

https://dspace.org/

The role of brachytherapy alone and in conjunction with teletherapy or chemotherapy in advanced oesophageal carcinoma

Sur, Ranjan K

2014-04-07
http://hdl.handle.net10539/14514

Downloaded from a DSpace repository. https://dspace.org/

patients in all disease stages, and 44% of those in stage 1 and 2. Group 2, in contrast had a 2 year survival rate of 4.3% for the patients in all stages of disease, and 9.1% for those in stage 1 and 2. The local control rate was 62.8% in group 1, significantly higher than 19.6% in group 2. The authors concluded that HDR ILBT following EBRT was an effective treatment modality for oesophageal carcinoma, especially in a limited stage of the disease.

The autopsy findings in 35 patients treated with radiotherapy for oesophageal carcinoma were subsequently reported (Hishikawa et al., 1988). Residual tumour was seen at autopsy and in 7 of 16 patients treated with HDR ILBT following EBRT; in 13 of 14 patients treated with EBRT of 50 Gy or more, and in all 5 patients treated with EBRT of <50 Gy . Incidence of lymph node metastasis at autopsy, did not differ between the combined radiotherapy group and the external irradiation groups. However, it did correlate with disease stage. It was observed in 11 of 17 patients with stage 1 and stage 2 disease, compared to 17 of 18 patients with stage 3 and stage 4 disease. Distant organ metastasis, at autopsy, did not differ between the combined radiotherapy group and the external irradiation groups either, but was also correlated with disease stage. It was found in 8 of 17 of the patients with stage 1 and stage 2 disease, compared to all 18 patients with stage 3 and stage 4 disease. Mean survival was different between the patients treated by HDR ILBT following EBRT, and those treated by EBRT alone: 11.3 months in the 16 patients treated with combined therapy,

compared to 6.9 months in the 14 patients who received EBRT of 50 Gy or more, and 3.6 months in the 5 patients who received EBRT of <50 Gy.

The use of ILBT alone in the treatment of small superficial squamous cell oesophageal cancer was subsequently reported (Hishikawa et al., 1989). 6 patients with small, superficial carcinoma of the oesophagus were treated with 18-24 Gy of HDR ILBT alone. All patients were examined with an endoscope within 1 month after therapy, and the tumour in all 6 had disappeared. Erosion induced by HDR ILBT was seen in 5 of the patients. 5 of the patients experienced no local recurrence, and endoscopic biopsy showed local recurrence in the remaining patient 7 months after radiation therapy. All patients survived 6-16 months. Oesophageal ulceration induced by ILBT occurred in 3 of the 6 patients; the ulcers however healed on conservative management. The authors suggested as a result, that HDR ILBT could be used in the treatment of patients with small, superficial carcinoma of the oesophagus.

In the last report from this center, Hishikawa et al (1991) described their experience using HDR ILBT in oesophageal cancer for 10 years. 148 patients with thoracic oesophageal cancer were treated with HDR ILBT, following EBRT. The protocol was to give 60 Gy in 30 fractions over 6 weeks and HDR ILBT of 12 Gy in 2 fractions over 1 week. HDR ILBT dose was prescribed at 1 cm from the center of the source axis. Patients were divided into 2 groups according to disease stage. 66 patients had limited stage disease (LD), and 82 patients had

extensive stage disease (ED). The 2 year survival rate was 37% in the LD group and 7% in the ED group. The 5 year survival rate of the LD group was 18%. The 1 and 2 year actuarial local control rate was 66% and 64% in the LD group, and 49% and 45% in the ED group, respectively. In the total group, ulceration, stricture, and fistula were found in 42 (28%), 15 (10%) and 6 (4%) of patients respectively. However, major complications, defined as those resulting in a second hospitalization or requiring surgical intervention, occurred in 3 of the 42 patients with ulceration, 1 of the 15 patients with stricture, and all of the 6 patients with fistula. In the LD group cause of death was attributable to local failure (14), local failure with distant metastasis (6), distant metastasis (15), and inter-current disease (16). No patients death was attributed to unknown reasons. The ED group results were 13, 24, 30, 9 and 1 respectively. From their experience, Hishikawa et al. reported that HDR ILBT boost after EBRT was a safe and effective way of treating oesophageal cancer.

Hishikawa's studies demonstrated that:

1. ILBT boost after EBRT improved outcome significantly in terms of dysphagia free survival and overall survival when compared with EBRT alone.
2. ILBT boost was a safe and effective modality of treatment.
3. ILBT could be used alone for treating superficial carcinoma of the oesophagus as the dose delivered locally was very high.

All the above reports were based on retrospective analyses, and there was no randomization. Further more, the question of dose optimization, could not be concluded from these reports. However, the reports of Hishikawa and others generated tremendous enthusiasm in the Radiation Oncology world on the use of EBRT in combination with ILBT and also alone in the radical treatment of early and locally advanced cancer of the oesophagus.

Initial Reports on the use of EBRT + ILBT in oesophageal cancer from Europe and North America

One of the earliest reports on the use of telebrachytherapy treatment in locally advanced, inoperable oesophageal cancer came from the University of Southern California School of Medicine, USA. During a 10 year period, 46 patients with unresectable or inoperable carcinoma of the oesophagus were treated with telebrachytherapy. (Hyden E.C. et al., 1988). There were 5 patients with stage I disease (11%), 23: stage II (50%), 6: stage III (13%) and 12 with stage IV (26%) disease. 13 patients were treated for recurrent disease including 11 patients initially treated with teletherapy and 2 with surgical resection previously. Radiotherapy was administered with EBRT in 33 and ILBT in all 46 patients. An average tumour dose of 50 Gy with EBRT and 20 Gy with ILBT was given. ILBT was the given 2 weeks after completion of EBRT. 25 of these patients had more than 1 brachytherapy application. The 5-year actuarial survival rate for 28 patients with stage I or II disease was 12%, with a median of 13 months. This compared with no 5 - year survivals and a median survival of 10 months for the

18 patients with stage III or IV disease. Failure at the primary site was seen in 16 (35%) patients. CR was seen in 20%, PR in 76% and no response in 4%. Treatment was well tolerated, : complications included oesophageal stenosis in 2 patients and trachea oesophageal fistula in 1. The study demonstrated that combination telebrachytherapy provided an effective treatment modality in unresectable or inoperable oesophageal cancer.

Another report describing the use of EBRT and ILBT was made from the University of British Columbia, Vancouver, Canada. Flores et al. (1989) described their initial experience of 211 patients with cancer of the oesophagus and cardia who were treated with a combination of EBRT and ILBT. Prior to the use of EBRT + ILBT, the overall 5-year survival was 9% for all patients treated by EBRT. The 5-year survival for patients selected for oesophagectomy was 20%. Most patients died of local failure (83%). The cause of death was aspiration pneumonia (82%) due to obstruction caused by persistent cancer. Using ILBT, either prior to EBRT or following it in 211 patients, the treatment was considered safe and simple, and preliminary analysis of treatment results suggested that this had improved the therapeutic ratio. The analysis of quality of life at 6 months following therapy as it related to performance status, swallowing ability, weight and pain indicated significant improvement in all of these parameters. Of 171 patients, 33% were still alive at 1 year, 26% at 2 years and 19% 3 years following treatment. EBRT was given 40 Gy in 15 fractions over 3 weeks. ILBT was given with a medium dose rate (MDR) after loading system to a dose of 15

Gy, which was prescribed at 1 cm from the center of the source axis. The authors suggested that the combination of ILBT and EBRT should be the optimum radiotherapy treatment arm for clinical trials, either as a primary form of treatment for upper oesophageal lesions, or as an adjuvant program to potentially operable cases, particularly in the lower oesophagus below the tracheal bifurcation.

A third report was made from Newcastle on Tyne in the U.K.. Dawes et al. (1989) reported results of a study that compared EBRT of 50 Gy in 20 fractions over 4 weeks and EBRT of 30 Gy in 10 fractions over 2 weeks + ILBT of 10 Gy by MDR at 1 cm from the center of the source axis. The actuarial survival with EBRT group at 1 year was 25%. With the EBRT + ILBT group it was 77%. The authors concluded that combined EBRT + ILBT provides good palliation in locally advanced oesophageal cancer. The optimal dose of EBRT lies between 30 Gy in 10 fractions and 50 Gy in 20 fractions when used with ILBT.

Caspers et al. (1988) reported their initial results with ILBT boost following radical EBRT. 16 patients were treated with EBRT of 60 Gy in 6 weeks. 2 - 3 weeks after treatment, ILBT was done using the Micro Selectron LDR. A dose of 15 Gy was given at 1 cm. The median follow-up was 6 months (1-14). Treatment was well tolerated, and no acute toxicity was observed. During the follow-up period, only 2 local recurrences were seen at 4-6 months following treatment. Both of these patients had metastasis. 2 other patients died with

distant metastasis. The other 12 patients were alive without significant dysphagia.

The initial 4 studies from various western centers confirmed the role of a ILBT boost following EBRT in the treatment of locally advanced oesophageal cancer. However, as is evident from the 3 retrospective reports, no consensus on the EBRT or the ILBT doses was evident. The studies of Dawes and Flores demonstrated that lower doses of EBRT and ILBT gave better results than radical EBRT alone. Again, all these reports were retrospectively analysed, often involving patients with unknown and ill-defined selection criteria. No conclusions could be reached on dose optimization.

Initial Reports on the use of EBRT+ ILBT from the Far East

The preliminary analysis of a randomised prospective study was reported from the Chinese Academy of Medical sciences at the Vth International Selectron Users Conference (Yin Wei-bo, 1989). The study of EBRT versus EBRT + ILBT was conducted between 1982-84 and involved 128 patients. EBRT was given 70 Gy in 35 fractions over 7 weeks. In the EBRT + ILBT group, EBRT of 50 Gy was given in 25 fractions over 5 weeks and 19.62 Gy or 26.16 Gy by ILBT. The survival results after 1 year were 67.2% for the EBRT group, and 82.8% for the EBRT + ILBT group. The 5 year survival rate was 10.5% for the EBRT group

and 30.6% for the EBRT + ILBT group. The patient selection criteria and the follow-up details of morbi and so forth were, however, not reported.

Nian-yong et al. (1990) reported their preliminary experience using HDR ILBT on 20 patients with locally advanced oesophageal cancer. EBRT was given to a dose of 50-60 Gy over 5-6 weeks. HDR ILBT of 8-18 Gy was given in 2 - 4 fractions over 2-3 weeks. After treatment completion, 18 of the 20 patients achieved complete tumour regression with restored peristalsis, whereas 2 of the 20 patients had complete regression, but with restricted peristaltic activity. 3 of the 20 patients developed retrosternal pain between 1 - 3 weeks after treatment. This was symptomatically controlled. 10% developed retrosternal pain for 6 months or longer: pain in 1 was caused by oesophago mediastinal fistula, and in the other oesophagitis. 4 of the 20 patients developed a localised oesophageal stricture at 3 months or longer, but in 2 of these there was no evidence of cancer. Of the remaining 2 patients, 1 developed a oesophago mediastinal fistula, and the other required a second course of HDR ILBT of 12 Gy for residual cancer. 1 of the 20 patients developed a benign, superficial oesophageal ulcer 2 weeks after treatment was completed. 2 of the 20 patients developed an oesophago-mediastinal fistula at 2 months and 7 months later. The authors recommended that the optimal dose by HDR ILBT should be 4 Gy per fraction to a total dose of 8-16 Gy at 0.5 cm below the oesophageal mucosa.

These studies therefore demonstrated that there was a definite role of ILBT boost in the treatment of oesophageal cancer with radiotherapy. However, at this stage, no conclusions could be drawn from the studies as regard to optimization of doses both by EBRT and ILBT with the only randomised prospective study from China was incompletely reported with no details of patient selection, follow up or complications. The results were all retrospectively analysed, and were based on different doses and fractionations, each of which reported almost similar results in locally advanced cases.

Experience of the Postgraduate Institute of Medical Education And Research, Chandigarh, India

The results of a prospective nonrandomised study were reported from this center, based on the experience of the Hyogo College of Medicine, Japan. In a preliminary report that used HDR ILBT as a boost in palliation of locally advanced oesophageal cancer (Sur et al., 1991a), 10 patients with a Karnofsky score > 70, lesion in the middle third 4-6 cm in length, dysphagia to solids and with no extra oesophageal spread on CT scan were treated with either EBRT 55 Gy in 25 fractions over 5 weeks (5 patients-group A) or EBRT 35 Gy in 15 fractions over 3 weeks (5 patients-group B) . This was followed with HDR ILBT of 12 Gy in 2 fractions over 2 weeks in both the groups. Relief of dysphagia was seen in 2 out of 5 patients in group A and 4 out of 5 patients in group B by the end of 6 months. Recurrence at the end of 6 months was seen in only 1 patient in group B. Stricture formation occurred in 3/5 patients in group A and 1/5 patients in

group B. Fistula formation occurred in 2/5 patients in group A only. All patients in group A who received radical EBRT and HDR ILBT had problems in the form of stricture or fistulae. The results on this small series indicated that EBRT of 35 Gy and HDR ILBT boost of 12 Gy could be used in the radical treatment of oesophageal cancer as an alternative to radical EBRT + ILBT in view of the high morbidity involved.

In a subsequent report from a prospective nonrandomised study (Sur et al, 1992a), 25 patients with squamous cell carcinoma arising from the middle third of the oesophagus, who fulfilled the selection criteria above, were treated radically with EBRT to a dose of 55-60 Gy . All patients had lesions <6 cm in length with no extra oesophageal spread on CT scan. 11 of these patients received additional ILBT of 12 Gy, 1 cm from the source axis in 2 sessions of 6 Gy each, a week apart. There was no difference in survival, dysphagia relief or local control in the 2 groups at 6 months. Thereafter dysphagia was worse in the group that received ILBT with EBRT. 3 of the 5 patients in the EBRT+ILBT group had fistulae at 9 months and 1 at 12 months following treatment. Strictures were observed with equal frequency in both groups, however strictures in the group that received ILBT boost were very narrow and often impossible to dilate. 4 such patients required gastrostomy. Ulcerations occurred in both groups. Addition of ILBT to radical EBRT was associated with significant complications, like stricture and fistulae accounting for the poor results. It therefore appeared that addition of ILBT to radical doses of EBRT, as was done

in the Japanese study, was associated with unacceptable morbidity in the form of strictures and fistulae. The results contrasted to the earlier reports from the Hyogo College. Possible factors associated with increased morbidity in this study were as follows : Patient selection, increased dose per fraction by EBRT in contrast to conventional fractionation in the Japanese study, and possibly type of tumour and stage in the 2 series.

