ILBT BOOST FOLLOWING EBRT IN LOCALLY ADVANCED OESOPHAGEAL CARCINOMA- IS IT REALLY CURATIVE OR JUST PALLIATION?

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ABSTRACT

INTRODUCTION

Oesophageal Cancer is usually associated with late presentation and poor prognosis. Unfortunately, advanced disease at presentation is seen in around 70% oesophageal cancer patients with limited curative option. The main objective of treatment remains palliation. Different treatment modalities were tried in locally advanced oesophageal cancer, but the median survival remains less than 10 months.[1-3] A combination of these modalities in advanced cases has marginally improved the results. Radiotherapy can be external beam (EBRT) alone, intraluminal brachytherapy (ILBT) alone or combination of both and nowadays IMRT/IGRT with different fractionation schedules have some promising results and needs further exploration through large clinical studies.

MATERIAL AND METHODS

We evaluated the efficacy and safety of EBRT followed by ILBT in locally advanced unresectable cases of carcinoma oesophagus and compared it with EBRT alone arm with boost.

All the patients were administered three cycles of three weekly neoadjuvant chemotherapy (NACT) with TPF and further received a total target radiation absorbed dose of 40 Gy/20 fractions/4 weeks. All patients were divided in two arms of 30-each. In arm-1, patients received 3 sessions of ILBT boost of 5 Gy each, a week apart. In this arm, ILBT boost was given using state of the art MicroSelectron HDR brachytherapy machine with $Iridium^{192}$ source. In arm-2, patients received EBRT boost of 20 Gy/10 fractions (Cobalt-60 Teletherapy machine) by three field isocentric technique using Simulix HP Simulator.

After completion of treatment, response was evaluated every month, in terms of local control, symptomatic relief like dysphagia, odynophagia, etc. All the patients were followed up regularly for five years.

RESULTS

Complete response at completion of treatment was 37% vs. 23% in arm-1 & arm-2 respectively although the results were statistically insignificant. There was marked difference in relief of dysphagia and odynophagia at the end of 1-year of completion of treatment and its proving the fact that brachytherapy has been widely performed for the palliation of dysphagia. At 5-year follow-up, 6-patients (20%) were having no evidence of disease (NED) in arm-1 while only 2-patients (6%) were disease-free in arm-2.

CONCLUSION

The overall prognosis in patients with locally advanced oesophageal cancer is generally very poor, with a mean survival of 2-10 months. HDR brachytherapy was found to contribute good palliation in a significant number of patients with inoperable oesophageal cancer. In some patients, total remission was achieved lasting more than six months.

KEYWORDS

Oesophagus; EBRT; Brachytherapy; ILBT; Oesophageal Cancer; Boost.

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INTRODUCTION: Oesophageal Cancer is usually associated with late presentation and poor prognosis.[1] Unfortunately, advanced disease at presentation is seen in around 70% oesophageal cancer patients with limited curative option.[1,2] Different treatment modalities include surgery (bypass, resection) laser, dilatation, chemotherapy, intubation, EBRT and ILBT and a combination of these modalities has marginally improved the results.

Radiotherapy can be EBRT alone, ILBT alone or combination of both.

An ILBT can be used following EBRT with or without neoadjuvant or concomitant chemotherapy. In unresectable, non-metastatic, locally advanced oesophageal cancer, curative attempt can be made with combination of EBRT and ILBT boost or EBRT alone. In this retrospective study, we analysed the merits and hazards of ILBT boost used with radical radiotherapy and reviewed the relevant literature.

AIMS AND OBJECTIVES: To evaluate the efficacy and safety of external beam radiotherapy (EBRT) followed by intraluminal brachytherapy (ILBT) in locally advanced unresectable cases of carcinoma oesophagus and to explore the feasibility status of this procedure and to compare it for symptomatic relief, locoregional control and 5-year survival with EBRT alone arm with boost.

