRT) is a protracted form of therapy administered in daily treatments over a period of 2 - 6 weeks. Various protocols have been used to palliate patients. Radiation doses ranging from 10-40 Gy given in various fractionations have been used. The mean survival period with external beam radiotherapy is 5 months, not significantly different from that of untreated patients (Rider & Mendoza, 1969). However, the quality of life was significantly better for most patients having dysphagia free survival until death.

Unlike external beam radiotherapy where the radiation is delivered externally, brachytherapy is a form of radiation treatment where the radioactive isotope is placed in and around a tumour. In the oesophagus, this is done by placing a catheter in the oesophageal lumen. A radioactive isotope, such as Iridium-192 or Cobalt-60, is then passed through the catheter by means of a remote after loading system, to deliver a high dose to the luminal aspect of the tumour. This part of the tumour is thought to be more hypoxic and therefore relatively radioresistant. Due to the close proximity of the radiation source, a very high dose of radiation is delivered to the luminal aspect of the tumour which undergoes rapid necrosis, thus rapidly restoring lumen patency. This allows the patient to rapidly restore swallowing which is maintained for a prolonged period of time. Further, high specific activity radiation sources, for example, small Ir-192

sources with an activity of 10 Ci (370 GBq) allows a dose rate of > 2 Gy / minute to be delivered in a very short time - so called High Dose Rate Intraluminal Brachytherapy (HDR ILBT), are used.

Further advantages also include:

1. Short treatment time - the whole treatment including the procedure takes about 20 minutes
2. No anesthesia is required - The procedure is done under Pethidine analgesia
3. The procedure can be performed on an out patient basis - Therefore no admission is required, which saves hospital beds for optimal utilization of resources.
4. There is minimal patient discomfort and morbidity of the treatment and procedure.
5. Risk of radiation to personnel is minimal.
6. Radiation dose to surrounding normal tissue structures due to rapid dose fall off, is minimal.
7. Many patients can be treated in one day on one HDR unit
8. It is a cost effective and safe method of treatment.

In view of the above, the rationale for these studies were formulated:

1. In the palliative situation, with limited life expectancy, the shortened duration of treatment and rapid response to HDR ILBT may improve the quality of life of the patient.

2. The virtual absence of mortality associated with properly administered HDR ILBT contrasts strongly with the 15-20% mortality associated with palliative surgery and even intubation (Mannell, 1987).

3. The costs of HDR ILBT are lower than those of surgical procedures or prolonged therapy.

4. In patients, in whom initial brachytherapy is not possible due to long lesions/tight strictures, initial high dose per fraction teletherapy may have a role in opening a constricted oesophageal lumen so that brachytherapy may be possible.

5. Chemosensitisation with teletherapy has been shown to improve results in oesophageal cancer. In the palliative situation, chemosensitization with brachytherapy may have a role in improving the dysphagia free survival in patients with advanced oesophageal carcinoma.

Although there are several prospective randomized studies on the use of EBRT in palliation of oesophageal cancers, there are very few studies prospective studies on the use of brachytherapy alone in the palliation of advanced oesophageal cancer (Sur and Levin, 1995b). Most studies are retrospective analyses done on patients on whom other forms of therapy have failed. No reports on the optimization of dose most likely to give the best results are available.

In this report, the optimization of brachytherapy dose is examined for the first time in a randomized prospective setting.

Further, there are no studies, prospective or retrospective, which examine the effect of chemosensitization with brachytherapy in the palliation of advanced and locally advanced oesophageal cancer.

This report also examines the role of chemosensitization with brachytherapy alone in the palliation of advanced oesophageal cancer for the first time in a randomized prospective setting.

A combination of external beam radiotherapy and brachytherapy as a local boost has been used by researchers in the past to palliate advanced oesophageal cancer.

In this report, the experience previously published (Sur et al., 1994a) and the use of teletherapy in high dose per fraction, in an attempt to open up the oesophageal lumen of patients in whom initial brachytherapy is not possible, is also examined for the first time.

Chapter 8

Aims and Objectives

STUDY I

In this study, brachytherapy was used alone to palliate patients with advanced oesophageal carcinoma (IA).

In those patients in whom initial brachytherapy was not possible, due to long lesions and/or tight strictures, initial teletherapy was given in an attempt to open the oesophageal lumen. This was followed by brachytherapy in 2 weeks time (IB). The following are the aims and objectives of the studies:

IA. Brachytherapy Alone

To optimize the dose of brachytherapy when used alone in patients with advanced oesophageal cancer (staged as CT stage III &IV*) with regard to -

a. Dysphagia free survival

b. Overall survival

c. Complication free survival

d. To identify prognostic variables that may have an impact on the treatment outcome

e. To evaluate the complications encountered in the various treatment groups. These include strictures, fistulae and procedural morbidity, and mortality following treatment

IB. TELEBRACHYTHERAPY IN PATIENTS IN WHOM INITIAL BRACHYTHERAPY IS NOT POSSIBLE:

In patients with long lesions and with locally advanced disease, causing total obstruction of oesophageal lumen, to evaluate the role of tele-brachytherapy in palliation of patients. To evaluate -

a. Dysphagia free survival

b. Overall survival

c. Complication free survival

d. To identify prognostic variables that may have an impact on the treatment outcome

e. To evaluate the complications encountered, specifically, strictures, fistulae, procedural morbidity and mortality following treatment.

STUDY II

Following completion of the above study I (A), to conduct a prospective randomized study to determine the value of :

CHEMOTHERAPY AS A SENSITIZER TO BRACHYTHERAPY IN PALLIATION OF PATIENTS WITH LOCALLY ADVANCED (CT STAGE III) OESOPHAGEAL CANCER.

This would be conducted by comparing :

a. Dysphagia free survival

b. Overall survival

c. Complications free survival

d. Identification of prognostic variables that may have an impact on the treatment outcome

e. Evaluating the complications encountered, specifically strictures, fistulae, procedure related morbidity and mortality following treatment.

*** CT STAGING OF OESOPHAGEAL CANCER (HALVORSEN & THOMPSON, 1984)**

Stage I	Intraluminal Mass
Stage II	Mass and wall thickening**
Stage III	Spread to adjacent structure
Stage IV	Distant Metastasis

** Wall thickening defined as > 5mm

Chapter 9

Hypothesis

STUDY IA : BRACHYTHERAPY ALONE

H_1 Brachytherapy contributes towards providing patients with advanced oesophageal cancer sustained dysphagia free survival and overall survival.

STUDY IB : TELEBRACHYTHERAPY

H_1 Initial teletherapy has a role in opening a constricted oesophageal lumen to permit brachytherapy to be performed. The role of teletherapy is to rapidly shrink the tumor in order to open the lumen, making brachytherapy possible.

H_2 Initial teletherapy with brachytherapy plays a role in providing dysphagia free survival and overall survival in patients with advanced oesophageal cancer, in whom it is not possible to pass a stainless steel guide wire for initial brachytherapy treatment in an effort to provide palliation.

STUDY II : CHEMOSENSITISATION WITH BRACHYTHERAPY

H_0 There is no difference in overall survival, dysphagia free survival and complication free survival in patients who receive chemosensitisation with brachytherapy when compared to those who receive brachytherapy alone.

H_1 When compared to those patients who receive brachytherapy alone, a difference in overall survival, dysphagia free survival and complication free survival is evident in patients who receive chemosensitisation with brachytherapy.

Chapter 10

Patients and Methods

STAGING

All patients in this study were staged by the computed tomography (CT) staging system described by Halvorsen and Thompson (1984). Most patients were worked up by the surgical units which referred the patients. They were deemed to be inoperable due to extensive para- oesophageal disease or lymph nodes as ascertained by CT. Radical Surgery was not possible in any of these patients and they were all referred for brachytherapy.

The CT system used was as follows :

Stage I	Intraluminal Mass
Stage II	Mass and wall thickening*
Stage III	Spread to adjacent structure
Stage IV	Distant metastasis

* Wall thickening defined as > 5 mm

MEASUREMENT OF TUMOUR LENGTH

Tumour length was made measurement on a barium/gastrografin swallow prior to the brachytherapy procedure, along with fiberoptic upper gastrointestinal endoscopy (g.i) whenever possible. For this report, it is accepted that underestimation of tumour length by this method of measurement may occur when compared to alternate ways of measurements as done by CT scan. However, this method was used as it was standard in all patients.

BRACHYTHERAPY PROCEDURE

REQUIREMENT : The patient must fast at least 12 hours before the procedure

ANALGESIA : with Pethidine 50 mg + Buscopan 1 amp given deep I.m. 30-45 minutes before the procedure

EQUIPMENT : Flexible fiberoptic upper G.I., Stainless steel guide wire (Figure I), Nucletron 6 and 4 mm intra oesophageal catheters, Marker wire (Figure II), Fluoroscopy control (C-arm) (Figure III), Brachytherapy Treatment Planning system (Figure IV), and afterloading microsource HDR unit (Figure V)

PROCEDURE :

1. Oral Gastrograffin is given to the patient, the tumour is localised and tracheo-oesophageal fistula is ruled out prior to the procedure (Figure VI).
2. Fiberoptic upper g.i. endoscopy is performed in all patients and the tumour is visualised (Figure VII, VIII).
3. Stainless-steel guide wire is passed across the tumour length under Endoscopic vision (Figure IX, X).
4. The Nucletron Intra Oesophageal Catheter with an outer diameter of 0.6 cm is passed across the tumour length over the guide wire (Figure XI).
5. Positioning of the Catheter is performed under fluoroscopic vision using a C Arm (Phillips BV29) after giving the patient oral Gastrograffin (Figure XII). A margin of 2 cm

is prescribed above and below the visible tumour, including the tumour (Figure XIII).

6. The catheter is connected to a remote after loading HDR unit (Microselectron HDR, Nucletron, The Netherlands) which has an Iridium-192 source of 10 Ci (370GBq) initial activity (Figure XIV, XV).

7. Treatment is given following dose optimization on the treatment planning system for brachytherapy treatment (Plato, Nucletron, The Netherlands) - see Figure XVI,XVII. The dose was prescribed at 10 mm from the center of the source axis, and included the tumour and a 2 cm margin proximally and distally to the tumour.

8. Treatment delivery is controlled from the remote console of the HDR unit (Figure XVIII, XIX).

TREATMENT TIME : The entire procedure depending on source activity, is 20-30 minutes; it is done on an out patient basis

IA. BRACHYTHERAPY ALONE

A total of 172 patients with advanced oesophageal cancer were randomised into a prospective randomised study.

