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NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

STUDY NUMBER: CASE 5217

ClinicalTrials.gov NCT #: NCT03335813

Protocol Date: 22 November 2017

STUDY TITLE: Endoesophageal Brachytherapy for Patients with Esophageal Cancer: A Balloon Repositioning, Multichannel Radiation Applicator for Optimizing Treatment Delivery (IRB# IP 30)

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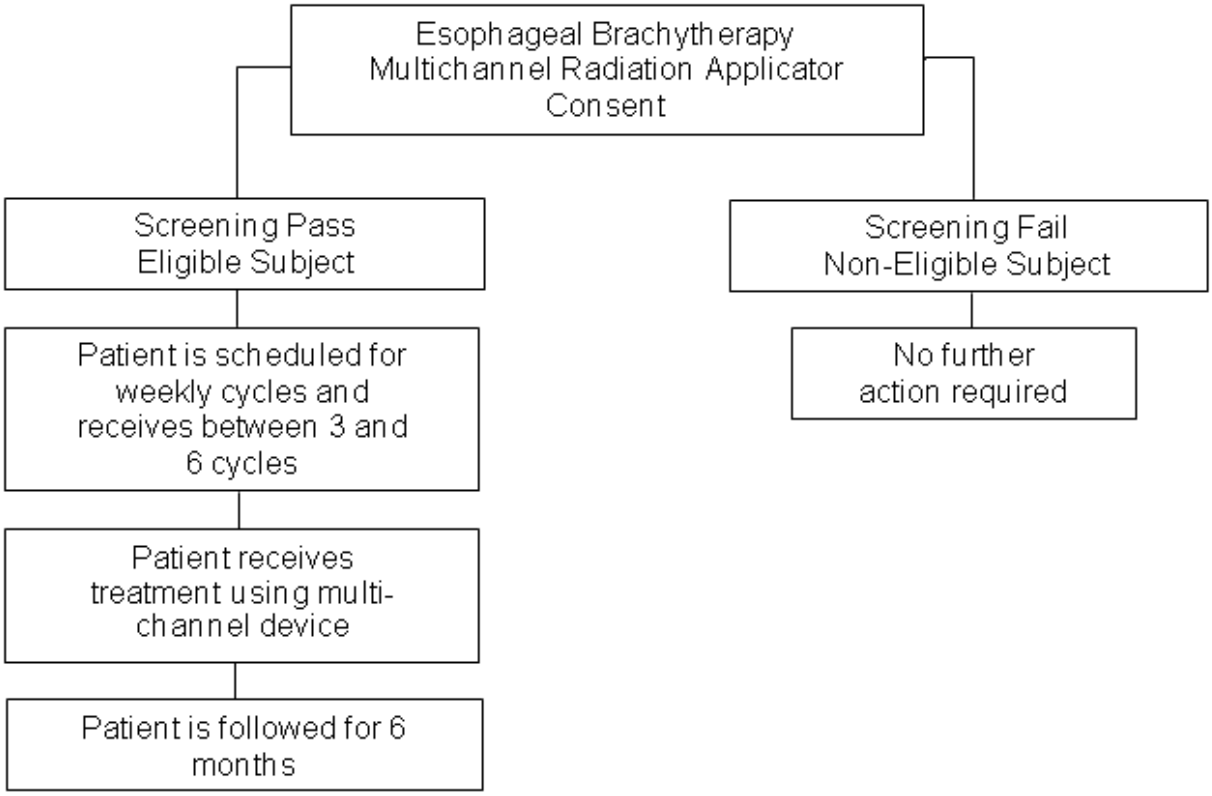
SPONSOR:	Case Comprehensive Cancer Center Cleveland Clinic - Innovative Practice Group
SUPPORT/FUNDING:	Cleveland Clinic
SUPPLIED AGENT*(S):*	N/A
IND #:	N/A
OTHER AGENT*(S):*	N/A

SUMMARY OF CHANGES

Please provide a list of changes from the previous approved version of the protocol starting at IRB approval. This table will remain blank until initial IRB approval. The list shall be a brief overview. When appropriate, a brief justification for the change should be included. This is a running list for the life of the study.

STUDY SCHEMA



PROTOCOL SUMMARY

Protocol Number/Title	CASE 5217
Study Phase	PILOT TRIAL
Brief Background/Rationale	This innovative study will be an improvement over our previously designed 3-tube endoesophageal brachytherapy technique in patients who are candidates for esophageal brachytherapy. The brachytherapy planning process will utilize our multichannel balloon applicator as described within.
Primary Objective	Pilot study of multichannel endoesophageal brachytherapy applicator to determine dose distribution and conformality of a 6 channel balloon repositioning applicator.
Secondary Objective(s)	1. To compare conformality and normal tissue doses versus previous 3-tube design. 2. To evaluate acute toxicity of multichannel endoesophageal brachytherapy applicator.
Exploratory Objective(s)	None
Correlative Objective(s)	None
Sample Size	Number expected to accrue: 5 Age: ≥18 Gender: Male and Female
Disease sites/Conditions	Esophagus / Esophageal Cancer
Interventions	Agent/Route: Endoesophageal Brachytherapy Cycle Length: Weekly Number of cycles: Between 3 and 6 cycles

ABBREVIATIONS

CCCC	Case Comprehensive Cancer Center
CRF	Case Report Form
DCRU	Dahm's Clinical Research Unit
DSTC	Data Safety and Toxicity Committee
FDA	Food and Drug Administration
ICF	Informed Consent Form
IRB	Institutional Review Board
PRMC	Protocol Review and Monitoring Committee
SOC	Standard of Care
CCF	Cleveland Clinic Foundation
UH	University Hospitals
IPC	Innovative Practice Committee

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1.0 INTRODUCTION

Esophageal cancer is a global health problem with over 400,000 new cases and a similar number of deaths occurring each year.[1] Although the highest incidence rates are observed in Southern and Eastern Africa and Eastern Asia, 16,980 cases are diagnosed each year in the United States and 15,590 deaths are attributed to this cancer annually.[2] Depending on a combination of patient factors and disease characteristics, patients are often treated with definitive chemoradiation therapy or surgical resection, with or without pre-operative chemoradiation therapy. For patients treated with a non-operative approach, phase III trials using concurrent chemoradiation therapy have revealed high local failure rates (crude local failure 45-55%) in patients receiving moderate radiation therapy doses (50 Gy).[3, 4] Even in patients undergoing dose escalation (64 Gy) using external beam radiation therapy, the local failure rate continues to be problematic (crude: 50%, 2 year actuarial: 56%).[4] Unfortunately, the nearby organs at risk (such as the lungs, heart, and spinal cord) limit the amount of radiation therapy that can be delivered via standard external beam radiation therapy techniques.