The next report compared the efficacy of similar biological doses, one delivered completely by EBRT and another by EBRT and ILBT (Sur et al, 1992b). Biologically both doses were "radical" as described by Beatty et. al previously, and were in the NSD range of 1602 - 1714 rets. In a prospective randomised setting, 50 patients with squamous cell carcinoma arising from the middle third of the oesophagus, with no apparent extra oesophageal spread on a CT scan and Karnofsky performance score of over 70, were randomised to receive a NSD (CRE) of 1729 reu by EBRT or 1741 by EBRT + ILBT . 25 patients received EBRT of 35 Gy /15 fractions / 3 weeks + EBRT boost of 20 Gy / 10 fractions / 2 weeks (group A) . Another group of 25 patients received EBRT of 35 Gy / 15 fractions / 3 weeks + ILBT boost of 12 Gy / 2 fractions / 1 week by HDR (group B). All patients were assessed symptomatically, endoscopically, and radiologically every 3 months. There was a marked difference at the end of 1 year in relief of dysphagia (37.5% in group A vs 70.6% in group B), and local control (25% in group A vs 70.6% in group B), although results were statistically insignificant ($p > 0.05$). Actuarial survival (44% in group A vs 78% in group B) was, however,

significant statistically (z= 2.83). Although the biological doses were similar with both the protocols, the biological effect was better with the EBRT + ILBT group. 8% of patients in group B had strictures in contrast to 4% of patients in group A. An analysis of the results showed that moderate doses of EBRT + ILBT gave better local response than EBRT alone for the same biological dose in the treatment of oesophageal cancer. The authors concluded, in the absence of any randomised prospective studies, that the optimal dose by EBRT lay between 35-45 Gy and 12-18 Gy by ILBT given in weekly fractions of 6 Gy each.

The use of ILBT boost was now extended to advanced cases in a randomised prospective setting (Sur et al., 1994a*). A series of 50 patients with squamous cell carcinoma of the oesophagus were randomised to 2 treatment groups with palliative intent. Group A (n = 25) received 35 Gy of EBRT followed 3 weeks later by 12 Gy of ILBT, while group B received 35 Gy of EBRT alone. Groups were comparable with regard to patient characteristics. The patients were followed up at 3-monthly intervals for 1 year clinically, radiologically and endoscopically. 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 ($p < 0.01$), while the corresponding values for relief or dysphagia were 84.2% and 12.5% ($p < 0.01$). Beyond 6 months, statistical comparison was not possible due to poor survival in group B. 4 patients in group A developed oesophageal strictures which were easily dilated. No other complications were encountered. The results clearly show that HDR ILBT

following EBRT provides better palliation than EBRT alone in patients with advanced oesophageal cancer. The local control improved, resulting in relief of dysphagia and the prolonging of symptom free survival.

In contrast to the Japanese studies, the PGI studies demonstrated that radical EBRT + ILBT was a poorer option than radical EBRT alone, as the incidence of complications in form of strictures and fistulae were unacceptably high. Decreasing the EBRT dose and combining it with ILBT boost in locally advanced and advanced cases, resulted in significantly better dysphagia free and overall survival than using radical EBRT or palliative EBRT alone respectively (Sur et al., 1994b).

Subsequent Reports on EBRT + ILBT

Nakajima et al. (1992) examined the contribution of ILBT to the prognosis of T_2M_0 oesophageal cancer, and patient selection . To determine the effect of patient selection, oesophagograms were used to assess the potential difficulty of inserting a tube for ILBT in 39 patients who were treated with EBRT prior to 1982. 22 patients were assessed as likely to have been able to undergo ILBT (group 1) while 17 were assessed as unlikely to have been able to undergo the procedure (group 2). Of the 36 patients treated after 1983, 19 patients were treated with the combination of ILBT and EBRT (group 3) and 17 by EBRT alone (group 4). The median survival times for groups 1, 2, 3 and 4 were 10.8, 6.4,

12.0, and 8.5 months, respectively. The prognosis of patients treated with combination therapy (group 3) was superior to that of those treated before 1982 (groups 1 + 2). However, there was no improvement in the prognosis of T_2N_0 oesophageal cancer treated by radiotherapy after the introduction of ILBT, and the difference between the survival rates of patients treated by combination therapy and with wide oesophageal lumen, was not significant. The study showed that the selection of patients according to the insertability of the ILBT tube affects the prognosis.

Hareyama et al. (1992) , during a 15 year period, between 1974-1988, treated 277 previously untreated patients diagnosed with, squamous cell carcinoma of the thoracic oesophagus, with time dose fractionation factor (TDF) of more than 99. Of these, 161 patients were treated with EBRT combined with ILBT. ILBT was performed in all patients in whom an applicator of 1 cm in diameter was possible and a relatively good performance score was seen and the end of EBRT treatment. Except for mild radiation induced oesophagitis, no acute radiation injuries were noted. The early clinical effect of radiation upon the oesophageal lesion was determined by oesophagography and oesophagoscopy. Approximately 1 month after the combined radiotherapy; a CR was observed in 86 (53.4%) of the 161 patients. After a 5-year follow-up, local control of oesophageal cancer was found to have been successful in 51 (31.7%) of the 161 patients. The highest rate of local control was associated with stage I, tumour length <5 cm, and superficial or tumourous types of tumour. The 5-year actuarial survival rates

were 43.3% for stage I, 21.1% for stage II, and 0% for stages III and IV. Benign radiation induced oesophageal ulcerations or strictures developed in 5 of the long-term survivors, suggesting that the dosage is close to the maximum tolerance of the oesophagus. Hareyama et al recommended that 15-20 Gy in 2 or 3 fractions, is the optimal dose ILBT of oesophageal mucosa after EBRT of 55-60 Gy in 5.5 - 6 weeks.

Sudarshan et al (1992) reported results of 10 patients with squamous cell carcinoma with good general condition, dysphagia to semisolids, lesion 6-8 cm in length, mid one-third, and no evidence of distant spread treated with EBRT of 40 Gy in 20 fractions over 4 weeks + 10 Gy ILBT by MDR given as a single fraction following 2 weeks after EBRT. 2 patients developed problems due to severe ulceration of the mucosa with hemorrhage and broncho oesophageal fistula. The follow-up period of this study ranged from 6-12 months, with most patients remaining asymptomatic during the period.

Kumar et al. (1992) reported a simple and locally developed method of treating the oesophagus with ILBT boost in the radical treatment/palliative treatment of carcinoma of the oesophagus . The technique described was a manual after loading technique that involved low does rate (LDR) and Cesium-137. Using this technique, Kumar et al. reported a response rate of 80% in patients receiving treatment with EBRT + ILBT.

The 7th International Brachytherapy Working Conference was held in Baltimore, Washington, U.S.A. between 6-8 September 1992. Flores A.D.(1992), described the experience of the British Columbia cancer agency since 1985. More than 600 patients with carcinoma of the oesophagus and cardia were treated using the treatment combination of EBRT + ILBT . 120 of these patients had their oesophagus resected after treatment. An analysis of the quality of life of these patients following treatment, in relation to the performance status, swallowing ability and weight indicated, a significant improvement in all of these parameters. The inter-operative and preoperative morbidity of patients resected also compared favorably with historical data using oesophagectomy alone, and only 1 patient died in the peri- operative period. Of the 297 patients who were suitable for analysis, with a minimum follow-up period of 3 years (median follow 31 months) the local control and survival appeared to be significantly superior than in patients treated previously (median survival 43 months). A randomised phase III study to evaluate the timing of brachytherapy before after EBRT was started in 1988, and a preliminary analysis of 170 patients entered into the study suggested no differences between the 2 groups.

Ardiet et al. (1992) reported the results of 21 patients who were treated with HDR ILBT. These cases consisted of 13 primary tumours, 3 second primary tumours in a previously irradiated area, and 5 local recurrences after radical EBRT. The 13 tumours received EBRT of 50-60 Gy and 2 or 3 HDR ILBT treatments of with a fractional dose 7 Gy. Recurrent tumours and second

primary tumours were usually treated with HDR ILBT alone. Immediate and delayed tolerance was estimated to be good or very good in 20/91 cases. Delayed healing with ulceration was also seen in 1 case, and moderate stenosis of grade 2 in 1 other case. 10/13 patients with primary tumours had CR while 3/3 patients with second primary tumours had CR. Recurrent tumours stabilised in 4/5 patients. The actuarial 15 month survival was 74% for the group of 13 patients with primary tumours.

Kovacs et al. (1992) reported the results of 43 patients who were treated with 30 Gy EBRT + 8 Gy HDR ILBT x 3, 1 week apart + 20 Gy EBRT with planned fields . 38/43 patients (88%) had no more dysphagia after treatment. Mean follow up duration was 7 months (1-30 months). The median duration of a dysphagia free period was 4 months. For the 7 cases who were T_2, the median survival was 9 months (mean 10); for the 12 patients who were T_3 the median survival was 6 months (mean 9) and, in the 24 patients who were T_4, 5 months- median (mean 7).

Onishi et al. (1993) reported the results of using HDR ILBT boost in 14 patients with advanced or in operable carcinoma of the oesophagus. The total dose of EBRT was 45-70 Gy/15-35 fractions and that of ILBT, 11.6-34.0 Gy/2-4 fractions at 0.5 cm depth from the inner surface of oesophageal mucosa. The TDF for the whole treatment was 116-186 (mean 146). 6 patients (43%) had CR, 3 (21%) had PR and 5 (36%) had no response (NR). Patients with oesophageal

carcinoma that showed exophytic growth, was less than 5 cm long, and showed favorable response to EBRT were good candidates for ILBT boost. Fistula formation occurred in 5 patients (36%), 4 of whom were irradiated to more than 140 TDF. All 6 CR patients were free from oesophageal tumours, but severe oesophageal stenosis due to radiation injury developed in 5 (83%) of them. They were irradiated to more than 135 TDF. 1 and 2 year survival rates were 98.6% and 14.3% respectively. The poor prognosis was ascribed to the frequent occurrence of fatal radiation stenosis and fistula formation, as was shown by Sur et al.(1991a). The authors suggested that an appropriate therapeutic dose for oesophageal carcinoma that would not cause severe radiation stenosis should be under 120 TDF.

Kumar et al. (1993) studied the influence of intraluminal brachytherapy dose, on the incidence of complications, in the telebrachytherapy treatment of oesophageal cancer . 75 patients with oesophageal cancer were entered into the study. Patients had a Karnofsky score of over 70, with no supraclavicular lymph nodes or distant disease. EBRT was given to 40-55 Gy (mean 52 Gy), 5 fractions a week, 2-2.06 Gy/fraction. This was followed by a single session of MDR ILBT using Cesium-137 sources with a dose range of 8-10 Gy (group 1-42 patients), 10-12 Gy (group 2-11 patients) and 12-15 Gy (group 3-22 patients). The actuarial figures at 1 year were 39% for overall survival, 29% for disease free survival and 38% for local control. 14 patients (18.6%) developed complications in the form of either an oesophageal stricture or fistula. These were dependent

on ILBT dose. For groups 1, 2 and 3, the actuarial local control was 28%, 45% and 63% ($p < 0.1$) and for complications 6%, 20% and 70% ($p < 0.001$) respectively. On applying the TDF formula on brachytherapy doses, it was found that the complication rate was 6% for TDF of <31, 25% for TDF of 32-37 and 70% for TDF of > 38 ($p < 0.001$). The authors recommended that EBRT in the range of 50-55 Gy followed by a dose of 10-12 Gy ILBT be used in the radical treatment of oesophageal cancer as the incidence of complications and local control were optimal with this combination.

In the same year, Armstrong (1993) reviewed the results with HDR ILBT in the treatment of oesophageal cancer. Armstrong summarised that HDR ILBT may be used as sole therapy in specific clinical situations. In general, it should be combined with EBRT. Limited prospective data available showed that ILBT may improve outcome of oesophageal cancer when added to EBRT. However, further prospective trials were required to confirm this.

Micaily et al. (1994) reported the initial results of 8 patients with squamous cell carcinoma of the oesophagus, stages I through III, who were treated with ILBT following EBRT. Within 3 months after completion of treatment, there was radiographic evidence of CR in 6 of the 8 patients. None of the responders recurred locally. All patients died with a mean survival of 17 months. Treatment was well tolerated with minimal acute toxicity. 1 patient developed stricture at

the site of tumour, but this was successfully dilated. The authors recommended that addition of systemic chemotherapy to this regimen warrants investigation.

Tio et al. (1994) reported on the use of endosonography to stage and predict the outcome in patients with inoperable oesophageal carcinoma treated with combined ILBT and EBRT. 63 patients with inoperable oesophageal cancer underwent endosonography followed by combined ILBT + EBRT. Staging was incomplete in 31 of 63 patients because of tight stenosis or difficulty in imaging celiac nodes. During a follow-up of 23 patients, reduction of tumour thickness and lymph node abnormalities was observed in 16. The median survival was 10.4 months. Survival time was correlated with initial number of metastatic lymph nodes found by endosonography. Paradoxically, the survival of patients with more extensive intraluminal tumour growth was significantly better than survival of those with less tumour growth. The authors summarised that the response to combined ILBT + EBRT could accurately be assessed with endosonography. Lymph node abnormalities and tumour thickness were closely related to survival rate.