SELECTION CRITERIA

Patient selection criteria included :

Figure I

Upper G.I. Fiberoptic scope and stainless steel guide wire

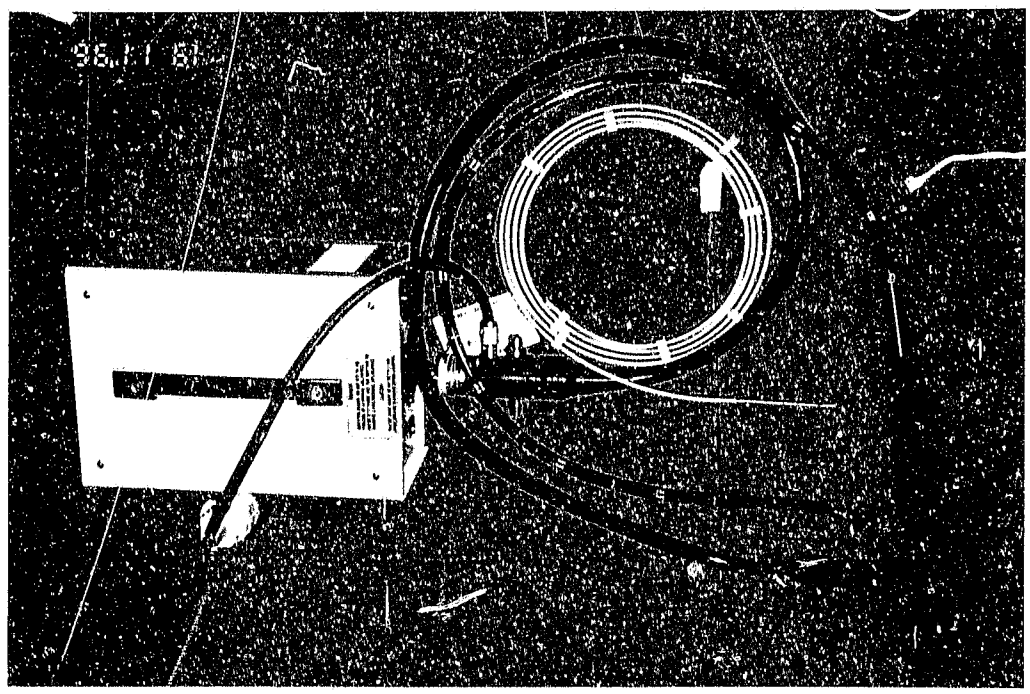


Figure II

Nucletron 4 and 6 mm Oesophageal catheters with marker wire

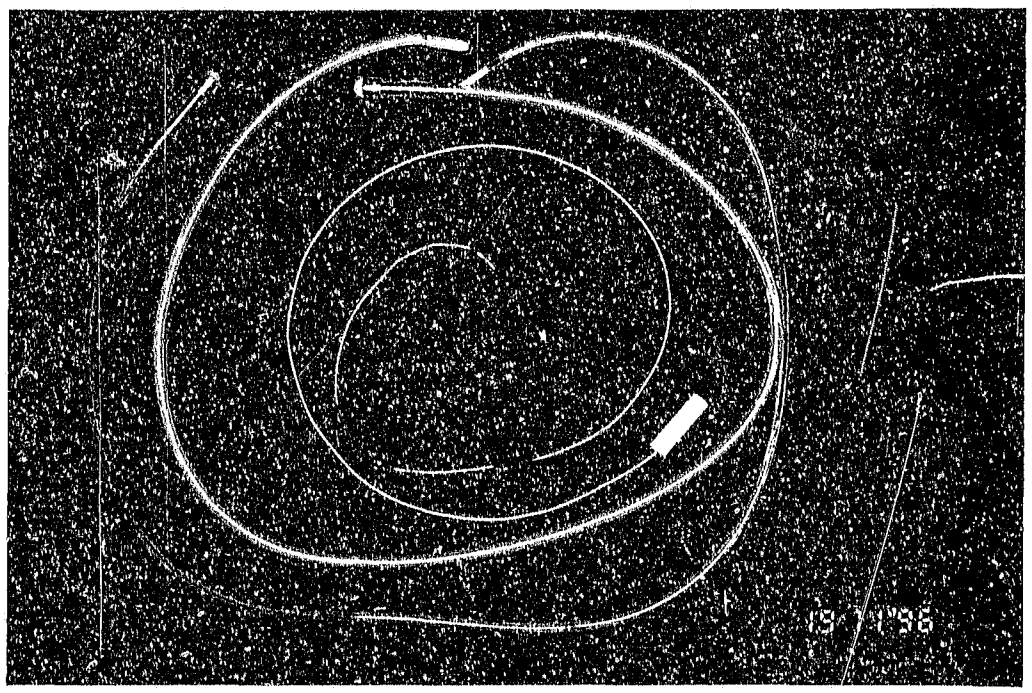


Figure III

Fluoroscopy control - c-arm

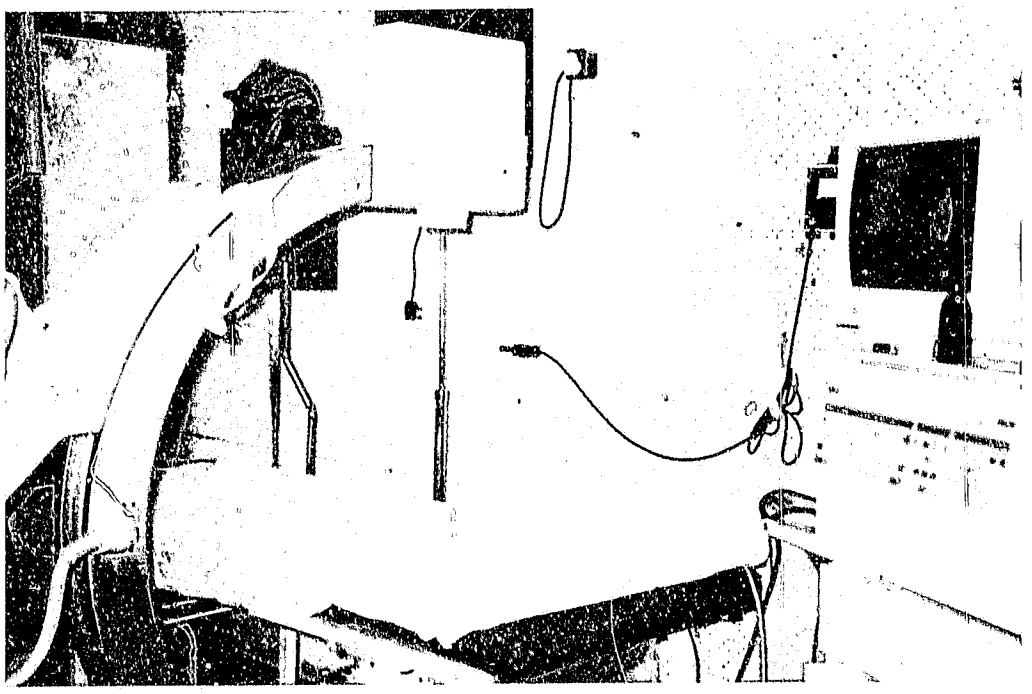


Figure IV

Brachytherapy Treatment Planning System

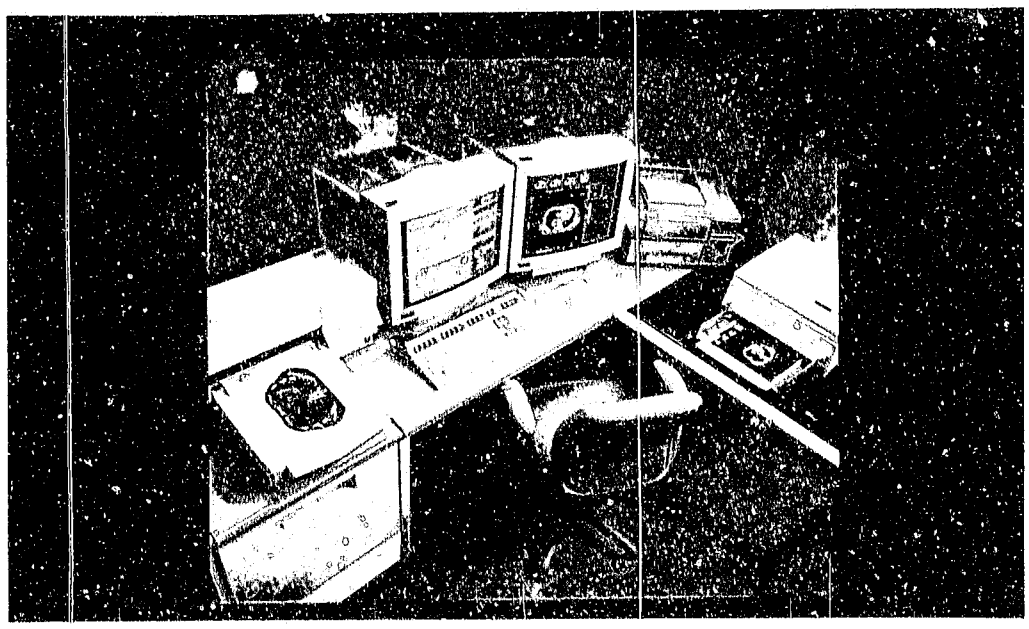


Figure V

Nucletron - Microselectron HDR - Remote After loading HDR unit

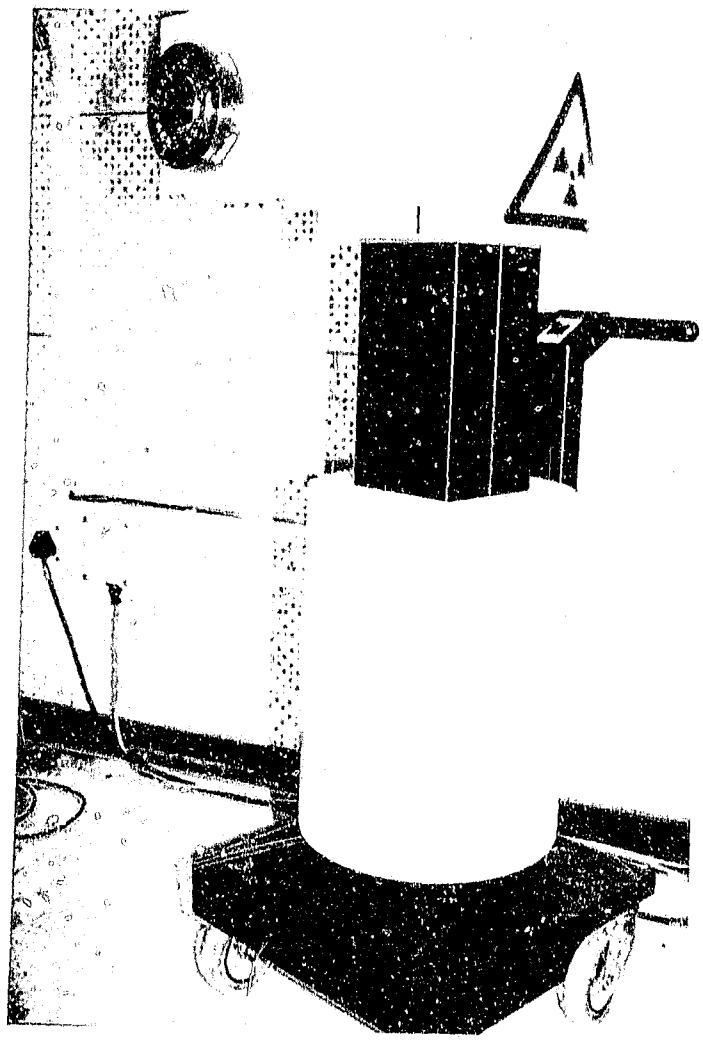


Figure VI

Visualization of the tumor after giving the patient 10 ml of Oral Gastrografin.
This also rules out presence of a tracheo-oesophageal fistula