1.1 Background

Brachytherapy is a radiation therapy treatment technique that allows for high doses of radiation to be delivered directly to the tumor volume while sparing the surrounding normal structures. Specifically, high-dose-rate (HDR) brachytherapy delivered using modern devices allows for high doses of radiation to be delivered directly to the tumor in a short period of time (minutes). In an effort to intensify therapy, multiple institutions investigated the role of esophageal brachytherapy in nonoperable patients. For example, Tamaki and colleagues demonstrated a local control rate of 79% at 5 years for 54 patients undergoing external beam radiation therapy followed by a 2-3 fraction brachytherapy boost.[5] Although some investigators such as Tamaki reported encouraging results, the concern with this approach was the high incidence of treatment-related toxicity.

A prospective Radiation Therapy Oncology Group (RTOG) trial was subsequently performed in patients undergoing definitive concurrent chemoradiation therapy for non-metastatic esophageal cancer.[6] Patients were treated to a dose of 50 Gy with concurrent chemotherapy, a two week break, and then three fractions of HDR brachytherapy at weekly intervals to a dose of 15 Gy (5 Gy per fraction per week). The brachytherapy applicator was prescribed to treat the tumor volume plus a one-centimeter margin proximally and distally. The dose was prescribed to a one cm depth from the source axis. Unfortunately, the high treatment-related toxicity (1-year actuarial fistula rate: 18%) observed with this approach limited its routine use and led to the development of strict selection criteria for patients to treated with brachytherapy by the American Brachytherapy Society (ABS).[7] According to the consensus guidelines, good candidates for the procedure as a boost to definitive treatment include those with a unifocal thoracic esophageal cancer $\leq$ 10 cm in length with no extraesophageal extension of disease, and no nodal or metastatic disease. Strict contraindications for esophageal brachytherapy included patients with an esophageal fistula, cervical esophageal location, or a stenosis that could not be bypassed during endoscopy.

In addition to nonoperable patients with esophageal cancer undergoing definitive therapy, patients with recurrent or metastatic disease may symptomatically benefit from HDR brachytherapy. In fact, a randomized controlled trial was recently performed in 209

patients with dysphagia from inoperable esophageal or gastroesophageal junction cancer treated with stent placement or a single dose (12 Gy) brachytherapy application. This trial showed a higher incidence of complications in patients undergoing stent placement (33% vs. 21%, p=0.02) with an improvement in quality-of-life and better long-term relief of dysphagia in patients undergoing brachytherapy.[8] Therefore, patients with unresectable local disease progression, thoracic esophagus lesions with distant metastasis, or those who recurred after definitive external beam radiation therapy can also be considered candidates for the procedure per the ABS guidelines.[7] In addition to these criteria, reported institutional series support the use of HDR brachytherapy in patients with symptomatic stenosis, dysphagia, or tumor hemorrhage as an alternative to endoscopy with coagulation or stent placement.[9]

1.2 Preclinical Data

As previously mentioned, one of the limitations of esophageal brachytherapy is the lack of the treating physician's ability to modulate the dose when using a single tube device. The currently utilized and innovative approach used in our department is a 3-tube technique. Use of the 3-tube technique improves the dose homogeneity and reduces the doses to heart, lungs, bronchus, trachea, and vertebral bodies.

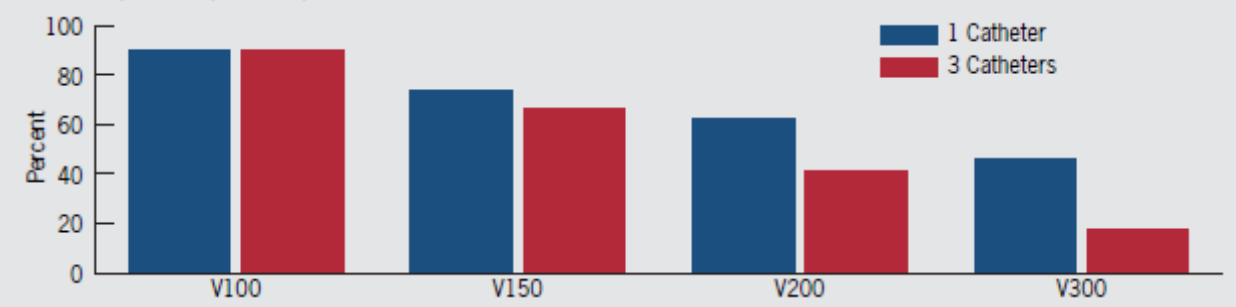


Figure 1. Bar graphs demonstrating the improved dose homogeneity with the 3-tube approach. V100, V150, V200, and V300 represent the volume receiving 100%, 150%, 200%, and 300% of the prescribed dose, respectively.

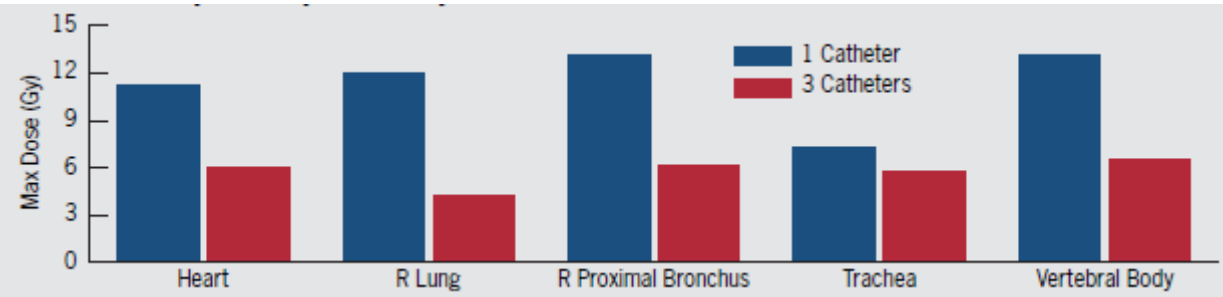


Figure 2. Bar graphs demonstrating the reduced maximum doses of radiation to the nearby critical structures when utilizing a 3-tube technique compared to a single tube technique.