The response to telebrachytherapy in 10 patients of advanced oesophageal cancer treated with EBRT and ILBT was reported from the University of the Witwatersrand (Sur et al., 1995d*). All patients had long lesions, 8-15 cm in length, and narrow lumen that did not allow the passage of a guide wire for dilatation. EBRT of 20 Gy was given in 5 fractions over 1 week. ILBT was

performed 2 weeks after completion of EBRT. Improvement in dysphagia by more than 2 grades was seen in 9 out of 10 patients. This finding was correlated with an increase in the size of the oesophageal lumen at the end of 6 weeks, following treatment by barium swallow. No complications of treatment were seen in any patient. The authors concluded that low doses of EBRT and HDR ILBT can provide quick and effective palliation in advanced metastatic oesophageal carcinoma.

In a preliminary report of this study from the University of the Witwatersrand, Johannesburg, high dose per fraction EBRT was used in an attempt to open the lumen of patients with oesophageal cancer so that ILBT was possible (Sur et al., 1994c*). Twenty patients with advanced oesophageal cancer with tumour lengths 6-11 cm (mean 9.35 cm), in whom it was not possible to pass an intra oesophageal catheter for ILBT due to tight stenosis from tumour, were scheduled for telebrachytherapy. EBRT of 20 Gy was given in 5 fractions, 4 Gy per fraction daily in an attempt to rapidly shrink the tumour and facilitate ILBT. 2 weeks following EBRT, all these patients received HDR ILBT of 10 Gy at 1 cm from the source axis. Relief of dysphagia was evident in all patients by the end of first month. However, by the end of second month 2 patients developed strictures (1 fibrotic, 1 tumour) and by the end of 4 months, 5 patients developed strictures (4 fibrotic, 1 tumour). In 1 patient, dilatation was not possible due to severe fibrosis and long tumour length. The authors concluded that High Dose per fraction EBRT and long tumour length contribute to increased

complications in the telebrachytherapy treatment of oesophageal cancer. Following results of the study, the EBRT dose was brought down to 15 Gy in 5 fractions, 3 Gy per fraction.

Mohanti et al. (1995) described their experience at the All India Institute of Medical Sciences in the treatment of advanced oesophageal cancer using a combination of EBRT and ILBT. 34 patients with inoperable cancer of the oesophagus, who were treated with ILBT during June 1991 to December 1993, were evaluated to assess its palliative effect . 17 of these patients had received additional Chemotherapy and EBRT. 13 patients received only radiotherapy (both EBRT + ILBT) and remaining 4 received only ILBT. They were followed up for a mean period of 8.3 months (range 2-28 months) during which 1 patient was lost to follow. 8 patients had a follow-up of less than 6 months. 8 (33%) amongst the remaining 25 patients were considered disease free, 15 had recurrent and progressive disease, 1 developed metastasis and 1 patient died. In 21 (66%) dysphagia markedly improved. 9 (26%) patients survived beyond 1-year and the median survival for all patients was 8 months. Associated radiation morbidity was documented in 13 (38%) patients. The authors concluded that combination of EBRT and ILBT was an effective and safe therapy for inoperable oesophageal cancer.

Taal et al. (1996) applied HDR ILBT before EBRT to induce fast relief of dysphagia in patients with oesophageal cancer. 74 patients with inoperable

oesophageal carcinoma (36 squamous cell, 38 adenocarcinoma) were treated with the combination of 10 Gy HDR ILBT, followed by 40 Gy EBRT in 4 weeks starting, 2 weeks later. Tumour response, as measured by endoscopy and/or barium swallow, revealed CR in 21 and PR in 38 (over all response rate 80%). Improvement of dysphagia was induced by brachytherapy within a few days in 39% of patients, and achieved at the end of treatment in 70% of patients. Further weight loss was prevented in 39 of the 59 patients who presented with weight loss. Pain at presentation improved in 12 of the 25 patients. Median survival was 9 months. No differences in either response rate or survival were found in patients with squamous cell or adenocarcinoma. Side effects were acute with minimal discomfort in 32 (42%) of patients, or late with painful ulceration in 5 patients (7%), occurring after a median of 4 months. Fistula developed in 6 patients, all with concurrent tumour. In conclusion, ILBT before EBRT was found to be a safe and effective procedure to induce rapid relief of dysphagia, especially when combined with EBRT.

Gava et al. (1996) reported on the use of HDR ILBT in oesophageal carcinoma in Italy . 134 patients with oesophageal carcinoma (110 men, 24 women) were treated in 10 Italian centers. 41 patients received radical treatment and brachytherapy was often combined with EBRT and/or Chemotherapy. Clinical response rates were-56% CR, 34% PR, 10% NR/disease progression/not assessed. 93 patients underwent palliative treatment; dysphagia was reduced in 80% of them and pain in 71% of them. Treatment induced oesophageal

damage consisted of G_3-G_4 oesophagitis (5% of patients), strictures (10%) and fistulae (3%). Complication rates were then correlated with fraction dose (9.5% complications for fraction doses <5 Gy, 20% with doses ranging from 5-8 Gy and 38% with fraction doses > 8 Gy). Moreover, the oesophagus was most severely injured when small tubes were used. When EBRT was combined with brachytherapy, dysphagia was relieved more than with brachytherapy alone (88% vs. 79%), and once again complication rates did not increase. Based on the analysis, it was concluded that in the radical treatment of oesophageal cancer HDR ILBT allows high radiation doses to be delivered with fair complication rates. As a palliative treatment, HDR ILBT is safe, has low morbidity and provides adequate relief of dysphagia in 80% of patients. Tubes > 6 mm in diameter and fraction doses ranging from 5-6 Gy were recommended.

Moni et al. (1996) reported on the effectiveness and toxicity of HDR ILBT as a complement to other treatment for local control and palliation in patients with oesophageal cancer. 47 evaluable patients received HDR ILBT as a complement to treatment for oesophageal cancer. They were divided into 3 treatment groups. Group A comprised 21 patients treated for primary non-metastatic disease. 15 patients (71%) received EBRT with HDR ILBT as a boost. Of these, 2 patients received HDR ILBT preoperatively and EBRT after resection of the oesophageal tumour. The median dose of EBRT was 45 Gy (range 30-64.8 Gy). 7 patients received adjuvant 5FU based Chemotherapy. Group B comprised 14 patients with recurrent non-metastatic disease. 14 patients received 20

treatments; 4 had EBRT for this recurrence to a median dose of 38.4 Gy (range 30-54 Gy). 10 patients had EBRT prior to this recurrence. None of the patients had surgical resection and only 1 patient had 5FU chemotherapy. Group C comprised 12 patients with metastatic disease. Of these, 7 had primary and 5 had recurrent tumours . 6 patients had EBRT to a median dose of 42.5 Gy (range 30-59.4 Gy), 4 had surgical resections and 1 had Chemotherapy. HDR ILBT was given using various doses and fractionations. For group A the median dose was 14 Gy, group B 14 Gy and group C 12 Gy all given in various dose per fraction. 12 of 21 group A patients had CR at the end of treatment (38%). The median survival was 11 months and the 2 year actuarial survival 27%. For group B, local control rates were 64% at completion of treatment, and median survival was 6 months. Only 17% (2/12) were locally controlled and a had a median survival of 5.5 months. For the total group, severe complications were seen in 36% of patients. Fistula occurred in 17%. The authors concluded that HDR ILBT was a reasonable approach in the treatment of oesophageal cancer.

Sur et al. described the results of the studies at the University of the Witwatersrand, Johannesburg South Africa. In the first report (Sur et al., 1996c*), 45 previously untreated patients with advanced inoperable oesophageal cancer, who failed ILBT due to long lesions or tight strictures, were treated with telebrachytherapy to a dose of 20 Gy in 5 fractions over 1 week (4 Gy per fraction by anterior posterior fields). 2 weeks later, HDR ILBT was given to a dose of 10 Gy at 1 cm from the source axis. Following initial evaluation of 20

patients at the end of 4 months, the dose was decreased to 15 Gy in 5 daily fractions due to the increased morbidity experienced with the higher dose per fraction (Sur et al., 1994c). This analysis was done at the end of 1 year and included 34 patients who received teletherapy of 20 Gy, and 11 patients who received teletherapy of 15 Gy. The dysphagia- free survival was 34% (20 Gy-37%, 15 Gy-33%) and the overall survival rate was 31% for the entire group (20 Gy-34%, 15 Gy-28%). The complication free survival rate was 55% for the 20 Gy group and 83% for the 15 Gy teletherapy group ($p > 0.05$). Age, race, sex, length of tumour, tumour grade or dose of EBRT made no significant impact on dysphagia- free, overall and complication- free survival ($p > 0.05$). In cases where tight strictures/long tumour lengths do not allow initial treatment with ILBT, telebrachytherapy can provide significant palliation in the management of these patients.

Schraube et al. (1997) reported their experiences with ILBT in combination with EBRT in the treatment of inoperable oesophageal carcinoma. Between 1988 and 1993, 54 patients were treated with primary radiotherapy. The mean age was 63 years (43-84 years range). All patients were considered unresectable due to tumour localization, extension, metastasis or limited general condition. 1 patient had stage I disease, 19 stage II, 25 stage III and 9 had stage IV disease. Patients were divided into 2 groups. The first group consisted of patients in good general condition (Karnofsky's score > 80) with a localised tumour extension so that the potential curative treatment goal was presumed (21

patients) . The aim of brachytherapy in these cases was to boost the local area for better eradication of the tumour. The second group consisted 33 patients in whom a more palliative treatment intent was presumed because of advanced disease, and reduced performance status. The aim of brachytherapy was to shorten the EBRT treatment time without compromising the local palliative effect. Mean EBRT doses of 60.3 Gy (range 58-70 Gy), and an additional HDR ILBT of 13.6 Gy (ranged 10-20 Gy) was applied for the curative group and, 44.9 Gy (range 14-53 Gy) with 17.5 Gy (range 5-30 Gy) was applied for the palliative group. Overall treatment time was 10 weeks (range 4.6-14.3 weeks) for the curative group and 9.3 weeks (range 4.1-13.9 weeks) for the palliative group. 6 weeks after treatment, a radiological remission was observed in 32 of the 33 palliatively treated patients (10 CR, 22 PR, 1 NR). In 13 patients of this group, local progression was observed after a median time of 7.1 months. The median survival of this group was 9 months. Radiological remission occurred in 18 out of 21 of the curatively treated patients (11 complete, 7 partial, 3 none). Median time to local progression (12 patients) was 4.5 months in this group and median survival was 7.7 months. The difference in time to progression reached statistical significance ($p = 0.05$). The only favorable factor for survival was an incomplete or complete radiological remission (median survival 7.5 vs 11.4 months, $p = 0.0024$). The prior estimation of the treatment goal was not confirmed by survival data. 8 of the 54 minor and 8 out of 54 major adverse events were observed. In 4 of these patients, major complications were caused by progressive tumour. ILBT in combination with EBRT was shown to be a

feasible method of treatment in inoperable cases. Good local tumour regression and functional results were achieved. The data from the study suggested that ILBT extends the time to local progression. In contrast to the literature, it was found that survival was not increased by this technique.

Gasper et al. (1997a) utilizing published reports and clinical experience, formulated the American Brachytherapy Society consensus guidelines for brachytherapy in oesophageal cancer. Recommendations made were divided into 2 categories:

Category A - definitive treatment: good candidates for brachytherapy include patients with unifocal thoracic adeno- or squamous cancers, < 10 cm length, with no evidence of intra-abdominal or metastatic disease. Contraindications include tracheal or bronchial involvement, cervical oesophagus location, and stenosis that cannot be bypassed. The oesophageal brachytherapy applicator should have an external diameter of 6-10 mm. If 5FU based Chemotherapy and 45-50 Gy EBRT are used, recommended brachytherapy is either-HDR 10 Gy in 2 weekly fractions of 5 Gy each, or MDR 20 Gy in a single fraction. All doses are prescribed at 1 cm from the center of the source axis. Brachytherapy should follow EBRT and should not be given concurrently with Chemotherapy.

Category B - palliative treatment: patients with adeno-or squamous cancers of the thoracic oesophagus with distant metastasis or unresectable local disease progression/recurrence after definitive radiation treatment should be considered for brachytherapy with palliative intent. After EBRT of 30 Gy, the recommended

brachytherapy dose is either 10-14 Gy in 1 or 2 fractions by HDR or 20-25 Gy by MDR as a single fraction. The need for EBRT in newly diagnosed patients with a life expectancy of < 3 months is controversial. In these cases, HDR ILBT of 15-20 Gy in 2 or 4 fractions, or MDR of 25-40 Gy may be of benefit.

Histological Studies Related to Telebrachytherapy Treatment

Histological findings of oesophageal injury induced by ILBT were reported from the Hyogo College of Medicine, Japan (Hishikawa et al., 1985b, 1993). In the oesophagus treated with ILBT, denudation and regeneration were found in the epithelium, degenerative changes of small vessels and fibrotic changes were found in the sub mucosa, and fibrotic changes were found in the muscle layer. Hishikawa suggested that these changes correlate with the additional dosage given by ILBT following EBRT.

Berry et al (1989) described the pathologic findings in 21 oesophagectomy specimens from patients who received pre operative ILBT and EBRT from the same center . 11 patients received 15 Gy ILBT and 40 Gy EBRT (group 1) and 10 patients received 15 Gy ILBT and 20-30 Gy EBRT (group 2). Effectiveness of radiotherapy was expressed as the ratio between depth of radiation effect, and depth of tumour invasion. Depth was expressed as 1 of 4 levels: level 1 being not deeper than the muscularis mucosa; level 2, involving but not penetrating deeper than the sub mucosa; level 3, involving but not penetrating deeper than

muscularis propria; and level 4, involving peri-oesophageal soft tissue. The depth of radiation damage to tumour cells was comparable between the 2 groups. However, a residual tumour was present in the peri-oesophageal tissue in only 1 of 11 patients after high dose EBRT compared to 8 of 10 patients with lower EBRT ($p < 0.01$). A ratio of 1 between radiation effect and depth of tumour invasion was present in 6 cases receiving high dose EBRT, and 1 patient received lower dose EBRT ($p < 0.05$). Berry et al. concluded that ILBT combined with EBRT gives good local tumour control in the majority of patients. Higher doses of EBRT gave a better radiation effect in deeper layers of the oesophageal wall. The ratio between depth of radiation effect and tumour invasion, provided a simple and objective approach to the pathologic analysis of oesophagectomy specimens.

