Organ motion in different time aspects in esophageal cancer radiotherapy – is a novel fiducial marker feasible?

Master thesis

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Spring 2018

Forord

Arkivfoto fra Bergens Tidende, tatt i Haugeveien på 1950-tallet, Publisert i Bergens Tidende 8.7.2013

Ideen til dette prosjektet var et resultat av en invitasjon fra Dr. Pham til et møte ved Medisinsk avdeling, der Simon Brouwers fra Cook Medical demonstrerte en ny nål for implantasjon av markører i spiserøret ved hjelp av endoskopisk ultralyd. Dette var en etterlengtet mulighet da det er store utfordringer med å fastslå tumors avgrensning for å definere et passende behandlingsvolum ved strålebehandling av kreft i spiserøret. Ved andre kreftdiagnoser har det vært vellykket å bruke markører som surrogat for tumor, for en mer presis strålebehandling, jeg ble derfor nysgjerrig på hvordan vi kunne nyttiggjøre oss markørene i bildeveiledet strålebehandling hos pasienter med spiserørskreft. Med suksessen ved bruk av gullmarkører i prostata i tankene kan dette ha virket liketil og greit, men i motsetning til prostata, som er velavgrenset og trivelig rund, er spiserøret langt og krokete, og klemt mellom organer som puster og slår uten stans. Det var ikke noe annet å gjøre enn å forsøke å beskrive hvordan markørene oppførte seg i disse omgivelsene. Nå er det opptil leseren å bedømme om dette er gjort på en tilfredsstillende måte.

Uansett, mine kollegaer tok godt imot ideen og har bidratt med utallige diskusjoner, ideer og gode råd underveis.

Først av alt vil jeg rette en **stor takk** til min hovedveileder Liv Bolstad Hysing for å ha stilt seg til disposisjon med sin faglige tyngde og hjelp og oppmuntring underveis. Takk også til Grete May Engeseth som var vikar for Liv ved hennes fravær. og til Una Ørvim Sølvik som var intern veileder fra Universitetet i Bergen. Jeg vil gjerne få rette en takk til Nils Glenjen og Khanh Pham for å la meg "kjanke[1]" prosjektet deres, gjennom god hjelp med søknad til Regional estisk komité og diskusjoner rundt temaet underveis. Jeg er også takknemlig for god tilrettelegging og støtte fra min nærmeste leder, Dagfinn Brosvik. Mine utmerkete stråleterapeut-kollegaer ved Haukeland Universitetssjukehus, spesielt John Vidar Hjørnevik, Else-Gunn Bø Fjell og Turid Husevåg Sulen, takkes for gode faglige innspill, oppmuntring og hjelpsomhet.

Til slutt vil jeg takke min familie for å ha holdt ut med en mor og ektefelle som har vært ganske fraværende både fysisk og i tanken, og likevel på alle måter støttet min innsats for å gjennomføre dette mastergradsprosjektet. Uten den støtten hadde dette ikke blitt noe av.

[1] Lokalt uttrykk fra Bergen, som refererer til en høy-risikosport utført av ungdommer i Bergen i det de holdt seg fast på støtfangeren til bussen og skled på skoene.

Content

Sammendrag

Introduksjon: En ny markør ble undersøkt for bruk i bilde-veiledet strålebehandling (IGRT) for pasienter med spiserørskreft, ved å karakterisere inter- og intra-fraksjonell organbevegelse.

Materiale og metode: Tolv pasienter med spiserørskreft som ble tilbudt strålebehandling deltok i denne pilotstudien. Markører (1-6 per pasient) ble implantert EUS-veiledet før planleggings CT (CT_p) med tillegg av 4DCT, og pasientene gjennomgikk IGRT (23-33 fraksjoner, 41,4-66,0 Gy) med daglig cone beam computed tomography (CBCT, n=302) og/eller ortogonale planare bilder (2D/2D, n=61) og et repetert CT- og 4DCT skann siste behandlingsuke. Markørenes tilstedeværelse, dekning av planning target volume (PTV), senterposisjon og ekstremposisjon for markørene på CBCT ble registrert per pasient og fraksjon. Inter- og intra-fraksjonell bevegelse ble karakterisert i alle pasienter og gruppert etter markørlokalisasjon.