As can be seen in Figure 3, with dose delivery using a single lumen (left picture), there are increased doses delivered to the surrounding normal structures. With use of the three-tube technique (right), the prescription doses can be shaped to match the tumor volume more accurately.

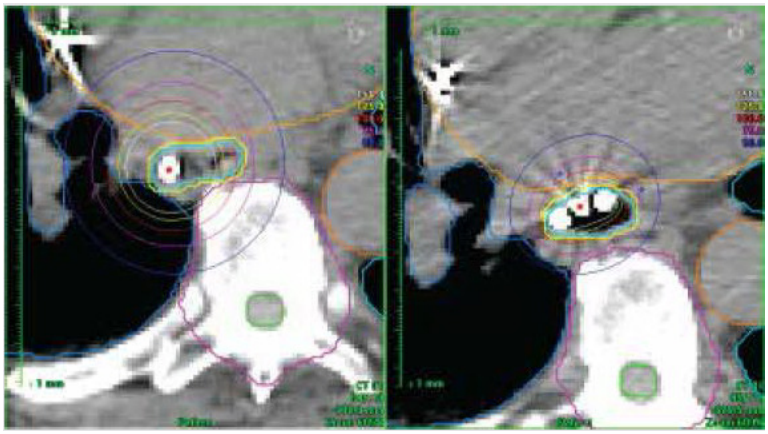


Figure 3. Axial CT treatment planning images for two patients undergoing HDR brachytherapy. Image on the left demonstrates the isodose distribution in a patient treated with a single tube, patient on right was treated with 3-tube technique. Note that all of the circles (representing isodose lines) are smaller with the 3-tube technique.

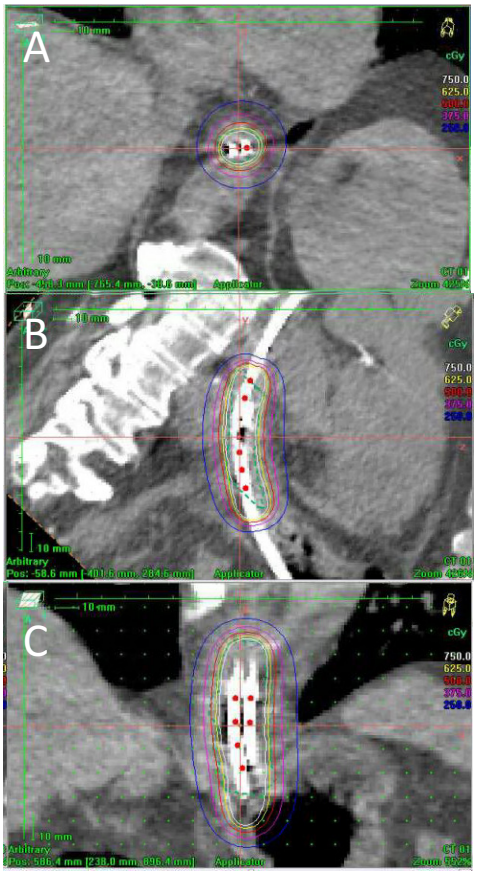


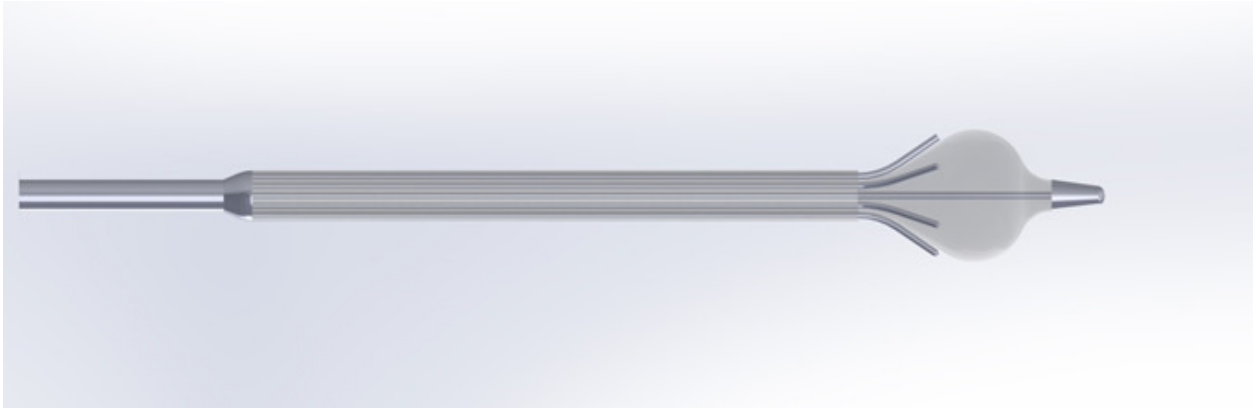
Figure 4. Axial (A), sagittal (B), and coronal (C) CT treatment planning images for a patient with a locally advanced esophageal cancer undergoing HDR brachytherapy. Two transesophageal tubes (each 1.0 meter length) were used to deliver a dose of 5 Gy

1.3 Clinical Data to Date

In an effort to further improve on our treatment technique, we have made substantial improvements by creating a novel balloon repositioning, multichannel brachytherapy applicator itself (i.e., 6 channels instead of 3-tubes). The following figures illustrate the current prototype of the new device designed specifically for this procedure. This new device contains a therapeutic balloon with a maximum diameter of 20 mm when inflated and an anchor balloon with a maximum diameter of 24 mm when inflated. A semi-hard tip was added to the end of the applicator tapering from the 10 mm diameter of the tube to 4-5 mm in diameter at the distal end to allow for easier placement through a narrow, stenotic tumor or strictured area, along with a guidewire channel added to the semi-hard tip. Finally, the seed channels have been designed to extend along the applicator and terminate at the midpoint of the anchor balloon to allow the inflated anchor balloon to push the seed channels closer to the gastroesophageal junction wall (closer to the tumor to improve dose delivery).

A previous prototype incorporating many of the above improvements was tested in a porcine model which showed ease of placement of the device and successful anchoring at the gastroesophageal junction.

Figure 5. Overview of the catheter with inflated balloons.