11.7 : LASER AND ILBT

Laser has been used in palliating oesophageal cancer by rapidly restoring lumen patency. However, the procedure needs to be repeated as the tumour grows back, and the patient thus requires repeated treatments. A combination of Laser and ILBT makes an ideal combination. Laser rapidly restores luminal patency, while ILBT gives a high dose of radiation to the oesophagus locally, thus maintaining luminal patency for prolonged periods of time, obviating the need for repeated laser treatment. A brief review of laser and ILBT is presented here as it is the other method of palliating oesophageal carcinoma in whom initial brachytherapy is not possible.

From Germany, Bader and others (1985) reported the possible use of laser and ILBT of 700 cGy in a single fraction for palliation of dysphagia induced by malignant stenosis . Although detailed results of the study were not reported, laser was used to make brachytherapy easier and feasible, and at the same time provided the patient with rapid and sustained relief from dysphagia through a combination of these techniques.

Hagenmuller and others (1987) reported the results of laser and ILBT in palliation of oesophageal cancer. 25 patients with advanced oesophageal carcinoma retreated with a combination of laser (neodymium- YAG laser) and ILBT of 7 Gy prescribed at 1 cm from the center of the source axis. HDR ILBT

was given up to 6 times, or even more, depending on the effect produced. The first 3 applications were performed at 1 week intervals. Further irradiation was carried out only in the case of recurrent stenosis due to tumour growth during the follow up period. The dysphagia free survival was 71 days (range 8-179) with laser and ILBT, in contrast, to 56 days (5-169) with laser alone. The incidence of complications were similar in both groups. The mean survival was 120 days in the laser and ILBT group, and 86 days in the laser only group. The study showed that when ILBT was combined to laser therapy, dysphagia free survival and overall survival improved.

Sander et al. (1991) reported the results on 39 patients with malignant stenosis of the oesophagus (22 adeno carcinomas, 17 squamous cell carcinomas) who were treated with Nd: YAG laser recanalization alone (N = 20) or with laser recanalization and subsequent ILBT with Iridium-192 at a dose of 3 x 7 Gy. Squamous cell carcinoma patients in the after loading group showed a prolonged first dysphagia free interval (65 vs.30 days,p <0.03), while patients with an adenocarcinoma did not share this benefit and had a need for more frequent endoscopy procedures (p < 0.05). The complication of oesophagitis was only seen following ILBT (21%). Restenosis occurred in all patients. Neither the duration of relative dysphagia, nor survival time was prolonged after ILBT in adenocarcinoma or squamous cell carcinoma patients. The authors felt that, after prior laser recanalization, palliative ILBT would seem helpful only in cases of

squamous cell carcinoma with a high-performance status, with the aim being to prolong the first dysphagia free interval.

Shmueli et al (1996) examined the combination of laser treatment and ILBT for malignant dysphagia in an attempt to reduce the need for follow-up treatment, and to improve survival in oesophageal cancer. 32 patients with inoperable oesophageal cancer (18 adeno; 14 squamous cell carcinoma) were initially treated by a median of 3 laser treatments. They were then treated with ILBT of 10-15 Gy at 1 cm from the source axis with a Selectron LDR system. ILBT was administered 1-4 weeks after laser therapy. Those with squamous cell carcinoma received 10 Gy intraluminally and 30-50 Gy externally in 10 daily fractions. Those with adenocarcinoma received 15 Gy intraluminally only. After the radiotherapy, 9 patients survived a median of 22 (range 4-40) weeks without requiring any further endoscopic treatment. The remaining patients survived a median of 40 (range 4-102) weeks and required a median of 3 follow-up endoscopic treatments over that time. 11 patients developed fibrous strictures with no intraluminal tumour, and were treated by dilatation. 12 patients required dilatation and repeat laser therapy for the combination of fibrous stricture and recurrent intraluminal tumour. 6 patients eventually required Atkinson's tubes. The combination of laser treatment and ILBT provided good palliation and reduced the need for repeated endoscopic treatments.

Spencer et al. (1996) reported on the use of laser and ILBT in the palliation of adenocarcinoma of the oesophagus and cardia . The logic behind addition of these 2 modalities is that although laser is an effective and safe treatment, it has to be repeated at 4-5 weekly intervals in order to maintain palliation. ILBT would augument the benefits of laser while reducing the need for repeat treatments. 19 patients with dysphagia due to advanced adenocarcinoma of the oesophagus or cardia were recruited. All patients received laser recanalisation until they were able to swallow a soft diet or better, before the application of a single dose of 10 Gy by HDR ILBT at 1 cm from the center of the source axis. Patients were followed up and treated promptly with other endoscopic means in the event of their dysphagia worsening. 6 patients (32%) required no further treatment until death at a median of 10 weeks (range 1-20 weeks). Further therapy was required at a median of 11 weeks (range 4-37 weeks) after brachytherapy for those 13 patients with recurrent dysphagia. Subsequent symptom control required endoscopic intervention at an average, or once every 9 weeks. There was no mortality associated with laser or brachytherapy. Median survival from treatment was 36 weeks. The authors concluded that laser combined with brachytherapy offered a safe, and more effective means of palliating malignant dysphagia due to adenocarcinoma, than a longer dysphagia free interval experienced by historical controls treated with laser alone.

11.8 : BRACHYTHERAPY ALONE IN PALLIATION OF OESOPHAGEAL CANCER

Following the successful use of laser and ILBT, the question arose as to whether ILBT alone was adequate to control the tumour locally, thus providing the patient with prolonged dysphagia free survival and therefore effective palliation. This had the advantages of being cheap, it could be done on an outpatient basis, did not require hospitalization, did not require anesthesia, and more importantly could be done in most cases regardless of performance scores.

The first report on the use of ILBT alone for palliation of advanced oesophageal cancer was published by Rowland and Pagliero (1985). 40 patients (22 males, 18 females, age range 47-83 years, median 76) were treated with palliative ILBT. In 5 patients dysphagia was complete, the rest could manage liquids only. All these patients were assessed to be inoperable, and many of them (60%) had metastatic disease. On histology, there were 24 squamous, 15 adeno carcinomas and 1 oat cell cancer. A dose of 1500 cGy was given with a 2 cm margin at 1 cm from the center of source axis, using a Selectron LDR that used Cesium-137 radioactive isotope. Good relief of dysphagia was obtained in 20 (70%) of the patients with squamous carcinoma, 12 (60%) with adeno carcinoma and the patient with oat cell carcinoma. The duration of relief from dysphagia was 8-50 weeks (median 50), 8-30 weeks (median 12), and 20 weeks respectively. 12 out of 14 cases showed improvement on barium examination. 2

patients were retreated at 30 weeks, and showed further improvement in swallowing. ILBT alone was found to be more effective than intubation in high palliation or advanced oesophageal cancer.

Wei-bo Yin (1989) reported the results of his studies at the department of Radiation Oncology, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China over a 14 year period. From 1970-74 a total of 203 patients with cancer of the oesophagus were treated with HDR Cobalt-60 ILBT. The prescribed dose was 7.5 Gy at 0.5 cm, and 2-4 insertions were given to each patient at intervals of 2-4 weeks. Therefore, a total of 15-30 Gy was given in 2-4 fractions. The survival rate was 34.5% at 1 year, 13.8% at 3 years and 8.4% at 5 years. The major complications comprised 66% acute oesophagitis with severe pain on swallowing, 49.3% back pain and 11.8% strictures. Patient details and selection criteria were unfortunately not available.

Fleischman et al. (1990) reported the results of a pilot study on 10 consecutive patients with advanced oesophageal cancer, who were treated with palliative ILBT alone. All patients received treatment of 20 Gy in a single fraction by MDR. The dose was prescribed at 1 cm from the center of the source axis. There were 6 males and 4 females with an average age of 66.8 years. The average length of the tumour was 8.5 cm. 6 patients had received some form of treatment previously e.g. chemotherapy, dilatation, cautery, laser or a combination of these. Previous treatment had failed in all these 6 patients. 9 out of 10 patients

achieved improvement in dysphagia. The average length of response was 5.1 months. There were no complications of treatment, and the survival ranged from 1-12 months. 2 patients had no evidence of disease at 10 months after treatment. The authors suggested that palliative ILBT could be used in place of palliative EBRT in quick and effective palliation of advanced oesophageal cancer.

Sur et al. (1991b) reported results on the use of HDR ILBT alone in palliation of advanced oesophageal cancer. 9 patients with advanced oesophageal cancer involving the middle third of the oesophagus with a length of 6-10 cm, lumen of at least 10 mm, who were unsuited for surgery and had a Karnofsky score > 70, were treated with HDR ILBT of 12 Gy in 2 fractions, given a week apart. The dose was prescribed at 1cm from the center of the source axis. All 9 patients were alive 9 months after treatment. At the end of 6 months, 4 patients had strictures which were dilated. At the end of 9 months, 6 patients had dysphagia, 4 of whom had strictures, and 2 had recurrence which was treated with further ILBT of 6 Gy. The authors concluded that HDR ILBT alone can be used in the high palliation of advanced oesophageal cancer and avoids intubation.

Pickering et al. (1992) treated 28 patients with advanced oesophageal cancer with LDR ILBT giving 15 Gy at 1 cm from the source axis. The response rate in terms of improvement of dysphagia was 22 out of 28 and in addition, 2 patients had relief of pain on swallowing. The overall response rate was 86%, and the survival following the procedure was between 1-68 weeks with a mean of 17

weeks. The authors concluded that ILBT should be the initial palliative treatment of choice in advanced oesophageal cancer. It is well tolerated with a low morbidity and mortality, and does not preclude the later use of intraluminal tubes if required.

Harvey et al. (1993) compared 10 patients who received 20 Gy/3 fractions at 1 cm by MDR ILBT to 12 patients who received 12.5 Gy in a single fraction by HDR ILBT at 1 cm. Dysphagia was relieved in 9 out of 10 MDR patients and 11 out of 12 HDR patients. The duration of palliation was 4.5 months for the single fraction HDR group, and 5.1 months for the fractionated MDR group. The life expectancy for the single fractionated HDR group (5.8 months) compared favorably with fractionated MDR patients (4 months) and EBRT patients (4.9 months).

Jager et al. (1992) reported the results of 36 patients with advanced oesophageal cancer who were entered into a study to determine the efficacy of palliation by a single session of ILBT. A dose of 15 Gy was administered 1cm from the center of the applicator. In 22 of the 32 patients alive 6 weeks after treatment, dysphagia improved in 14 (complete). Reobstruction occurred in 8 of the 22 responders, but a second treatment with ILBT caused improvement in 6. Intra oesophageal prostheses were needed in only 6 of the 36 patients. The authors concluded that ILBT was safe, easy to administer, and formed a useful addition to the therapeutic possibilities for palliation of oesophageal cancer.

In an updated follow up report, Jager et al. (1995) reported the results of 51 patients with oesophageal cancer, who were treated by a single section of ILBT of 15 Gy, prescribed at 1 cm from the center of the source axis using an MDR after loader; and 37 patients who were treated with HDR after loader. All patients were inoperable either because of loco regional tumour extension (n = 18), the presence of distant metastasis (n = 22), for other medical reasons, including poor performance status (n = 33), or a combination of these factors (n = 15). The improvement of dysphagia, assessed 4-6 weeks after treatment, was noted in 50 of 75 (67%) evaluable patients, whereas swallowing ability was restored in 47% of them. Relapse of dysphagia occurred in 28 (37%) patients during follow-up. Additional palliative treatment consisted of intubation in 14 (19%) patients, a second course of brachytherapy in 13 (17%), 1 or more dilatation in 11(15%) and laser treatment in 4(5%) patients. 1 nonfatal hemorrhage and 5 fistulae occurred, all in the presence of tumour. 2 severe obstructions without evidence of tumour were noted, both managed by combined curative treatment. The median survival of the group was 5.5 months. In a multivariate analysis, the presence of distant metastasis (p = 0.0028), weight loss (p = 0.0051) and an exophytic growth pattern (p = 0.0199) were associated with a lower survival rate. The authors concluded that single fraction ILBT was appropriate in palliating dysphagia in patients with inoperable oesophageal cancer showing bad prognostic signs.

Greene et al. (1995) described the role of oesophagogastroscopy in application and follow-up of patients with oesophageal cancer treated with HDR ILBT. 24 patients (21 oesophageal, 3 GE junction) were treated using HDR ILBT, which was delivered through endoscopically placed catheters. Radiation doses range from 5 Gy to 8 Gy delivered to the tumour bed in 3 sessions. All patients were assessed for swallowing ability, endoscopic evidence of tumour reduction, and complications resulting from ILBT. 15 patients had reduction in intraluminal tumour based on endoscopic evaluation. 7 had partial or complete relief of dysphagia. 9 patients required gastrostomy tube placement for alimentation before or after therapy. 4 patients had complications of perforation (1), fistula (1), or bleeding (2) after HDR ILBT. Overall survival ranged from 2 to 27 months (mean 8.9 months) after the first HDR ILBT treatment.

A dose searching study on the optimal dose of single fraction HDR ILBT was conducted at the University of the Witwatersrand, Johannesburg (Kulhavy et al., 1995). 51 untreated patients with advanced oesophageal cancer arising from the thoracic oesophagus were entered into a randomised prospective study. Patients were randomised to receive 10 Gy (group A, n = 12), 12 Gy (group B,n = 14), 15 Gy (groupC, n = 14) and 18 Gy (group D, n = 11) single session HDR ILBT. Patients were followed up every month for 4 months. Relief of dysphagia and weight gain were seen in all patients in groups B and C. Improvement in performance status was seen in all evaluable patients in group C at the third and fourth month. 4 patients (2 in group A and 2 in group B) developed strictures

due to persistent disease after 3 months of follow-up. 4 patients developed fibrotic strictures (1 in group C and 3 in group D) within 4 months of follow-up. 1 patient in group D developed tracheoesophageal fistula and required intubation. Single fraction HDR ILBT of 12-15 Gy gave the best results in terms of relief of dysphagia, weight gain and improvement of performance status. Based on the results of the study, the authors expressed the view that patients receiving between 12-15 Gy would experience the least morbidity in terms of strictures and fistulae, in palliation of advanced oesophageal cancer by HDR ILBT.