Resultater: Ved behandlingsslutt var 92 % av markørene som var synlig på CT_p fremdeles tilstede. PTV tok høyde for variasjoner i markørenes posisjon i >95 % av behandlingsfraksjonene for 92 % av pasientene. Total 3D inter-fraksjonell variasjon var >1cm for 23 % og >0,5cm for 58 % av markørene. Median(IQR) intra-fraksjonell bevegelse for alle markører var 1,2cm (0,4cm) i longitudinal retning, 0,11cm (0,51cm) i ventral retning og 0,0cm (0,13cm) i lateral retning.

Konklusjon: Den undersøkte markøren kan være nyttig i IGRT ved spiserørskreft da tapet av markører underveis i behandling var begrenset. Inter- og intra-fraksjonell variasjon var betydelig, med størst bevegelse i longitudinal retning og mest uttalt i kaudale del av spiserøret.

Nøkkelord: Spiserørskreft, strålebehandling, markører, organbevegelse, intrafraksjonell variasjon, interfraksjonell variasjon, bildeveiledning.

Abstract

Introduction: A novel fiducial marker was explored for use in image-guided radiotherapy (IGRT) of esophageal cancer patients by characterizing inter- and intra-fractional organ motion.

Material and methods: Twelve esophageal cancer patients proposed for radiotherapy participated in this pilot-study. Makers (1-6 per patient) were implanted EUS- guided prior to radiotherapy planning CT (CT_p) with additional 4DCT, and the patients received IGRT (23-33 fractions, 41.4-66.0 Gy) with daily cone beam computed tomography (CBCT, n=302) and/or orthogonal planar images (2D/2D, n=61) and a repeated CT- and 4DCT the last treatment week. Marker presence, planning target volume (PTV) coverage, centroid position and extreme positions on CBCT were recorded per patient and -treatment fraction. Inter- and intra-fractional motion were characterized, in all patients and grouped according to marker location.

Results: At treatment end, 92% of markers visible at CT_p were still present. The PTV accounted for marker variation in >95% of treatment fractions for 92% of the patients. Overall 3D inter-fractional variation was >1cm in 23% and >0.5cm in 58% of the markers. Median (IQR) intra-fractional motion of all markers was 1.2 cm (0.4 cm) in the longitudinal, 0.11 cm (0.51 cm) in the ventral and 0.0 cm (0.13 cm) in the lateral direction.

Conclusion: The use of the investigated fiducial marker may be beneficial for IGRT in esophageal cancer as the marker loss during radiotherapy was limited. Inter- and intra-fractional variation was substantial with largest motion in the longitudinal direction and more pronounced in the caudal part of esophagus.

Keywords: Esophageal cancer, radiotherapy, fiducial markers, organ motion, interfractional variation, intrafractional variation, image guidance.

1. Introduction

Esophageal cancer has a growing incidence, with an increase of approximately 50% from 2005-2014 (Cancer Registry of Norway, 2015). Contrary to several other cancer types, the disease is expected to increase in the years to come (Napier et al., 2014). The disease is four times more common in men than in women. In Norway, 397 patients were diagnosed with esophageal cancer in 2015, including cancers in the esophagogastric junction (Frøland et al., 2016). This makes it the 8th most common cancer type. The disease is often diagnosed in advanced stage and the prognosis is therefore poor. Depending on how far the disease has progressed at diagnosis, localized disease, regional disease and disease with distant metastasis have a 5-year survival of 27%, 18% and 0%, respectively. The overall survival is 13.8% (Cancer Registry of Norway, 2015).