Figure VII

Tumor as visualized on fiberoptic endoscopy

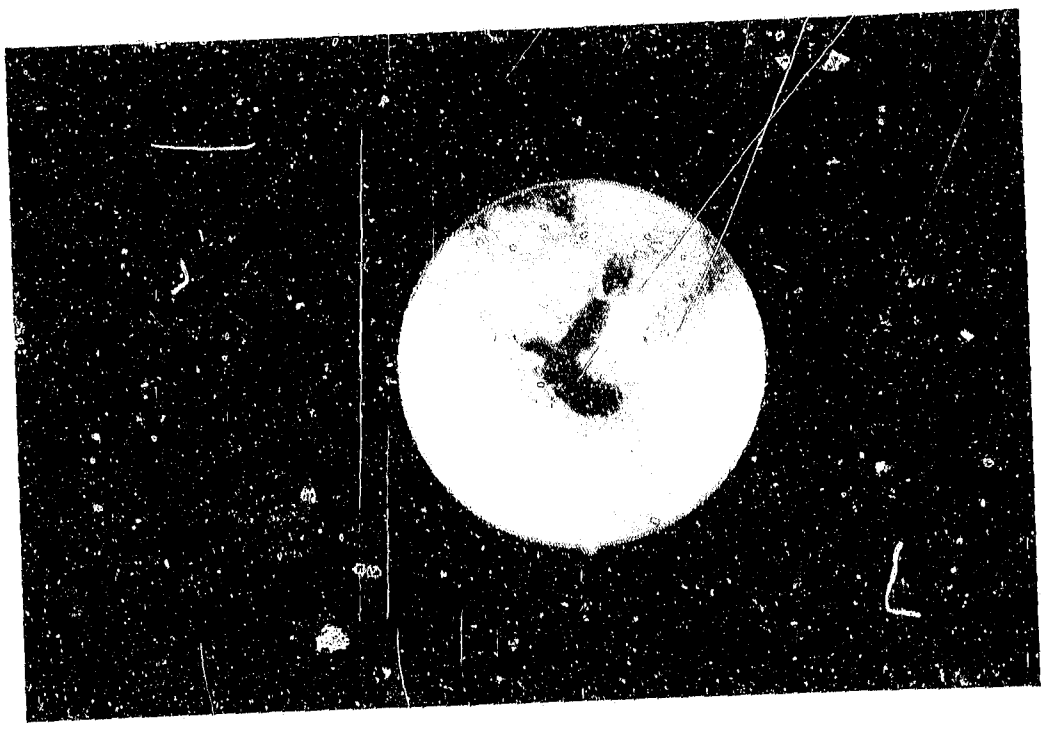


Figure VIII

Tumour as visulised on fluoroscopy with a c-arm

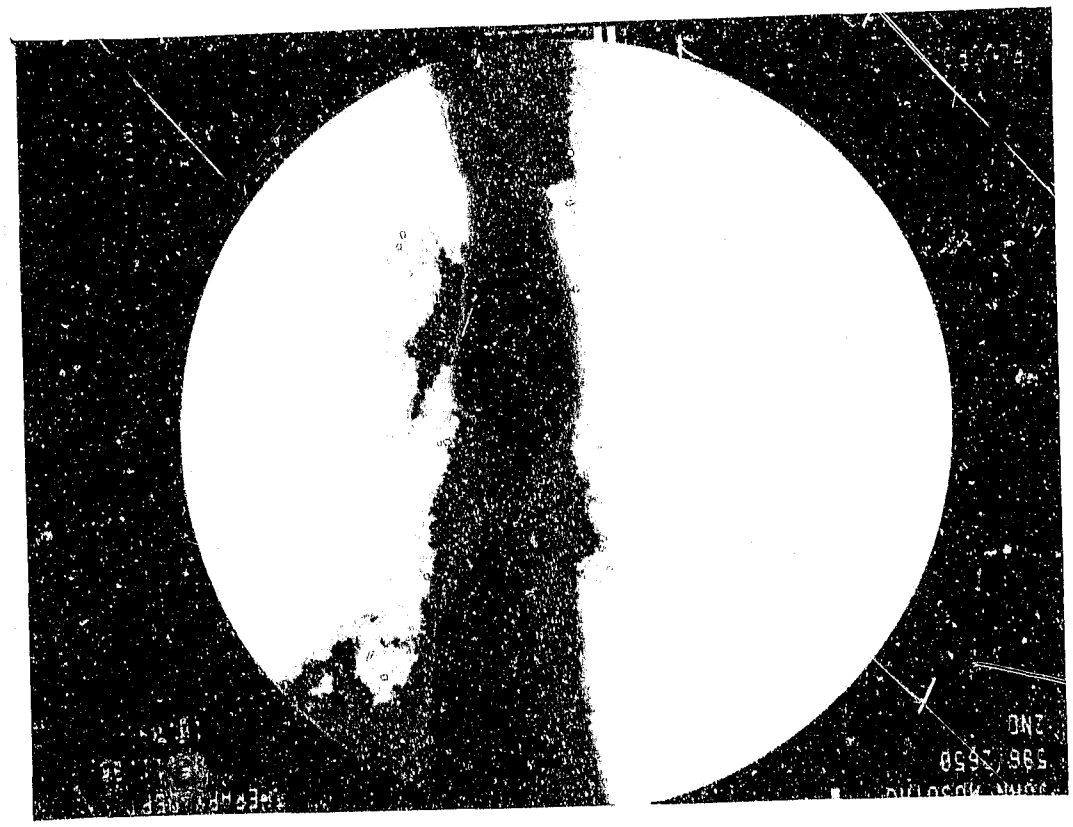


Figure IX

Stainless steel guide wire passed across the tumor length under endoscopic vision

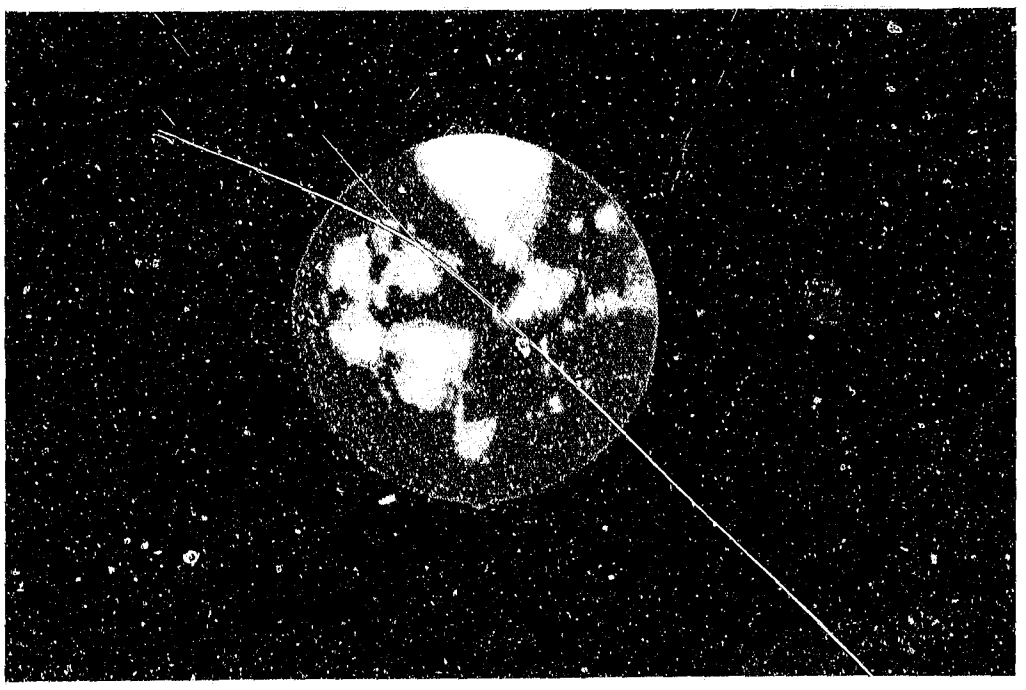


Figure X

Stainless steel guide wire passed across the tumor length as seen on fluoroscopy with a c-arm



Figure XI

Nucletron Intra-oesophageal catheter passes across the tumor length through the guide wire as seen on fluoroscopy with a c-arm

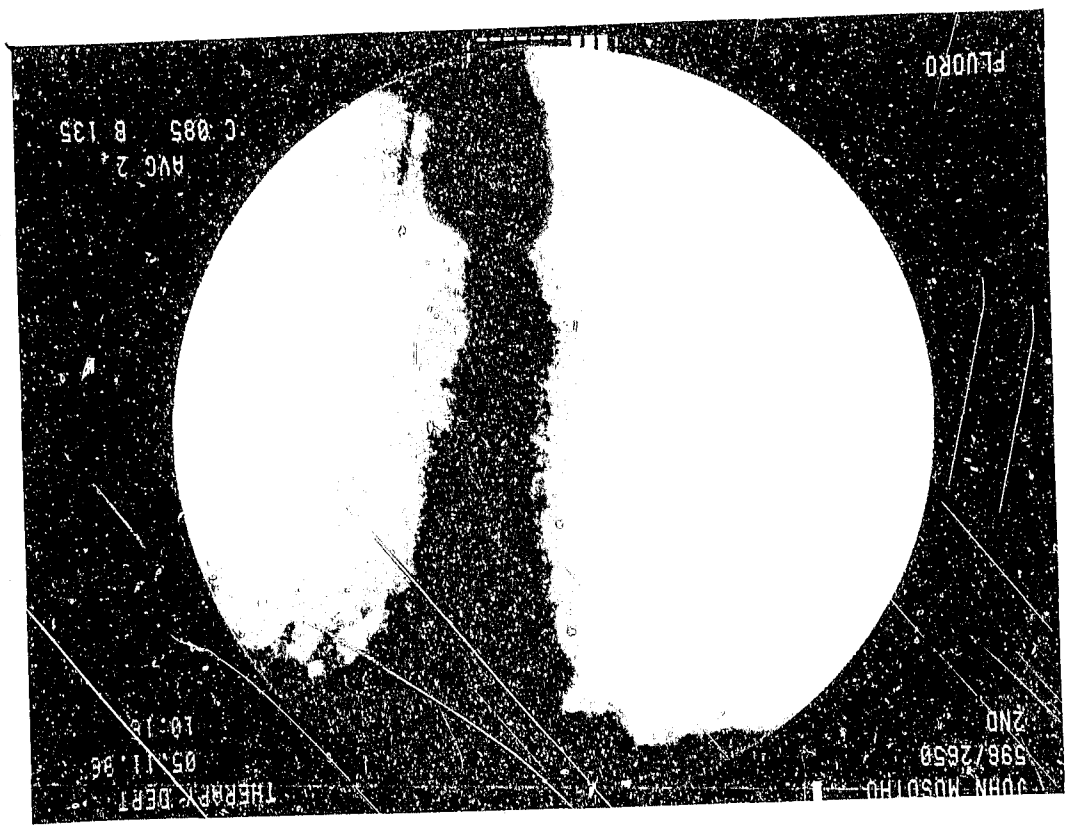


Figure XII

Catheter positioning done under fluoroscopic control after giving the patient 10 ml of oral Gastrografin.

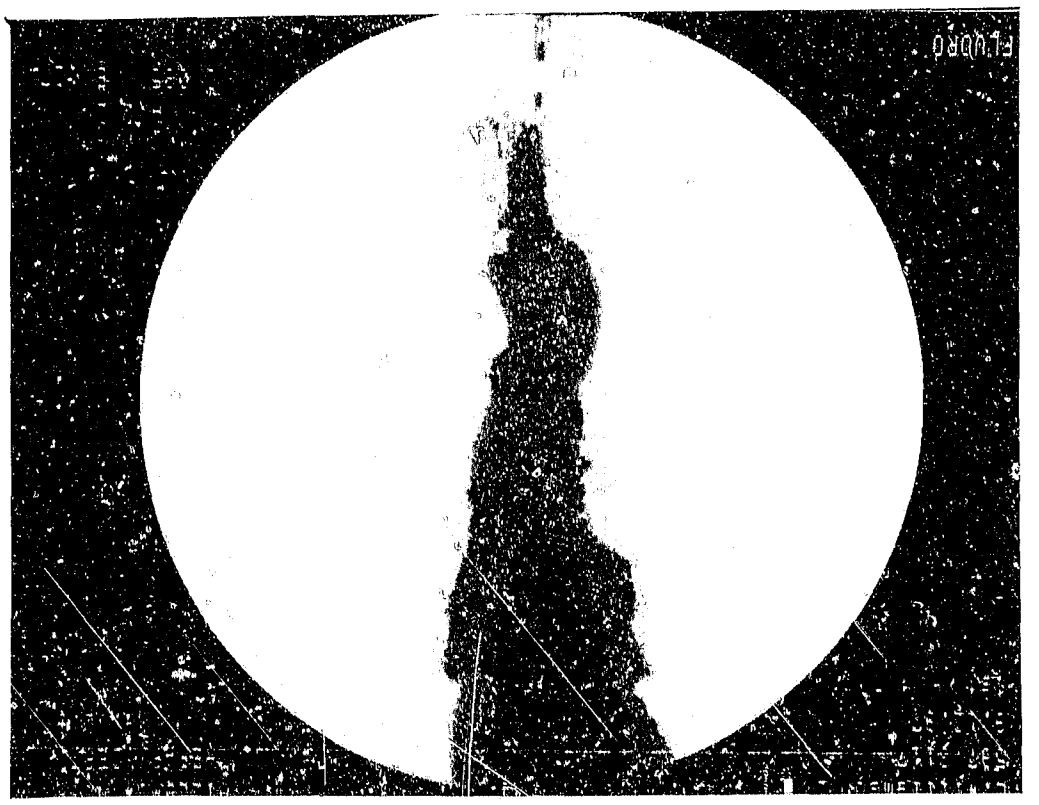


Figure XIII

Catheter in place with at least 2 cm margin proximally and distally to visible tumor