Brewster et al (1995) described their experience using intraluminal brachytherapy in the palliation of carcinoma of the oesophagus from the Christie hospital and Holt Radium Institute in Manchester. There were a total of 197 patients in their study with median age of 73 years and M:F ratio of 1.2:1. 14% of patients had previously undergone oesophagectomy, 37% had been treated with palliative dilatation and 6% with laser therapy. 12 patients (6%) received prior EBRT delivered between 2 and 4 months prior to the intraluminal treatment. 1 patient received a single fraction of 12.5 Gy and 2 patients received 50 Gy in 15 fractions. The remaining 9 patients received doses ranging from 20 Gy in 4 fractions to 39.4 Gy in 16 fractions. 50% of the patients had lesions of 7 cm or more in length, and 14% had known metastatic disease at presentation. Treatment was given with a micro-Selectron HDR. 94% of patients presented with a dysphagia score of 3 or more, 11% had a score of 5, 43% had

a score of 4 and 40% a score of 3. 72% of patients had suffered a weight loss of 6.4 kg or more. In the 161 patients in whom dysphagia scores were reassessed at 6 weeks, 87 sustained an improvement (54%). Of these, 80 (91%) were able to tolerate a soft diet or better. 42% remained stable, and 4% had deteriorated. Improvement was maintained for a median of 123 days. This compared well with the overall median survival for the group of patients as a whole, which was 136 days. Those in whom reassessment score was available (either because they were unable to attend or because initial follow-up was arranged elsewhere) had a median survival of 71 days. The median survival of those patients who improved was 193 days, compared with 121 days for those who remained stable, and 118 days for those who deteriorated. Statistical analysis of survival confirmed that those who sustained an improvement in dysphagia did demonstrate a small survival advantage ($p = 0.0001$). Predicted survival at 1 year of those patients who had improved following treatment was 19.5 months, compared with 12.2 months for those who were stable. Those with no reassessment score had a predicted survival at 1-year of 3.5 months. This clearly did not imply that the treatment itself conferred any survival advantage, but it does suggest that an improvement in dysphagia following treatment may be a good prognostic indicator. The response rate was similar for those patients with severe pretreatment dysphagia (56%), and those who could tolerate a soft or semisolids diet (48%). 6 patients who developed recurrent dysphagia after sustaining an initial improvement were re-treated with a dose of 10 Gy at 1 cm. None of these patients experienced an improvement in

dysphagia scores when assessed 1 month after treatment. 61% of patients with adenocarcinoma improved following treatment, compared to 46% of those with squamous cell carcinoma ($p \approx 0.02$). 63% of lesions in the upper third of the oesophagus improved, 55% in the middle third and 47% of those in the lower third. This difference was not significant statistically, but suggested that the effect of pathology on response rate was not related to the site within the oesophagus. Those patients who received prior EBRT had a similar response rate (42%) when compared to the group as a whole. 4 patients developed severe adverse reactions. Marked acute oesophagitis occurred in 3, all of whom had received EBRT previously. 1 patient developed stricture. Overall response rate, when compared with EBRT was 57%. However, all the patients who responded tolerated a solid diet following treatment, compared with a total of 34% of patients who tolerated a solid diet following brachytherapy alone.

Leung and Kuan (1995) reported a retrospective review of 11 patients who were treated at the Peter MacCallum Institute, Australia, with LDR ILBT. 8 patients had recurrent oesophageal carcinoma and had undergone previous treatment. The remaining 3 were new presentations with no previous treatment. The mean age of the patients was 63 years (25-88). 8 patients were male and 3 female, 9 had squamous cell carcinoma, and had 2 adenocarcinoma. Only 1 patient had distant metastasis at the time of ILBT. Most patients had received other treatment prior to brachytherapy: 1 patient had an oesophagectomy and 8 had laser treatment with 6 having 2 or more ablations, 7 had previous dilatations,

and 8 had received prior EBRT with a mean dose of 48.4 Gy and a range of doses from 20 to 60 Gy. 6 patients had received prior chemotherapy. The indication for ILBT was dysphagia, which was scored on the basis of swallowing ability of the patient. ILBT was given using a LDR Selectron and a mean dose of 18.6 Gy (7.1-60 Gy), and was prescribed at 1 cm from the surface of the applicator. Patients were assessed 4 weeks after ILBT, and then at regular intervals. Improvement or stabilization of swallowing was defined as a therapeutic response and survival was measured from the date of ILBT. 1 patient died because of widespread disease. Of the remaining 10, 2 had a dysphagia score of 2 pre-ILBT, 6 had a score of 3 and 2 had a score of 4. Response was noted in 9 of the 10 patients. The 1 non-responding patient progressed from a dysphagia score of 3 to 4, and had an oesophageal dilatation 2 months later, but was lost to further follow-up. All responding patients were able to swallow at least a semisolids diet until death. No complications were seen in this series, and the median survival from the date of ILBT was 3 months.

Makarewicz et al. (1996) reported the use of palliative ILBT in 15 patients with advanced carcinoma of the oesophagus. Most of these patients had failed other palliative modalities including EBRT, chemo radiotherapy, laser therapy and dilatation. ILBT was given in 3 fractions to a dose of 22.5 Gy. 3 months after treatment, complete endoscopic regression was seen in 1 patients, partial regression in 8 patients, no response in 1 and progressive disease in 5. The median survival was 6.2 months, in which time no complications had occurred.

HDR ILBT was shown to be an effective means of palliation, where other palliative modalities had failed.

The preliminary results of a randomised prospective study on fractionated HDR ILBT alone in palliation of advanced oesophageal cancer, was reported from the University of the Witwatersrand (Sur et al., 1996a*). 68 patients with stage III and IV carcinoma of the thoracic oesophagus were entered into a randomised prospective study. Patient selection criteria included: 1. lesion in the thoracic oesophagus >6 cm length, 2. histologically proven carcinoma, 3. Karnofsky score > 50, 4. normal blood parameters, 5. ability to swallow at least liquids, and 6. no evidence of trachea bronchial fistula on bronchoscopy and/or barium swallow. The presence of distant metastasis was not considered a contraindication for entry. Patients were randomised to 3 groups. Group A received 12 Gy in 2 fractions over 2 weeks (6 Gy per fraction, weekly); group B, 16 Gy in 2 fractions over 2 weeks (8 Gy per fraction, weekly) and group C, 18 Gy in 3 fractions over 3 weeks (6 Gy per fraction, weekly). All patients were followed monthly and assessed for relief of dysphagia, and for weight gain. At 6 months, the dysphagia free survival for all patients was 46% (A-35%, B 83%, C 51%). Patients in group B did significantly better than those in the other groups (A vs B, p=0.0497; A vs C, p=0.663; B vs C, p=0.118). The overall survival was 86% for the whole group (A 76%, B 95%, C 94%; p > 0.05). The complication free survival was 78%, 82% and 42% for groups A, B and C respectively. 10 patients in group A had persistent tumour causing dysphagia, and when compared with

other groups, results were significant statistically (p=0.01517). No patients died as a result of the procedure or treatment, nor were any perforations present. On the whole groups B and C were comparable and there was no statistical difference evident in the outcome. Following the results of this analysis, the arm of 12 Gy in 2 fractions was dropped (Group A), and randomization continued between groups B and C. HDR ILBT provided better results when compared with other currently available palliative modalities of treatment.

Histological Studies related to ILBT alone

Freund and others (1989) investigated the tolerance of intact oesophageal mucosa in 15 pigs given HDR ILBT. Doses of 6 Gy and 12 Gy were administered. No macroscopic or microscopic alterations of the mucosa were found after 6 Gy. On the other hand, a single dose of 12 Gy produced more severe side effects, including vascular occlusion due to fibrosis of the intima, formation of fistulas, and perforations of the oesophageal wall. The authors recommended that further investigations be conducted to elaborate the schemes for dosage and fractionation.

Sur et al (1996) reported the morphological alterations in oesophageal squamous cell carcinoma who were given preoperative HDR ILBT. Total oesophagectomy specimens from 4 patients, who were given preoperative HDR ILBT of 20 Gy in 2 fractions of 10 Gy each weekly, were reviewed for radiation changes.

Oesophagectomy was performed 2 weeks following brachytherapy in all patients. In all patients, preoperative biopsy specimens showed moderate to poor differentiation in squamous cell carcinoma, with minimal to negligible keratin production. The oesophagectomy specimens were sampled at the resection margins; the edge of irradiated length, 1 cm from the proximal and distal edge of visible tumour, and the center of the tumour and lymph nodes. Radiation change in the form of fibrosis was limited to the sub mucosa at the resection margins, the circular muscle layer at the edge of irradiated length, and full thickness at 1cm from the edge of the visible tumour and the center of the tumour. Surface epithelium did not show any changes at the resection margins but did show basal cell hyperplasia at the edge of the irradiated length, at 1cm from the edge of the visible tumour and the center of the tumour. Endarteritis obliterans was seen only at 1 cm from the edge of the visible tumour, and at the center of the tumour. Necrosis, intense keratin formation, and giant cell reaction were observed at the center of the tumour. When compared with pre-radiation biopsies, the amount of keratin in the post radiotherapy specimens was extensive. It may be concluded that HDR ILBT may cause induction of keratin gene in the irradiated cells to stimulate differentiation towards better differentiated cells.

As can be seen from the review, all previously reported series have been retrospective with no defined selection criteria. Often ILBT was chosen as other modalities had failed, or because the patient had recurred after radical

treatment. Further, no dose optimization was determined excepting a previous report from this department (Kulhavy, 1995). The lack of these parameters therefore necessitated the need for a randomised prospective study for dose optimization. This forms the basis of this report here.

11.9 : OTHER STUDIES

The following studies mentioned here have a bearing on various aspects of oesophageal cancer treatment, but do not specifically fall under the various subheadings of treatment mentioned in the review.

Casper et al. (1988) retrospectively analysed a group of 107 patients with oesophageal cancer, treated with EBRT of different dose levels. It was found that 70.5% of the patient showed improvement of dysphagia, and that 54% remained palliated with respect to food passage until their death. The 2 major prognostic variables with respect to the palliative effect on dysphagia, as well as survival, were the passage score and the radiation dose. Patients with severe dysphagia (PASS 0 or 1) had a median actuarial dysphagia free interval, and survival of 3.7 and 6.4 months respectively, in contrast to 16 and 8.7 months for patients who were able to ingest solid food (PASS 2 and 3). The median actuarial dysphagia free interval, and the overall survival of patients treated with a relatively low dose (<50 Gy in 5 weeks), was 2.5 and 4.8 months respectively, compared with 10.1 and 8.3 months respectively for patients treated with a higher dose.

O'Rourke et al. (1988) evaluated the incidence and etiologic factors of importance in the development of strictures of radiotherapy for carcinoma of the oesophagus, and analysed the outcome of patients who develop such strictures.

80 patients with carcinoma of the oesophagus were treated with radiotherapy (50 radical, 30 palliative). 69 patients had squamous cell carcinoma, 4 adeno carcinoma, 1 had sarcoma, 1 mucoepidermoid carcinoma, and 5 had undifferentiated tumours. 40% developed no stricture, 30% had benign fibrotic stricture, and 28% of patients developed malignant stricture. The etiologic factors analysed included age, pretreatment swallowing score, histology and length of tumour, stage of disease, dose of radiotherapy, and the use of chemotherapy. None of these factors were shown to be of etiologic importance. The survival of patients who developed benign strictures was found to be significantly longer (1 year survival-88%) than those who developed no stricture (50%) or malignant stricture (19%). Patients who developed benign strictures had a median survival from the development of stricture to time of death of 14.1 months, when compared to 1.3 months for patients with malignant stricture ($p < 0.001$)

Leslie et al. (1992) reported an audit of 244 patients with carcinoma of the thoracic oesophagus registered at the Mount Vernon Center for Cancer treatment, UK, between 1980 and 1989. The median survival of the group who had localised disease, were deemed unsuited for surgery, and had been treated solely with radiotherapy, was 8.2 months (0.2-54 months). Dysphagia was improved by radiotherapy in 77.3% of cases. The median duration of relief was 24 weeks (0-208 weeks), and was maintained until death in 40% of the cases. Life table analysis showed that radical compared with less than radical regimens

of radiotherapy gave significantly superior relief of dysphagia and were unlikely to be attributable to patient selection.

Kinsman et al. (1996) reported that patients who had prior radiation and/or chemotherapy have an increased risk of severe complications following placement of a self expanding metallic stents. Self expanding Gianturco-Rosch Z stents were placed successfully in 59 patients with obstructing oesophago gastric malignancies. Early procedure related complications occurred in 6 patients (10%) and were overall minor. 23 late complications occurred in 22 patients (37.5%). Life-threatening complications occurred in 9 patients (15%) including gastrointestinal bleeding (7), perforation (1), and trachea oesophageal fistula (1). These complications contributed to all 5 deaths. 8 of the 22 patients with prior radiation and/or Chemotherapy (36.4%) had life-threatening complications compared to 1 of 37 (2.5%) without prior therapy ($p = 0.001$). Stent related mortality occurred in 5 of the 22 (23%) patients with prior therapy, compared to none of the 37 without prior therapy ($p = 0.005$). Multivariate analysis confirmed the association between prior radiation and/or Chemotherapy and life-threatening complications ($p = 0.032$; odds ratio 13.9). There was no association with tumour location or length, histologic type, age, presenting dysphagia score, or previous surgical resection.