The primary treatment choice for curative treatment is surgery, but chemo radiation has also shown similar treatment results (Frykholm et al., 2011). About 20% of patients are eligible for surgical treatment (Johnson et al., 2015). Radiotherapy is offered as an option for curative treatment of stage I disease, as neoadjuvant treatment in combination with chemotherapy for stage II-III disease, and as palliative treatment. It has been estimated that around 80% of patients with esophageal cancer could benefit from radiotherapy, while the actually number of patients receiving radiotherapy is considerably lower (51% in U.S. and 31% in United Kingdom) (Delaney et al., 2004).

Technological achievements give possibilities for treatment refinement in radiotherapy. Image-guided radiotherapy has been proposed to have a major importance in increasing the cure rate by radiotherapy, because it provides better positioning and control with organ motion and changes. In patients with esophageal cancer the normal tissue effects have been dose limiting and a hinder for dose escalation. Image guidance in combination with implanted fiducial markers is a newer area of research in Haukeland University Hospital (HUH). The implantation techniques have been improved and a new preloaded needle for ultrasound-guided endoscopic implantation is being tested to aid

target delineation. This gave an opportunity to explore the possibility the implanted marker gave to refine treatment delivery trough image-guidance during radiotherapy.

1.1 Theoretical aspects

1.1.1 Anatomy and pathology

The esophagus extends from the upper esophageal sphincter at 15 cm from the incisors, descends behind the trachea and passes through the diaphragm at 38 cm, just in front of the aorta. Finally it enters the stomach at the esophagogastric junction through the lower esophageal sphincter at 40 cm from the incisors. It is divided in the cervical part, the upper-, mid- and lower thoracic part, and the esophagogastic junction, which reaches 2 cm distally from cardia (Figure 1-1). The anatomical site of a tumor is specified according to the epicenter of the tumor, and its extension is endoscopically measured from the incisors.

The esophageal wall has got two muscular layers and a loose layer of connective tissue named adventitia. It is surrounded by numerous vital organs like lungs, trachea, heart, aorta, spinal cord and stomach (Ellis and Mahadevan, 2013)(page 47-50). The surrounding organs can easily be invaded by an esophageal tumor due to the esophagus' absent serosa (Frykholm et al., 2011). Further, lymphatic spread throughout the lymph nodes depends on the depth of infiltration, and the direction of the spread follow the site of the tumor (Lordick et al., 2013). Distant metastases are most often found in the lungs, peritoneum and liver.

Histologically, the two main cancer types are adenocarcinoma (AC) and squamous cell carcinoma (SCC) (Cancer Registry of Norway, 2015). AC has a growing incidence and now represents nearly 80% of the cases, while the incidence of SCC is decreasing. Both histological types are related to lifestyle; SCC relates to high consume of tobacco and alcohol, while AC is associated with overweight and esophageal reflux (Frøland et al., 2016, Johnson et al., 2015). Adenocarcinomas that occur in the esophagogastric junction are often

classified according to Siewert's classification system, were the tumors with their epicenters placed within the proximal two cm of the junction are classified as Siewert type I/II (Rice et al., 2017). The tumor/node/metastasis (TNM) classification differs for the histological types and how the staging is performed (clinical, cTNM or pathological, pTNM) (Rice et al., 2017).

