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High-dose rate intraluminal brachytherapy for oesophageal cancer using MR imaging: A clinical implementation

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Abbreviations

ABS	American brachytherapy society
BED	Biological effective dose
CT	Computed tomography
DVH	Dose volume histogram
EBRT	External beam radiotherapy
EQD_2	Equivalent dose in 2 Gy per fraction
EUS	Endoscopic ultrasound
FDG	^{18}F-fluoro-deoxy-D-glucose
FRFSE	Fast recovery fast spin echo
HDR	High-dose rate
IR FSE	Inversion recovery fast spin echo
LDR	Low-dose rate
MDR	Medium-dose rate
MR	Magnetic resonance
OAR	Organ at risk
PDR	Pulsed-dose rate
PET	Positron emission tomography
PTV	Planning target volume

Popular scientific summary in Swedish

Strålbehandling är en vanlig behandlingsteknik för behandling av cancer. Behandlingen kan levereras på två olika sätt: internt eller externt. Vid extern strålbehandling bestrålas tumören med en strålkälla som befinner sig utanför kroppen. Vid intern strålbehandling, även kallat brachybehandling, placeras strålkällan inuti kroppen, i eller i nära anslutning till tumören. Själva tumören får därmed mycket strålning samtidigt som omkringliggande vävnad skonas.

Vid brachybehandling av cancer i matstrupen förs en radioaktiv strålkälla ner i matstrupen genom en sond. Strålkällan stannar i ett antal bestämda positioner till dess att tumören mottagit den dos läkaren har ordinerat. Dagens behandlingsplaner utförs på en röntgenbild med hjälp av markörer som markerar tumörens utsträckning. På grund av otillräcklig information i röntgenbilden kan inte tumörens volym bestämmas, vilket kan medföra att tumören erhåller felaktig dos.

Information om tumörens volym kan däremot fås genom tredimensionella bilder från en magnetisk resonanstomografi (MR) kamera. Dessa bilder ger möjligheten att urskilja olika vävnader i kroppen, vilket gör det lättare att separera tumören från omkringliggande vävnad.

Syftet med projektet är att utforma en behandlingsmetod för cancer i matstrupen med MR som bildunderlag vid planering av behandling. Vid avbildning av matstrupen uppstår tekniska utmaningar då både hjärtats aktivitet och andningsrörelser bidrar till störningar i MR-bilder. Ett MR protokoll har utarbetas under denna studie och en tumör i matstrupen hos en patient har kunnat avbildas med tillräckligt god bildkvalité för att kunna användas som underlag för behandling.

Abstract

Purpose: The aim of this study was to investigate a new methodology for brachytherapy of oesophageal cancer using magnetic resonance (MR) imaging for treatment planning. That includes finding a suitable oesophageal applicator that can be visualised on MR images and to create dose and fraction schedule that should be used brachytherapy treatments.

Material and Methods: A total of six patients were involved to determine a suitable MR sequence for visualisation of the oesophageal tumour. The patients were scanned with two different T2-weighted sequences, inversion recovery fast spin echo (IR FSE) and fast recovery fast spin echo (FRFSE). The imaging was performed on a 3.0 T MR scanner from GE Healthcare. Dose planning was performed on MR images using two different methods. In the first method the dose was prescribed at 10 mm from the applicator centre, as currently used at Skåne University Hospital. In the second method the dose planning was performed by manually adjusting the dwell times until tumour coverage was reached. An MR safe oesophageal applicator could not be found on the market. Therefore a duodenal tube was used and modified. Different contrast agents were studied in order to render the tube visible on MR images.

Results: The oesophageal tumour was successfully visualised and delineated on T2-weighted images with FRFSE sequences. Furthermore, improved dose coverage to the tumour was observed when the dose planning was manually optimised to the tumour volume, where $V_{100\%}$ to the tumour was increased from 70% to 95%. Moreover, the applicator was filled with a saline solution and was visualised on the MR images.

Conclusion: Brachytherapy treatment for oesophageal cancer with MR imaging provides an improved tumour visualisation and the manifesting of DVH parameters enables dose coverage to the tumour.

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1. Introduction

1.1 Background

Cancer of the oesophagus is the ninth most common carcinoma worldwide and has a high cancer-related mortality (Pennathur et al., 2013, Torre et al., 2015). The most common symptoms of oesophageal cancer, dysphagia and weight loss, arise first when the carcinoma has reached an advanced stage, hence the poor prognosis. A good outcome of the carcinoma is associated with early stage diagnosis. Oesophageal cancer has a 5-year overall survival rate with less than 20 % of survival, making it one of the lowest long-time survival rates among different cancer diagnoses (Pennathur et al., 2013, Hujala et al., 2002).

The primary curative approach of oesophageal cancer is radical surgery, however about 60-70% of the patients are not suitable to undergo the procedure due to unfavourable diagnosis, i.e. the cancer has progressed into an inoperable stage. Heavy alcohol intake and long-time smoking are often associated with the carcinoma, consequentially contributing to poor health conditions making surgery impractical (Fabrini et al., 2010, Pennathur et al., 2013). When surgery is not possible, external beam radiotherapy (EBRT) with or without concurrent chemotherapy is another treatment approach. Intraluminal brachytherapy is also preferred as a boost following EBRT (Muijs et al., 2012, Murakami et al., 2012).

The main purpose with palliation treatment of oesophageal cancer is dysphagia relief (Hujala et al., 2002). A variety of modalities are used for treatment, such as external radiation therapy and/or intraluminal brachytherapy, oesophageal stenting and laser procedures (Hujala et al., 2002, Lettmaier and Strnad, 2014). The two latter therapies have presented a more rapid relief in dysphagia compered to intraluminal brachytherapy. However, intraluminal brachytherapy provides a more long-lasting effect and should be used for patients with longer life expectancies (Bergquist et al., 2005, Homs et al., 2004). Intraluminal brachytherapy has the advantage of delivering high doses to the target volume and low doses to surrounding normal tissue. This is considered as an advantage when intraluminal brachytherapy is used as a boost to EBRT, since the window for additional radiation exposure to critical organs such as the spinal cord after EBRT is small (Folkert et al., 2013).

Because of the adjacent radiosensitive organs, i.e. organs at risk (OAR), an accurate dose planning is essential. Dose planning is currently performed with x-ray imaging combined with the information from endoscopy for brachytherapy. The treatment trajectory is based on two-dimensional (2D) images, which lack the ability to provide information regarding the volume of the tumour. Furthermore, due to treatment uncertainties, additional longitudinal margins are added to the tumour. By introducing three-dimensional (3D) images, the margins of the tumour's delineation can be decreased. Additionally, 3D-images provide dose volume information of the tumour and the OARs (Potter et al., 2006).

Magnetic resonance (MR) imaging provides a great soft-tissue contrast and is a non-invasive technique. The utility of MR in dose planning has been seen in malignancies in other sites, such as cervix and prostate cancer (Groenendaal et

al., 2012, Dimopoulos et al., 2012). To this stage, the evidence of MR for dose planning and tumour delineation for oesophageal cancer is limited, but the idea is promising (van Rossum et al., 2015).

1.2 Aim

The purpose of this study is to evaluate a method for treating oesophageal cancer with brachytherapy using MR-imaging. This includes evaluating the imaging modality for dose planning, creating a dose and fraction schedule, as well as finding a suitable applicator. Ultimately, this method will be implemented at Skåne University Hospital in Lund, Sweden.

2. Theory

2.1 Anatomy of the oesophagus

The oesophagus is a hollow muscular tube with a length of 25 to 30 cm with a diameter of 2 cm, connecting the pharynx with the stomach. The oesophagus runs in front of the spinal cord, traverses through the diaphragm and runs behind the trachea and heart. The oesophagus is anatomically divided into three distinct regions: cervical, thoracic and abdominal oesophagus (Figure 1) (American Cancer Society, 2015).

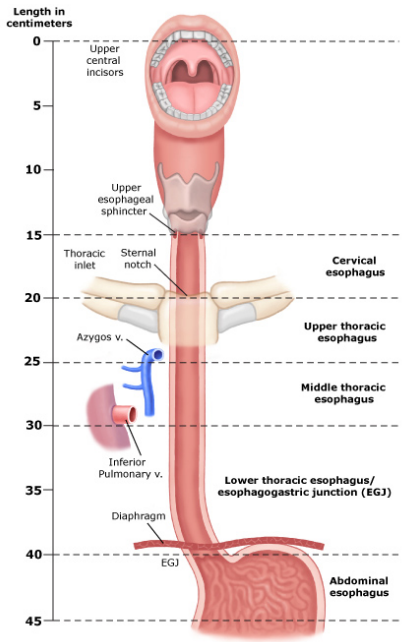


Figure 1. The anatomy of the oesophagus (http://www.seattlecca.org/client/Esophagus-large.jpg).

