

Full Length Research Paper

The effectiveness of high dose rate brachytherapy using a special applicator set with external beam radiation treatment and chemotherapy followed by surgery as a treatment of adenocarcinoma of the esophagus: A case series of single institution with literature review

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Our study looked at patients with esophageal adenocarcinoma treated with high dose rate brachytherapy (HDR-BT) followed by external beam radiation treatment (EBRT) and chemotherapy with and without surgery to find local response using special HDR-BT delivery catheter, Bonvoisin-Gerard Esophageal Applicator (BG Applicator). We reviewed eight patients' charts with adenocarcinoma of esophagus (Median age = 63.5 years, median follow up = 32 months). They received HDR-BT using BG Applicator that provides advantages such as: (1) Proper radiation source positioning; (2) Decrease hot mucosal spots; (3) Bougienage of the obstruction by use of bougie tube, and (4) Decrease rate of local side effects. Descriptive analysis was performed and biopsy/surgical pathology results were reported to determine the local histopathological response. Two patients did not receive surgery and had a complete local response; one of which developed cancer at a lymph node site with no cancer at primary site on follow-up. Five patients completed treatment, of which four showed complete local response and only one of those four developed distant bony metastasis with negative primary site. One patient died due to stroke. HDR-BT with BG applicator gives promising locoregional response in esophageal cancer that needs to be confirmed by further systematic randomized trials.

Key words: High dose rate brachytherapy, external beam radiation therapy, Bonvoisin-Gerald Applicator.

INTRODUCTION

Esophageal cancer is the sixth most common cause of cancer related death in world but has a low incidence rate in United States with limited literature for standard of care for treatment. There is a trend showing shift in the pathological type from squamous cell carcinoma to adenocarcinoma of the esophagus over last few decades (Tew et al., 2005; Blot et al., 1999).

Surgery is the most common treatment approach for resectable esophageal tumor. It had been shown that neoadjuvant chemoradiotherapy followed by surgery improves local response and prolongs survival which is now followed as standard of care by many clinicians for treatment of esophageal cancers (Hyngstrom et al., 2010; Urschel et al., 2003; Meluch et al., 2003; Spigel et al., 2010).

Research over last two decades had shown that concurrent use of high dose rate brachytherapy (HDR BR) with chemotherapy and external beam radiation treatment achieves better local control in esophageal

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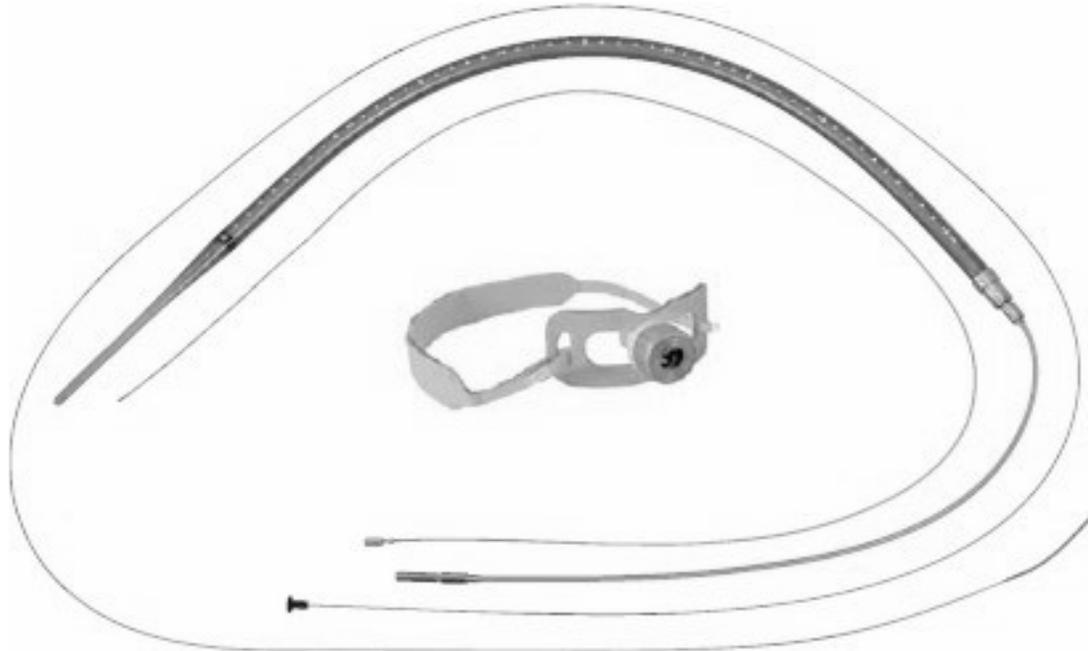