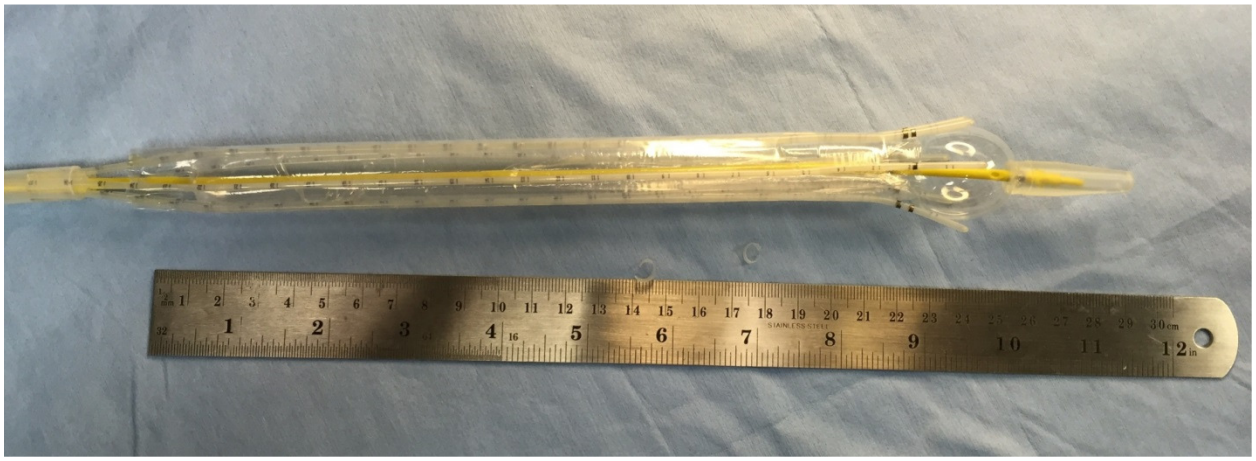


Figure 6. View of seed delivery channels (A) and cross-view (B)

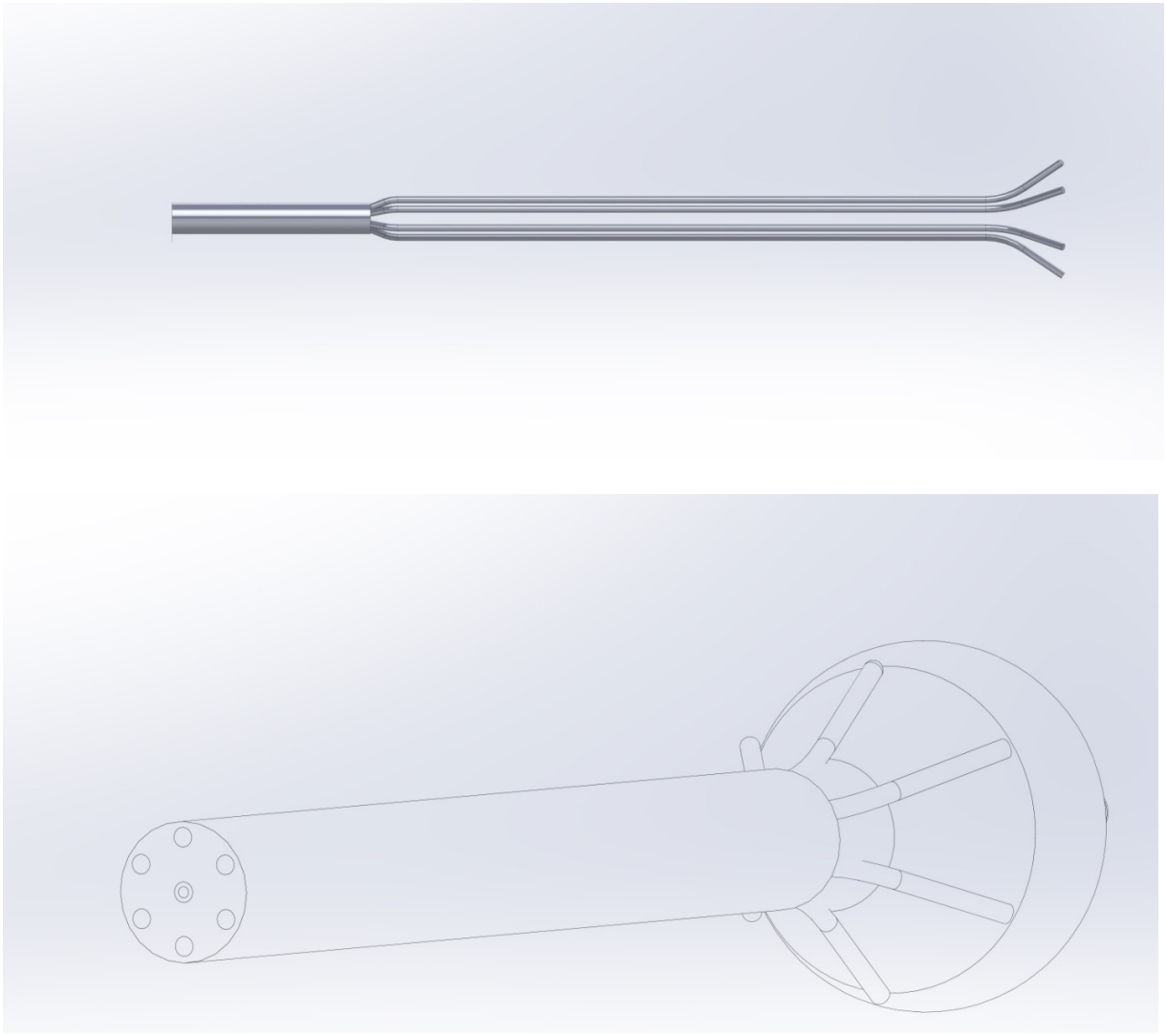
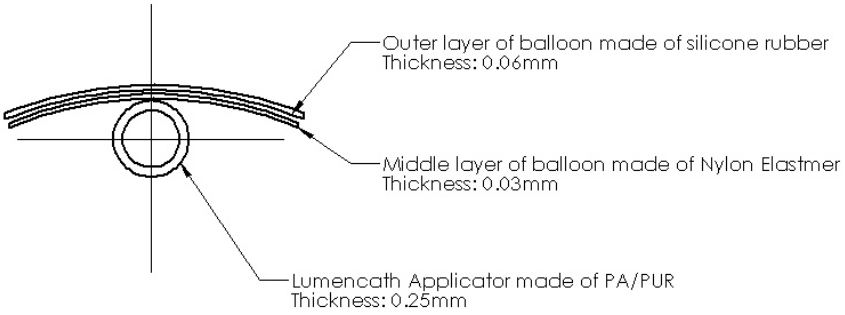