41 patients with oesophageal cancer who developed strictures after HDR ILBT, were dilated using a slow continuous dilator (Didcott dilator). The dilator

remained in the patient for 5-7 days (Sur et al., 1996b*). After dilatation, all patients were evaluated monthly to monitor relief of dysphagia. At the end of the first month, 41 patients were evaluable, and 28 had no dysphagia while 13 had improvement. At the end of the third month, 34 patients were evaluable, 24 had no dysphagia, and 10 had improved. 3 patients developed a worsening of dysphagia due to tumour recurrence among 32 patients who were evaluable at the end of the fourth month. 5 patients developed worsening of dysphagia among the 26 patients evaluable at 5 months due to tumour. These patients were treated with further brachytherapy after slow continuous dilatation. At the end of 6 months, 14 patients were evaluable, 7 had no dysphagia, and 7 showed improvement over their presenting dysphagia score. Slow continuous dilatation using, the Didcott dilator as is practiced in Johannesburg, was an effective way of dilatation of strictures following HDR ILBT in oesophageal cancer. Dilatation is prolonged and sustained and a single dilatation is usually enough to maintain patency.

Sargeant et al. (1997) reported that radiotherapy enhances laser palliation of malignant dysphagia. This was based on the results of a randomised study in which 67 patients with inoperable oesophageal or gastric cardia cancers, who had satisfactory swallowing after initial laser recanalisation, were randomised either to palliative EBRT (30 Gy in 10 fractions) or to no radiotherapy. All patients underwent a check endoscopy 5 weeks after initial recanalisation, and were subsequently re-endoscoped only for recurrent dysphagia, which occurred

in 59 patients. Dysphagia was relieved equally well in both groups and improvement was maintained with further endoscopic treatment. The initial dysphagia controlled interval, and the duration between the procedures required to maintain lifelong palliation (treatment interval) had increased from 5 to 9 weeks (median) in the radiotherapy group ($p < 0.01$ both parameters). Radiotherapy was well tolerated in all but 3 patients. 1 perforation occurred and 2 fistulae opened after dilatation in patients who received EBRT. The authors concluded that additional radiotherapy reduces the necessity of therapeutic endoscopy for a patient's remaining life. It has an important role in relatively well patients who are likely to survive long enough to benefit.

11.10 : STUDIES COMPARING RESULTS WITH VARIOUS PALLIATIVE TECHNIQUES IN THE ADVANCED CASES

Desa and others (1988) reviewed the management of 120 consecutive patients with carcinoma of the oesophagus, treated at the North Tees General Hospital in the UK, over a period of 10 years. The treatment options included endoscopic methods, radiotherapy, and surgery, or a combination of these. Adeno carcinoma was the most frequent histological type (51%) and 41% of patients had squamous carcinoma. In addition to survival, the quality of swallowing and incidence of late complications following the treatment options were assessed. Primary surgery was carried out in 21 cases (operability rate 17.5%) and 81% of these cases were resectable. The overall operative mortality rate was 14.3% (6% in resected cases) and the 5 year survival rate was 9.5%. After primary radiotherapy, only 5% of patients survived 2 years. The majority of patients were treated by endoscopic intubation with an overall mortality of 16.6%, and a mean survival of 5.5 months. Patients treated surgically experienced the best symptomatic relief and had the lowest incidence of late complications, when compared to those treated differently. The overall results of surgery were poor, and the authors felt that there was due cause for combining surgery with radiotherapy.

Sawant and Moghissi (1994) compared and contrasted the potentials of palliation afforded by various management methods, in a retrospective study of all

patients referred to one surgical team over a 20 year period. 537 patients had unresectable oesophageal cancer. There were 5 treatment groups:

Group 1- dilatation + EBRT (n = 95)

Group 2- gastrostomy + EBRT (n = 18)

Group 3- permanent intubation (n = 329)

Group 4- esophageal bypass (n = 70)

Group 5- YAG laser + ILBT (n = 25).

Groups 1 and 2 had high mortality (4% and 25%) and poor symptom relief, with an average survival of 2.5 and 3.5 months respectively.

Group 3 had a 20% mortality rate, moderate to good symptom relief, and an average survival of 4.2 months. This method was best for lower oesophageal cancer.

Group 4 had a 22% mortality rate, good symptom relief, and an average survival of 10.5 months. The bypass method was suitable for patients with oesophago-airway fistula and those with lower oesophageal cancer found unresectable at operation.

Group 5 had a hospital mortality rate of 8%, good symptom control, and an average survival of 6.2 months. This treatment was suitable for all patients (excluding those with fistula). The authors recommended that the palliative modality must be selected to suit the characteristics and location of the tumour.

11.11 : OESOPHAGEAL STENTS

Carapeti et al. (1996) described the use of oesophageal stents in palliation of advanced oesophageal carcinoma at a district general hospital. 30 stents were inserted in 27 patients: 19 with adenocarcinoma, 7 with squamous cell carcinoma, and 1 patient with mixed adeno squamous carcinoma. In addition, some patients had received radiotherapy (4), Chemotherapy (6), surgery and Chemotherapy (2) and laser (1). The follow-up ranged from 6 weeks to 16 months (mean 4.5). 8 patients died, their survival ranging from 2 weeks to 4.5 months post stenting. No deaths occurred following stenting, or as a direct consequence of it. Swallowing improved in all but 1 patient who could manage a fluid diet. In 16 patients, the ability to manage a semisolid diet was maintained until death, while 10 could sustain a near normal solid diet. 3 patients underwent re-stenting for complete dysphagia due to growth of tumour through the mesh fenestration. Stents are evidently a very useful method of palliating oesophageal carcinoma. However, the problems with stents are essentially the same as those of intubation. These include tumour growth through the fenestration and above the stents, blockage of the stents, perforation, infection, halitosis due to food rotting , bleeding, and mediastinitis. Further stent insertion requires general anesthesia, hospitalization, and is an expensive method of palliation.

11.12 : STUDIES ON CHEMOSENSITIZATION WITH BRACHYTHERAPY

While increasingly successful use of ILBT boost following EBRT were reported from the Hyogo College of Medicine, Jordaan et. al (1987) at the University of Natal, South Africa used a different approach in treating oesophageal cancer involving a combination of chemosensitisation and ILBT. Using a Selectron HDR which used Cobalt-60 pellets as its source, a dose of 0.5 Gy per fraction was repeated 3 times per week for 2 weeks, followed by a 2 week rest, followed by the same treatment given to a total dose of 6 Gy. The dose was prescribed at 2 cm depth from the center of the source axis. At the same time cis-platinum was infused at a dose of 35 mg/m^2 per radiation fraction giving a total Dose of 400 mg/m^2 over the 12 factions. Sudden and acute arterial intra thoracic bleeding occurred in 2 patients, with subsequent death. The number of fractions was decreased to 8 for the whole period with a 2 week break in between. This resulted in a 4.0 Gy total tumour dose over 8 fractions, with a total simultaneously administered dose of cis-platinum 280 mg/m^2. 36 patients were treated by this technique. Hematological and renal toxicity were seen in less than 5% of the patients. Relief of pain was experienced by 92% patients, while 91% had subjective and objective relief of dysphagia for liquids, and 85% had subjective and objective relief of dysphagia for solids. Unfortunately the survival results were not reported and no conclusions could be drawn from this study on the effectiveness of chemosensitisation with brachytherapy. There are no other

reports in the literature on chemosensitisation with brachytherapy alone, in the treatment of oesophageal cancer.

11.13 : STUDIES ON TELE-BRACHY-CHEMOTHERAPY SENSITIZATION

Dinshaw et al. (1991) reported the results of a randomised pilot study to test the efficacy of ILBT and concurrent 5FU infusion. 50 patients with locally advanced carcinoma of the oesophagus received treatment with EBRT to a dose of 50 Gy in 28 fractions in 5 1/2 weeks. 2 weeks after completion of EBRT, patients were randomised to receive either ILBT 25 Gy at 1 cm using a Selectron LDR alone, or ILBT of 25 Gy with a 24-hour 5FU infusion. The dose of 5FU was 500 mg/m^2 , and the infusion was started 12 hours before the initiation of ILBT and discontinued after its removal. All 50 patients were evaluated every 6 weeks after completion of treatment, ranging from a period of 6-27 months. Significant improvement in dysphagia was recorded in 76% of the patients. No comparison was made of the 2 groups with regard to dysphagia status in the report. CR was seen in 22/25 patients in the ILBT group and in all the patients in the ILBT + 5FU group. The overall survival at the end of 2 years was 15% for the ILBT group, and 22% for the ILBT + 5FU group ($p > 0.05$). 10 patients developed strictures, 4 severe obstructions, and 5 developed tracheoesophageal fistulae. The distribution amongst the 2 groups was not reported. The addition of 5FU for chemosensitisation to ILBT did not appear to influence the results significantly as per the study.

Peddada et al.(1993) described the results of Chemotherapy, HDR ILBT, and oesophagectomy on patients with cancer of the oesophagus. Examination of the

surgical specimens revealed a CR in only 13% of patients. Locoregional recurrence was disappointing. There were no operative deaths or major complications attributable to the preoperative treatment. 2 year survival was 33%, not different from that achieved by primary surgery or by primary EBRT. The authors concluded that HDR ILBT + Chemotherapy is insufficient for locoregional control, and must be supplemented by oesophagectomy or EBRT for even modest long-term survival.

Fietkau et al.(1994) reviewed the records of 52 patients with inoperable but localised squamous cell carcinoma of the oesophagus, to determine the influence of different treatment modalities on survival, dysphagia, and sites of recurrence. 22 patients were treated by concurrent chemo radiotherapy with cisplatin/5FU or carboplatin/5FU; 19 patients by radiotherapy alone; 6 patients by chemotherapy followed by irradiation, and 5 patients by concurrent chemo radiotherapy with various drugs. EBRT consisted of treating the primary lesion (mean dose 53 Gy) and lymphatic areas (mean dose 31 +/-26 Gy) at the rate of 2 Gy/day for 5 days/week. Additional HDR ILBT was done in 13 patients with single fractions of 6 Gy as boost. Minimum follow-up was 12 months, median follow-up 4.3 years. For the whole group, a remission rate of 65% (34/52 patients) was achieved (CR 18/52 patients = 35%; PR 16/52 patients = 31%). Relief of dysphagia accompanied tumour regression. Median survival was 11 months; the 3 year survival rate was 23%, and the 5 year survival rate 7.6%. An analysis of recurrence revealed a high rate of local failures (26/52 patients=50%) and

distant metastasis (9/52 patients = 18%). Comparing the different modalities, the best results were achieved by concurrent chemo radiotherapy. CR could be determined in 46%, and median survival was 14.9 months. Additional ILBT resulted in a slightly better local control rate (54% vs 46%) and a 3 year survival rate (30% vs 20%), compared to EBRT alone. The authors concluded that concurrent chemo radiotherapy is superior to all other treatment modalities in inoperable carcinoma of the oesophagus. Additional ILBT may result in an increase in local control.

Preliminary results from a large Australasian multicentric study using combined modality therapy for oesophageal cancer were published in 1995 (Burmeister et al., 1995). 294 patients were treated using 3 prospective unrandomised protocols that used concurrent radiation, cisplatin, and a modest dose infusional 5FU. Protocol 01- "definitive" chemo radiation: 137 patients were treated with radiation of 60 Gy in 6 weeks, together with 2 courses of cisplatin (80 mg/m^2) and 5FU (800 mg/m^2/day over 4 days) during the first and fourth weeks of radiation. Protocol 02- "pre-operative" chemo radiation and surgery: 78 patients received chemo radiation using the same chemotherapy, but with 30-35 Gy EBRT in 3 to 4 weeks prior to surgery. Protocol 03- "palliative" chemo radiation: 79 patients deemed incurable were treated palliatively, with the same chemo radiation protocol, but without surgery. Follow-up ranged from 6 months to 7 years (mean 22 months) in live patients. Durable palliation of dysphagia in all 3 treatment groups was reflected by encouraging 3-year survival expectations of

43.2 +/-5% in definitively treated patients, 40.3 +/-7.65% in surgically treated patients, and 8.5 +/-3.9% in the palliatively treated patients. There were early indications that female patients fared better than males. Toxicity levels were modest in all 3 groups. Following definitive treatment, severe myelotoxicity occurred in 19% of patients, severe oesophagitis in 11%, and moderate or benign strictures in 17% depending on age and sex of the patients, being worse in the case of female patients. This study demonstrated that concurrent addition of modest doses of cisplatin and 5FU to radiation in the definitive, preoperative and palliative settings contributed to high rates of durable dysphagia free survival, with improved overall survival.

Sakai et al (1995) reported on the feasibility of concurrent chemo radiotherapy for patients with inoperable squamous cell oesophageal cancer. 28 patients with inoperable squamous cell oesophageal cancer were treated with concurrent chemo radiotherapy using protracted low dose continuos infusion of 5FU (250-300 mg/m^2/24 hours), and standard EBRT. In 25 patients who received a total dose of > 60 Gy and concurrent 5FU infusion for more than 5 weeks, the CR rate was 52%. Local progression free rate in this chemo radiotherapy group was significantly higher than that of historical controls treated with EBRT alone ($p < 0.05$). A multivariate analysis showed that treatment scheme (concomitant chemo radiotherapy opposed to radiotherapy alone) was a significant factor in local control ($p < 0.01$). Swallowing pain (39%), anorexia (39%) and nausea (32%) were the most frequent over reactions. No late radiation morbidity was

observed. Concurrent chemo radiotherapy using protracted low dose continuous infusion of 5FU and standard radiotherapy, was shown to be an effective and safe method of obtaining improved local control in inoperable oesophageal squamous cell carcinoma.

Mantravadi et al. (1995) analysed the local control, survival, toxicity and palliation of dysphagia in 40 patients with carcinoma of the oesophagus. 29 patients with squamous cell carcinoma and 11 with adenocarcinoma were treated with a combination of EBRT, concurrent chemotherapy, and ILBT boost to the primary site, with no oesophagectomy. 32 patients had either American joint committee on cancer stage II or III malignancy. The treatment protocol consisted of 2 courses of 96 hour continuous intravenous infusion of 5FU (1 g/m^2) plus cisplatin (100 mg/m^2) or Mitomycin (10 mg/m^2) on day 1 during the first and last weeks of an EBRT dose of 40-55, given in 5-6 weeks. All patients received a HDR ILBT boost of 5 Gy x 2, given weekly, the dose prescribed at 1 cm from the center of the source axis. Complete follow-up was available in all patients with a median of 36 months. Complete tumour response was seen in 85% of the patients, as documented by periodic endoscopy, biopsy and barium swallow. Tumour control in the oesophagus was achieved in 77.5% of patients, with an acceptable acute and long term treatment related morbidity. 8 patients developed grade 3 (severe dysphagia or odynophagia with dehydration or weight loss of > 15% from pretreatment baseline requiring nasogastric tube feeding, intravenous fluids of hyper alimentation); whereas all recovered completely with

only supportive care. Toxicity in the form of oesophageal stricture (grade 4) developed in 9 patients who required periodic dilatation of the oesophagus. On review, all these patients were found to have an annular, and lesion >5 cm in length. Near normal swallowing returned in 72% of patients at 3 months, and maintained in 62% of patients at 3 years, with the actuarial overall and recurrence free survival rates at 3 years being 36% and 55% respectively. The authors concluded that combined chemotherapy, and EBRT and HDR ILBT was an effective treatment in the management of carcinoma of the oesophagus, with acceptable acute and long-term toxicity.