The oesophageal wall is composed of four layers: *mucosa*, *submucosa*, *muscularis propria* and *adventitia* (Figure 2) (Jobe et al., 2009).

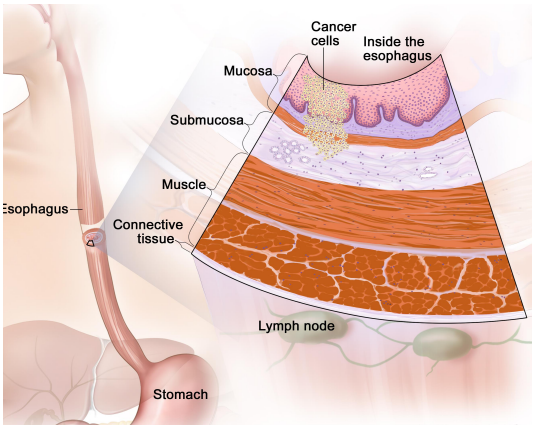


Figure 2. The layers of the oesophageal wall.
(http://www.cancer.gov/images/cdr/live/CDR752730.jpg)

The *mucosa*, the innermost layer is composed of three sublayers. The first sublayer, the epithelium, covers the inner surface of the oesophagus with a stratified non-keratinized squamous epithelium lining. Lamina propria, the second sublayer of the mucosa, is a connecting tissue that connects the epithelium with the muscularies mucosae, which is the third sublayer. The muscularies mucosa consists of a double layer of smooth muscles. The *submucosa* contains loose connective tissue, lymphocytes, plasma cells, nerve cells, a vascular network and submucosal glands. The glands secrete mucus to support and ease the passage of food through the oesophageal. The thick layer of *muscularis propria* is responsible for the motor function and helps the food to pass the oesophagus by rhythmic movements. The *adventitia* is the outermost external layer of the oesophagus and it connects it to neighbouring structures. The *adventitia* is composed of loose connective tissue (Jobe et al., 2009, American Cancer Society, 2015).

2.2 Cancer of the oesophagus

Cancer of the oesophagus emerges from the innermost layer, the epithelium, and spreads out to the outer layers. Squamous cell carcinoma and adenocarcinoma are the two most prevalent histological types of oesophageal cancer, representing about 90% of the diagnoses (American Cancer Society, 2015). Other less common histological types are melanoma, leiomyosarcoma and small-cell carcinoma (Pennathur et al., 2013). The incidence of oesophageal cancer increases with age and the risk of getting oesophageal cancer is four times higher for men than women (Torre et al., 2015).

Squamous cell carcinoma derives from the squamous dells in the lining of the oesophagus. The carcinoma is dominant in developing countries and is prevalent in populations of lower socio-economics development. Risk factors associated

with squamous cell carcinoma are a long-time tobacco use, heavy alcohol intake, achalasia and history of head and neck cancer (Pennathur et al., 2013, American Cancer Society, 2015). The incidence of squamous cell carcinoma has decreased or stayed constant over the last decades. The occurrence is also related to ethnicity. For instance, African-Americans are more likely to develop squamous cell carcinoma than adenocarcinoma, and the opposite applies for the Caucasian population (Jobe et al., 2009).

Adenocarcinoma derives from the gland cells, which usually do not thrive at the epithelium lining of the oesophagus. In order for adenocarcinoma to develop gland cells must replace the squamous cells. A disease that eliminates squamous cells from the epithelium is thus associated with adenocarcinoma. Gastro-oesophageal reflux disease (GORD) is a condition that occurs when the acid and enzymes existing in the stomach aimed to digest the food leak to the lower part of the oesophagus. GORD and its associated conditions, such as Barrett's oesophagus have shown to be risk factors to adenocarcinoma. Barrett's oesophageal disease develops after a long time occurrence of GORD, where the epithelium of the oesophagus will be damaged and the squamous cells will be replaced with gland cells. Adenocarcinoma is therefore more prevalent in the lower part of the oesophagus (American Cancer Society, 2015). The carcinoma has shown an increased incidence in higher socio-economic classes and obesity. Adenocarcinoma is dominated in the western nations, such as North America and Western Europe (Jobe et al., 2009).

2.3 Brachytherapy

Brachytherapy is a treatment modality that has been used since the beginning of the 20th century. In brachytherapy radioactive source are placed near into a target volume. Brachytherapy has the ability to deliver high doses to the tumour volume and low doses to surrounding normal tissue due to the steep dose gradient of the radioactive source (GEC ESTRO Handbook of Brachytherapy, 2002).

The radiation doses can be delivered interstitial, intracavitary, intraluminal or by surface brachytherapy. For interstitial brachytherapy the radioactive source are placed into body tissue. This treatment therapy is common for prostate cancer where the needles are pierced into the prostate. For intracavitary brachytherapy the source are placed in pre-existing body cavities adjacent to the treatment volume. Intracavitary therapy is used for gynaecological and nasopharynx malignancies (Metcalfe et al., 2007). Treatment of sites such as oesophagus, bronchus and biliary duct are referred to as intraluminal brachytherapy. Surface brachytherapy is used for skin cancers and soft tissue carcinoma. (GEC ESTRO Handbook of Brachytherapy, 2002).

Treatment with brachytherapy can be delivered with different dose rates:

- Low- dose rate (LDR) 0.4-2 Gy/h
- Medium-dose rate (MDR) 2-12 Gy/h
- High-dose rate (HDR) >12 Gy/h

Low-dose rate brachytherapy is used for both temporary and permanent treatments. For temporary treatments the radioactive source is taken out of the patient after a period of time. For permanent implants the radioactive sources, usually in encapsulated seeds, are to deliver the dose over several months to the target volume. In high-dose rate (HDR) brachytherapy, sources with high activity are used. In HDR brachytherapy the dose is delivered step by step in predetermined positions (dwell points) covering the entire tumour over a course of minutes (Metcalfe et al., 2007). In pulsed-dose rate (PDR) the dose is delivered in many short exposures, administering the same total dose as for LDR treatments. PDR brachytherapy uses thus the physical advantages of HDR treatment and the radiobiological advantages of LDR treatment (GEC ESTRO Handbook of Brachytherapy, 2002, (Metcalfe et al., 2007).

To deliver the dose, a remote afterloading machine is preferred (Figure 3). The afterloading machines have the capability to alter the positions of the source and the time in each position (dwell time) corresponding to the predetermined dose plan (Metcalfe et al., 2007). The machines have a safe where the radioactive source is stored and the source can easily be delivered from the safe to the patient. The afterloading machine can be controlled outside the treatment room and thus prevent radiation exposure to the staff.

Figure 3. Varian GammaMedplus iX HDR/PDR remote afterloader (www.varian.com)

The radioactive sources are sealed and encapsulated with metal to avoid leakage of the isotopes and to absorb beta particles. The most prevalent radioactive source used today in HDR brachytherapy is iridium-192 (^{192}Ir), which decays through emission of β -particles and electron capture (EC). The β- particles will be absorbed in the encapsulated material and not contribute to the dose. The average energy of the emitted photons is 370 keV (Metcalfe et al., 2007). The decays of ^{192}Ir with a yield greater than 5 % are presented in Table 1.

Table 1. Decays of ^{192}Ir with a yield greater than 5 % (http://www.nndc.bnl.gov/useroutput/192ir_mird.html).

Decay	Yield (%)	Energy (keV)
β^-	41.4	162
β^-	48.0	210
β^-	5.60	71,6
γ	28.7	296
γ	29.7	309
γ	82.7	317
γ	47.8	468
γ	8.20	604
γ	5.34	613
γ	8.00	7.24

2.4 Brachytherapy of oesophageal cancer

2.4.1 Curative treatment

Brachytherapy is given both as a sole treatment modality and as a boost following external beam radiotherapy for curative treatments. Data from brachytherapy as a sole treatment modality is limited and the therapy is preferred for very early stages of the carcinoma (Lettmaier and Strnad, 2014). Brachytherapy is predominantly used as a boost following external beam radiotherapy with or without concomitant chemotherapy. A higher survival rate is obtained with concomitant chemotherapy for patients in general good health conditions (Gaspar et al., 1997). Chemotherapy is contraindicated for patients with poor health conditions due to the high toxicities and patients should be evaluated if they are appropriate candidates to receive chemotherapy.