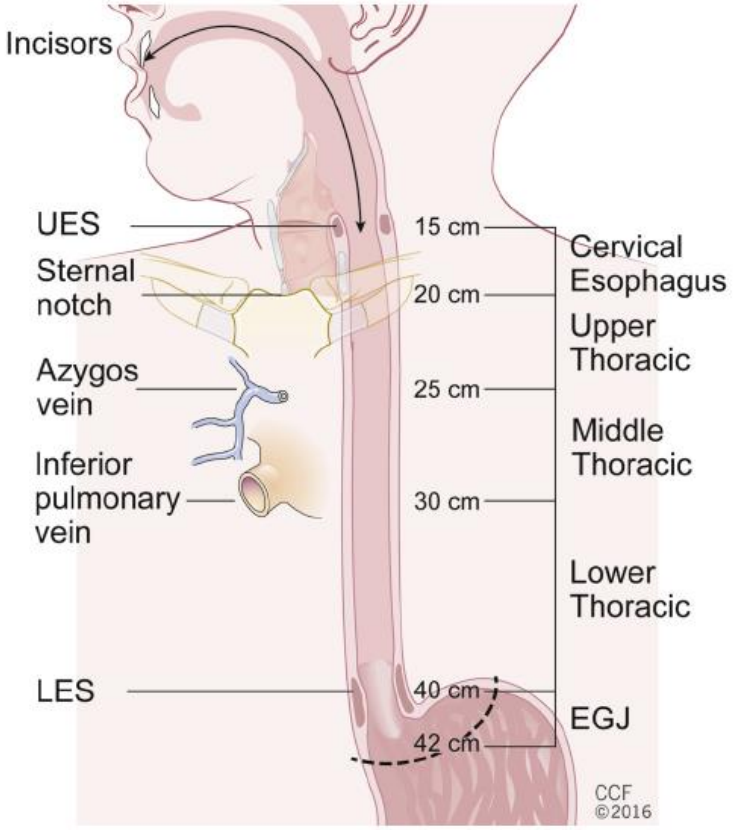

Figure 1-1-1: Anatomy of the esophagus. Illustration from(Rice et al., 2017)

1.1.2 Brief introduction to the physics and radiobiology in radiotherapy

Radiotherapy (RT) is used to treat medical conditions with ionizing radiation. A range of different technologies and radiation types are available, but here the focus will be on external beam therapy with megavolt (MV) photons. The most common treatment machine is the linear accelerator, which produces high energy radiation by accelerating an electron beam towards a target (Symmonds et al., 2012)(p125). When the electron beam reaches the target a beam of photons is produced. Modern accelerators most often deliver 1-2 photon energies in the range of 4-25 MV.

Passing through tissue the photons may pass straight through without interacting with the atoms, or it may be absorbed, scattered or a combination of both. The interactions cause ionizations, and scattered electrons may cause damage on the cell-DNA, that leads to cell damage or cell death. Energy is deposited through the interactions, and as the energy is absorbed it may cause chemical changes and next, biological effects (Joiner and Kogel, 2009). The deposited energy is referred to as absorbed dose (or just dose) and is defined as the mean energy measured in Joules absorbed per mass unit Joules/kilogram. The unit for dose is Gray (Gy).

The deposition of dose in tissue depends on density, but also the quality of the radiation beam. A photon beam can be characterized by a percent depth-dose curve (%DD curve) (figure 1-2), which describes how a photon beam with a specific energy attenuates in matter. A 15 MV beam reaches the maximum dose (d_{max}) deeper than the 6MV beam (Figure 1-2). It also continues to give an approximately 10% higher dose in the depth.