Sola et al (1996) reported the results of concurrent chemo radiotherapy in 18 patients (squamous cell carcinoma 15, adenocarcinoma 2, undifferentiated carcinoma 1) with oesophageal carcinoma. All patients had inoperable lesions for unresectable disease (11 patients) or concomitant illness (7 patients). The median Karnofskys score was 70 (range 60-80). According to the 1988 AJCC staging of oesophageal cancer, 1 patient was staged as IIA, 2 staged as II B, 12 patients as stage III, and 3 as stage IV. Treatment consisted of 2 courses of chemotherapy by cis-platin (75 mg/m^2 i.v. on days 1 and 29), and 5FU (1,000 mg/m^2/24 hours by continuous infusion from days 1 to 4, and from days 29 to 32), along with 1 course of concomitant radiotherapy at 45 Gy in 25 fractions over 5 weeks. 15 to 30 days after EBRT, all patients received 7 Gy by HDR ILBT. All patients were assessed for toxicity, and 17 for response. The combined treatment was generally well tolerated. Only 1 case of WHO grade III toxicity

occurred. 8 patients had a CR (47%); 4 had a PR (24%); 4 a minimal response (24%), and 1 patient showed stable disease (5%). Only 1 patient developed local progression, and 4 developed distant metastasis. All patients with CR were alive without local recurrence (2 distant metastasis), with a mean follow-up of 6 months. The treatment regime provided good local tumour resolution with no major toxicity.

The Trans Tasman Radiation Oncology group reported on the factors that influence outcome following radio Chemotherapy of oesophageal carcinoma (Denham et al., 1996). 373 patients with oesophageal cancer were entered into 3 prospective but unrandomised protocols, which involved radiation with concurrent cisplatin and infusional 5 FU. Centers in Australia and New Zealand contributed patients. Cause specific survival in 92 patients treated preoperatively with 35 Gy, infusional 5 Fluorouracil and cisplatin was 25.5 +/-6.0% at 5 years, was similar to the 5 year expectations of 169 patients treated with 60 Gy and 2 courses of the same chemotherapy (23.8 +/-4.7%). Analysis of failure in these groups suggested that local relapse precedes the development of metastasis, and competes as a cause for ultimate failure. Although patients treated surgically were less likely to relapse locally, survival was no better because most developed metastasis. The 112 patients who were treated palliatively with 30-35 Gy concurrent chemotherapy without surgery had a 5-year survival figure of 7.7 +/-3.4%. Apart from variables related to disease stage and performance status at presentation, tumour site emerged as a strong predictor for outcome.

Prognosis worsened, the nearer the tumour was to the stomach. The group concluded that concurrent radio chemotherapy protocols can improve outcome in patients fit enough to tolerate these approaches.

A pilot study was performed with 5 patients having inoperable, advanced adenocarcinoma of the oesophagus, with good performance score, normal blood parameters and with no metastatic disease with telebrachychemotherapy at the University of the Witwatersrand (Sur et al., 1996d). Treatment was given with EBRT of 45 Gy in 25 fractions over 5 weeks with anterior posterior fields that included both the supra-clavicular fossa, the entire mediastinum and oesophagus, the gastroesophageal junction, and the celiac nodes. Chemotherapy with 5FU 800 mg/m^2 was given as a bolus after adequate hydration from day 1 to day 5 and from day 21 to day 25 of EBRT. ILBT was administered immediately after completion of EBRT, and a dose of 10 Gy was given by HDR ILBT at 1 cm from the center of the source axis. 3 of the 5 patients died due to severe grade IV toxicity within 3-4 weeks of treatment. 2 were dysphagia free, but had lost a significant amount of weight. Their Karnofsky score had deteriorated to less than 40%. These 2 patients died after 2 months. The cause of death could not be ascertained, but they did not die of grade IV toxicity. Based on this study, the authors recommended that although telebrachychemotherapy treatment has its place in the palliation of advanced oesophageal cancer, caution should be exercised in the selection of patients. Karnofsky's score of these patients should be between 90-100% which would

allow them to tolerate the regime. Administration of the chemotherapeutic agent should be as a slow continuous infusion rather than a bolus. The dose of EBRT should be moderate and the brachytherapy fractionated as far as possible, as these factors may also contribute to increased morbidity.

Dosoretz et al. (1997) described their experience using EBRT + ILBT with or without chemotherapy in the treatment of inoperable oesophageal cancer. 35 patients with biopsy proven squamous cell (21) or adenocarcinoma (14) of the oesophagus and no evidence of distant metastasis were treated with the combination of EBRT + HDR ILBT. All these patients were unsuited for surgery due to advanced age or poor performance status. The median EBRT dose was 61 Gy (range 36-68.4 Gy). The median HDR ILBT dose was 15 Gy, and most patients had 3 HDR procedures with a fractions size of 5 or 7 Gy. HDR ILBT was given 2 weeks following completion of EBRT. Chemotherapy was given in 71% (25) of the patients. Chemotherapy was not given to 10 patients due to age, concomitant medical problems, or patient refusal. Combination of 5FU and cis-platin was used, typically given at doses of 1 gm/m^2 per 24 hours during 4 days and 75 mg/m^2 respectively. The probability of progression free survival at 12 months and 24 months was 52% and 28% respectively. The progression free survival at 12 months was 62% for patients receiving chemotherapy, compared to 30% for those not receiving chemotherapy ($p = 0.02$). In a multivariate analysis, chemotherapy, histologic diagnosis, tumour location and swallowing ability were associated with survival. Late complications included stricture

formation and were mild to moderate in 44%, and severe in 12% of patients. Chemotherapy did not appear to increase the incidence of strictures. No fistulae or deaths were seen as a result of the study.

Gasper et al. (1997b) reported a preliminary toxicity report of a phase I/II study of EBRT, ILBT and concurrent Chemotherapy in localised cancer of the oesophagus, conducted prospectively in multi-institutions. This study was designed to determine the feasibility and tolerance of EBRT + concurrent Chemotherapy and ILBT in potentially curable adenocarcinoma or squamous cell carcinoma of the oesophagus. EBRT was delivered 50 Gy in 25 fractions over 5 weeks followed 2 weeks later by HDR/LDR ILBT of 5 Gy, and on weeks 8,9 and 10 for a total of 15 Gy by HDR, or 20 Gy on week 8 by LDR. The protocol was later revised to exclude the LDR alternative, owing to poor accrual and to decrease in the HDR dose to 10 Gy (i.e., 5 Gy on weeks 8 and 9). Chemotherapy was given on weeks 1, 5, 8 and 11, with cisplatin 75 mg/m^2 and 5FU 1,000 mg/m^2 per 24h, 96 hour infusion. 56 patients were entered on the HDR arm. 6 patients were declared ineligible due to tumour extension to the gastroesophageal junction (3 patients) or involved celiac lymph nodes (3 patients). Of the 50 eligible patients, the planned ILBT dose was 15 and 10 Gy, in 40 and 10 patients respectively. 46 of the eligible patients had squamous cell histology and 3 adenocarcinoma. Life-threatening toxicity or treatment related death occurred in 13 (26%) and 4(8%) of the 50 eligible patients respectively. Treatment related oesophageal fistulas occurred in 3 patients (12% overall, 14%

of patients starting ILBT) at 0.5-6.2 months from the first date of brachytherapy, leading to death in 3 patients. The fourth death was secondary to renal toxicity and infection, attributed due to chemotherapy. No correlation was found between the development of fistula and location of primary tumour, brachytherapy active length or applicator diameter. So far 5 of the 6 treatment related fistula occurred following 15 Gy ILBT. 35 patients (70%) were able to complete EBRT , ILBT and at least 2 courses of Chemotherapy. Estimated survival rate at 12 months was 48% with an estimated 11 month median survival. Survival following EBRT + concurrent Chemotherapy + ILBT did not appear to be significantly different from the survival seen following EBRT + Chemotherapy only. The authors recommended extreme caution in using ILBT boost following concurrent EBRT + Chemotherapy.

Again, all the above studies were retrospective with no selection of patient criteria, and with no standardization. Further more, subjecting a patient with oesophageal cancer in advanced stages to a course of 7-9 weeks treatment, without significantly altering survival was a waste of resources that could be used in the treatment of more radical patients with cancers at other sites. A combination of 5 FU for chemosensitisation with ILBT was earlier attempted by Jordaan (1987), with poor and insufficient results. Dinshaw et al (1991) demonstrated that there was no advantage of chemosensitisation with ILBT following EBRT. The question of chemosensitisation with 5 FU + ILBT alone, as an effective means of palliation has never been answered as there has never

been a study conducted in the past. Both 5 FU and HDR ILBT are cheap and have been shown to be effective. The present report examines the possible role of chemosensitisation and ILBT in palliation of advanced oesophageal cancer.

Histological Studies related to chemosensitisation

Soejima (1992) conducted experiments on the oesophagus of rabbits, in order to describe the side effects on the normal part of the oesophagus, following ILBT boost therapy. Oesophageal ulcer was observed in the specimen receiving are dose of 15 Gy during 7-28 days after irradiation. Before mucosal changes were observed, oedema and cell infiltration were found in the lamina propria. Chronic injury such as necrosis and degeneration of epithelium, and degeneration of the walls of blood vessels, were seen at 6 months. No marked changes were found in the specimen that received 5 and 10 Gy. The influences of administering a mucosa protection agent and a cancer chemotherapeutic drug were also studied. Administration of mucosa protection agent protected the occurrence of severe ulcer and accelerated the recovery from mucosa damage. Administration of cancer chemotherapeutic agent enhanced the radiation injury by ILBT of the oesophagus. The author suggested that single dose of HDR ILBT should been reduced to less than 10 Gy to prevent the oesophagus from severe injury.

11.14 : NORMAL TISSUE DOSE FOLLOWING BRACHYTHERAPY

An estimate of the maximum dose reaching the adjacent normal tissue structures (spinal cord, posterior pericardium and left and right hilum) was obtained from radiographs in the anterior-posterior and lateral views for patients who received HDR ILBT for oesophageal cancer (Peterson et al., 1996). Doses to the posterior pericardium ranged from 20.33%-64.38%, 13.3%-33.1% to the spinal cord, 27.5%-81.7% to the left hilum, and 16.3%-114.6% to the right hilum depending on the dose prescribed at 1 cm from the center of the source axis. Doses to the spinal cord showed the least variability, with a standard deviation of 0.98, while doses to the right hilum showed the greatest variability with a standard deviation of 5.66. Use of one tailed single sample t test, mean spinal cord dose, mean posterior pericardial dose, and mean left and right hilar doses, was found to be significantly less than tolerance doses of these structures ($p < 0.05$). HDR ILBT was found to be a safe and effective method of palliation in oesophageal cancer either alone or in combination with EBRT.

Chapter 12

Results

For the sake of continuity and easy reference, a brief summary of the treatment regimes used in the various studies are mentioned at the beginning of the results

STUDY I (A) : BRACHYTHERAPY ALONE

A total of 172 patients were entered into this randomised prospective study using random number tables. Patients were randomised into 3 treatment groups. Each group received treatment by HDR ILBT of a varying dose.

Group A : 12 Gy given in 2 fractions over 2 weeks , 6 Gy per fraction given a week apart. Dose was prescribed at 1 cm from the center of the source axis, and included the tumour and 2 cm margin proximal and distal to the tumour.

Group B : 16 Gy given in 2 fractions over 2 weeks, 8 Gy per fraction given a week apart. Dose was prescribed at 1 cm from the center of the source axis, and included the tumour and 2 cm margin proximal and distal to the tumour.

Group C : 18 Gy given in 3 fractions over 3 weeks, 6 Gy per fraction given a week apart. Dose was prescribed at 1 cm from the center of the source axis, and included the tumour and 2 cm margin proximal and distal to the tumour.

Variables : Distribution of patients into the 3 treatment groups is shown in Table VIII. Distribution by age ranges, tumour length and weight is shown in Table IX. Distribution by mean age, mean length and mean weight is shown in Table X. Distribution by sex is shown in Table XI. Distribution by length of lesion is shown in Table XII, and distribution by race is shown in table XIII. Distribution

according to presenting dysphagia score is shown in Table XIV, and distribution according to histology and grade is shown in table XV and XVI respectively. Distribution amongst the groups based on initial Karnofsky performance score is shown in table XVII.