MATERIAL & METHODS: In this retrospective study, patients of locally advanced oesophageal carcinoma were analysed from the year 2005 to 2009 in Regional Cancer Centre, Rohtak, and a total of 30 patients who received definitive treatment in form of EBRT followed by ILBT boost were assessed and compared with other subsets of 30 patients who received EBRT followed by EBRT boost. Total 60 patients of locally advanced histopathologically proven patients of squamous cell carcinoma of oesophagus which were deemed unresectable were evaluated in this study.

The pre-treatment evaluation in all patients included complete history, general physical examination and complete systemic examination. The assessment of patient's general condition was done using Karnofsky Performance Status (KPS). Haematological assessment was done by complete haemogram and biochemistry profile. Radiological assessment including chest X-ray, abdominal ultrasonography and barium swallow was done in all patients. The patients were staged according to American Joint Committee on Cancer (AJCC) 2010 staging system.

Patients included in the study were those having locally advanced unresectable biopsy positive patients of squamous cell carcinoma of oesophagus, KPS> 70, Hb>8.0 g/dL, TLC>4000/cmm, platelet count >100,000/cmm, blood urea <40 mg/dL, serum creatinine <1.5 mg/dL, SGOT <35 IU/L, SGPT <40 IU/L. The patients having prior radiation, surgery or chemotherapy for the disease; KPS <60; pregnant or lactating patient; associated medical conditions; tracheo-oesophageal fistula/ deep ulcerative lesion, stenosis which cannot be bypassed, cervical oesophagus involvement; histopathology other than squamous cell carcinoma were excluded from the study.

All these patients were administered three cycles of three weekly neoadjuvant chemotherapy (NACT) with taxane, platinum and 5-FU based chemotherapy (Docetaxel 75 mg/m^2 or Paclitaxel 175 mg/m^2, Carboplatin 300 mg/m^2 and 5-FU 650 mg/m^2).

All the patients were simulated and proper field placement and verification were done on the Simulix HP Simulator having Digital Therapy Imaging (DTI) facility. After proper positioning and immobilisation, simulation and fluoroscopic visualisation was done to know the extent and localisation of disease. All the patients received a total target radiation absorbed dose of 40 Gy/20 fractions/4 weeks by AP-PA field. All patients were divided in two arms of 30 each.

In arm-1, patients received NACT with TPF followed by EBRT 40 Gy/20 fractions/4 weeks followed by 3 sessions of ILBT boost of 5 Gy each, a week apart. In this arm, ILBT boost was given using state of the art MicroSelectron HDR brachytherapy machine with Iridium^{192} source. The geometrically optimised dose distributions were generated using a PLATO software program. The reference point of dose calculation was done at a distance of 5.0 mm from the applicator surface. In all the patients, the length treated was 8.0-12 cm. The dose prescribed was 5 Gy in three fractions a week apart. The overall treatment time including external beam radiotherapy and brachytherapy ranged from 6-9 weeks.

In arm-2, patients received NACT with TPF followed by EBRT 40 Gy/20 fractions/4 weeks followed by EBRT boost of 20 Gy/10 fractions (Cobalt-60 Teletherapy machine) by three field isocentric technique using Simulix HP Simulator.

After completion of treatment, response was evaluated every month, in terms of local control, symptomatic relief like dysphagia, odynophagia, etc. Barium swallow, upper GI endoscopy and contrast enhanced computed tomography (CECT) chest were performed to rule out residual disease. There was no treatment-related mortality. All the patients were followed up regularly for five years. Data were analysed using IBM SPSS Statistics version 15.0 software (SPSS Inc., Chicago, IL) and Microsoft® Excel® 2013 (version 15.0.4805.1001).