Figure 7.Partial views of the catheter



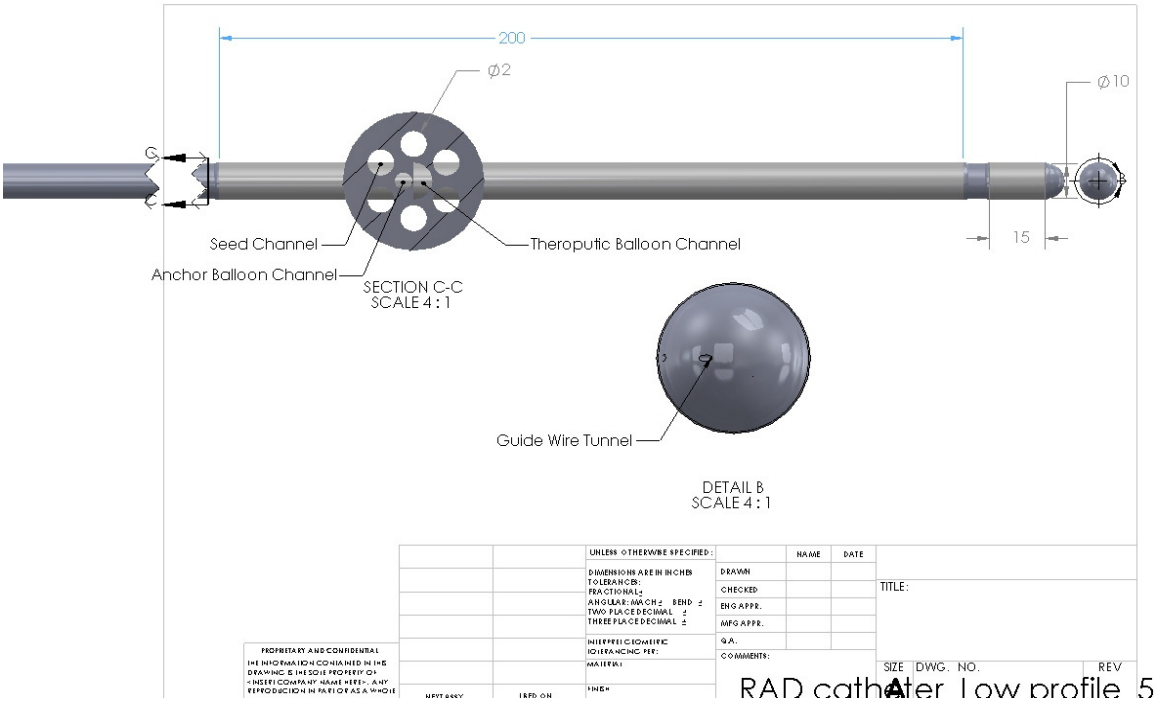
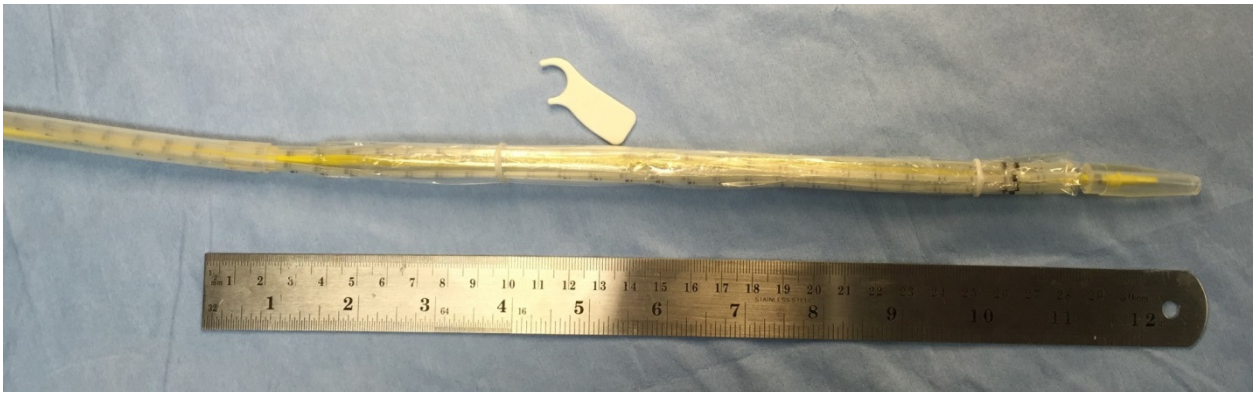


Figure 8.Deflated applicator (without outer sheath)



1.4 Rationale

Although patient access to endoscopy centers has expanded and the incidence of esophageal cancer continues to increase, one of the key limiting factors in the more widespread use of esophageal brachytherapy is the limitations of the current single catheter approach. Therefore, in an effort to improve on this technique, patients in our department have been treated using a novel 3-tube technique. This 3-tube technique makes the dose more conformal and reduces the "hot spots" of radiation (doses above the prescription dose) in the esophageal wall. We evaluated the clinical outcomes of the initial thirteen patients treated for medically unresectable, stage 0-IVA, esophageal cancer with our 3-tube design: Five patients were treated with HDR brachytherapy alone and eight were treated with a combination of HDR brachytherapy and external beam radiation therapy. Across all patients, the 18-month local control, disease-free-survival, and overall survival rates were 81%, 74%, and 92%, respectively. Moreover, no patients have suffered a fistula as a result of treatment and only two patients have required dilation for esophageal strictures. A majority of the patients (11 of 13) continue to be free of dysphagia at a median of 17 months of follow-up. These promising initial results have fueled our interest in further innovation of our delivery technique in an effort to broaden the utility of esophageal brachytherapy as well as provide more effect cancer-directed therapy while maintaining a patient's quality of life.

2.0 OBJECTIVES

2.1 Primary Objective

Pilot study of multichannel endoesophageal brachytherapy applicator to determine dose distribution and conformality of a 6 channel balloon repositioning applicator.

2.2 Secondary Objective(s)

a. To collect data in order to show how the 6-tube endoesophageal brachytherapy technique will be an improvement (more conformed dose distribution) over our previously designed 3-tube endoesophageal brachytherapy technique in patients who are candidates for esophageal brachytherapy

b. To evaluate acute toxicity of novel endoesophageal brachytherapy applicator.