Figure 1. Bonvoisin-Gérard esophageal applicator set. The figure shows the catheter used in the treatment delivery of HDR-BT. The applicator assists in the dilatation and provides excellent source centering. The bougie tube also helps to easily access the target site beyond obstruction and the source tube in the center provides radiation at the target site. Image courtesy of Nucletron. Figure retrieved from: http://www.nucletron.com/Resources/Documents/308880-05_applicator_guide_2009_digital.pdf.

tumor but at a cost of higher incidence of local toxicity like tracheo-esophageal fistula (TE Fistula) due to high dose of local radiation from brachytherapy (Gaspar et al., 1997a). Multiple efforts have been made to decrease the incidence of toxicity and improve local response rate. Research studies have tried to achieve the safe dose of HDR BT as well as to improve the delivery method by developing new delivery systems in order to accomplish better local control and reduce the local toxicity (Yorozu et al., 1999a).

Our research is a descriptive case series of eight patients with advanced local esophageal cancer who received HDR BT using special applicator set called Bonvoisin-Gerald Esophageal applicator set (B. G. Applicator, Nucletron B. V., Veenendaal, The Netherlands) (Figure 1) followed by EBRT and chemotherapy with or without surgery. The primary goal of this study is to describe the locoregional response rate with combined modality treatment, while comparing results to prior research.

METHODS

Patient population and disease characterization

This study is a case series involving retrospective data review of total eight patients diagnosed with locally advanced adenocarcinoma of the esophagus and treated in between 2006

and 2009 with radical treatment intent. Among the patients, there were seven males and one female with an overall median age of 63.5 years (Range: 48 to 86 years) and median follow up was for 32 months (Table 1). Of the eight patients, one patient did not receive full course of HDR-BT secondary to nontolerance to the treatment and only received one fraction of 4Gy (Table 2). Out of remaining seven patients, one patient was not able to complete the EBRT secondary to stroke which subsequently resulted in his death. The other patients did receive all the treatment modalities. Table 1 describes the age and gender of patients with pertinent findings of the cancer including the site, size at the time of diagnosis, histology type, and TNM scoring. All the patients in the study had Karnofsky performance score of more than 70 before the start of treatment.

Patient evaluation

Total, eight patients' charts were reviewed. The institutional review board (IRB) application was approved by Sanford Hospital, Fargo, IRB Board as well as IRB Board of University of North Dakota, Grand Forks. Patients were treated in between 2006 to 2009 with follow up till December 2009. All patients received history taking, physical examination, imaging study, TNM staging, and endoscopy evaluation before the treatment. Informed consent was obtained for delivery of radiation treatment. All of the patients were also evaluated for surgery and then referred for neoadjuvant or radical chemoradiotherapy. Surgically treatable candidates were referred to surgery after the HDR-BT and neoadjuvant chemoradiotherapy. Typical treatment included sequence of HDR-BT boost followed by subsequent EBRT and chemotherapy. After that, patients were evaluated and treated by surgery if agreeable.

Table 1. Patient and tumor characteristics including tumor size, and classification.

ID	Age (Years)	Gender	Size of tumor (cm)	Stage TNM
1	86	M	2	T3N0M0
2	58	F	2	T3N1M0
3	48	M	10	T3N0M0
4	84	M	5	T3N0M0
5	62	M	6	T3N0M0
6	54	M	7	T3N0M0
7	65	M	7	T3N0M0
8	74	M	9	T3N1M0

All tumors reported here were in distal esophagus and of adenocarcinoma histology.