The American Brachytherapy Society (ABS) (1997) has published consensus guidelines for brachytherapy of cancer in the oesophagus. The guidelines include recommendations for patient selection and dose and fractional schedule for curative treatment with intraluminal brachytherapy (Table 2). For patients receiving external beam radiotherapy with concurrent chemotherapy, an external dose of 45-50 Gy, in fractions of 1.8-2.0 Gy, is given. For patients unable to receive chemotherapy, the dose is increased to 60 Gy. Intraluminal brachytherapy is recommended to begin 1-3 weeks after external radiotherapy in order for the acute reactions to subside.

Table 2. Guidelines for dose recommendations and patient selection for curative intraluminal brachytherapy treatment of oesophageal cancer.

Good candidates	
	Unifocal squamous or adenocarcinoma of the thoracic oesophagus
	Length of primary tumour ≤10 cm
	No regional lymph node or metastatic disease
Contraindications	
	Oesophageal fistula
	Cervical oesophageal location
	Stenosis that cannot be bypassed
Dose recommendations (After 45-60 Gy EBRT)	
	HDR 10 Gy, 5 Gy/fraction over two weeks*

* The doses should be prescribed 1 cm from the midsource or mid-well position.

Newer consensus guidelines for brachytherapy of oesophageal cancer have yet to be published. A few studies have implemented different doses and fraction schedules for curative treatment of oesophageal cancer (Table 3).

Muijs et al. (2012) analysed a study where external beam radiotherapy in combination with intraluminal brachytherapy was used to treat oesophageal cancer. Eligible patients for this study were patients with tumour stage T1-4 N0-1 M1a without distant metastasis and patients with a tumour length ≤ 6 cm. However, after 2005 the tumour length criteria were excluded. The brachytherapy was delivered one week before and one week after the external beam radiotherapy treatment. The dose was prescribed 10 mm from the centre of the applicator and an applicator with an outer diameter of 6 mm was used. Severe toxicities such as acute bleeding, stricture and ulcers occurred in 10 patients (16%). The authors concluded that due to a high rate of severe toxicities and the high doses to the oesophageal wall, intraluminal brachytherapy should only be considered for well-selected patients.

Murakami et al. (2012) presented results from a long-term study of superficial oesophageal cancers treated with intraluminal brachytherapy in combination with external beam radiotherapy. Patients with thoracic oesophageal cancer were eligible for this study. Patients with tumours in the muscularis mucosa or a deeper invasion were given intraluminal brachytherapy as a boost following external beam radiotherapy. Brachytherapy was given five times a week and was performed immediately after completed external beam radiotherapy irradiation. The brachytherapy dose was prescribed 5 mm from the applicator surface and the diameter of the applicator was 16 or 20 mm. The acute toxicities that occurred were esophagitis, leukopenia and thrombocytopenia and late toxicities pneumonitis. The authors deduced that the results obtained for treatment of submucosal cancer with intraluminal brachytherapy as a boost following external beam radiotherapy were not satisfactory and a consideration towards a more intensive treatment should be done.

Tamaki et al. (2012) studied intraluminal brachytherapy as a boost following external beam radiotherapy for superficial oesophageal cancer. All the patients in this study had cancer in the thoracic part of the oesophagus. Low-dose rate brachytherapy was delivered to 19 patients and delivered once a week and high-dose rate brachytherapy was delivered twice a week to the remaining 35 patients.

The brachytherapy dose was prescribed 5 mm from the applicator surface and an applicator with the diameter 15-20 mm was used. A total of 11 patients (20%) had tumour recurrence. The authors encourage the use of HDR as a boost following external beam radiotherapy in the curative setting for patients with superficial oesophageal cancer.

Gaspar et al. (2000) studied radiation therapy with concurrent chemotherapy for localised carcinoma of the oesophagus. The brachytherapy treatment was given with concurrent chemotherapy two weeks after completion of external irradiation. The HDR brachytherapy was first given as total dose of 15 Gy with a weekly fraction dose of 5 Gy but then decreased to a total dose of 10 Gy with the same fractional dose. The dose was prescribed 10 mm from the centre of applicator and an applicator with an outer diameter of 4-6 mm was used. The authors concluded that combining brachytherapy with chemotherapy should be closely evaluated due to the high incidence of toxicities.

Table 3. Overview of studies for curative intraluminal brachytherapy as a boost following external beam radiotherapy for oesophageal caner.

Author	n	EBRT dose	Intraluminal brachytherapy dose	Local control	Complications	Overall survival
Muijs et al. (2012)	62	60 Gy	12 Gy (6 Gy/fraction)	71% (1y)	Esophagitis Ulcerations (11%) Strictures (16%) Severe toxicities (10%)	11% (5y)
Murakami et al. (2012)	87	50-61 Gy	10 Gy (2-2.5Gy/fraction)	[a]49%, [b]75% (5y)	Acute effects (34%) Late effects (20%)	[a]31%, [b]84% (5y)
Tamaki et al. (2012)	54	56-60 Gy	10 Gy (5 Gy/fraction)[c] 9 Gy (3 Gy/ fraction)[d]	79% (5y)	Late effects (10%)	61% (5y)
Gaspar et al. (2000)	49	50 Gy	10-15 Gy (5 Gy/fraction)	37% (1y)	Fistulas (12%) Severe toxicities (59%) Life-threatening (24%)	49% (1y)

[a]Submucosal cancer and [b]mucosal cancer
[c]Doses with LDR brachytherapy
[d]Doses with HDR brachytherapy

2.4.2 Palliative treatment

The main intent with palliation treatment is to improve patients swallowing ability and to increase quality of life. A high priority is therefore to use a therapy modality with low side effects and low intervention (Bergquist et al., 2005). The main modalities advocated for palliative treatments are intraluminal brachytherapy, stent placement and laser therapy (Nd:YAG laser and photodynamic therapy) (Homs et al., 2005, Lettmaier and Strnad, 2014)

A few studies have been made comparing the efficacy between the different treatment modalities. Homs et al. (2004) conducted a multicentre randomised trial comparing single dose brachytherapy with stent placement of oesophageal cancer. The outcome was that a more instant relief of dysphagia was obtained after stent placement compared to single dose intraluminal brachytherapy. However, intraluminal brachytherapy provides with a more long lasting effect

and is thus preferred for patients with a life expectancy greater than 3 months (Figure 4). Furthermore, more complications are associated with stent placement than brachytherapy treatment such as stent migration, tumour growth or fistula formation. These results were emphasised by a randomised trial performed by Bergquist et al. (2005). Laser procedures have also shown an instant improvement in swallowing capability but the disadvantage with the procedure is the need of frequent repetition because of the continuous growth of the tumour and the expensive treatment costs (Sargeant et al., 1992).

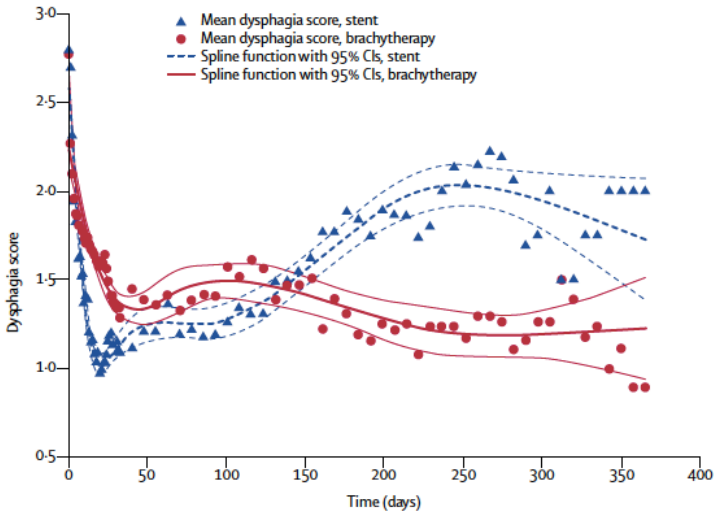


Figure 4. Dysphagia score after stent placement and single dose brachytherapy treatment. The dysphagia score has a range from 0 to 4 where 0 represents normal swallowing ability (no dysphagia) and 4 represents complete dysphagia (Homs et al., 2004).