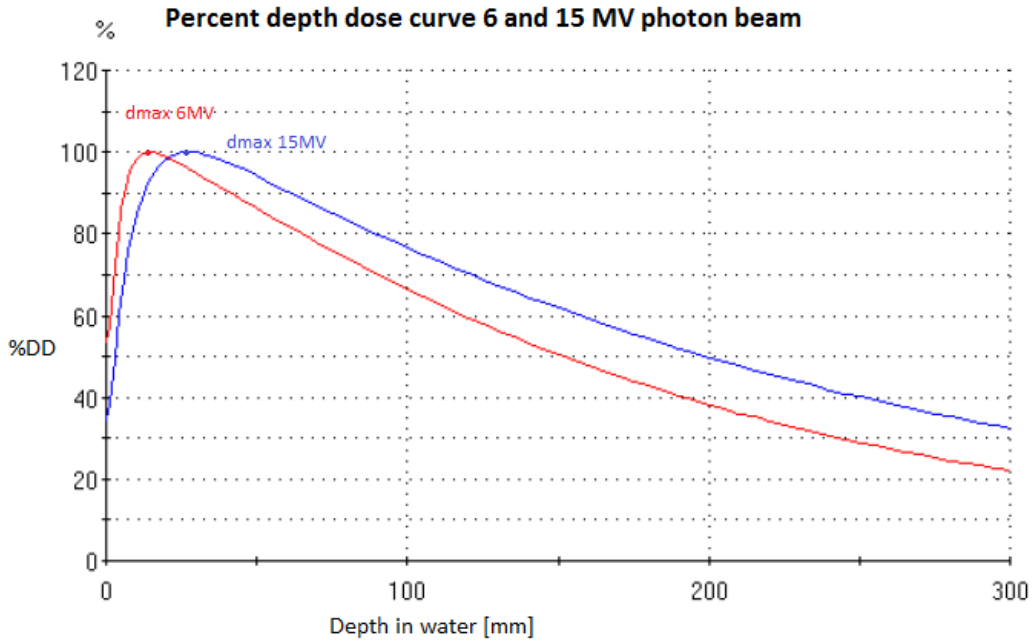

Figure 1-1-2: Percent depth dose curve (%DD curve) for 6MV and 15 MV photon beam. The 6 MV curve shows a build up until it reaches d_{max} at 1.4 cm depth. A 15MV photon beam will reach deeper and have a d_{max} at 3 cm depth. Authentic curves from a linear accelerator in Haukeland University Hospital, courtesy of Medical Physisist Harald Valen.

The relationship between dose and tumor control and effects on healthy tissue can be demonstrated in a dose-response curve, which have a sigmoid shape

(Joiner and Kogel, 2009), Figure 1-3. The therapeutic window is given by the difference in response between tumor and normal tissue (Joiner and Kogel, 2009), shown as the distance between the two sigmoid curves in Figure 1-3. This illustrates the possibility of giving a sufficient dose to achieve tumor control with an acceptable level of normal tissue damage. In radiobiology tissues are divided into three types; early responding normal tissues, late responding normal tissues and tumors.

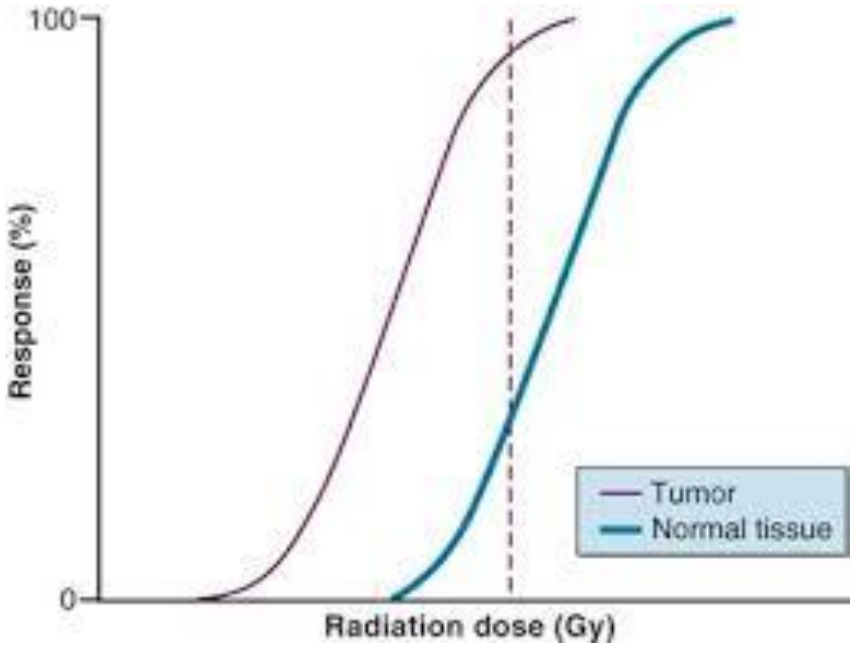

Figure 1-1-3: Illustration of the relationship between dose and effect on tumor and normal tissue. (Horsman et al., 2015)

Dose fractionation means to divide the total radiation dose into fractions that is delivered over several days. Fractionation is done to balance the effect of radiation on normal tissues and tumor, by allowing cell repair between fractions and repopulation of cells. On the other hand, fractionation increases the damage to the tumor when the tumor tissue is reoxygenated between fractions and the tumor cells are reassorted into sensitive phases of cell cycle. A daily dose of 1.8-2.0 Gy, given five days a week, is referred to as the conventional fractionation schedule. The total dose given depends on tumor histology, tumor size and tumor localization, and weather one treats macroscopic disease or

microscopic disease. Total dose is normally ranging from 40-70Gy for macroscopic disease (Joiner and Kogel, 2009).