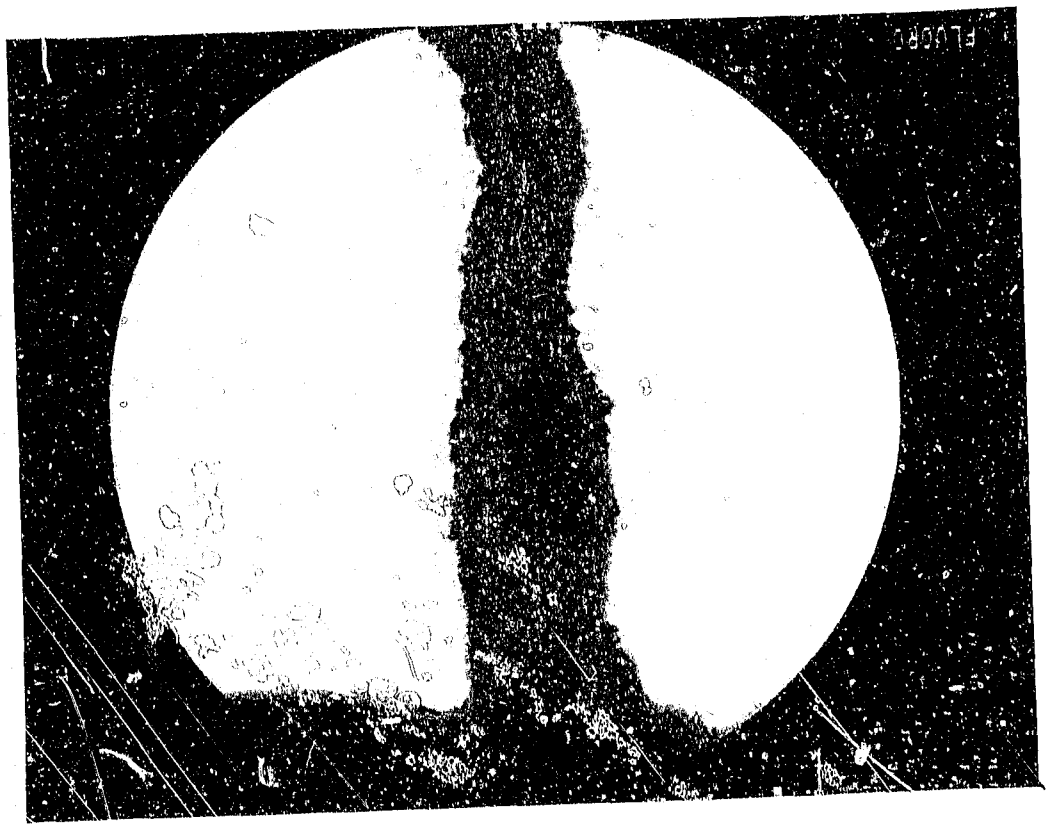


Figure XIV

Microselectron HDR with 18 treatment channels

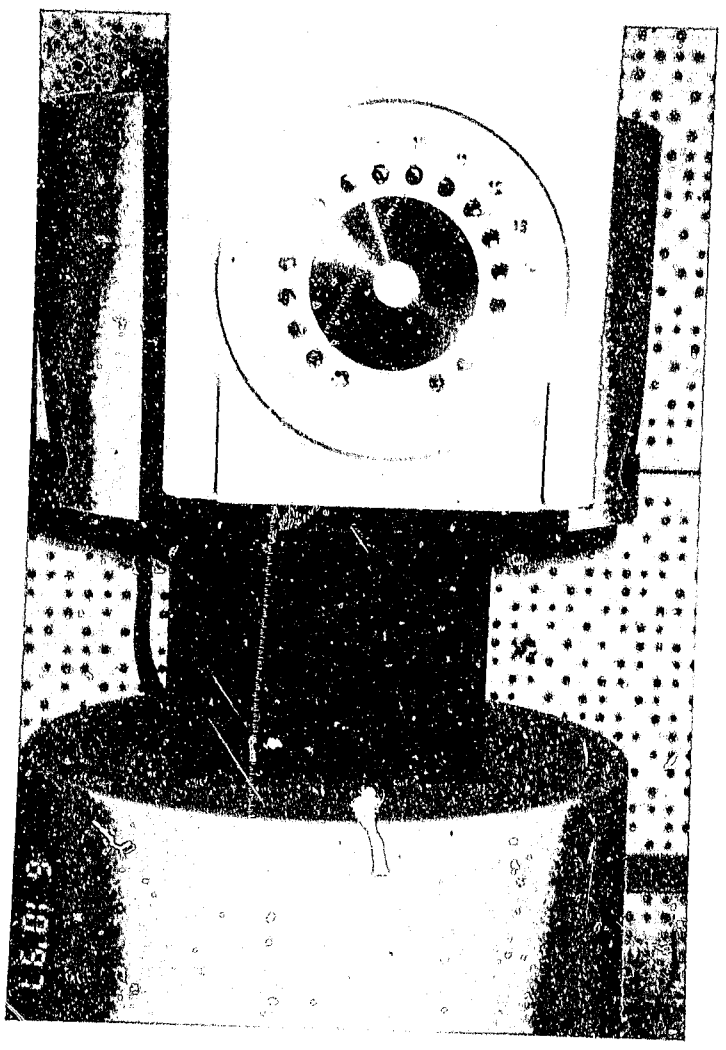


Figure XV

Intra-oesophageal Catheter connected to the HDR Microselectron unit for treatment

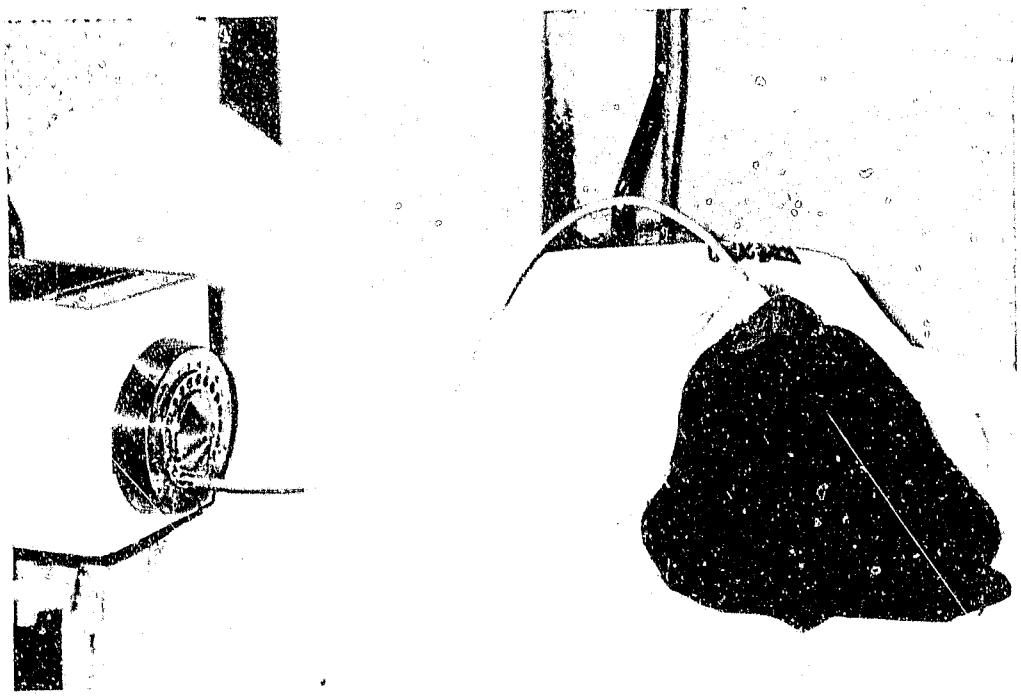


Figure XVI

Isodose curves superimposed on x-rays in AP view to show dose optimization. Dose prescribed at 1 cm from center of the source axis with a 2 cm proximal and distal margin to tumor or as prescribed. Dose fall off is very rapid as can be seen from the x-rays

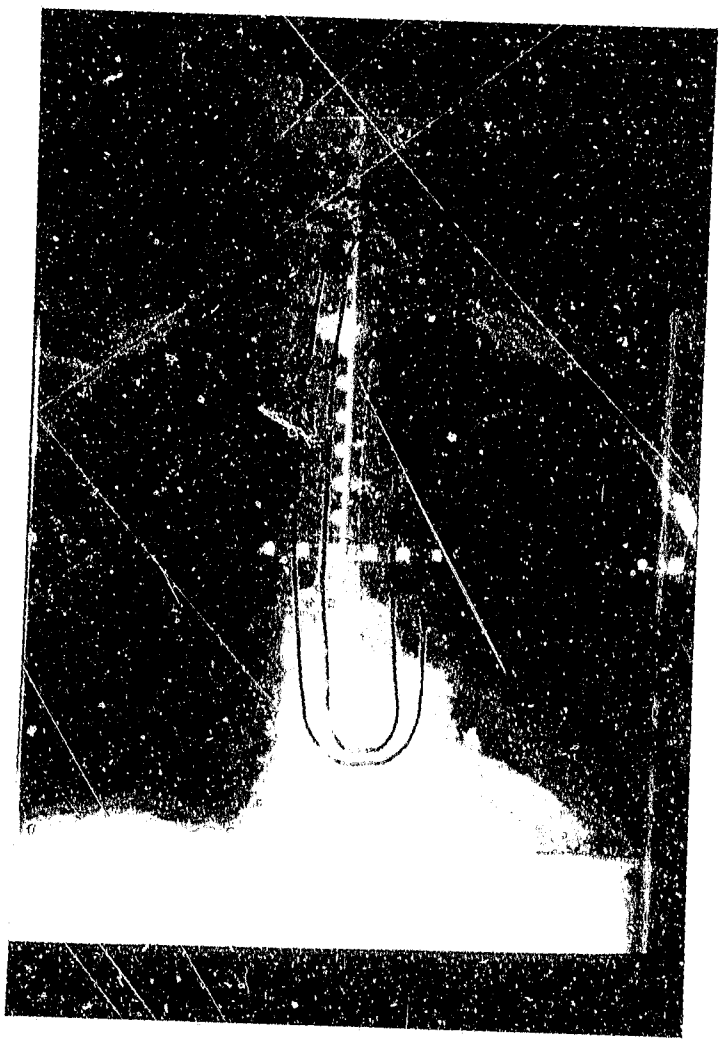


Figure XVII

Isodose curves superimposed on x-rays in lateral view to show dose optimization. Dose prescribed at 1 cm from center of the source axis with a 2 cm proximal and distal margin to tumor or as prescribed.