Dose recommendation and patient selection from ABS for palliative HDR brachytherapy treatment is presented in Table 4. The dose recommendations are dependent on previous treatments and life expectancy. ABS encourages intraluminal brachytherapy as a boost following external beam radiotherapy for patients with a greater life expectancy than 6 months. As for curative treatment the HDR brachytherapy is recommended to begin 2-3 weeks after external radiotherapy is completed.

Table 4. Guidelines on dose recommendations for palliative intraluminal brachytherapy treatment.

Candidate for palliative treatment
Adeno- or squamous cancers of the thoracic oesophagus with distant metastases
Unresectable local disease progression/recurrence after definitive radiation treatment
Dose recommendations*
Short life expectancy or recurrent cancer after EBRT
HDR – total dose 10-14 Gy, with 1 or 2 fractions
No previous EBRT
EBRT - 30-40 Gy, 2-3 Gy/fraction
HDR – total dose 10-14 Gy, with 1 or 2 fractions
No previous EBRT and life expectancy > 6 months
EBRT - 40-50 Gy, with 1.8-2.0 Gy/fraction
HDR – total dose 10 Gy, 5 Gy/fraction once a week

* The doses in the table are prescribed 1 cm from the midsource or mid-well position.

An overview of palliative treatment results from different studies treating oesophageal cancer with intraluminal brachytherapy is summarized (Table 5).

Rosenblatt et al. (2010) conducted a randomised trial of the International Atomic Energy Agency to investigate the efficacy of external beam radiotherapy with and without intraluminal brachytherapy. The HDR intraluminal brachytherapy treatments were given a median of five days apart and prescribed 10 mm from the centre of the applicator. The external beam radiotherapy treatment consisting of 30 Gy, 3 Gy/fraction began one week after the second brachytherapy treatment. No significant difference in overall survival was noticed between the two study arms. An improvement in dysphagia relief was observed in the combined therapy arm with an absolute benefit of 18% after 200 days nonetheless.

Bergquist et al. (2005) presented the results of a randomised controlled clinical trial for palliative treatment of advanced cancer in the oesophagus and gastro-oesophageal junction. Patients eligible for this study were patients with cancer in the oesophagus or gastro-oesophageal junction with metastatic disease and with a dysphagia score of at least grade 2 (able to drink and eat semisolid food). The brachytherapy treatments were delivered in an interval of 1-2 weeks apart and prescribed 10 mm from the applicator surface. A clinical relevant improvement regarding eating scale, problems with choking and the ability to eat solid and semisolid food was observed 3 months after the treatment.

Homs et al. (2004) conducted a multicentre randomised trial with a single dose brachytherapy treatment. Dysphagia control, with an improvement of at least one dysphagia score, was detected in 73% of the patients after 1 month. Major complications after the treatment occurred in 13 (13%) patients, which consisted mainly of haemorrhage and fistula formation. The brachytherapy dose was prescribed 10 mm from the centre of the applicator. Furthermore, Kulhavy et al. (1995) presented in his study that 12-15 Gy is the optimal dose for single HDR brachytherapy.

Skowronek et al. (2004) reported results after HDR brachytherapy treatment for palliative treatment. The authors also concluded that patients with a higher Karnofsky Performance Status, smaller tumour size and a lower clinical stage had a longer survival. Complications in form of esophagobronchial fistula occurred in 9 patients (10%) during the first 6 months. Furthermore, an association between fistula occurrence and low Karnofsky score and tumour size was noted. The brachytherapy dose was prescribed at 10 mm from the centre of the applicator.

Sur et al. (2002) presented a randomised trial where HDR brachytherapy was received with a dose and fraction schedule of 18 Gy, 6 Gy/fraction and 16 Gy, 8 Gy/fraction. The total dose of 18 Gy was delivered during 5 days, one fractional dose every second day and total dose of 16 Gy was delivered during 3 days, one fractional dose every second day. The dose was prescribed 10 mm from the applicator centre. No significant difference in dysphagia relief, overall survival or complications was observed between the two study arms.

Table 5. Overview of studies of palliative intraluminal brachytherapy treatment for oesophageal cancer.

Author	*n*	Total dose (fractional dose)	Dysphagia improvement, (recurrent dysphagia)	Complications	Survival (median)
Rosenblatt et al. (2010)	109	16 Gy (8 Gy/fraction)	66.7 %[b]	Fistulae (7%)	188 days
	110	16 Gy (8 Gy/fraction)[a]	82.7%[b]	Fistulae (19%) Dilation (14%)	
Bergquist et al. (2005)	31	21 Gy (7 Gy/fraction)		Perforation (6%) Fistulae (3%)	106 days
Homs et al. (2004)	101	12 Gy (single fraction)	73% (43%)	Major complications (13%), minor complications (8%)	155 days
Skowronek et al. (2004)	91	22.5 Gy (7.5 Gy/fraction)	(80%)	Esophagobronchial fistula (10%)	246 days
Sur et al. (2002)	120	16 Gy (8 Gy/fraction)	?[c]	Strictures 11% Fistulae 10%	207 days
	112	18 Gy (6 Gy/fraction)	?[d]		273 days

[a]Additional external beam radiotherapy 30 Gy, 3 Gy/fraction
[b]One year dysphagia relief survival
[c]The median dysphagia free survival was 182 days
[d]The median dysphagia free survival was 238 days

2.4.3 Applicator

The diameter of the applicator used for intraluminal brachytherapy of oesophageal cancer has a crucial role on the dose distribution to the tissue, especially the mucosa. The ABS recommends an applicator with an external diameter between 6-10 mm. As above-mentioned, the dose gradient of the brachytherapy sources is very steep and a diameter narrower than 6 mm will contribute to high doses to the mucosa and possibly fistula developments and ulceration. Furthermore, a diameter greater than 10 mm can increase the risk of abrasions and perforations of the oesophagus.

2.5 Imaging techniques for dose planning

In current treatments of oesophageal cancer endoscopy combined with planar x-ray imaging is used to visualise the tumour and treatment trajectory (Figure 5). Due to uncertainties in the tumours proximal and distal boarders, a longitudinal margin of 20-30 mm is applied in both directions to include possible microscopic disease (Gao et al., 2007). In addition to the lack of accuracy in tumour delineation, the imaging technique fails to provide any information about the tumour volume, which can lead to inadequate coverage of the treatment volume. A study performed by Homs et al. (2004) showed that 43% of the patients treated with a single dose brachytherapy presented persistent or recurrent dysphagia caused by tumour persistence or tumour regrowth. This is most likely due to an inadequate coverage of the treatment volume and unwanted dose exposure to healthy parts of the oesophagus. Introducing 3D imaging a more accurate dose

coverage of the target volume can be obtained. When dose planning with 3D images the ordinated dose is prescribed to the target volume and the dose coverage of the tumour can be evaluated by the use of dose volume histogram (DVH) parameters. Additionally, the dose to the OARs can be evaluated by the DVH parameters (Potter et al., 2006).

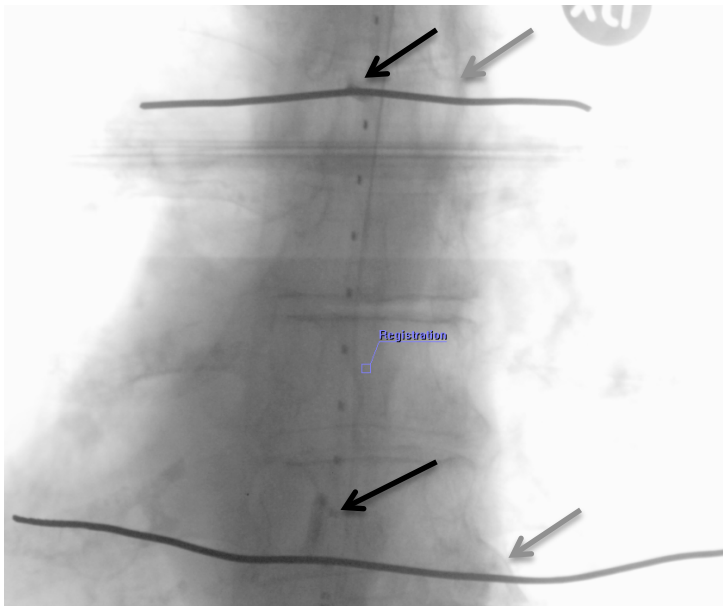


Figure 5. X-ray image used for treatment planning, visualising clips that marks the distal and proximal boarders of the tumour (black arrows) and a marker wire that presents the dwell positions of the source. External lead skin markers are also visualised in the image (grey arrows).