RESULTS: Median age at presentation was 53 years (Range: 47-65 years). Male to female ratio was 2:1. Overall, 90% patients were from rural areas while 10% patients belonged to urban background. In this study, overall 95% patients were smokers, while 5% patients were those who never smoked and 70% were alcoholic. Total patients with KPS 80 were 80% and KPS 90 were 20%. Most common presenting symptoms include dysphagia in 90%, odynophagia in 50% and weight loss in 60% of patients. Duration of symptoms ranged from 1-6 months. Middle oesophagus was most common presenting primary ICD site observed in 80% cases while 20% were of lower third oesophagus. The length of lesion ranged from 6.0-9.0 cm (Median length: 7.0 cm).

This study was carried out only on histopathologically proven cases of squamous cell carcinoma, which revealed that the most common subtype was MDSCC being 60% in all groups followed by PDSCC being 25% and WDSCC being 15%.

All the patients have completed the prescribed neoadjuvant TPF based chemotherapy regimen within intended time frame. 10% patients during the neoadjuvant treatment developed febrile neutropenia but managed conservatively and none of the patients required any dose reduction during the treatment time and further there was

no delay of any scheduled chemotherapy cycle during the treatment phase.

All the patients received a total target radiation absorbed dose of 40 Gy/20 fractions/4.0 weeks and received ILBT boost of 5 Gy each, a week apart in arm-1 and EBRT boost of 20 Gy/10 fractions in arm-2 respectively.

All the patients completed the intended prescribed treatment with toxicities as mentioned in Table 1.

Sl. No.	Treatment related toxicity	Toxicity profile (n=60)	No. of patients; n=60 (%)
1	Haematological toxicity after NACT	Anaemia Grade III	45(75%)
		Anaemia Grade IV	04(07%)
		Neutropenia Grade III	06(10%)
		Febrile Neutropenia	05(08%)
2	Non-haematological toxicity after NACT	Nausea	40(67%)
		Vomiting	18(30%)
		Oral mucositis	10(17%)
		Diarrhoea	21(35%)
3	EBRT related toxicity after 40Gy/20fractions/4-weeks in both the arms	Stricture	08(13%)
		Fistula	01(02%)
		Weightloss(SWOG Grade II)	39(65%)
		Weightloss(SWOG Grade III)	18(30%)
		Skin reactions(RTOG Grade I & II)	52(87%)

Table 1: Showing Treatment Related Toxicity (n=60)

Sl. No.	Response to treatment		No. of patients n=60, (%)
1	Response Rate after NACT	Overall Response Rate(ORR)	48(80%)
		Complete Response(CR)	06(10%)
		Partial Response(PR)	42(70%)
		Progressive Disease(PD)	12(20%)
2	Response Rate after completion of EBRT	Overall Response Rate(ORR)	52(87%)
		Complete Response(CR)	12(20%)
		Partial Response(PR)	40(67%)
		Progressive Disease(PD)	08(13%)

Table 2: Response Rate after NACT and after Completion of EBRT in Both the Arms (n=60)

Sl. No.	Response Rate	Arm-1 with ILBT boost (n=30)	Arm-2 with EBRT boost (n=30)	P value
1	Overall Response Rate (ORR)	27(90%)	26(87%)	0.687 (not significant)
2	Complete Response(CR)	11(37%)	07(23%)	0.259 (not significant)
3	Partial Response(PR)	16(53%)	19(64%)	0.432 (not significant)
4	Progressive Disease(PD)	03(10%)	04(13%)	0.687 (not significant)

Table 3: Showing Response Rate in both the Arms after Completion of Respective Treatment(n=30)

Sl. No	Toxicity	Arm-1 with ILBT boost n=30(%)	Arm-2 with EBRT boost n=30(%)	P value
1	Stricture	17(57%)	11(37%)	0.120 (not significant)
2	Fistula	01(3%)	00(00%)	0.313 (not significant)
3	Ulceration	02(7%)	04(13%)	0.389 (not significant)

Table 4: Comparing Toxicity Profile of ILBT Boost with EBRT Boost in both the Arms after 6 Months of Follow-up (n=30)