HDR-BT radiation treatment

All patients were screened by a single radiation oncologist before HDR brachytherapy and underwent endoscopy before each round by a gastroenterologist. All of the HDR-BT and EBRT treatments were delivered in an outpatient setting and none of the sessions required hospitalization. During each session, the patient received sedation and the esophageo-gastro-duodenoscopy (EGD) were performed. It was done to evaluate the extent of the tumor and mark the upper and lower margins of tumor by inserting radio-opaque surgical clips 1 cm each above and below the tumor. With the help of the gastroenterologist, the esophageal applicator set (Bonvoisin-Gerald Esophageal applicator set, Nucletron B.V., Veenendaal, The Netherlands) was inserted on the guide wire under direct visualization in the stomach and then fixed to the mouth piece for immobilization. CT Imaging was done for treatment planning and determining the limit and location of the tumor using the surgical clips (Poon et al., 2009). After the planning CT was performed and while the treatment plan was being implemented, the patient was given an oral suction with a pediatric tube to remove any saliva that he is generating and not able to swallow due to the B-G tube. The treatment was planned using PLATO planning system (Plato software, Nucletron B.V., Veenendaal, The Netherlands).

One fraction of brachytherapy in dose of 4 Gy was then administered with Nucletron high dose rate ¹⁹²Ir remote afterloader (Microselectron; Nucletron B.V., Veenendaal, The Netherlands). Total of 20 Gy dose of HDR Brachytherapy by 5 fractions of 4 Gy each usually twice weekly was delivered in similar fashion. Details of the individual dose received by each of the patients are described in Table 2.

EBRT

EBRT treatment began after completing the HDR-BT. Target volume was determined using the endoscopy information, careful review of pathology and planning CT images. The treatment planning included a 3-dimensional simulation using a planning CT scan (GE Discovery ST-4 PET/CT scanner, GE Medical Systems, Waukesha, Wisconsin). The contouring of the target, the organs at risk and the treatment planning used the ADAC software system (Philips Medical System, Madison, WI, USA).

EBRT was delivered using primarily two techniques: (1) 3D four field conformal technique, and (2) Intensity modulated radiation treatment (IMRT). EBRT was given either in multiple conformal portals using a high energy linear accelerator with photon beams or using IMRT seven field techniques with 6 MV photons of energy.

Total dose was 50 Gy to the esophageal tumor site and lymph nodes at risk in 25 fractions. Individual patient dose in details is described in Table 2.

Chemotherapy

Radiation sensitizing chemotherapy was administered along with the EBRT treatment by an oncologist. Type of the chemotherapy received by individual patient is described in Table 2.

Surgery

As surgery is the ideal treatment modality for esophageal cancer all patients were evaluated by a surgeon after establishing the diagnosis. Surgeons either referred the patients for neoadjuvant chemoradiotherapy before surgery or declared the cancer non-resectable. In this study, two patients were declared having non-resectable cancer and received chemoradiotherapy with radical intent. Out of the remaining six patients screened for resectable cancer, one patient died during treatment from secondary cause (stroke) and did not receive surgery. Out of other five patients, three received Ivor-Lewis Esophagectomy and two received Transhiatal Esophagectomy. All the Ivor-Lewis resection was performed in Mayo Clinic, Rochester, MN. Transhiatal Esophagectomy was performed at Sanford Hospital, Fargo, ND. Details of each patient treatment are described in Table 2.

Follow up

Patients were usually assessed biweekly during the HDR-BT, weekly during the EBRT by radiation oncologist and weekly by the medical oncologist delivering the chemotherapy during the chemotherapy cycles. Total median follow up was for 32 months. After the chemoradiotherapy EGD with biopsy was carried out for evaluating the response to the treatment. Depending on the requirement and response, patients also received imaging studies for evaluation of tumor progression that included CT scan and PET scan. Patient who were treated by surgery were also followed by surgeons with follow up EGD for evaluation of the disease status. For the purpose of the study, we did not evaluate the detailed schedule of surgical follow up.