The conventional imaging technique for 3D dose planning is computer tomography (CT). Studies have demonstrated difficulties in to accurately distinguish the proximal and distal margins of oesophageal tumours from CT images due to the poor soft tissue contrast. A more accurate estimation of the longitudinal tumour extent can be obtained from an endoscopic ultrasound (EUS) examination, but unfortunately the information obtained from the EUS is difficult to translate to CT images (Muijs et al., 2010). Using positron emission tomography (PET) with ^{18}F-fluoro-deoxy-D-glucose (FDG) radiotracer functional information based on metabolic activity can be obtained. Combining the functional information with the anatomical information from a CT the visualisation of the tumour may be improved. However, not enough studies have been made to implement PET/CT as an imaging technique for oesophageal tumour delineation in radiotherapy and further clinical validation is needed (Leong et al., 2006, Muijs et al., 2010).

Magnetic resonance (MR) imaging has shown to be useful in delineation of the tumour and organs at risk for numerous of clinical sites such as the prostate, cervix and head and neck. MR imaging provides a great contrast in soft tissue and distinction of tumour and normal tissue. High-resolution T2-weighted MR images have shown to provide detailed images of the oesophageal wall and surrounding structures (Riddell et al., 2007). However, there are some technical difficulties regarding imaging of the oesophagus due to motion artefacts from

blood flow in the aorta and the respiratory and cardiac movements. To reduce respiratory motion technical innovations for the compensation of respiratory and cardio motions have been introduced (van Rossum et al., 2015, van Rossum et al., 2013).

3. Method and material

3.1 Current treatment methodologies in Scandinavia

To find out which methodologies are used today to treat oesophageal cancer with brachytherapy in Scandinavia, a questionnaire was created. The questionnaire was sent to five hospitals in Sweden, three in Denmark and one in Norway and Finland respectively. The questionnaire was sent through a survey and included 12 questions (Appendix I).

3.2 MR imaging

The next step was to investigate the possibility to use MR as an imaging technique for brachytherapy of oesophageal cancer. The MR imaging was performed at the Oncology Department at Skåne University Hospital in Lund on a 3.0 T scanner from GE Healthcare, located next-door to the brachytherapy treatment room. The imaging part of this study included a total of six patients with oesophageal cancer. The first four patients were scanned with T2-weighted inversion recovery fast spin echo (IR FSE) sequences but due to poor image quality the two latter patients were scanned with a different sequence, T2-weighted fast recovery fast spin echo (FRFSE) sequences. The oesophagus was scanned in the sagittal plane for assessment about the cranio-caudal tumour extent and in the axial plane for assessment on tumour depth and ingrowth to nearby structure. Furthermore, to compensate for the respiratory motion a navigator that tracks the movement of the diaphragm was used. By following the movement of the diaphragm, the scanning was triggered when the diaphragm was on its end position. CINE scan was performed in the sagittal and axial planes for visualisation of the tumours movement. Additionally, the MR-images of patient number 5 were compared with the patient's CT images. An experienced radiologist evaluated the obtained images regarding image quality and the ability to delineate the tumour. This study was approved by the Regional Ethics Board of Lund, Sweden (EPN Lund, Dnr 2013/742).

3.3 Applicator

An oesophageal applicator would be ideal to use since its construction is made for brachytherapy of oesophageal cancer. However, after some research, an MR safe oesophageal applicator could not be found and a duodenal tube was used as an applicator (Figure 6). In order for the chosen duodenal tube to work in this setting, some modifications had to be done. Since the tip of the duodenal tube is important to be visualised on an MR image, in order to decide dwell positions for the radioactive source, the duodenal tube had to be sealed on its distal end.

Furthermore, the tube was made out of a plastic material and thus not visualised on MR images. In order to make the tube visible in MR images, the tube was as filled with contrast agents with different concentration. Measurements were performed with a 0%, 2% and 4% concentration of gadolinium (Gd) in a saline solution.

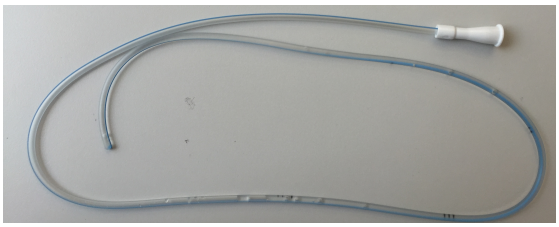


Figure 6. Duodenal tube used as an oesophageal applicator with a sealed distal end.

3.4. Dose planning

Dose planning on MR images was performed for one patient, patient number 5, in BrachyVision (version 13.0, Varian Medical Systems). An oncologist delineated the oesophageal tumour and the OARs consisting of the aorta, heart, spinal cord and trachea. The dose planning was performed using two methods. In the first method, the ordinated dose was prescribed at 10 mm from the applicator centre. In the second method, the dose planning was based on manual optimisation of the dwell times until adequate dose coverage (approximately 100%) of the tumour was reached.

The dose to the oesophageal tumour and the OARs was assessed by the use of DVH parameters. The dose to the oesophageal tumour was assessed by the minimum dose delivered to 90% ($D_{90\%}$) and 98% ($D_{98\%}$) to the tumour volume and the volume that received 100% of the ordinated dose ($V_{100\%}$), i.e. 7.5 Gy. The dose to the OARs was evaluated by the minimum dose in the most irradiated tissue volume, of $2cm^3$ (D_{2cc}), adjacent to the applicator.

3.5 Dose and fractional schedule

The effective dose for different fractionations schemes were evaluated by calculation of the biological effective dose (BED), using

$$\mathrm{BED} = nd\left(1 + \frac{d}{\alpha/\beta}\right) \quad (1)$$

where n is the number of fractions, d is the dose per fraction and the α/β ratio is the parameters of the linear quadratic model of cell survival.

Equivalent dose in 2 Gy per fraction (EQD_2) was calculated for the dose and fractional schedules mentioned in Table 3 and Table 5 using

$$\mathrm{EQD}_2 = \frac{\mathrm{BED}}{1+\frac{2}{\alpha/\beta}} \quad (2)$$

where the α/β ratio for the oesophageal tumour was equal to 10. The dose and fractional schedule was then decided in consensus with the brachytherapy oncologists.

3.6 Clinical test patient

Patient number 6 was scheduled to undergo intraluminal brachytherapy of oesophageal cancer during the course of this thesis. Two clips to mark the tumour's macroscopic longitudinal extent were inserted during endoscopy. After the endoscopy, the applicator was inserted in the oesophagus through the patient's nose. Prior to the treatment, the applicator was filled with a saline solution for visualisation on the MR images. Inside the applicator a bronchial catheter was inserted, in where the source wire (radioactive source) will run. To be certain that the bronchial catheter is in the bottom of the applicator, the catheter was marked when it reached the bottom. The bronchial catheter was cut to a length corresponding to the source wire's length by a so-called length cutter.

The patient then underwent an MR scan for the purpose of visualising the applicator in vivo and for further optimisation of the MR sequence. When the MR imaging was completed, the patient was transferred to the treatment room to receive brachytherapy. A planar x-ray imaging, fluoroscopy, was used for treatment planning. The dose planning x-ray image included visualisation of the clips and a marker wire that showed the dwell positions of source (Figure 5). Longitudinal margins of 20 mm in the proximal and distal direction were added and the dose was prescribed at 10 mm from the applicator centre. The patient was ordinated a total dose of 22.5 Gy with a weekly fractional dose of 7.5 Gy.

4. Results

4.1 Questionnaire

The questionnaire was sent out to 10 hospitals in total and 6 hospitals (60%) responded. None of the hospitals used 3D imaging for dose planning of oesophageal cancer.

Uppsala University Hospital only treats oesophageal cancer with HDR brachytherapy in the palliative setting. High-dose rate brachytherapy is given when external beam radiotherapy and concurrent chemotherapy are unfavourable or no longer an option. Brachytherapy is consequently used as a sole treatment modality. Planar x-ray imaging is used for dose planning and the patients receive a total dose of 5-15 Gy, with a weekly fractional dose of 5 Gy.

Sahlgrenska University Hospital also treats patients in the palliative setting with HDR brachytherapy, and they also use planar x-ray image for dose planning.

Sahlgrenska combines external beam radiotherapy with brachytherapy and an EBRT dose of 18-20 Gy with 2 Gy/fraction is given. Brachytherapy is given in different dose schedules, where a total dose of 14 Gy, with 7 Gy/fraction is must common.