Complete response at completion of treatment was 37% vs. 23% in arm-1 & arm-2 respectively although the results were statistically insignificant (p value=0.259). There was marked difference in relief of dysphagia at the end of 1 year of completion of treatment (67% in arm-1 vs. 37% in arm-2). Similarly, after completion of treatment, odynophagia was relieved in 75% of patients of arm-1 and 45% relieved in arm-2 (p value=0 .000015; statistically significant), while there was no significant improvement seen in weight loss in any of the treatment arms. At 5-year follow-up, 6 patients (20%) were having no evidence of disease (NED) in arm-1 while only 2-patients (6%) were disease free in arm-2. The chi-square statistic is 2.3077 and p-value is .128735 and is not significant.

DISCUSSION: Carcinoma oesophagus is considered as aggressive disease as at the time of presentation most cases present as advanced or metastatic disease with five-year survival rate of 5-10%, and median survival ranges from 2.5–9.9 months with advanced or metastatic disease.[1-3] The reported 2-and 5-year survival rates range from 30-40% and 10-25% respectively, regardless the tumor stage and treatment options.[4] Moreover, the prognosis is much worse

in patients with stage IV and in those with inoperable advanced cancer.

Carcinoma of the oesophagus forms 4% of all cancer patients attending Regional Cancer Centre, Rohtak and out of these nearly 70% of the patients present in locally advanced disease condition.[4] A recent meta-analysis has proved that people with relatively high intakes of fruit and vegetables have a 40–50% lower risk of total oesophageal cancer and also suggest that intake of fruit and vegetable is inversely associated with the risk for squamous cell carcinoma.[5] Most common presenting symptoms, as seen in our present study also, include dysphagia in 90%, odynophagia in 50% and weight loss in 60-70% of patients.[1-3]

Intraluminal brachytherapy for radical intent in oesophageal cancer is being practiced at Regional Cancer Centre, Rohtak since 2005 with high dose rate brachytherapy system. This study includes patients treated with radical intent with intraluminal brachytherapy with EBRT and its comparison with EBRT boost. Brachytherapy as compared to EBRT offers rapid tumour reduction of luminal aspect, thus rapidly restoring the swallowing function and at the same time delivers relatively low dose to the surrounding normal tissues particularly lung, spinal cord and adjacent normal oesophageal mucosa.[6-8] HDR brachytherapy limits the dose to critical structures with dose escalation to primary site but with a limited role in this setting with the use of CT/RT protocols.[6] Many studies in different socio-economic conditions and geographical distribution have highlighted the effect of ILBT boost following EBRT, and also claimed clinical superiority of EBRT following ILBT boost compared to EBRT boost arm.[1,8,9] Our study in third world country like India with patients of poor socio-economic strata have also shown the similar results.

The other factor which determines the efficacy and toxicity of brachytherapy are treatment related factors such as sequencing, timing and fractionation, total dose of EBRT and brachytherapy parameters including target definition, applicator diameter, dose rate, active length, interval, dose prescription point and brachytherapy fractionation schedule etc.[8,9] In our study, brachytherapy boost of 5 Gy in 3 fractions was well tolerated with manageable toxicities and good compliance.

Stricture formation, fistula and oesophageal ulceration are the common late toxicities of HDR brachytherapy. Post radiation strictures reported by various authors' ranges from 12–44% and in our series 37% in arm-1 and 57% in arm-2 developed strictures.[8-10] Out of these, 5 patients underwent endoscopic dilatation and 2 patients underwent endoscopic stunting. Sur et al. reported the local control rate approximately doubled when HDR brachytherapy was used and results of our study are in concurrence with this showing complete response at completion of treatment was 37% vs. 23%, in arm-1 and arm-2 respectively but were not statistically significant; p value=0.259.[1,8,9]

In present study, EBRT doses were given 40 Gy followed by 15 Gy (5 Gy per fraction) by HDR–ILBT could explain the less toxicity in form of fistula and ulceration. However, the incidence of strictures formation rate (57% vs. 37%) was higher for the brachytherapy modality (p value=0.120, statistically non-significant), could have resulted from the use of narrower intraluminal fibre optic applicator with diameter 6.0 mm. As existing in the literature that brachytherapy has been widely performed for the palliation of dysphagia, hence proved in our present study also by showing the statistically significant improvement in palliation by relieving dysphagia in 57% and relieving odynophagia in 75% patients of arm-1 using HDR –ILBT (p value= 0.000022). Hence, the present study recommends the use of ILBT arm for palliation in locally advanced oesophageal cancer.