Analysis

The objective of this study was descriptive evaluation of locoregional response rate of the HDR-Brachytherapy using special delivery device followed by combined chemoradiotherapy. The objective was evaluated by doing extensive chart review and reporting the comprehensive analysis of disease status, treatment regimen and response. We used findings of EGD with biopsy after completing the treatment and surgical specimen pathology following surgery to report the loco-regional response. Patient characterization and follow up time analysis were done manually using standard statistical methods. We also reported the recurrence of tumor in local area or distant metastasis during follow up period. Charts were also reviewed for any major HDR-BT treatment related complications like perforation, stricture and TE Fistula. Death and cause of death was also reported.

RESULTS

A total of eight patients were treated with HDR-BT followed

Table 2. Treatment and result.

ID	HDR BT	EBRT	Chemotherapy	Surgery	EGD + Biopsy* (post chemoradiation) or post surgery	Local response	Response - pathological in surgical specimen	Recurrence local vs. distal	Toxicity **	Follow up (Months)
1	10 Gy	43.2 Gy	Carboplatin + Capecitabine (5 cycles)	No surgery	Negative for cancer	Complete remission	N/A	Lymph node in arch of aorta	0	36
2	16 Gy	50 Gy at tumor site + 45 Gy at lymph node site	Cisplatin and 5-FU (1 cycle)	Ivor lewis esophagectomy	Not done	Complete remission	Tumor free specimen and lymph nodes Benign	No	0	36
3	20 Gy	60 Gy at tumor site and 50 Gy at lymph node site	Taxol + Cisplatin + 5-FU (3 cycles)	Ivor lewis esophagectomy	Post surgery EGD negative for cancer	Complete remission	0.4 cm residual tumor microscopic in specimen. Lymph nodes benign	No	0	34
4	4 Gy	50 Gy at tumor site and 45 Gy at lymph node site	Taxol + Carboplatin (4 cycles)	No surgery	Negative for any cancer	Complete remission	N/A	No	0	36
5	20 Gy	45 Gy at tumor site	Taxol + Cisplatin+ 5-FU (3 cycles)	Transhiatal esophagectomy	Post surgery EGD negative for cancer	Near complete remission	2.2 × 1.8 cm grade 3 invasive adenocarcinoma, margins free and lymph nodes benign	No	0	24
6	19.4 Gy	50 Gy at tumor site	Taxol + Cisplatin + 5-FU (2 cycles)	Transhiatal esophagectomy	Post surgery EGD negative for cancer	Complete remission	No cancer in specimen and lymph nodes benign	Distant bone metastasis	0	30 – died due to metastatic disease
7	20 Gy	50 Gy at tumor site and 45 Gy at lymph node site	Cisplatin + 5-FU (1 cycle)	Ivor lewis esophagectomy	Post surgery EGD negative for cancer	Partial local response	4.3 × 2.6 cm size residual grade 3 tumor and 4/30 paraesophageal lymph nodes positive for adenocarcinoma	Local recurrence and distal metastasis	0	24- died due to metastatic disease
8	20 Gy	20 Gy at tumor site and 18 Gy at lymph node site	Cisplatin + 5 FU (1 cycle)	Last EGD for treatment showed good local response to radiation treatment without any serious adverse event. Patient died of stroke in the middle of the treatment from his severe carotid artery stenosis.						

*EGD was done in case of patients not undergoing surgery for evaluating local response. ** Toxicity analysis included – reporting of esophageal perforation or TE fistula.

by chemoradiotherapy with or without surgery. Out of total eight patients, one patient (ID: 8) did not complete treatment due to death secondary to stroke from his severe carotid artery stenosis.

Two patients were screened as having non-resectable adenocarcinoma of the distal esophagus and underwent HDR-BT and chemoradiotherapy with radical intent (ID: 1, 4). Both of them had excellent local response with complete remission after the treatment. Response was confirmed by doing EGD and biopsy from multiple sites. During follow up, a patient (ID 1) developed recurrence of disease in one of the lymph node site at the level of the arch of aorta. All the follow up EGD with biopsy for him were negative for local recurrence in esophagus.