Karolinska University Hospital and Kuopio University Hospital have not treated oesophageal cancer with brachytherapy during the last years. However, Karolinska University Hospital is currently discussing new routines regarding treatment of oesophageal cancer with brachytherapy. Furthermore, neither Rigshospitalet in Copenhagen or Västerbotten County Council treat oesophageal cancer with brachytherapy.

4.2 MR imaging

The images from the first four patients were not considered to have a good enough image quality to be used for dose planning (Figure 7). The high degree of motion artefacts made it hard to visualise the tumour. Moreover, the images were blurry and the oesophagus tumour was difficult to distinguish from the surrounding tissue.

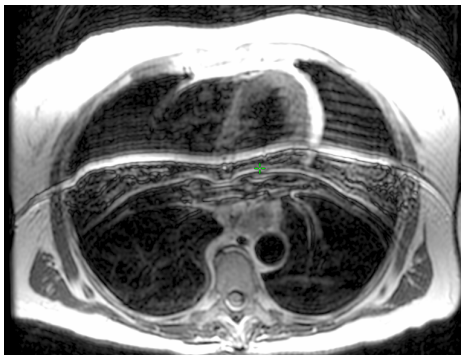


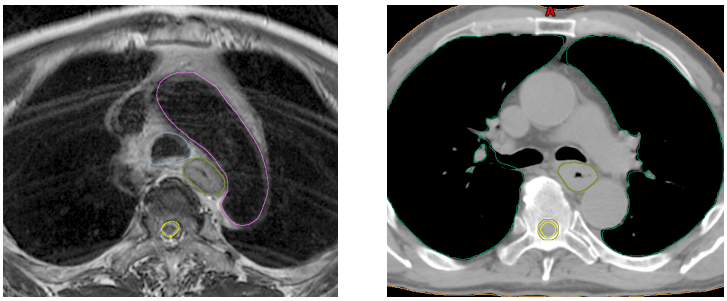
Figure 7. T2-weighted MR image with an IR FRSE sequence. The motion artefacts in the image make it difficult to delineate the oesophageal tumour. These images were not used for treatment planning.

The MR sequence used for the two latter patients, i.e. the FRFSE sequence, provided a better image quality and the tumour could be visualised and outlined (Figure 8a). The parameters for the FRFSE sequence are presented in Table 6.

Table 6. Parameters used for MR scans in the sagittal and axial plane.

Parameters	Sagittal plane	Axial plane
Slice thickness	3 mm	3 mm
Spacing	10 %	0 %
Pixel size	0.9 mm × 0.9 mm	1 mm × 1mm
Echo time	102 ms	102 ms
Parallel imaging acceleration factor	3	4
Frequency encoding direction	Sup/Inf	R/L

The MR and CT images for patient number 5 are shown in Figure 8. The radiologist and oncologist concluded that the tumour was more easily delineated in the MR images. In the MR images the oesophageal tumour can be more clearly distinguished from the mediastinum, i.e. the adjacent tissue. Moreover, the residual motion artefacts in the MR image were deemed not to disturb the visualisation of the tumour.



A B

Figure 8. The oesophagus tumour (green) delineated on an MR image (A) and on a CT image (B). In the MR image the OARs have been delineated, aorta (pink), spinal cord (yellow) and the trachea (blue).

4.3 Applicator

Measurements with a T2-weighted sequence were performed for different concentrations of Gd in a saline solution are presented in Figure 9. The highest signal was obtained when no Gd was used in the saline solution (can to the left). Since T2-weighted images are used to visualise the oesophagus, a contrast agent that reduces the T1-relaxation time was desired. This because a reduced T1-relaxation time increases the signal in T2-weighted images, hence the use of Gd. However, as it appears in the images the contrast also reduces the T2-relaxation time and therefore there was no advantage of using Gd in this setting.

4.4 Dose planning

DVH histogram for the oesophageal tumour for the two different methods to perform dose planning is presented in Figure 10. The DVH parameters for the oesophageal tumour are presented in Table 7 and for the organs at risk i.e. the heart aorta, trachea and spinal cord are presented in Table 8.

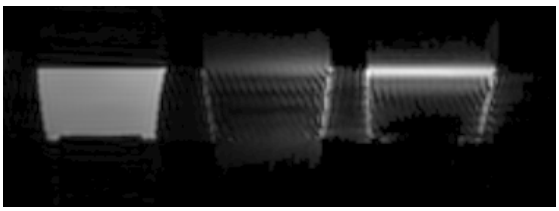


Figure 9. Measurements with different concentrations of Gd in a saline solution; 0% Gd to the left, 2% Gd in the middle and 4% Gd to the right.

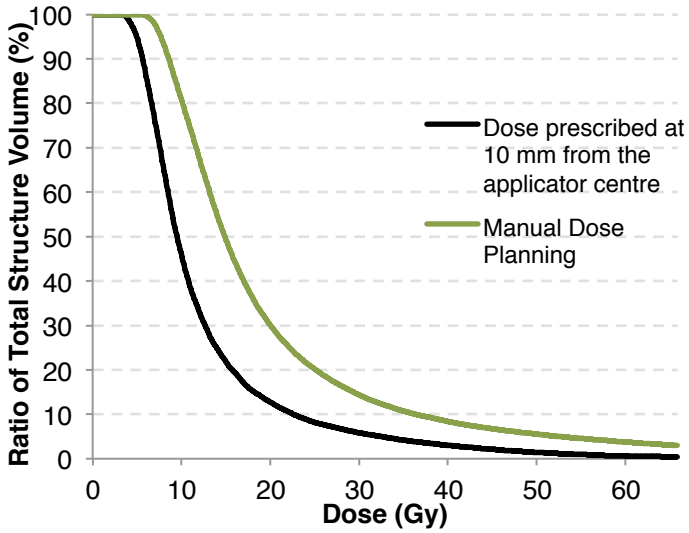


Figure 9. The dose-volume histogram for the oesophageal tumour when the dose is prescribed at 10 mm from the applicator centre (black line) and when the dose planning is performed manually, i.e. until dose coverage was reached to approximately 100% of the tumour (green line).

Table 7. Dose-volume histogram parameter for the tumour when dose planning is performed with different two methods.

	$D_{98\%}$	$D_{90\%}$	$V_{100\%}$
Dose prescribed at 10 mm from the applicator centre	4.3 Gy	5.6 Gy	70 %
Manual dose planning	6.9 Gy	8.5 Gy	95%

Table 8. The dose to 2 cm^3 of the risk organs when dose planning is performed with two different methods.

	Aorta	Heart	Spinal cord	Trachea
Dose prescribed at 10 mm from the applicator centre	4.8 Gy	3.7 Gy	1.4 Gy	4.6 Gy
Manual dose planning	6.9 Gy	5.0 Gy	2.0 Gy	7.3 Gy

Sagittal and transversal images for the two dose planning methods are shown in Figure 11 and Figure 12. The blue line in the figures represents the planning target volume (PTV) and the white dotted line in Figure 11 shows the slice of the transversal images. A difference in the dose distribution between the two dose planning methods can be visualised in Figure 11, where improved dose coverage to the PTV is obtained when the dose planning is performed manually. The cutoff of the PTV in the images is a consequence due to inadequate scanning of the tumour in the transversal plane, where the oncologist outlined the tumour. In

the transversal images an improved dose coverage to the PTV for manual dose planning can also be visualised.

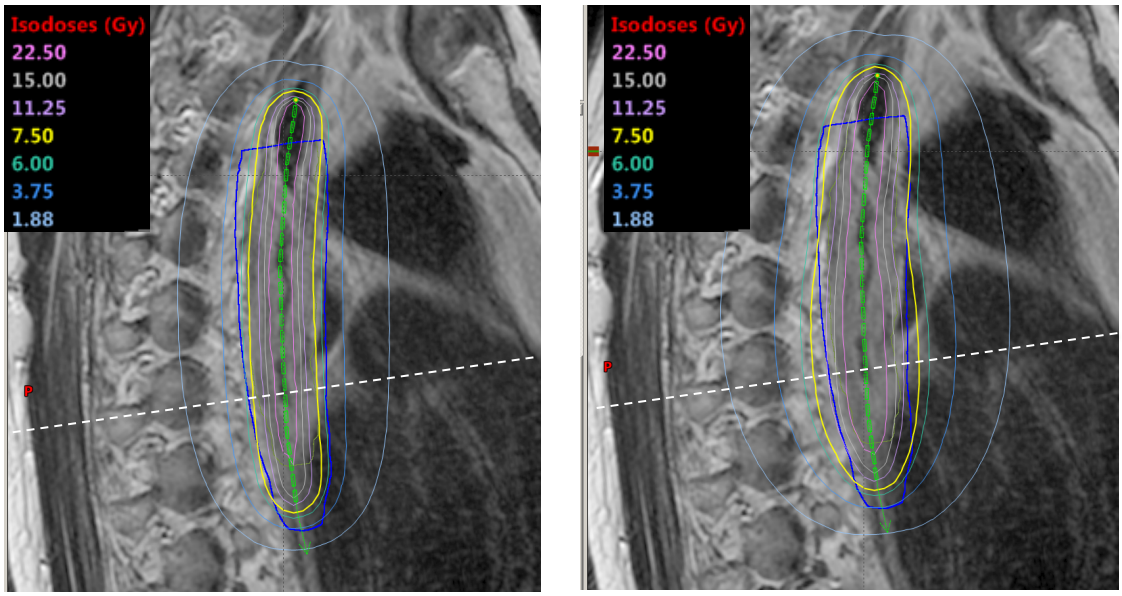


Figure 10. Sagittal isodose images where the dose is prescribed at 10 mm from the applicator centre (left image) and where the dose planning is performed manually (right image). The blue line presents the PTV and improved dose coverage to the PTV is obtained when the dose planning is performed manually. The white dotted line shows the slice of the transversal image in Figure 12.