1.1.3 Imaging in planning and guidance of radiotherapy

Medical imaging plays a key role in the radiotherapy process. This section will focus on computed tomography (CT) used for treatment planning, and CBCT and planar kV imaging for treatment verification in the treatment room.

1.1.3.1 Computed tomography(CT)

CT is used to produce cross-sectional images from a set of x-ray images taken from numerous angles through a patient. A CT scan produces a volume of data that can be reconstructed in various planes and as 3D structures. CT technology has evolved since the first scanner which was in clinical use in 1974, and here the third generation technology is described. The scanner consists of an x-ray source that is mounted in a circular gantry, and at the opposite side of the circle there is a row of detectors, Figure 1-4. The x-ray source and the detectors are rotating simultaneously around the patient. The x-ray beam is fan-shaped and the table is moved along the center axis of the gantry to obtain volumetric information of the scanned object (helical scan). The scanner may have several rows of detectors (up to 320), which results in a shorter scan time, but also gives a more cone shaped beam.

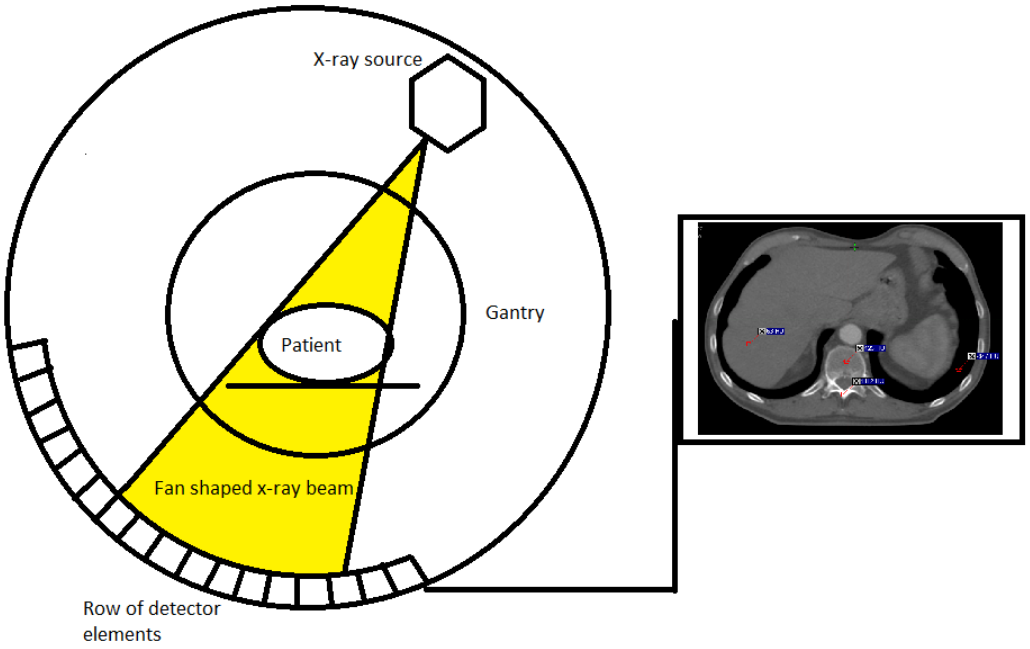

Figure 1-1-4: Illustration of a third generation computed tomography (CT) scanner, and a CT image from one of the patients in this study (right).

The technology is the same whether the CT is used in diagnostics or for treatment planning In RT. However, there are a few things to consider when the CT is to be used in the purpose of RT planning; a flat table top like the one used at treatment machines, position lasers and a large gantry to allow for place demanding patient fixation devices. In RT the CT scan is used for treatment volume definition and dose calculations.