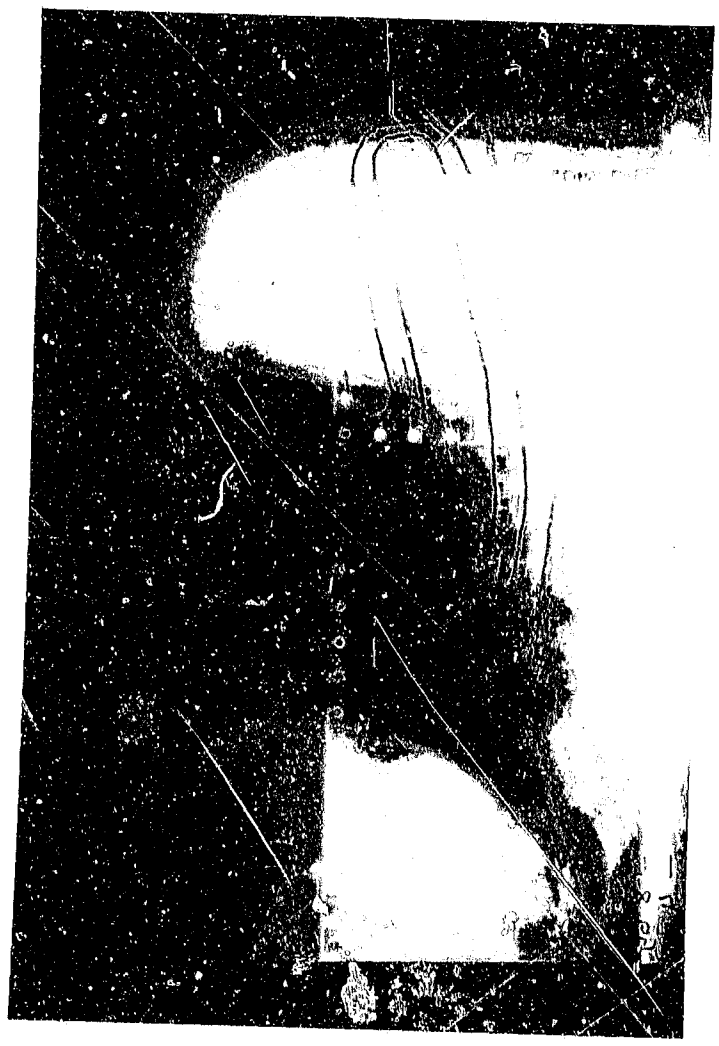


Figure XVIII

Intra-oesophageal catheter connected to the HDR after dose optimisation

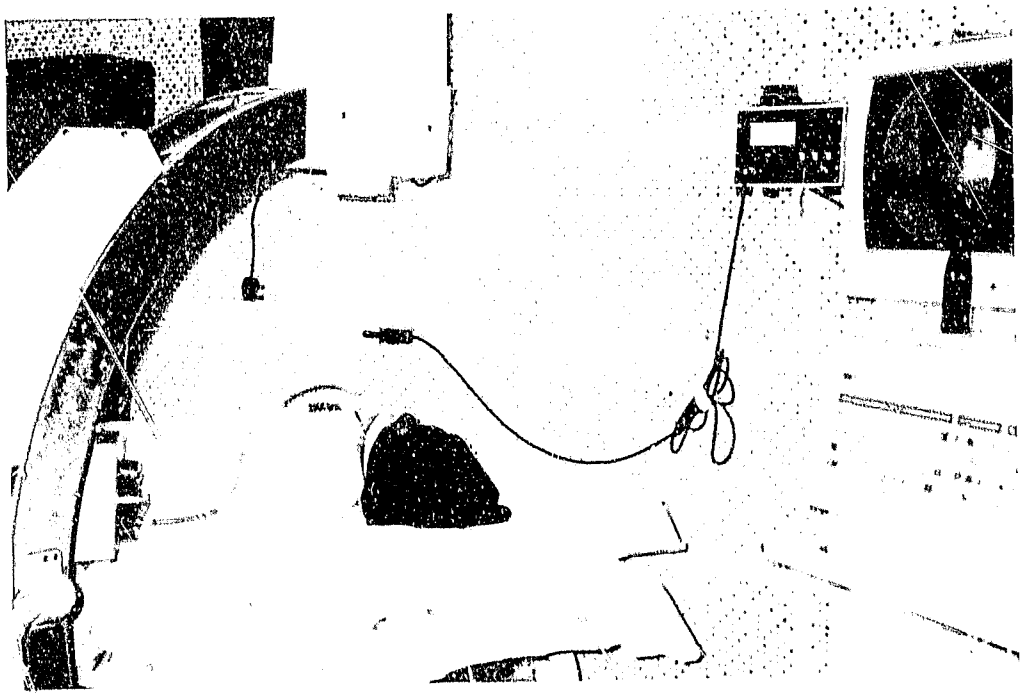
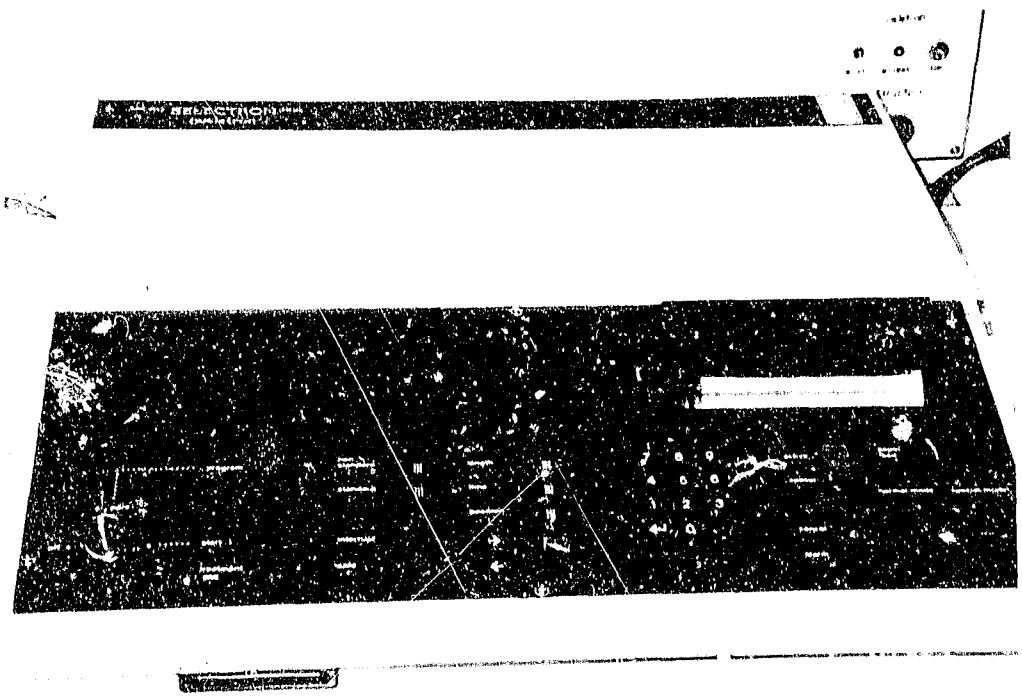


Figure XIX

Remote console of the HDR unit ready for patient treatment



1. Lesions in the thoracic oesophagus
2. Lesions longer than 6 cm
3. Histologically proven carcinoma
4. Karnofsky score of more than 50
5. Normal hematological and biochemical parameters
6. Ability to swallow at least liquids
7. No evidence of tracheo / broncho-oesophageal fistula on bronchoscopy and/or barium swallow
8. Advanced inoperable oesophageal carcinoma (stage III & IV)

The presence of distant metastasis was not considered a contraindication for entry into the study. CT scans were done in all patients who showed evidence of extensive peri-oesophageal disease. Following investigations, all patients were staged as CT stage III or IV advanced stage disease (Halvorsen and Thompson (1984).

Randomisation

Randomisation was performed using random number tables. Patients were randomised into three treatment groups.

Group A

Patients in this group received HDR ILBT of 12 Gy in weekly fractions of 6 Gy each

GROUP B

Patients in this received HDR ILBT of 16 Gy in weekly fractions of 8 Gy each;

GROUP C

Patients in this group received HDR ILBT of 18 Gy in weekly fractions all 6 Gy each.

Treatment was given as described above.

RATIONALE FOR BRACHYTHERAPY DOSE SELECTION

This was based on the preliminary analysis of a randomised prospective dose searching study, conducted previously in the department of Radiation Oncology, University of the Witwatersrand, Johannesburg, and based on the recommendations of Hishikawa et al.

In the study previously reported from the department of Radiation Oncology, University of the Witwatersrand (Kulhavy, 1995), patients were randomised to receive 10Gy, 12 Gy, 15 Gy and 18 Gy in a single fraction by HDR ILBT. It was observed that doses of 12 - 15 Gy given in a single fraction by HDR ILBT gave the patient the best palliation. Doses below this were associated with treatment failures, while doses above this were associated with recalcitrant strictures.

Hishikawa et al (1985) have recommended 6 Gy in one fraction or 12 Gy / 2# as standard dose, and 18 Gy / 3# as the maximum dose that can be delivered when using HDR ILBT. They concluded that although better local control can be achieved with higher doses, severe oesophageal injury can be caused. They estimated that a course of fractionated HDR ILBT should not exceed 20 Gy.

Therefore in this study where fractionated brachytherapy was used, 12 Gy in 2 fractions (#) over 2 weeks, 6 Gy per #; 16 Gy in 2 # over 2 weeks, 8 Gy per #, and 18 Gy in 3 # over 3 weeks, 6 Gy per # were chosen.

Ethics

Ethics approval for this study was obtained from the Committee for Research on Human Subjects (Medical), University of the Witwatersrand, Johannesburg (Clearance Certificate No. M940415)

Preliminary Analysis

A preliminary analysis of 68 patients, treated and who a completed six-month follow-up, was undertaken in the earlier part of the study. Patients who received 12 Gy in two fractions did significantly worse than patients who received 16 Gy in two fractions or 18 Gy in three fractions, in terms of dysphagia free survival and persistent disease, causing oesophageal lumen obstruction after treatment. The arm of 12 Gy in two fractions was therefore discontinued, and patients were then alternated into groups B and C.

Follow up

All patients were assessed monthly for relief of dysphagia, weight gain, relief of other presenting symptomatology, and development of complications. Whenever a patient complained of increasing dysphagia, fiberoptic endoscopy was performed, and if gross tumour was visible, a biopsy was taken. In cases where strictures were found on endoscopy, dilatation was performed using the Didcott dilator (Sur et al., 1996f). Dysphagia scoring was done as follows: 0 = no dysphagia; 1 = dysphagia to solids: 2 = dysphagia to semisolids; 3 = dysphagia to liquids; 4 = total dysphagia.

Statistical analysis

Statistical analysis of the data was done using the SAS software package (SAS Institute, Cary, NC, USA). Prognostic variables were analyzed using the chi square and log rank tests. Survival curves were the drawn using the Kaplan Meier method and multivariate survival analyses were done using the Cox proportional hazards model.

TELEBRACHYTHERAPY

Study from the Postgraduate Institute of Medical Education and Research, Chandigarh, India

Between July 1988 and December 1989, a randomised prospective study was conducted at the Postgraduate Institute of Medical Education and Research, Chandigarh, India. The subjects of the study consisted of 50 untreated cases of

squamous cell carcinoma, arising from the middle third of the oesophagus, who fulfilled the following selection criteria (Sur et al., 1994a):

1. Biopsy proven squamous cell carcinoma of the middle third oesophagus
2. Lesions between 5-10 cm in length as assessed at barium swallow and endoscopy
3. Patients with dysphagia to solids
4. Karnofsky score over 70.

Each patient underwent hematological and biochemical studies followed by chest x-ray, barium swallow, ultrasonogram of the abdomen and oesophago - gastroscopy. Computed tomography was done in 27 of these patients. Following confirmation of the diagnosis at endoscopic biopsy and/or brush cytology, the patients were randomly assigned into one of the two treatment groups of 25 patients each.

GROUP A

Patients in this group received EBRT followed by ILBT. EBRT was given by two parallel opposed fields, anterior and posterior, so as to deliver a dose of 35 Gy in 15 fractions over three weeks, 233.33 cGy per fraction by a Cobalt-60 Teletherapy unit (Theratron 780 C, AECL, Canada). Each case was planned on the simulator with fluoroscopic control. Field size ranged from13x6 cm to15x7 cm, depending on the length of lesion. All these patients had a repeat barium swallow three weeks after completion of EBRT, when they were taken for ILBT.

ILBT was given in the same way as described in the text except that the diameter of the catheter was 0.8 cm, and the remote after loader used was a Selectron HDR, which used Cobalt-60 pellets as its source. Therapy was given in two sessions of 6 Gy each a week apart, to a total dose of 12 Gy delivered 1 cm from the center of the source axis.

GROUP B

Patients in this group were treated with EBRT alone, as were the patients in group A, with parallel opposed fields to deliver a total dose of 35 Gy in 15 fractions over three weeks.

Patients in both groups were followed up every three months for one year. At every visit, symptomatic improvement of dysphagia was noted, and a thorough clinical examination was done. Clinical examination included a general systemic examination, and examination for any metastatic disease, especially in the liver or the lymph nodes in the supraclavicular fossae. Barium swallow and endoscopy examinations were done at each visit, and samples for histology and cytological analysis were taken when indicated. Data was analysed for complications, relief of symptoms, and survival patterns at the end of the study. Survival was calculated using the life table method. Statistical significance was then calculated by using the z test and chi square test.