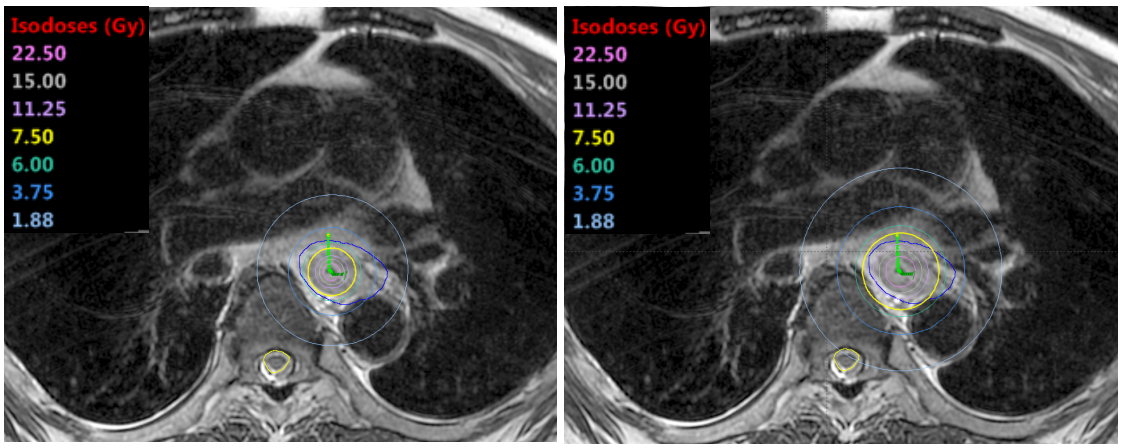


Figure 11. Transversal isodose images where the dose is prescribed at 10 mm from the applicator centre (left image) and where the dose planning is performed manually (right image). The ordinated dose at 7.5 Gy is shown in yellow and the PTV in blue.

The dose as a function of the distance for the two dose planning methods for a representative slice is shown in Figure 13. The dose at the applicator surface for an applicator with the outer diameter of 6 mm is 26 Gy when the dose is prescribed at 10 mm from the applicator centre. Furthermore, when the dose planning is performed by manual optimisation of the dwell times the dose at the applicator surface is 39 Gy. In the case of the clinical test patient, an applicator with an outer diameter of 4.7 mm will result in an applicator surface dose of 34 Gy and 58 Gy, respectively.

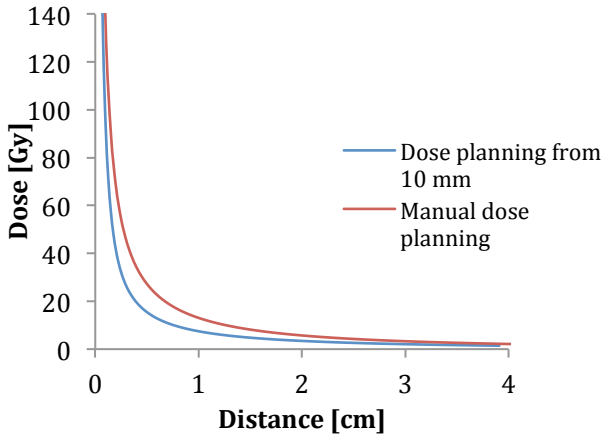


Figure 13. The dose as a function of the distance for two different ways of dose planning: when the dose is prescribed at 10 mm from the applicator centre and when the dose is manually optimised by adjusting the dwell times until tumour coverage is reached.

4.5 Dose and fractional schedule

The calculated EQD_2 and the point where the dose was prescribed are presented in Table 9 and Table 10 for curative and palliative treatments, respectively. The outer diameter of the applicator for the curative treatment is presented in Table 9.

Table 9. The EQD_2 dose for the different dose and fractional schedules presented in Table 3.

Author	EQD_2	Dose prescription	Outer diameter of the applicator
Muijs et al. (2012)	76 Gy	10 mm from the applicator centre	6 mm
Murakami et al. (2012)	70 Gy	5 mm from the applicator surface	16-20 mm
Tamaki et al. (2012)	73 Gy[a] 70 Gy[b]	5 mm from the applicator surface	15-20 mm
Gaspar et al. (2000)	69 Gy	10 mm from the applicator centre	4-6 mm

[a]LDR brachytherapy
[b]HDR brachytherapy

Table 10. The EQD_2 dose for the different dose and fractional schedules presented in Table 5.

Author	EQD_2	Dose prescription
Rosenblatt et al. (2010)	57 Gy / 24 Gy	10 mm from the applicator centre
Bergquist et al. (2005)	30 Gy	10 mm from the applicator surface
Homs et al. (2004)	11 Gy	10 mm from the applicator centre
Skowronek et al. (2004)	33 Gy	10 mm from the applicator centre
Sur et al. (2002)	24 Gy / 24 Gy	10 mm from the applicator centre

Based on the results from Table 9 and Table 10 the dose and fractional schedule that will be used at our clinic is the following:

- For curative treatments, HDR intraluminal brachytherapy will be delivered as a boost following external beam radiotherapy. The external beam radiotherapy dose of 50-60 Gy will be given in 2 Gy fractions, five times per week, followed by a brachytherapy dose of 10 Gy with a weekly fractional dose of 5 Gy. The total EQD_2 is 63-73 Gy.

- For palliative treatments, HDR intraluminal brachytherapy will be delivered as a sole treatment modality. For patients with a longer life expectancy, a total dose of 22.5 Gy with a weekly fractional dose of 7.5 Gy will be given (EQD_2 = 33 Gy). However, for patients with shorter life expectancy, a single dose of 10 Gy will be given (EQD_2 =17 Gy), which can be repeated once or twice if necessary.

4.6. Clinical test patient

The MR images from the patient that underwent intraluminal brachytherapy for oesophageal cancer are presented in Figure 14. The oesophageal tumour could be visualised in the images, but there were some difficulties in determining the tumours proximal and distal boarders due to the motion artefacts in the image. No dose planning was performed on these images. For this patient an applicator with an outer diameter of 4.7 mm was used due to the patient's narrow lumen and the applicator was visualised on a transversal image. Furthermore, the diameter of the bronchial catheter was 1.67 mm.

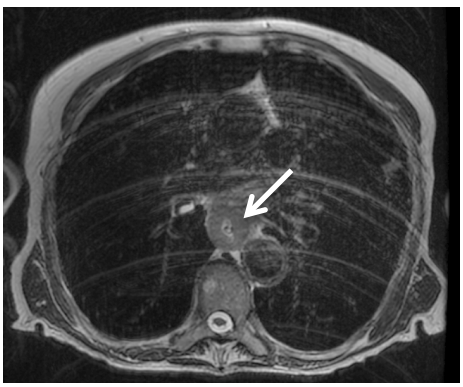


Figure 12. T2- weighted MR image with the applicator in vivo (white arrow).