3.0 STUDY DESIGN

This innovative study will be an improvement over our previously designed 3-tube endoesophageal brachytherapy technique in patients who are candidates for esophageal brachytherapy. The brachytherapy planning process will utilize our multichannel balloon applicator as described above.

Intraoperative procedure
In the operating room, the patient's pulse, pulse oximetry, and blood pressure are obtained prior to the procedure and during the procedure. The patient is typically medicated with Demerol (100 mg IV) and Versed (4 mg IV) throughout the procedure and Benzocaine topically prior to the procedure as per standard anesthesia practices for esophageal brachytherapy patients. The endoscope is passed through the mouth under direct visualization and advanced distally, typically to the stomach or 2nd portion of the duodenum. The scope is then gradually withdrawn and the mucosa is examined. Of note, if a significant area of stenosis is identified, this is dilated to allow for a sufficient diameter for insertion of the brachytherapy applicator. Once the cancerous mucosa is visualized, radio-opaque markers (endoclips or metallic seeds) are placed with ~2 cm margins on the proximal and distal ends of the tumor. A guidewire is then passed to the stomach and the endoscope is removed. Over the guidewire, the brachytherapy applicator device is then placed under fluoroscopic guidance ensuring that the distal end travels past the most distal radio-opaque endoclip and typically into the stomach. The brachytherapy applicator is then stabilized and secured by inflating the anchor balloon and/or fixing to the mouth guard after removal of the guidewire.

After applicator placement, the patient is transported to the Department of Radiation Oncology for a CT simulation. Metal dummy seeds are placed into the channels. The treatment balloon is inflated to move the channels in close proximity to the esophageal tumor. The patient is placed in the supine position and undergoes a planning CT scan of the neck and thorax. The CT images are downloaded into the Oncentra treatment planning system and then tumor volume as well as normal critical structures are outlined by the treating radiation oncologist. During the treatment planning phase, the patient is transported to the nursing unit for observation. Following completion of treatment planning, the patient is transported to the HDR brachytherapy treatment room and maintained on the transport cart in the supine position. The exterior portions of the brachytherapy channels are connected to the remote afterloader HDR device. AnIridium-192 seed will enter the channels to deliver the planned course of brachytherapy. After treatment delivery, the brachytherapy channels are disconnected from the HDR afterloader device. After deflation of the anchor and treatment balloons and disconnection from the mouthpiece the multichannel applicator is removed gently from the patient. No devices will remain in the patient. The patient is subsequently transported to the nursing unit for vital sign monitoring for approximately one-half hour prior to discharge to home.

Radiation therapy treatment planning
Patients will be planned using our standard 3D, CT-based, Oncentra treatment planning system. The target volume will be identified during endoscopy and an approximately 2 cm proximal and distal margin will be added to account for microscopic tumor extension (beyond the gross macroscopic disease) and to account for any spatial inaccuracy of the applicator device positioning. The dose will be prescribed to treat the target volume with modification if necessary to decrease doses to the normal surrounding tissues.

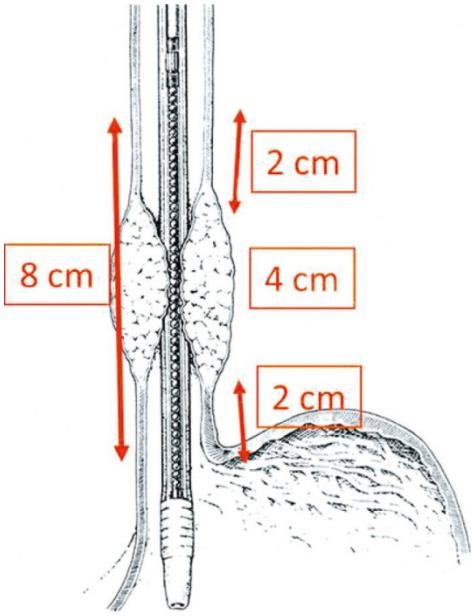


Figure 9. Diagram demonstrating the treatment volume for a 4 cm esophageal tumor treated with a HDR brachytherapy applicator. A 2 cm margin is added on either end to account for microscopic tumor extension and to account for any spatial inaccuracy of the applicator device positioning.[9]

Patients will be treated using standard radiation therapy dosing guidelines, typically in 2-6 sessions separated by weekly intervals. In addition to identifying the treatment volume (CTV, PTV), the organs at risk will be identified. Typical dosimetry constraints, such as the dose delivered to 90% of the tumor volume (D90) and the volume of the tumor receiving the prescription dose (V100) will be reviewed to ensure that an acceptable treatment plan is designed. The use of our new applicator will improve the dose homogeneity as well as lower the dose to the nearby normal organs.

Data Collection:
The focus of the data collection includes but is not exclusive (or limited) to:

A. Date of the procedure
B. Radiation therapy dosimetry and treatment planning parameters
C. Patient tumor characteristics
D. Video of the endoscopy procedure
E. All CT imaging datasets acquired for patient treatment
F. Screen shots from the treatment plan
G. Comments and feedback from members of the treatment team
H. Acute toxicity

Data Collection (cont'd)

I. Tumor Response: CR, PR, SD, PD
J. Esophageal Ulceration (Yes / No)
K. Esophageal Fistula (Yes / No)
L. Esophageal Stricture (Yes / No)
M. Need for Dilation (Yes / No)

Data Analysis:
As this application is specifically for a new device to deliver the same doses of radiation therapy previous administered using single or multi-tube approaches, we will analyze data on patient outcome and dosimetry data in comparison with our historical controls. Specifically, we will use endoscopic follow-up images and correlate the visual changes with the radiation therapy doses delivered to the tumor, esophageal wall, and nearby organs at risk.

3.1 Study design / cohorts

There is only one cohort for this trial. Subjects will be eligible based on meeting the inclusion/exclusion criteria.

3.2 Number of Subjects

Approximately 5 subjects will be enrolled in this trial.

3.3 Replacement of Subjects

If subject does not receive the esophageal brachytherapy treatment, they will be excluded from the trial and another subject will be selected.

3.4 Expected Duration of Treatment and Subject Participation

The initial treatment session will occur after the patient has been found to be eligible, the consent form has been completed, and the treatment plan has been created. The patient will undergo subsequent weekly treatments for 3 to 6 weeks after the initial treatment.