IB : Study from the University of the Witwatersrand, Johannesburg, South Africa

At the department of Radiation Oncology of the University of the Witwatersrand, 45 previously untreated patients with advanced, inoperable oesophageal cancer involving the thoracic oesophagus, were entered into a prospective phase I/II study. All patients were assessed with a detailed clinical examination, chest x-ray, barium swallow, endoscopy, biopsy, computed tomographic scan, and abdominal sonar in addition to hematological and biochemical tests. Following investigations, all patients were evaluated as having American Joint Committee on cancer stage III/IV and assessed inoperable by the surgical team.

Selection Criteria

Patient selection criteria included:

1. Dysphagia to semisolids
2. Karnofsky performance score > 50
3. Inability to pass of stainless-steel guide wire for ILBT due to narrow lumen and/or long lesions
4. Histologically proven squamous cell carcinoma
5. Lesion in the thoracic oesophagus.

RATIONALE

Criteria 3 above necessitated a means of opening the oesophageal lumen to pass the intra oesophageal applicator. EBRT was selected as the least invasive method of accomplishing this.

ETHICS

Ethics approval for this study was obtained from the Committee for Research on Human Subjects (Medical), University of the Witwatersrand, Johannesburg (Clearance certificate No. M 940418)

Fiberoptic endoscopy was performed in all patients in an attempt to pass a stainless-steel guideline through the tumour. It was not possible to pass the guide wire across the tumour in all the 45 cases due to risk of perforation, tight stenosis, or long tortuous lesions.

TECHNIQUE

In an attempt to shrink the tumour rapidly, EBRT of 20 Gy was given in five fractions over one week, 400 cGy per fraction by anterior and posterior portals. A Cobalt-60 teletherapy unit was used for the process, after planning on the therapy simulator. The patient was placed on the therapy simulator and screened after being given oral Gastrografin. The tumour was visualised and a margin of 4 cm was prescribed on either side of visible tumour proximally and distally, in addition to a margin of 2 cm prescribed at the sides. Verification films were taken

and the patients were treated on a Cobalt -60 teletherapy unit at 80 cm SAD. A dose of 20 Gy was prescribed in 5 fractions over one week using antero-posterior portals.

Two weeks following completion of EBRT, endoscopy was performed for assessment of the efficacy of EBRT in opening the lumen, and for insertion of a stainless-steel guide wire. The 6mm intra oesophageal catheter was then guided in position across the tumour length. Catheter placement and treatment length was decided under Gastrografin fluoroscopy using a c-arm image intensifier. The treatment length included 2cm margins above and below the tumour as described above. A dose of 10 Gy was given at 1cm from the center of the source axis using the Microselectron HDR described above.

Preliminary Analysis

A preliminary analysis of the first 20 patients treated was undertaken following four months of treatment. It was found that the incidence of strictures with this regime had increased. It was thought that the high dose per fraction when using EBRT was the probable cause. EBRT dose was therefore brought down to 15 Gy given in five fractions, 3 Gy per fractions over one week.

Follow up

All patients were followed up monthly and assessed for relief of dysphagia and complications in the form of strictures and fistulae for one year.

Statistical Analysis

Statistical analysis of the data was performed using the chi square and log rank tests, and survival curves were drawn using the Kaplan-Meier method.

CHEMO-BRACHYTHERAPY

Following the preliminary analysis of the brachytherapy alone group, it was found that 16 Gy in two fractions and 18 Gy in three fractions gave similar results in terms of dysphagia free survival and overall survival of the patients. A randomised prospective study was then devised to look at the effect of chemosensitisation with 5 Fluorouracil (5 FU) and brachytherapy. 200 patients were randomised into four treatment groups using random number tables.

Selection Criteria

Patient selection criteria included:

1. Squamous cell carcinoma oesophagus
2. WBC count > 4,000, Platelet > 150,000, hemoglobin > 11 grams/dl, Serum creatinine <1.5, normal liver function tests
3. Karnofsky performance score > 50, age range from 17-70 years
4. Disease length >5 cm as demonstrated on barium swallow and/or endoscopy
5. Able to swallow at least liquids or soft porridge with ease
6. Locally advanced cases (U. T. stage III-all T2-4, N0-1, M0).

Exclusion criteria included :

1. Fistula between trachea / bro. :hus and oesophagus
2. Prior treatment
3. Distant metastasis
4. Prior malignancy within the last five years.

GROUP A

Patients in this group received injection 5 FU 500 mg/m^2/daily for five days as a slow continuous infusion. HDR ILBT of 16 Gy was given 8 Gy per fraction on days 2 and 4 of chemotherapy .

GROUP B

Patients in this group received brachytherapy as in Group A but without chemotherapy

GROUP C

Patients in this group received Inj 5 FU 500mg/m^2/daily for five days, as a slow continuous infusion. HDR ILBT of 18 Gy was given 6 Gy per fraction on day 1, 3 and 5 of chemotherapy

GROUP D

Patients in this group received brachytherapy as in Group C, but without chemotherapy

Ethics

Ethics approval for this study was obtained from the Pharmaceutics and Therapeutic Committee and the Committee for Research on Human Subjects (Medical), University of the Witwatersrand, Johannesburg (Clearance No. M 950815).

Follow up

Following treatment, all patients were assessed monthly for relief of dysphagia, weight gain, relief of other presenting symptomatology and development of complications. Whenever a patient complained of increasing dysphagia, fiberoptic endoscopy was performed, and if gross tumour was visible, a biopsy was taken. In cases, where strictures were found on endoscopy, dilatation was performed using the Didcott dilator (Sur et al., 1996f). Dysphagia scoring was done as follows: 0 = no dysphagia; 1 = dysphagia two solids: 2 = dysphagia to semisolids; 3 = dysphagia to liquids; 4 = total dysphagia.

Statistical Analysis

Statistical analysis of the data was done using the SAS software package (SAS Institute, Cary, NC). Prognostic variables were analysed using chi square and log rank tests. Survival curves were then drawn using the Kaplan Meier method. Multivariate survival analyses were done using the Cox proportional hazards model.

Table I

Results of Bypass Surgery for Oesophageal Cancer

From : Horvath O.P. and Lukas L. Palliation of Oesophageal Cancer - Palliative Rescection and Bypass surgery. Dis Esoph. 1996; 9: 117-22

Author	Number of pts	Morbidity Rate	Mortality Rate	Mean Survival
Orringer, 1984	37	59%	24%	5.9 months
Mannell, 1988	124	40%	4%	5 months
Segalin, 1989	37	57.1%	20.4%	6.2 months
Muller, 1990	906	71%	20.4%	6months - 13.3%
Hirai, 1993	102	-	12.7%	12 months
Voros, 1993	48	-	16.6%	5 months
Fok, 1994	118	-	27.9%	-
Baldan 1995	19	-	15.8%	8.6 months
Horvath, 1995	20	40%	20%	6.3 months

Table II

Palliative Resection - Oesophageal cancer

From : Roth J.A., Lichter A.S., Putnam J.B., Forastiere A.A. Cancer of the Esophagus in Principles and Practice of Oncology IVth ed. 1993; Devita V.T., Hellman S., Rosenberg S.A. eds., Philadelphia, Lippincott J.B. pb 1993: 776 - 817

Author	Resection Technique	No. of pts	Operative Mortality	Operative Morbidity	5 year survival
Lozac'h et al., 1991	Ivor Lewis	100	4%	22%	25 % -3 years
Ellis, 1989	Ivor Lewis	275	2.2%	25%	21%
Mansour & Downey	Ivor Lewis	100	3%	27%	15%- stageII 10%- stage III
Gupta, 1990	Trans hiatal	40	12%	71%	-
Gotley et.al., 1990	Trans hiatal	54	11%	26%	10%
Hankins et al. 1990	Trans hiatal	26	8%	85%	10%
Mannell & Becker, 1991	Total	93	12%	-	13%
Hankins et al., 1989	Total	52	6%	75%	10%
Roth et al., 1988	Total	36	0%	39%	5%

Table III

Oesophageal Cancer - Results of Palliative External Radiotherapy

Author	No. of pts	Dose	Survivial
Beatty, 1979	168	< 40 Gy	0% - 2years
Schuchmann, 1980	127	45 Gy	3.9 months - median
Brady, 1965	26	30 Gy	5 months - median
Hishikawa, 1987	30	<50 Gy	3.5 months - mean
Casper, 1988	52	<50 Gy	4.8 months - median
Sur, 1994	25	35 Gy	16%-1year

Table IV

Oesophageal Cancer - Results of Combination Chemotherapy

From : Roth J.A., Lichter A.S., Putnam J.B., Forastiere A.A. Cancer of the Esophagus in Principles and Practice of Oncology IVth ed. 1993; Devita V.T., Hellman S., Rosenberg S.A. eds., Philadelphia, Lippincott J.B. pb 1993: 776 - 817

Author	Chemotherapy	Evaluable pts	Complete + Partial Response	Medial Response duration	Meadian survival
Chapman, 1987	DDP+MGBG+VBL	36	11	13 weeks	3.4 months
Kelsen, 1986	DDP+MGBG+VDS	20	40	3 months	4 months
De Basi, 1984	DDP+Bleo+MTX	31	26	5 months	5 months
Coonley , 1984	DDP+Bleo	17	17	6 months	4 months

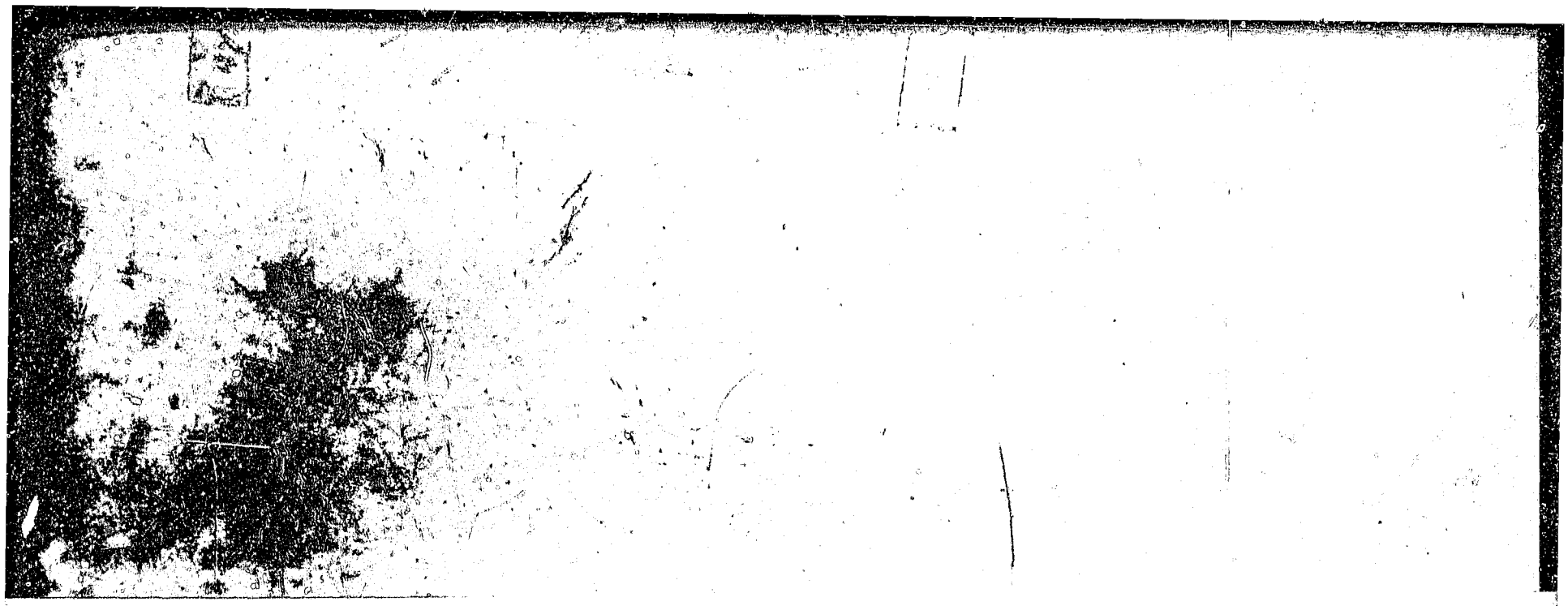


Table V

Oesophageal Cancer - Results of Laser Treatment Alone

From : Roth J.A., Lichter A.S., Putnam J.B., Forastiere A.A. Cancer of the Esophagus in Principles and Practice of Oncology IVth ed. 1993; Devita V.T., Hellman S., Rosenberg S.A. eds., Philadelphia, Lippincott J.B. pb 1993: 776 - 817