Table VIII

Patient distribution by protocol

Group	Protocol	Numbers
A	12 Gy/2#; 6 Gy/#	36
B	16 Gy/2#, 8 Gy/#	68
C	18 Gy/3#, 6 Gy/#	68
Total - all patients		172

Table IX

Patient distribution by age, length and weight groups

Variable	Range	Number
Age	31-40 years	13
	41-50 years	41
	51-60 years	63
	61-70 years	55
Turnour Length	6-8 cm	20
	9-11 cm	96
	12-14 cm	47
	15+ cm	9
Weight	21-40 kg	34
	41-60 kg	102
	61+ kg	15
	Unknown	21

Table X - Median Age, Mean length, Mean weight

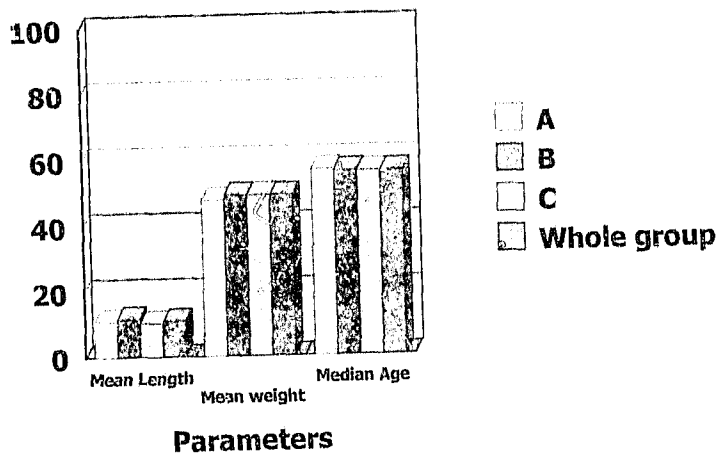


Table XI
Sex Distribution

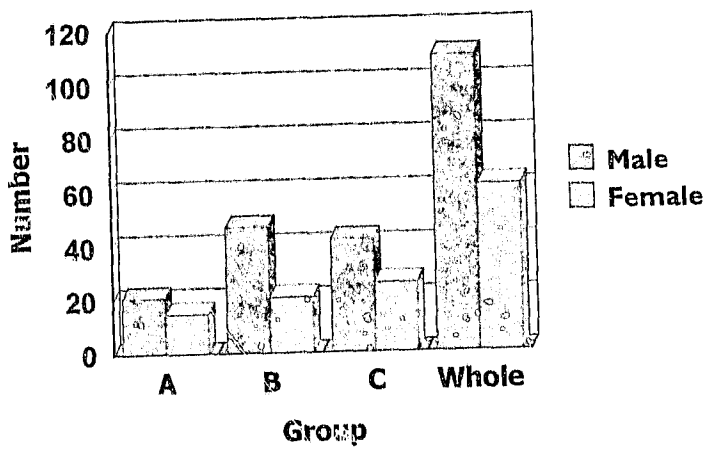


Table XII Distribution by length of lesion

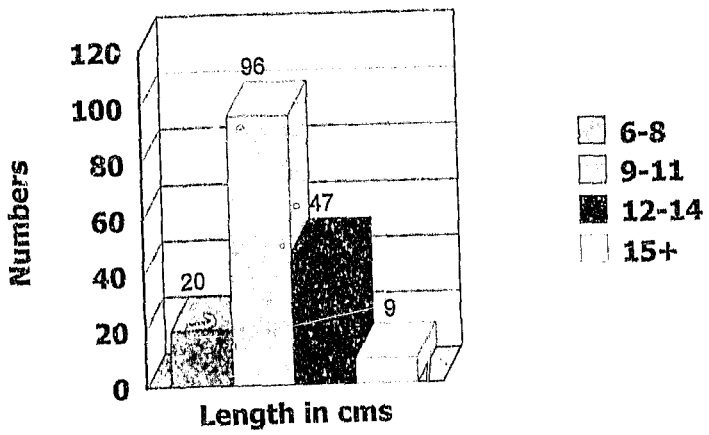


Table XIII

Distribution by Race

Race	Group A	Group B	Group C
Black	33	59	62
White	1	2	2
Asian	0	3	0
Colored	2	4	3

Racial Distribution - Whole group

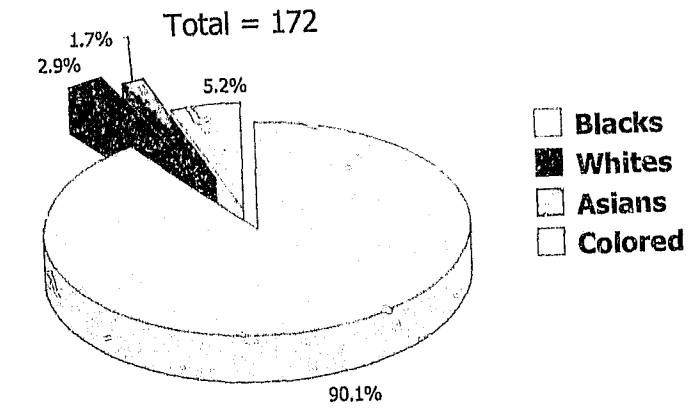


Table XIV-Presenting Dysphagia Score

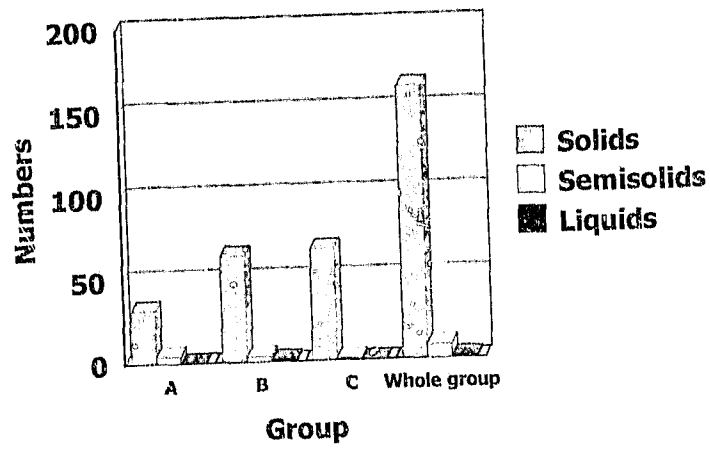


Table XV - Histology

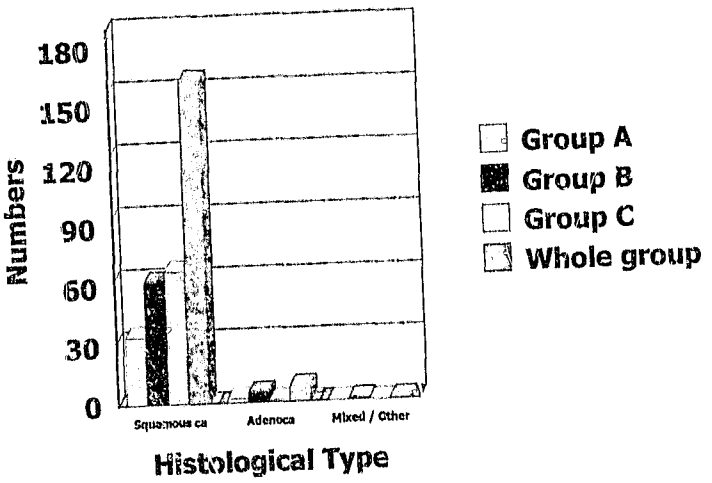


Table XVI
Histology - Grade

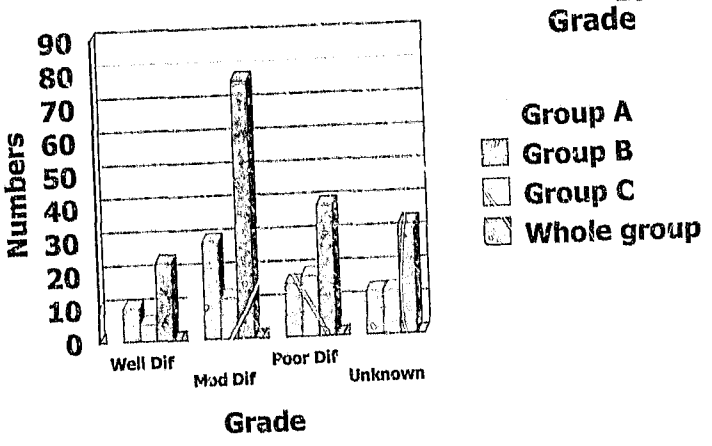
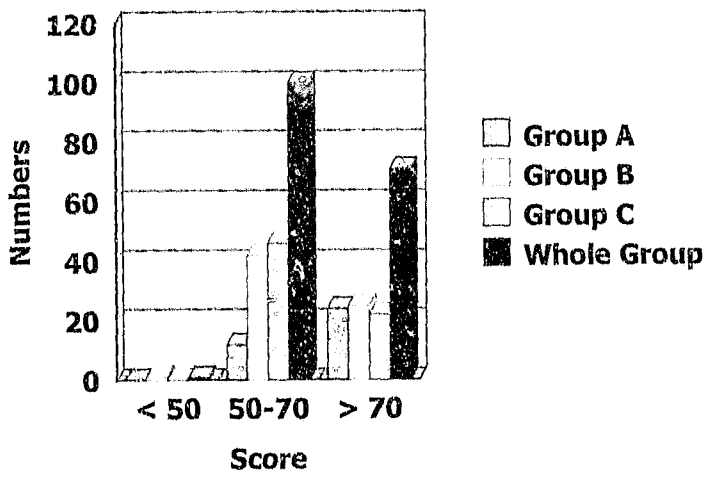


Table XVII - Karnofsky score



172 patients were entered into this study. 22 of these patients died before completing their treatment due to poor general condition and/or advanced disease. Their distribution into the 3 groups is shown in Table XVIII.

TABLE XVIII

DETAILS OF TREATMENT COMPLETED

PROTOCOL	COMPLETED	INCOMPLETE
A	35	1
B	60	8
C	55	13
TOTAL	150	22

Preliminary Analysis : From July 1994 to December 1994, a total of 68 patients were entered into the trial. A preliminary analysis was undertaken to evaluate the results at the end of 6 months. The patient characteristics are shown in table XIX.

TABLE XIX

PATIENT CHARACTERISTICS - Preliminary Analysis

	Group A (26)	Group B (21)	Group C (21)	Overall (68)
Median Age	56 (32-94)	57 (40-76)	55 (39-91)	56 (32-94)
M:F	17:9	17:4	12:9	46:22
Mean Tumour Length	10 (7-25)	11 (7-14)	10 (7-14)	10 (7-25)
Race	25 Blacks 1 Whites	21 Blacks	18 Blacks 3 Whites	64 Blacks 4 Whites
Dysphagia	21 Solids 5 Semisolids	18 Solids 2 Semisolids 1 Liquid	21 Solids	60 Solids 7 Semisolids 1 Liquids
Mean Weight	45	50	52	49
Histology:				
Squamous	25	20	21	66
Adenocarcinoma	1	1	0	2
Grade:				
Well Diff	4	5	1	10
Mod Diff	13	6	10	29
Poor Diff	2	6	6	14
Unknown	7	4	4	15

Diff - Differentiated, Mod- Moderately, M- Males, F- Females

The patients were comparable with each other with regard to their variables . 6 months after treatment, the dysphagia free survival was 35 % for group A, 83% for group B and 51% for group C. When analysed statistically, group B patients

did the best when compared to other groups. (A vs B, p=0.0497, A vs C, p=0.663, B vs C, p=0.118, chi square test). The overall survival at 6 months was 76% for group A, 95% for group B and 94% for group C. The overall survival rate was 86%. This, however, was insignificant statistically (p=0.279, chi square test). At 6 months, the complication free survival rates in the 3 groups were 69% for group A, 82% for group B and 42% in group C. Complications encountered included fibrotic strictures only in the preliminary analysis. Patients in group B had the lowest incidence of strictures followed by groups A and C. This was, however, not significant statistically (p>0.05, log rank test). No patients died as a result of treatment and no procedural morbidity were evident.

6 prognostic variables were analysed and their impact on dysphagia free, overall and complication free survivals were analysed using the log rank test. None of these variables had any impact on dysphagia free, overall or complication free survivals (Table XX).

TABLE XX

DYSPHAGIA FREE SURVIVAL - Preliminary Analysis

Analysis of Prognostic Variables at the end of 6 months

Variable		% Survival		p value
Age	Below Mean Above Mean	35 57		0.306
Sex	Males Females	45 50		0.862
Tumour Length	Below Mean Above Mean	60 68		0.286
Presenting Dysphagia Status	Solids Semisolids + Liquids	45 42		0.368
Tumour Diff-erentiation	W D M D P D Unknown	67 29 47 91	WD vs PD MD vs PD WD vs MD	0.431 1.0 0.751
Prior dilatation	Done Not done	66 60		0.343

W- Well , M- Moderately P- Poorly D- Differentiated

At 6 months, no treatment group showed improvement in mean weight. During follow up tumour recurrences, fibrotic strictures and distant metastasis were the only events recorded. This is shown in Table XXI.

TABLE XXI

FOLLOW UP - EVENTS - Preliminary Analysis

Feature	Gr A	Gr B	Gr C	p value
Tumour Recurrence/Persistence	10	1	1	0.01517
Fibrotic Strictures	4	3	8	0.186
Distant Metastasis	2	1	2	-

Gr.- Group

Tumour persisting after brachytherapy causing obstruction and persistent dysphagia was seen in 12 patients in the entire group. Of these, 10 patients belonged to group A, and when compared to the other 2 groups, results were found to be statistically significant (p=0.01517, chi square test). 16 patients developed fibrotic strictures requiring dilatation. Although this was highest in group C, it was not significant statistically. As the ILBT dose in group A was causing persistent disease, the radiation dose was inadequately giving local control to give the patient lasting relief from dysphagia, and as the results in terms of dysphagia free survival and persistent tumour were significant statistically, it was decided to discontinue with the 12 Gy / 2 fractions group (Group A) and the arm was dropped, following the preliminary analysis of patients from this stage onwards, who fulfilled the selection criteria previously described. They were then alternated into groups B and C.

Author Surer K
Name of thesis The Role Of Brachytherapy Alone And In Conjunction With Teletherapy Or Chemotherapy In Advanced Oesophageal Carcinoma Surer K 1998

PUBLISHER:
University of the Witwatersrand, Johannesburg
©2013

LEGAL NOTICES:

Copyright Notice: All materials on the University of the Witwatersrand, Johannesburg Library website are protected by South African copyright law and may not be distributed, transmitted, displayed, or otherwise published in any format, without the prior written permission of the copyright owner.

Disclaimer and Terms of Use: Provided that you maintain all copyright and other notices contained therein, you may download material (one machine readable copy and one print copy per page) for your personal and/or educational non-commercial use only.

The University of the Witwatersrand, Johannesburg, is not responsible for any errors or omissions and excludes any and all liability for any errors in or omissions from the information on the Library website.