The results of this study are encouraging and found to be well tolerated and showed better response in terms of complete and partial response. Despite advances in multimodality treatment for carcinoma oesophagus, EBRT followed by ILBT seems to prove good palliation with manageable toxicity.

Now a days, IMRT with concurrent systemic therapy in the definitive treatment of oesophageal cancer using an integrated boost concept with doses up to 60 Gy is feasible and yields good results with acceptable acute and late overall toxicity. Hence, further comparative studies are required to compare ILBT arm with IMRT/IGRT arm to establish the treatment protocols.

CONCLUSION: HDR brachytherapy was found to lead to regression of dysphagia in a significant number of patients with inoperable oesophageal cancer. In some patients, total remission was achieved lasting more than six months. Nowadays, IMRT with concurrent systemic therapy in the definitive treatment of oesophageal cancer using an integrated boost concept has shown good results with acceptable toxicity and downgraded the pathway for ILBT users, but still ILBT has proved good palliative results. Further validation with well-designed, larger clinical trials with comparison of EBRT+ILBT arm with IMRT/IGRT arm is required to establish the future treatment protocols. However, in Cancer Centres not equipped with IMRT/IGRT facilities, EBRT followed by ILBT is still a reasonable approach with good palliation in locally advanced unresectable oesophageal cancer.

REFERENCES

1. Sur RK, Singh DP, Sharma SC, et al. Radiation therapy of oesophageal cancer: role of high dose rate brachytherapy. Int J Radiat Oncol Biol Phys 1992;22(5):1043-1046.
2. Schottenfeld D. Epidemiology of cancer of the oesophagus. Semin Oncol 1984;11(2):92-100.
3. Sharma V, Mahantshetty U, Dinshaw KA, et al. Palliation of advanced/recurrent oesophageal carcinoma with high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 2002;52(2):310-315.

4. Das BP. Cancer pattern in Haryana: twenty-one years' experience (A retrospective analysis of 15968 patients). Health Administrator 2005;1052:29-49. Available from: http://medind.nic.in/haa/t05/i1/haat05i1p29.pdf
5. Dhull AK, Nupur B, Atri R, et al. The integrated relations of fruits and vegetables with cancer. J Cancer Prev Curr Res 2015;2(5):00053. DOI: 10.15406/jcpcr.2015.02.00053.
6. Brewster AE, Davidson SE, Makin WP, et al. Intraluminal brachytherapy using the high dose rate MicroSelectron in palliation of carcinoma of the oesophagus. Clin Oncol 1995;7(2):102-105.
7. Gaspar LE, Nag S, Herskovic A, et al. American brachytherapy (ABS) consensus guidelines for brachytherapy of oesophageal cancer. Int J Radial Oncol Biol Phys 1997;38(1):127-32.
8. Sur RK, Kochhar R, Singh DP. High dose rate intracavitory therapy in advanced carcinoma oesophagus. hid J Gastroenterol 1991;10:43-45.
9. Sur RK, Donde B, Levin CV, et al. Fractionated high dose intraluminal brachytherapy in palliation of advanced oesophageal cancer. Int J Radiation Oncology Biol Phys 1998;40(2):447-453.
10. Fleischman EH, Kagan AR, Belloti JE. Effective palliation for inoperable oesophageal cancer using intensive intracavitory radiation. J Surg Oncol 1990;44(4):234-237.