Author	No. of patients	Mortality (%)	Morbidity (%)	Dysphagia Relief (%)	Median Survival
Holting, 1991	29	2	-	80	5 months
Loizou, 1991	43	0	2	63	6 months
Segalin, 1989	50	0	0	83	4 months
Buset, 1987	28	0	4	100	7 months



Table VI

Oesophageal Cancer - Results of Treatment with Dilatation or Intubation

From : Roth J.A., Lichter A.S., Putnam J.B., Forastiere A.A. Cancer of the Esophagus in Principles and Practice of Oncology IVth ed. 1993; Devita V.T., Hellman S., Rosenberg S.A. eds., Philadelphia, Lippincott J.B. pb 1993: 776 - 817

Author	Technique	No. of pts	Mortality (%)	Morbidity (%)	Dysphagia Relief (%)	Median Survival
Lundell, 1989	Dilation	41	0	5	100	-
Loizou, 1991	Intubation	30	0	13	90	5 months
Segalin, 1989	Intubation	254	10	17	0	4 months
Pattison, 1990	Intubation	110	15	29	-	-
Unruh , 1985	Intubation	88	18	41	-	3-4 months

Table VII

BRACHYTHERAPY ALONE - PALLIATIVE RESULTS

AUTHOR*	N	DOSE	HDR/ MDR	DYSPHAGIA RELIEF	SURVIVAL	COMPLICATIONS
Rowland	40	15 Gy/1#	MDR	70%-15 wks -SCC 60%-12 wks-ACC+others	NR	Esophagitis 5
Wei-bo-Yin	203	15-30 Gy/ 2-4#	HDR	NR	34.5%-12 mo	66%-Esophagitis 49.3% back pain 11.8% strictures
Fleischman	10	20 Gy/3#	MDR	5.1 mo mean 9/10	1-12 months (range)	NR
Sur	9	12 Gy/2#	HDR	3/9- 9 mo	9 mo	4- Strictures 2-Failures
Harvey	10 12	20Gy/3# 12.5 Gy/1#	MDR HDR	5.1mo mean (9) 4.5 mo mean (11)	4 mo mean 5.8 mo mean	3-Esophagitis 9-Esophagitis
Jager	51 37	15 Gy/1# 15 Gy/1#	MDR HDR	67% 5 mo median	5.5 mo - mean 20% -12 mo	5-Fistulae 1-Hematemesis 2-Ulceration
Browster	197	7.5 Gy/1# -3 10 Gy/1# -23 12.5 Gy/1# - 7 15 Gy/1# - 163 20 Gy / 1# -1	HDR	42% 4.1 mo median	4.5 mo median	4-Esophagitis
Kulhavy	12 14 14 11	10 Gy/1# 12 Gy/1# 15 Gy/1# 18 Gy/1#	HDR	5 mo mean 5 mo mean 6 mo mean 8 mo mean	NR	2-Failures 2-Failures 1-Stricture 3-Strictures; 1-Fistula
Pickering	28	15 Gy / 1#	MDR	86%	4.25 mo mean	-
Greene	24	15-14 Gy / 3#	HDR	15/24	8.9 mo mean	Perforation 1 Fistula 1 Bleeding 2
Leung & Kuan	11	18.6 Gy mean	LDR	9/10	3 mo median	-
Makarewicz	15	22.5Gy/3#	MDR	9/15	6.2mo median	-

Mo-Months; HDR-High Dose Rate; MDR-Medium dose rate; NR-Not reported, N-number of patients; SCC - Squamous cell carcinoma; ACC - Adenocarcinoma ; * Numbers in parenthesis indicate references

Chapter 11

Review of Literature

The following review of literature primarily deals with brachytherapy, telebrachytherapy, chemo-tele-brachytherapy, and chemo-brachytherapy in the treatment of oesophageal carcinoma. For the sake of comparison, a brief review of other modalities of palliative treatment is also mentioned.

This review also reviews the published work of the author from this thesis which is marked with an * and which is now a part of published literature.

11.1 : TREATMENT OPTIONS IN OESOPHAGEAL CANCER

Various options have been described in the palliative treatment of oesophageal cancer. These include :

1. Surgery
2. External Beam Radiotherapy
3. Chemotherapy
4. Laser
5. Intubation
6. Intraluminal Brachytherapy
7. Combination of the above techniques

The results of treatment of advanced oesophageal cancer using various treatment modalities is shown in tables I through VII. This review deals mainly with a review of ILBT reports, used alone or in combination with laser and chemotherapy with or without EBRT . A brief review of previous work done at this university, and of the other palliative modalities of treatment, is also mentioned for the purposes of comparison.

11.2 : SOME HISTORICAL REPORTS IN OESOPHAGEAL CANCER TREATMENT

Intraluminal brachytherapy has been used in the treatment of oesophageal cancer since the beginning of the century. The first literature report on the use of ILBT in oesophageal cancer came from France, where Guisez described the use of this method by radium bougienage (Guisez, 1909, 1925). A source chain containing Radium seeds was swallowed as a bougie by the patient and the source remained inside the patient for 3-10 days so as to achieve the desired dose. The technique was abandoned due to the high risk of exposure to the radiation personnel handling the radioactive isotope.

In 1969, Pearson reported the results of treatment by surgery and radiotherapy in 1870 patients with primary carcinoma of the oesophagus seen in the Radiotherapy or Surgical departments in Edinburgh, U.K. . The series comprised of all patients with squamous cell carcinoma alone. Based on his experience from 1931 to 1967, Pearson summarised that the surgical management of carcinoma of the cervical and upper thoracic oesophagus was not satisfactory. This was because the operative mortality was very high. Regardless of the treatment method used, not more than 20% of patients were cured. Judging by the Edinburgh experience, the expectation of long survival is better than it is after operation, after megavoltage radiation, although local failure is common.

The main reason for this difference is the absence of treatment mortality following irradiation.

Rider and Mendoza (1969), reported their experience with cancer of the oesophagus at the Princess Margaret hospital in Toronto, Canada, from 1950 to 1964. 446 patients were seen during this time. Based on the analysis, they found no survivors after 5 years in patients who had received less than 4500 cGy. There were between 10-20% survivors in the range of 4500-5500 cGy and no survivors in the over 6,000 cGy range where the total radiation was delivered by external beam in the conventional 5 fractions per week, 1,000 cGy per week. Of the 446 patients treated by various modalities of treatment, 21 patients received no treatment. The medial survival was 4 months. 148 patients received palliative external beam radiotherapy, the dose ranging between 2,000-4,000 cGy. Their medial survival improved to only 5 months but quality of life was significantly better when compared to that of untreated patients. Out of 55 patients who received radiation and surgery, the 3-year crude survival was around 8%. 15 patients in this series received treatment with a combination of Cobalt-60 EBRT and a radium bougie as ILBT. The method of treatment involved administration of 3500-4000 cGy external Cobalt-60 radiation in 3.5-4 weeks to the whole mediastinum, followed by the insertion of radium bougie on 3 consecutive days. The dose delivered by the bougie was 1,000 cGy per day, as measured on the surface of the bougie 13 mm in diameter. Thus a maximum tissue dose of 7,000 cGy was reached in a period of about 4-5 weeks. For the 3

patients who had a tumour in the upper third, the median survival was 5 months. For patients, with a tumour in the middle and lower third, the median survival was 24 months. If the radium bougie was inserted immediately after EBRT, necrosis occurred commonly. If, however, there was an interval of a week or more between the 2 treatments, necrosis was absent. 1 patient treated by this method survived 11 years. The report demonstrated the possible use of brachytherapy in combination with EBRT in the treatment of oesophageal cancer.

Pearson in 1977 reported that in patients with a tumour length of 6 cm or more, 35 of 100 of these patients had demonstrable cancer beyond hope of cure. If the remaining 65 out of every 100 (with apparently localised tumours) were treated with megavoltage radical radiation, 33 (55%) would be alive 1 year later and only 10 (15%) would be alive after a period of 5 years. If treated by surgery, only 20 (30%) would be alive 1 year later, and 7 (10%) 5 years later. The difference is mainly due to operative mortality. With radical radiotherapy Pearson reported an overall 32% and 9% survival rate over a 1 and 5 year period respectively. The main reason for failure of treatment was the prevalence of disseminated disease.

Beatty et al. (1979) reported the results with of patients with carcinoma of the oesophagus. who were treated at the Princess Margaret hospital in Toronto, Canada between 1969-1975. 168 of these patients were treated palliatively. 176 patients were treated by a radical dose of radiation, surgical resection, or both.

Analysis of pretreatment assessment parameters indicated that all patients with T1 lesions (length <5 cm, circumference incomplete), and all patients with stage I disease, responded to treatment. Patients who were female, aged > 70 years, N_0, or had well differentiated squamous cell histology, responded to treatment in at least 80% of cases. No patients with extra lymphatic distant metastasis responded to treatment. The presence of other major disease did not affect response to treatment. 30 patients had surgical resection and survival was not significantly greater than the 146 patients who had radical radiation alone. Survival analysis revealed an optimum range of nominal standard dose (NSD) of 1602-1714 rets (median 1679 rets) for patients treated by radiation alone. 67% of the patients treated with radical doses of radiation developed oesophageal strictures post radiation and on the basis of radiological, endoscopic or histological evidence 75% of the strictures were considered to be associated with the persistence of malignancy. On the basis of postmortem examinations and death certificates, an overall 80% failure to control the disease locally was evident, and 95% of strictures were associated with persistence of malignancy in the oesophagus. 31 of the 146 patients who received radical radiation alone had palliation for oesophageal obstruction following radiotherapy. The construction a physiological bypass (e.g.colon) resulted in a mean survival of 215 days (7.2 months) which was much longer than the survival observed with rigid oesophageal tubes (35 days, 1 month) or gastrostomy tubes (58 days, 2 months).

These historical studies have demonstrated that the prognosis of oesophageal cancer was poor, regardless of the treatment modality used. This was because treatment in most patients failed locally (80% in Beatty's series), and had distant metastasis in spite of radical surgery or radiotherapeutic techniques. In most patients local failure caused recurrence of dysphagia and disseminated disease as well. This was further complicated by aspiration pneumonia and problems including infections and so forth in these patients, who had decreased immunological status as a result of their poor general condition, exacerbated by cancer. Further, most patients already have advanced disease at presentation. Therefore most treatment options are mainly palliative, the aim being to provide the patient with dysphagia free survival.

11.3 : PREVIOUS REPORTS FROM THE UNIVERSITY OF THE WITWATERSRAND, SOUTH AFRICA

Mannell, in 1987, reported on using surgical resection at Baragwanath hospital in Johannesburg. The study included 92 patients with squamous cancer involving the thoracic oesophagus. More than half of the patients (54) in this series had stage III disease, specifically, tumours just beyond the walls of the oesophagus and/or positive regional lymph nodes. In 12 patients, the tumour could not be staged accurately. Of the 19 patients with stage IV disease, all had metastasis to lymph nodes and 1 patient had liver metastasis. Lesions of the middle and upper third of the thoracic oesophagus were treated by near total oesophagectomy of the McKeown type (61 cases). Patients with cancers involving the distal third of the thoracic oesophagus underwent an Ivor - Lewis oesophagogastrectomy (31 cases). In addition to resection, most patients received adjuvant therapy in form of radiation therapy (48), radiation therapy + Bleomycin (15), no treatment (24) or cytotoxic drug therapy (5). The mortality rate was 12%. The 1-year survival rate was 55%, and the 5 year survival was 10%. Factors which had an impact on survival included the stage of the disease, adjuvant therapy, and incomplete excision of the tumour. The addition of radiotherapy to surgery also appeared to be an important factor influencing survival. The median survival with palliative resection was 5 months. Recurrence was seen locally in 11 patients, locally and distant in 4 patients and distant in 18 patients. The study showed that in the advanced stage of the disease, surgery did not improve survival of patients significantly from those who

were untreated (median survival 4 months). The difference was that their quality of life was better. However, this involved hospital stay, intensive care units and costly medication with no significant improvement in outcome. Another factor is that patients have to be selected for this modality of treatment.