A 4 dimensional CT scan (4DCT) is a CT scan where the breathing motion of the patient as the fourth dimension is taken into account. The images are sorted on breathing phase, and reconstructions of the images can demonstrate how anatomical structures move during breathing. An average reconstruction is a computation of the image data from a 4DCT scan and will demonstrate structures as smeared out during the breathing, and is thus comparable to the volumetric scan of the CBCT which is taken during several breathing phases due to its long scan time.

The construction of a cone beam computed tomography (CBCT) scanner is different from the ordinary CT, and uses a cone-shaped x-ray beam (Figure 1-5)

while the table is in a fixed position. It produces a volumetric scan in one rotation around the patient. In RT the CBCT is typically mounted on the gantry of the treatment machine, with an x-ray tube on one side and a planar detector on the opposite side, and is used for image-guidance in treatment position, see chapter 1.1.3.1. The scan time is limited by the rotation speed of the gantry of the treatment machine. It may take about 30-60 seconds for a scan. The scan length is limited by the x-ray field size and the size of the planar detector, and may be around 18 cm.

Different types of artefacts may occur in CT and CBCT imaging, and can be defined as a visualization of structures that are not present in the object being imaged. For instance metal artefacts (or exponential edge gradient effect) that is caused by high-attenuation objects (like metal) in the field of view, and motion artifacts caused by patient- or organ motion (Schulze et al., 2011). Artefacts are known to compromise image quality.
Another known issue in CT imaging is the partial-volume effect which is caused by the fact that a volume unit (voxel) may house both low density and high density objects, and that the voxel is visualized as a averaged pixel in the image. This blur the contrast between objects of differing density (Smith and Webb, 2011) page 12.

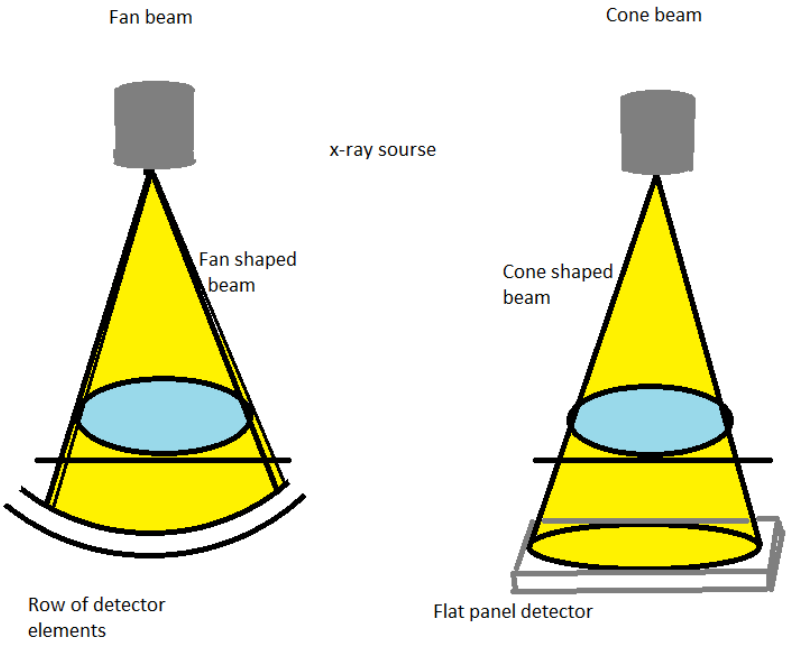

Figure 1-1-5: Illustration of the difference between a fan beam and a cone beam. The x-ray beam to the left is fan-shaped and scans through a narrow slice of the patient at each rotation. The cone-shaped x-ray beam at the right scans through a volume of the patient in one rotation.

1.1.3.2 Planar kV imaging

In planar x-ray imaging the images is produced by directing a x-ray source towards the patient, and by detecting the x-rays which passes through the patient using a solid state flat panel detector placed just behind the patient (Smith and Webb, 2011). The basis for image production is the same as in CT, and depends on differential absorption of x-rays in various tissues of the body. This is also the basis for dose calculation and is discussed further in the next section.