The subject will be expected to participate in the trial throughout its entirety. The participation period is 6 months of which the patient will be evaluated and seen at months 3 and 6.

4.0 SUBJECT SELECTION

Each of the criteria in the sections that follow must be met in order for a subject to be considered eligible for this study. Use the eligibility criteria to confirm a subject's eligibility.

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment:

1. Biopsy-proved esophageal adenocarcinoma or squamous cell carcinoma

2. Disease that can be encompassed in the radiotherapy treatment field

3. Age ≥ 18 years: Because no dosing or adverse event data are currently available on the use of esophageal brachytherapy in subjects ≤18 years of age, children are excluded from this study."

4. Women of childbearing potential must practice adequate contraception

5. Subjects must have the ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

The presence of any of the following will exclude a subject from study enrollment.

1. Concurrent chemotherapy at the time of brachytherapy treatments

2. Tracheal or bronchial involvement

3. Cervical esophagus location

4. Stenosis that cannot be bypassed or dilated to allow for applicator placement

5. Not willing or unable to provide informed consent

6. History of esophageal fistula

4.3 Inclusion of Women and Minorities

Men and women at or over the age of 18, and members of all races and ethnic groups are eligible for this trial.

5.0 REGISTRATION

All subjects who have been consented are to be registered in the OnCore™ Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through Cleveland Clinic Florida's Maroone Cancer Center and will be provided a study number by contacting Kim Thomas at (954) 487-2254 or thomask11@ccf.org.

Eligible subjects will be enrolled into the trial and treated as per standard of care.

6.0 TREATMENT PLAN

6.1 Radiation Therapy

6.1.1 General Guidelines and Timing

Radiation therapy treatment planning

Patients will be planned using our standard 3D, CT-based, Oncentra treatment planning system. The target volume will be identified during endoscopy and an approximately 2 cm proximal and distal margin will be added to account for microscopic tumor extension (beyond the gross macroscopic disease) and to account for any spatial inaccuracy of the applicator device positioning. The dose will be prescribed to treat the target volume with modification if necessary to decrease doses to the normal surrounding tissues.

Intraoperative procedure

In the operating room, the patient's pulse, pulse oximetry, and blood pressure are obtained prior to the procedure and during the procedure. The patient is typically medicated with Demerol (100 mg IV) and Versed (4 mg IV) throughout the procedure and Benzocaine topically prior to the procedure as per standard anesthesia practices for esophageal brachytherapy patients. The endoscope is passed through the mouth under direct visualization and advanced distally, typically to the stomach or 2nd portion of the duodenum. The scope is then gradually withdrawn and the mucosa is examined. Of note, if a significant area of stenosis is identified, this is dilated to allow for a sufficient diameter for insertion of the brachytherapy applicator. Once the cancerous mucosa is visualized, radio-opaque markers (endoclips or metallic seeds) are placed with ~2 cm margins on the proximal and distal ends of the tumor. A guidewire is then passed to the stomach and the endoscope is removed. Over the guidewire, the brachytherapy applicator device is then placed under fluoroscopic guidance ensuring that the distal end travels past the most distal radio-opaque endoclip and typically into the stomach. The brachytherapy applicator is then stabilized and secured by inflating the anchor balloon and/or fixing to the mouth guard after removal of the guidewire.

6.1.2 Equipment and Techniques to be used

After applicator placement, the patient is transported to the Department of Radiation Oncology for a CT simulation. Metal dummy seeds are placed into the channels. The treatment balloon is inflated to move the channels in close proximity to the esophageal tumor. The patient is placed in the supine position and undergoes a planning CT scan of the neck and thorax. The CT images are downloaded into the Oncentra treatment planning system and then tumor volume as well as normal critical structures are outlined by the treating radiation oncologist. During the treatment planning phase, the patient is transported to the nursing unit for observation. Following completion of treatment planning, the patient is transported to the HDR brachytherapy treatment room and maintained on the transport cart in the supine position. The exterior portions of the brachytherapy channels are connected to the remote afterloader HDR device. AnIridium-192 seed will enter the channels to deliver the planned course of brachytherapy. After treatment delivery, the brachytherapy channels are disconnected from the HDR afterloader device. After deflation of the anchor and treatment balloons and disconnection from the mouthpiece the multichannel applicator is removed gently from the patient. No devices will remain in the patient. The patient is subsequently transported to the nursing unit for vital sign monitoring for approximately one-half hour prior to discharge to home.

6.1.3 Target Volumes
Patients will be treated using standard radiation therapy dosing guidelines, typically in 2-6 sessions separated by weekly intervals. In addition to identifying the treatment volume (CTV, PTV), the organs at risk will be identified.

6.1.4 Dose to Target and Organs at Risk Constraints
Typical dosimetry constraints, such as the dose delivered to 90% of the tumor volume (D90) and the volume of the tumor receiving the prescription dose (V100) will be reviewed to ensure that an acceptable treatment plan is designed. The use of our new applicator will improve the dose homogeneity as well as lower the dose to the nearby normal organs.

6.7 Criteria for Removal from Study

In the absence of treatment delays due to adverse events, treatment may continue for up to 6 cycles or until one of the following criteria applies:

• Disease progression,

• Intercurrent illness that prevents further administration of treatment,

• The investigator considers it, for safety reasons, to be in the best interest of the subject.

• General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator,

• Subject decision to withdraw from treatment (partial consent) or from the study (full consent),

• Pregnancy during the course of the study for a child-bearing participant

• Death

• Sponsor reserves the right to temporarily suspend or prematurely discontinue this study.
The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments.

6.8 Duration of Follow Up

Subjects will be followed for 6 months after the initial procedure or until death, whichever occurs first.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

8.0 ADVERSE EVENTS AND POTENTIAL RISKS

8.1 Radiation Therapy

All patients will be seen weekly by their treating radiation oncologist while undergoing EBRT. Any observations with respect to the following symptoms/side effects will be recorded:

- Bowel/rectal irritation manifesting as cramping, diarrhea, urgency, proctitis, or hematochezia
- Urinary frequency, urgency, dysuria, hematuria, urinary tract infection, or incontinence
- Radiation dermatitis

Clinical discretion may be used in managing radiotherapy-related side effects. Diarrhea/rectal frequency/urgency may be managed with diphenoxylate or loperamide. Bladder irritation may be mitigated with phenazopyridine. Urinary frequency/urgency can be managed with anticholinergic agents or alpha-blockers such as tamsulosin. Erectile dysfunction can be managed with phosphodiesterase (PDE) inhibitors such as sildenafil.