In a subsequent report, Mannell and others (1988) published the early and late results of bypass surgery in 124 patients with unresectable oesophageal cancer from Johannesburg, South Africa. Patients were grouped according to the extent of disease :

Group A included patients who had a tumour localised to the oesophagus, but in whom severe pulmonary disease contraindicated oesophagectomy (n = 9)

Group B included patients who had a tumour < 10 cm in length with mediastinal invasion (n = 81)

Group C included patients with a tumour > 10 cm in length with mediastinal invasion and / or fixed malignant lymph nodes (n = 33).

Extent of disease was not reported in 1 patient. The operative mortality was 4%, but 9 other patients died in hospital (hospital mortality 11%). Mortality was increased in patients undergoing colon bypass and those with a large tumour load, but these differences were not significant statistically. The most frequent

complication was neck sepsis, secondary to leakage from the proximal end of the extruded oesophagus. 89% of the survivors could eat a normal, unrestricted diet on discharge and 82% of survivors had complete and lasting relief from dysphagia. Median survival after bypass was 5 months but survival was significantly increased by radiotherapy to the tumour ($p < 0.001$). Gastric bypass with radiotherapy was recommended in patients with extra oesophageal spread of malignancy, and in patients with tumours localised to the oesophagus who were unfit for resection. The authors recommended that Bypass surgery could be contraindicated in patients with a primary tumour > 10 cm in length and / or fixed lymph node metastasis, since the mortality rate would increase and survival time after operation would be short.

In 1988, Mannell and Murray reported an analysis of 1926 cases of oesophageal cancer seen in South Africa from November 1985 to August 1988. There were 1438 men and 488 women (M:F-3:1) and their ages ranged from 20-100 years (mean age 56 years). 24% were admitted to the hospital with total dysphagia. Performance status was excellent or good in 49% of patients and fair in 29%. Those in poor or desperate condition included 13% of the patients with tracheo-oesophageal fistula. The most common site of cancer was the mid thoracic oesophagus (53%), but 8.3% of the patients had tumours longer than 10 cm, involving 2 or more oesophageal segments. Using the AJC system of staging, 2.8% of the patients were assessed as stage I, 19.8% as stage II, and

77.4% as stage III. 37% of the patients were treated by oesophageal intubation, 35% by EBRT, 22% by Chemotherapy and 17% by surgery.

In a later report, Mannell and Winters (1989) reported their experience with Carboplatin in 11 patients with advanced oesophageal cancer. A partial response (PR) was seen in 1 patient and minor responses in 2. The median survival was 12 months in the responders, and 3 months in the non-responders. Toxicity in the form of myelosupression was seen in 1 patient. The authors stated that Carboplatin may have a role as a substitute for Cisplatin in combination chemotherapy regimens, and as a radio sensitizer. However the patients needed to be in a good performance score and general condition so as to be capable of tolerating intense cytotoxic drug therapy.

These studies from the Surgery department of the University of the Witwatersrand demonstrated that in South Africa, most patients present in advanced stage disease (>75%). Treatment options in these cases are essentially palliative. Surgery in advanced cases is associated with significant mortality (12%) and the median survival shows no significant increase. Also, increased hospital costs were involved as patients required hospitalization, theatre and intensive care facilities. Further for radical surgery, it was essential for the patient to be in a good performance score. Most patients of oesophageal cancer are, however, in poor performance status. In South Africa, patients present with longer lesions, are in more advanced stages, and manifest poorer

performance scores than are generally found in western countries like the U.S.A. or U.K.. As the results of palliation had not improved in any way, an alternate method of palliation required investigation. Quick and effective palliation was necessary, so that the limited available resources could be used in the more radical treatments of potentially curable patients.

11.4 : INTRALUMINAL BRACHYTHERAPY - MANUAL AFTER LOADING

Following the report of Rider in 1969, ILBT was abandoned due to the high risk of exposure to radiation personnel. In 1979 , Bottrill et al. proposed a system of treating the oesophagus using remote after loading by manual methods using Iridium-192 wires. In 1980, George reported his results on the use of intra oesophageal radioactive Iridium-192. In his study, 24 patients were selected for brachytherapy because of persistent or recurrent biopsy proven carcinoma after external radiation, or because external radiation alone had not consistently relieved dysphagia and similar cases (George F.W., 1980). 18 of the patients had lesions in the upper or middle third of the oesophagus, making them less amenable to surgical resection. All lesions were squamous cell carcinoma, predominantly grades III and IV. They were considered unresectable due to spread of the cancer beyond the oesophagus, as determined by x-ray examinations, Gallium - 67 scans, oesophagoscopy or surgical exploration. 1 patient had recurrent carcinoma at the side of mid thoracic oesophagogastroscopy after resection for a lower oesophageal cancer 3 years earlier. 4 patients had a gastrostomy and 1 a jejunostomy for feeding purposes. All patients presented with aphagia or severe dysphagia. External beam radiation to a dose of 4,000-5,000 cGy was administered in 5-6 weeks. This was followed by an intraluminal insertion of Iridium-192. A Dose of 1200-1500 cGy was given 0.5 cm below the surface of the mucosa. After 3 weeks, a second intraluminal insertion was used in some patients. After treatment there was

consistent regression of aphagia or dysphagia. Swallowing function after the final intra oesophageal therapy session was ranked excellent in 12 patients, fair to good in 10, and poor in 2. Return of dysphagia occurred in 2 patients, in 1 after 4 months, and in the other 1 year after the completion of brachytherapy. Oesophagectomy were required in both patients. The study demonstrated that ILBT could be used for effective palliation in patients who had failed previous radiotherapy. This was because a much higher dose could be delivered to the luminal aspect of the tumour than was possible by EBRT alone. Issues of normal tissue tolerance did not arise as dose fall off was rapid. Therefore high doses could be delivered.

11.5 : ADVENT OF REMOTE AFTER LOADING TECHNIQUES

The system of manual after loading technique still had the disadvantage of radiation exposure to the Radiation Oncologist handling the radioactive isotope. The advent of remote after loading techniques ushered in an era of radiation therapy where there was none / minimal risk of exposure to the radiation personnel. Kitagawa et al. described an after loading technique for radiation of lesions in deep seated organs (Abe and Kitagawa , 1981). An after loading procedure using Iridium-192 seeds was developed for the control of both localised primary lesions that were difficult to remove, and superficial residual lesions that remained after the partial removal of tumours in relatively inaccessible, deep seated organs. The technique allowed the delivery of a maximal radiation dose to lesions in deep seated organs. The seeds could be adjusted at appropriate intervals in proportion to the amount of radioactivity desired. Another advancement was the development of high specific activity cylindrical Iridium-192 sources of 1.1 mm diameter and 3.5 cm length, but with a source activity of 10 Ci (370GBq). This allowed the delivery of a radiation dose of 12 Gy per minute instead of the conventional 2 Gy per hour. A high radiation dose could now be delivered in a much shorter time and treatment time reduced to minutes instead of days. Also, no patient hospitalization was required, and larger numbers could be treated on an outpatient basis.

Using this technique, Abe and Kitagawa (1981) reported results of HDR ILBT in 15 patients with oesophageal cancer. 13 untreated patients with oesophageal cancer were given 1,000-2750 cGy at 0.5 cm from the inner surface of the oesophagus by HDR ILBT after EBRT of 5,000 cGy. 7 cases survived 1 year and 1 case 2 years. Local recurrence was seen in 5 out of 7 cases surviving 1 year. 2 recurrence cases after radical EBRT showed improvement on x-ray picture through ILBT. The era of HDR ILBT began after a series of reports were made from the Hyogo College of Medicine in Japan advocating its use.

11.6 : STUDIES WITH EBRT AND ILBT

A combination of EBRT and ILBT has been used in the radical and palliative treatments of oesophageal cancer. EBRT is meant to treat the disease in the deep oesophageal wall and plexus, while ILBT is meant to deliver a very high dose to the luminal aspect of the tumour, thought to be more hypoxic and therefore relatively radioresistant. A combination of both is therefore meant to treat the luminal disease and the surrounding areas of spread. This is the rationale behind the following studies using EBRT and an ILBT boost.

Experience of the Hyogo College of Medicine, Japan

In the first report made by Hishikawa (1983), 25 patients with oesophageal cancer were treated with a high dose rate remote controlled after loading unit used as a booster therapy for the intraluminal irradiation, following external irradiation. All patients were observed in a follow up program which continued for more than 1 year after the beginning of radiation treatment. At the end of 1 year, 7 patients were alive and had no local recurrence. 18 patients had died, of whom 9 had local failure. Local control rates at 6 months and 1 year were 67.3% and 62.1% respectively, significantly better than those in the group treated with EBRT only ($p < 0.01$). Side effects were seen in 12 patients, but no special treatment became necessary. As for complications, oesophageal ulcers were found in 24 patients, who, with the exception of 2 patients, were all cured

by conventional treatment. Other complications included 5 cases of strictures, 4 of oesophago-bronchial fistula, 1 oesophago-aortic fistula, 1 of pulmonary fibrosis, and 1 of radiation osteitis. No radiation myelitis occurred. Hishikawa concluded that HDR ILBT proved effective in delivering a sufficient dose to the oesophagus in order to control the turnour locally, without risk of injuring the surrounding normal tissues. Based on the experience of 22 patients who developed ulcers in the field of intraluminal radiation, Hishikawa (1984a) recommended that the total dose of ILBT should be less than 20 Gy. In a subsequent updated report on 31 patients, using regression analysis, Hishikawa (1984b) reported that the rate of possible local control by EBRT was 23%. The rate of possible local control increased to 62% when ILBT was used following EBRT .

The use of ILBT was extended to the treatment of early oesophageal cancer. In the next report, Hishikawa et al. (1985a) reported on 5 patients with early oesophageal cancer who were treated with 6-12 Gy ILBT, following 50-60 Gy of EBRT as a boost therapy. Surgery was not performed in these cases. None of the patients had local recurrence after radiation therapy, as demonstrated by radiology and endoscopy. 3 patients were alive for 1- 3 years and 10 months. Oesophageal ulceration induced by a ILBT had occurred in 3 of the 5 patients. These, however, resolved on treatment. As a result intracavitary irradiation was recommended to follow EBRT as a boost therapy for the treatment of early oesophageal carcinoma.

A multiple regression analysis for predicting local control of oesophageal cancer treated by intracavitary radiation was subsequently reported (Hishikawa et al. 1986). In phase I, the value of predicting local control (VPLC) was determined by 5 parameters:

VPLC = 1.38950-0.01571x (age) + 0.04517x (tumour length) + 0.62167x (stenosis) + 0.94811x (deep ulcer)-0.02969x (total Dose of ILBT).

From correlations between VPLC and local control observed in 19 phase I patients, it was determined that the VPLC value of 0.5 or more predicted local failure and a VPLC of <0.5 signified successful local control. In phase II, prediction of local failure or local control was made for another 24 patients by calculating VPLC, and 22 of the 24 cases (91.7%) were correctly predicted. These results indicated that VPLC was a useful index for predicting local control after ILBT in oesophageal carcinoma.

In 1987, Hishikawa et al., reported a series of 119 patients with squamous cell carcinoma of the oesophagus, who were seen over a 10 year period . Patients were analysed retrospectively in terms of survival rate and local control rate, in relation to treatment method and disease stage. All patients were treated with radiotherapy. 43 were treated with EBRT and HDR ILBT (group 1), 46 with EBRT alone with 50 Gy or more (group 2), and 30 with EBRT of <50 Gy (group 3). All patients in group 3 died within 8 months (mean 3.5 months) after the initiation of radiotherapy. In group 1, the 2 year survival rate was 27.9% for the

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