All remaining five patients received surgery after HDR-BT and chemoradiotherapy. Detailed description of the type of treatment received and findings of the surgical specimen is described in Table 2. Two patients (ID: 2, 6) were having complete response that was confirmed on biopsy report of surgical specimen as having no residual cancer. One patient (ID: 6) out of those two who developed distant bony metastasis during follow up and died due to complications of metastatic disease. There was no local recurrence of disease in both the cases confirmed by biopsy.

One patient (ID: 3) reported to have microscopic residual tumor on surgical specimen of 0.4 cm in size and of three quarter invasive adenocarcinoma histology with clear margins and benign lymph nodes. After the surgery, he did not have any local recurrence on follow up EGD and biopsy. There was no distant metastasis reported and patient is in complete remission.

Two patients (ID: 5, 7) demonstrated partial local response to the treatment and surgical specimen suggested residual tumor on both of them (Table 2). Patient ID 7 had three quarter grade invasive adenocarcinoma with 4.3 × 2.6 cm size and 4/30 lymph nodes positive for adenocarcinoma in surgical specimen. He reported to have local recurrence of the disease at GE junction at the site of surgical anastomosis and died due to complications of metastatic disease. Other patient had 2.2 × 1.8 cm tumor in the surgical specimen with clear margins and negative lymph nodes. He had negative EGD in follow up and no local recurrence of disease in 2 year follow up period.

None of the patients reported to have any major side effects including perforation at the site of tumor, stricture or TE Fistula. During the entire treatment and follow up period, none of the patients had any radiation treatment related side effect that required hospitalization and/or treatment.

In summary, four of the eight patients reported complete local response and no local recurrence but one of them had bony metastasis and one had lymph node disease progression at the level of the arch of aorta. Out of remaining four, three showed partial local response to initial treatment and two of them achieved complete

remission after surgery, and one of them developed local recurrence at the site of surgical anastomosis. One patient died due to stroke from severe carotid artery stenosis. Detailed description of the results is displayed in Table 2.

DISCUSSION

Modality of treatment is comparable for both the histological types of esophageal cancer including squamous cell cancer and adenocarcinoma of the esophagus. This study is directed to identify local response rate of multimodality treatment and possibility of reducing the side effect by using a specially designed applicator set.

The esophageal tumor treatment lacks specific guidelines and most of the treatment is driven based on findings of researches over the last two decades. Due to low incidence rate in the United States, there is paucity of literature and research for treatment standard establishment. Currently, most clinicians use a multimodality approach in lower esophageal cancer based on past research that includes HDR – BT boost before or after concurrent chemotherapy and EBRT followed by surgery (Siersema et al., 2008). Though surgery was thought to be the ideal treatment for resectable esophageal cancer, it had been shown that neoadjuvant chemoradiotherapy improves local response rate and improves survival as compared to surgery alone (Urschel et al., 2003).

Intraluminal brachytherapy had slowly made its way from palliative treatment to definitive treatment group. Research had shown that intraluminal brachytherapy via HDR-BT increases the radiation dose to local tumor site and improves local pathological response rate with improved survival (Yorozu et al., 1999a; Sur et al., 1992).

In light of years of research, the American Brachytherapy Society developed guidelines for definitive brachytherapy use and dosage standards for esophageal cancer which were not revised over the past 10 years (Gaspar et al., 1997b; Gaspar et al., 2000). Most of the studies for standardization of treatment are conducted in Japan where the rate of esophageal cancer is extremely high.

The optimal dose of the HDR-BT boost is unknown but it optimized by multiple research study. One study in Japan showed that esophagus can take total of 70 Gy dose from combined BT and EBRT (Hishikawa et al., 1991). Brachytherapy may bring the risk of late toxicity in form of tracheo-esophageal fistula, perforation and stricture and thus the dose and fractionation must be carefully chosen (Akagi et al., 1999; Gava et al., 1996; Sur et al., 1998). These complications lead many researchers to develop different delivery system of brachytherapy to reduce the hot spots in local mucosa and optimize adequate delivery of radiation to target

tissues. Over the years, multiple changes in the radiation delivery devices have been done. It had been shown that better local control of non resectable esophageal tumor has been achieved by using balloon type of esophageal applicator set (Yorozu et al., 1999b). The high rate of local side effect may be caused by the design of the applicator set which is studied barely. Multiple researcher groups have conducted the use of different applicator sets including balloon type applicator, and bougie devices in esophagus that will provide more beneficial outcomes (Yorozu et al., 1999a, b; Akagi et al., 1999; Calais et al., 1997; Ell et al., 1993). Still there are chances of local toxicity depending on the dose of the HDR-BT (Yorozu et al., 1999 b). The area of HDR-BT is still controversial and is undergoing constant revision by research studies.