5. Discussion

5.1 MR imaging

MR imaging of oesophageal cancer has over last years provided a poor imaging quality due to motion artefacts (van Rossum et al., 2013). To reduce the motion artefacts, faster sequences with cardiac and respiratory gating have been recommended (van Rossum et al., 2015). In this study a T2-weighted gated FRFSE was used to visualise the oesophageal tumour. The sequence provided a good image quality making it possible to delineate the oesophageal tumour. However, one limitation with this sequence is that the image quality is strongly dependent on the navigator that triggers the scanning. For the navigator to achieve its function, the patients must have a respiration with deep breathing and a stable respiratory cycle. The effect on the image quality for patients unable to fulfil these criteria can be seen in Figure 14. The patient was breathing very superficially, with difficulties to take deep breaths, hence the motion artefacts. The need of a stable respiratory cycle and a respiration with deep breathing could become a problem since the majority of patients receiving brachytherapy due to oesophageal cancer, will be in the palliative setting. These patients are therefore usually in a poor health condition and difficulties in deep breathing may occur. One way to get around this is by instructing the patients when to inhale and exhale while they are lying in the MR camera. Additionally, prior to the scanning, the patient could receive breathing training. Furthermore, since the MR sequence has been performed on two patients, a larger sample is needed for further optimisation of the MR sequence.

Accurate tumour delineation is essential for optimisation of the treatment planning. The ability to distinguish the oesophageal tumour from surrounding tissue is therefore of high importance. The great soft tissue contrast MR imaging provides makes it desirable for dose planning. Achieving accurate tumour delineation may provide an improvement in local control and less treatment related toxicities, which will ultimately lead to better treatment results and a better quality of life (van Rossum et al., 2015).

When dose planning is performed manually, an increased dose to the adjacent organs may be obtained as a consequence due to improved dose coverage to the tumour volume (Table 7 and Table 8). Moreover, the dose to adjacent organs is highly dependent on the size and location of the tumour. The advantage with MR based brachytherapy is the ability to evaluate the dose to the organs at risk and the tumour volume by DVH parameters. However, no DVH recommendations or constraints for the organs at risk or the oesophageal tumour have been found in the literature.

Uncertainties that can occur in the MR images are susceptibility artefacts, which arise in areas between air and tissue, along with geometric distortion due to nonlinearities. By increasing the frequency bandwidth in the images, the susceptibility artefacts can be reduced. Moreover, geometric distortion due to nonlinearities in the gradient system is mainly associated with the greater field of views. For scanning of the oesophagus the average value of the geometric distortion is less than 1 mm, according to phantom measurements performed on

the 3.0 T MR-camera. In general, geometric distortion due to nonlinearities leads to pixel shifts and intensity variations on MR images. In this study the geometric distortion on the reconstruction of the applicator has not been investigated, focus was put on the visibility of the applicator.

5.2 Applicator

The applicator has a crucial role in the determination of the accuracy of dose delivery. The dose of the radioactive source decreases with the inverse square of the distance, and high doses to the mucosal can be reached (Figure 13). Since treatment-related complications are associated with high mucosal doses the diameter of the applicator has an important role (Folkert et al., 2013). In the curative setting, a diameter of at least 10 mm is recommended (GEC ESTRO Handbook of Brachytherapy, 2002). However, in the palliative setting the diameter of the applicator is dependent on the patient's lumen and sometimes an applicator with a diameter less than the recommendations must be used. Moreover, the late complications are not of importance for palliative treatments.

Another aspect that requires attention is the centration of the source wire in the oesophageal applicator, which is a limitation with the applicator introduced in this study. The bronchial catheter will help with the centration of the source wire since it will transverse the catheter. However, the bronchial catheter also has the ability to move radially in the duodenal tube. The degree of movement is dependent on the diameter of the duodenal tube, where the radial movement increases with the size of the duodenal tube. For patient 6 in this study, the inner diameter of the duodenal tube that was used was 3.5 mm and the bronchial catheter with an outer diameter of 1.67 mm could theoretically move 1.83 mm radially.

Oesophageal applicators on the market today have the possibility to centre the source wire, but the applicators found are not MR safe. Manufacturing MR safe oesophageal applicators would improve the accuracy of dose delivery.

5.3 Dose planning

The two-dimensional imaging technique that is used for dose planning today fails to provide any information about the tumour volume. The dose planning is performed based on clips that mark the distal and proximal boarders of the tumour and prescribed at 10 mm from the applicator centre. By introducing 3D imaging, the tumour volume can be visualised. DVH parameters can also be obtained and the dose coverage to the tumour and organs at risk can be evaluated. In the DVH parameters for the oesophageal tumour presented in Table 7 an under-dosage of about 30 % of the tumour volume was obtained when the dose was prescribed at 10 mm from the applicator centre. A clear benefit with manual dose planning based on dose coverage to the tumour was thus noted for this patient. Obtaining inadequate dose coverage to the tumour is not surprising since tumours are generally different in shapes; therefore, it is essential that the tumour volume should be taken into consideration for dose planning. Improving

the tumour coverage could potentially lead to better treatment results and better patient comfort/quality of life.

To the author's knowledge, this is one of the first clinical brachytherapy of oesophageal cancer utilizing 3D imaging. To date, no information regarding DVH recommendations and constraints to the target volume or the organs at risk have been published. Future studies are thus needed for DVH recommendations and constraints to be determined.

For further development of this methodology, collaborations have been made with the University Medical Center in Utrecht. As for today, no patients with oesophageal cancer have yet received treatment with MR as an imaging technique for dose planning in Utrecht. However, a study protocol has been carried out.

5.5 Dose delivery

Before MR-based brachytherapy can be delivered uncertainties regarding the dose delivery needs to be further investigated. One uncertainty is the movement of the applicator from the moment the MR imaging is performed until the dose is delivered. The distance from the applicator tip and the tumour is of great importance since the dose planning is based on this distance. While the clips can be visualised on an MR image, an x-ray image can be used as a reference image to ensure correct positing. By inserting a marker wire in the applicator, the distance from the first dwell position and the tumour can be visualised on an x-ray image and an adjustment can then be made to correlate to the MR planning images. Moreover, margins can be added in the cranio-caudal direction to compensate for uncertainties. Further studies are needed to ensure a safe and accurate dose delivery.

5.6 Dose and fractional schedule

The optimal dose and fractional schedule for oesophageal cancer have yet to be reached. Studies with different dose and fractional schedules have been reviewed and summarised in section 2.4. By calculating the EQD_2 and by studying the point where the dose was prescribed and the treatment results, fractional and dose schedules for curative and palliative treatments have been determined for this clinic. For manual dose planning, the OARs can receive high doses due to improved dose coverage to the tumour volume compared to when the dose is prescribed at a specific distance. Therefore, a consideration between the dose to the tumour volume and the OARs has to be made if the dose to the adjacent organs is considered to be too high.

In summary, the ordinated dose is dependent on the patient's health condition and the tumour size and location. In palliative treatments the secondary effects on the OARs is of less importance.

6. Conclusion

In this study, a new methodology utilising MR for treatment of oesophageal cancer with brachytherapy has been investigated. The major benefit with MR based brachytherapy is the improved tumour visualisation, manifesting DVH parameters enabling dose coverage of the tumour. The next step is to construct clinical studies to determine dose-volume recommendations and constraints to the tumour and organs at risk based on this methodology.

7. Acknowledgement

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Appendix I

Brachytherapy of esophageal cancer

0%

1a. What type of imaging technique do you use when dose planning patients with esophageal cancer?

- ☐ CT
- ☐ MRI
- ☐ Fluoroscopy
- ☐ Other

1b. Have any observed restrictions with your current imaging technique occured? If yes, is a supplementary method used?

2. How do you decide which patients to treat? Do you follow any guidelines?

3a. What histology do your patients have? Please specify the approximate percentage in the box to the right.

- ☐ Adenocarcinoma
- ☐ Squamous cell carcinoma
- ☐ Other

3b. Is there any difference in treatment between different type of histology?

4. What kind of treatment technique do you use?

- ☐ HDR
- ☐ PDR
- ☐ Other

5. What applicator do you use and what is the size of its diameter?

6. What fractions and doses do your patients get treated with?

7. What dose-volume criteria are used for tumour and organs at risk?

8. In which purpose do you treat esophageal cancer?

- ☐ Curative
- ☐ Palliative
- ☐ Comment

9a. Is brachytherapy combined with external radiation therapy?

- ○ Yes
- ○ No

9b. If yes, what fractions and doses do the patients receive?

10. How is the treatment performed? Are clips used to define the tumour´s boarders?

11. Has any side effects occurred due to the treatment?

12a. Do you follow up your patients after the treatment has finished?

- ○ Yes
- ○ No

12b. If yes, what is the approach?

Thank you for answering this questionnaire. Please fill in your name and the hospital you represent in case I need to ask further questions.

Name

Hospital

Submit