8.3 Definitions

8.3.1 Adverse Event

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

8.3.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR
    - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR

- The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependant on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

For the purpose of this study the following events would not be considered adverse events and would not be recorded in the database:

- Abnormal laboratory findings considered associated to the original disease

8.3.3 Adverse Event Evaluation

The investigator or designee is responsible for ensuring that all adverse events (both serious and non-serious) observed by the clinical team or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's medical records. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, result in a delay or dose modification of study treatment, or judged relevant by the investigator), should be reported as an adverse event.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE)
- Description of the event
- Date of onset and resolution
- **Expectedness of the toxicity**
- **Grade of toxicity**
- **Attribution of relatedness to the investigational therapy/agent- (this must be assigned by an investigator, sub-investigator, or treating physician)**
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received conmed or other intervention, etc.
- Outcome of event

Descriptions and **grading scales** found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version **4.0** will be utilized for agent AE reporting.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

Protocol must specify if attribution is required for individual components of the treatment regimen or the treatment regimen as a whole.

8.4 SAE Report Form

SAE's related to radiation therapy only will be recorded into OnCore and reported to IRB according to local IRB policies and procedures.

SAEs related to agent therapy will be recorded on the FDA Form 3500A (MedWatch) but should only be reported as instructed below. The electronic FDA SAE reporting forms should not be used.

8.5 Reporting Procedures for Serious Adverse Events

For the purposes of safety reporting, all adverse events will be reported that occur [Please insert appropriate time frame, e.g. on or following first day of RT, on day of registration, etc.] through 30 days after the final dose of study radiation therapy/drug. Adverse events, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

8.5.1 SAE Reporting Requirements

- Participating investigators (all sites) must report all serious adverse events to the Lead Site Principal Investigator (e.g. Sponsor-Investigator) within **24 hours** of discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE until final resolution.
    - John F. Greskovich Jr., M.D.: (954) 659-5840 / Fax: (954) 487-2816
    - Study Coordinator: Kim Thomas (954) 487-2254 / thomask11@ccf.org.

- The Lead Site Principal Investigator will review the SAE and report the event to the FDA, external collaborator(s), and IRB as applicable.
- It is the Sponsor-Investigator's responsibility (e.g. lead site PI) to ensure that ALL serious adverse events that occur on the study (e.g. ALL SAEs that occur at each enrolling institution) are reported to all participating sites.

Institutional Review Board Reporting Requirements:

- Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

8.6 SAEs and OnCore

- All SAEs will be entered into OnCore.
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into Oncore.

8.7 Data Safety and Toxicity Committee

It is the responsibility of each site PI to ensure that ALL SAEs occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with their submission to the sponsor and/or other regulatory bodies

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

8.8 Data and Safety Monitoring Plan

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section #8.

10.0 CORRELATIVE STUDIES N/A

11.0 STUDY PARAMETERS AND CALENDAR

11.2 Calendar

Patients will be treated weekly for 3 to 6 weeks.
Follow up visits will take place at 3 and 6 month intervals.
A visit window of **+/- 1** day is allowed for treatment/procedure visit
A visit window of **+/- 7** days is allowed for the 3 and 6 month follow-up visits.

12.0 MEASUREMENT OF EFFECT

-Tumor Response: CR, PR, SD, PD
-Esophageal Ulceration
-Esophageal Fistula
-Esophageal Stricture
-Need for Dilation

13.0 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The OnCore™ Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore™ is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore™. Access to data through OnCore™ is restricted by user accounts and assigned roles. Once logged into the OnCore™ system with a user ID and password, OnCore™ defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore™ Administrator at OnCore-registration@case.edu.

OnCore™ is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the OnCore™ database. A calendar of events and required forms are available in OnCore™.

13.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical

information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. For multi-center studies, participating sites must inform the sponsor-investigator of pending audits.

14.0 STATISTICAL CONSIDERATIONS

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9).

A variety of statistical methods will be employed to analyze the trials's data. Data will be periodically analyzed using descriptive statistics and correlative measures for significance when comparing demographic and dosimetric data. Typical dosimetry constraints, such as the dose delivered to 90% of the tumor volume (D90) and the volume of the tumor receiving the prescription dose (V100) will be reviewed to ensure that an acceptable treatment plan is designed. The use of our new applicator will improve the dose homogeneity as well as lower the dose to the nearby normal organs.

As this application is specifically for a new device to deliver the same doses of radiation therapy previous administered using single or multi-tube approaches, we will analyze data on patient outcome and dosimetry data in comparison with our historical controls. Specifically, we will use endoscopic follow-up images and correlate the visual changes with the radiation therapy doses delivered to the tumor, esophageal wall, and nearby organs at risk. One of the limitations of esophageal brachytherapy is the lack of the treating physician's ability to modulate the dose when using a single tube device.

The currently utilized and innovative approach used in our department is a 3-tube technique. Use of the 3-tube technique improves the dose homogeneity and reduces the doses to heart, lungs, bronchus, trachea, and vertebral bodies. In addition to nonoperable patients with esophageal cancer undergoing definitive therapy, patients with recurrent or metastatic disease may symptomatically benefit from HDR brachytherapy. In fact, a randomized controlled trial

was recently performed in 209 patients with dysphagia from inoperable esophageal or gastroesophageal junction cancer treated with stent placement or a single dose (12 Gy) brachytherapy application. This trial showed a higher incidence of complications in patients undergoing stent placement (33% vs. 21%, p=0.02) with an improvement in quality-of-life and better long-term relief of dysphagia in patients undergoing brachytherapy.[8] Therefore, patients with unresectable local disease progression, thoracic esophagus lesions with distant metastasis, or those who recurred after definitive external beam radiation therapy can also be considered candidates for the procedure per the ABS guidelines.[7]

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APPENDIX I

PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	Percent	Description
0	Normal activity. Full active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% if waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead

APPENDIX II

DATA COLLECTION SHEET

Esophageal Brachytherapy / IRB# IP 30

MRN	Date	Tumor Response: CR, PR, SD, PD	Esophageal Ulceration (Yes / No)	Esophageal Fistula (Yes / No)	Esophageal Stricture (Yes / No)	Need for Dilation (Yes / No)