Our research is an effort to show the effect of HDR-BT using special applicator set (Bonvoisin-Gerald esophageal applicator set) with optimum fractionated HDR-BT followed by other treatment. There are distinct advantages of the B-G Applicator:

1. It has an outer catheter which is flexible and has a treatment unit in the center that is equidistance from the margins of the outer catheter. This allows for proper radiation source centering at the site of primary tumor.
2. This structural advantage provides opportunity to minimize the local hot spot at the area of radiation delivery, which will lead to decrease rate of local side effect and mucosal toxicity.
3. Due to proper source centering, it is easy to achieve delivery of effective radiation dose to the cancer site and minimize the damage to the surrounding structure as well as improve the local response rate.
4. The device also has a tapering tip with bougie bag on the tip of the device that makes it amenable to insert the catheter through obstruction at the site of cancer. This technical specification also provides distinct advantage of making the procedure easy for treatment provider as it has the treatment unit included in the catheter.
5. The bougie bag is radio-opaque that provides distinct advantage in treatment planning by deciding the tumor load and volume at the site of location using CT planning.

The outcome was measured by local histopathological response rate. Our study showed promising findings. It showed that out of seven patients completing treatment (with or without surgery) six patients showed complete or near complete local response and showed no local recurrence in follow up period. Only one patient had local recurrence of disease. Of the first six patients showing complete or near complete response, one had bone metastasis and one had recurrence at the lymph node site at the level of the arch of aorta but still both of them showed no disease at primary site on multiple EGD and biopsy follow up.

There is lack of sufficient literature comparing effectiveness of the HDR-BT using different devices and

the studies that we have are around ten years old. It is to note that the use of B-G Applicator in our study resulted in no local toxicity like TE Fistula or perforation and stricture as compared to other research using conventional esophageal applicator set which reported higher rates of TE Fistula and other treatment related toxicity (Vuong et al., 2005). Marinello et al. (1992) have described that tissues in the hyperdose sleeve area are at high risk of developing complications such as necrosis and perforation. Our research suggested that the incidence of such side effect can be decreased by using special applicator and reducing the hyperdose sleeve/mucosal hot spot area.

Another factor that could have contributed to our lower incidence of complications with the HDR-BT is the timing of the procedure. In our study, the patients underwent their HDR-BT prior to their EBRT-Chemotherapy treatment. So the tumor was still bulky at the time of HDR-BT and esophageal mucosa and tissue were not inflamed or friable from the exposure to combined modality of EBRT-Chemotherapy.

Our study showed results suggesting promising local histopathological response in locally advanced esophageal cancer along with low incidence of side effect using HDR-BT with B.G. Applicator set followed by EBRT and chemotherapy with and without surgery.

The limitation of the study is that it is a retrospective descriptive case series involving only eight patient's chart review. There is paucity of literature in Unites States about esophageal cancer. In lights of our findings, there should be further prospective research which should take into consideration the use of more aggressive radiation treatment via HDR-BT with special delivery device like B.G.Applicator to improve local response rate.

Conclusion

The use of HDR-BT with special esophageal applicator set such as B-G Applicator set can improve the local response rate of esophageal cancer. Use of B-G Applicator can also decrease the severe local side effects like TE Fistula and perforation due to the structure of the device that helps in reducing the local hot spots. Authors suggest that based on these preliminary findings, there should be some organized randomized prospective trials for HDR-BT boost followed by neoadjuvant chemoradiotherapy with and without surgery for curative treatment intent in esophageal cancer where special preference is given to technical aspect of treatment delivery like use of devices that can improve the outcome. These findings will encourage further research which can be later on converted to standards of care if found to be effective on large scale.

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