1.1.3.3 Hounsfield units

Different tissues attenuate the x-rays according to its varying density. The detectors will register the amount of radiation that passes through the patient. The radiographic image displays the distribution of the attenuation coefficients (Hounsfield Units, HU) like a gray scale pattern. The gray scale is calibrated relative to the attenuation of water and air, where water is 0 HU and air -1000 HU. Materials of higher density have higher HU, soft tissues vary between 100-300 HU and bone from 300-3000 HU (Figure 1-6). In the conventional

radiographic image dense structures like bone will appear as white and less dense structures appear darker.

In RT the CT images are used for dose planning, where the HU gives information to the dose planning system of the attenuation of the beam in the patient, and this information is crucial to the calculation of dose distribution. The HU in CBCT is not directly comparable to the CT as HU, but this a issue that is object to investigation (Srinivasan et al., 2014). CBCT is today normally not used for dose calculations.

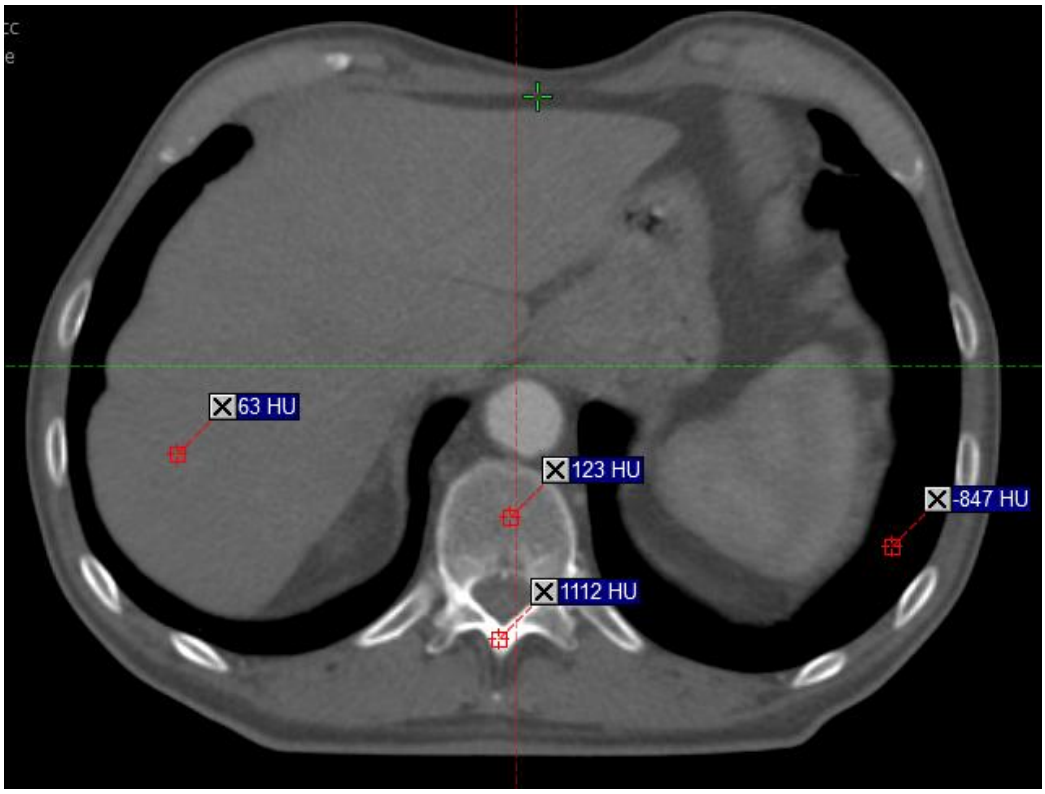

Figure 1-6: Axial computed tomography (CT) image through the upper part of the abdomen. The blue fields show examples of Hounsfield Units (HU) values in some pixels in the image. The image is from one of the study patients.

1.1.3.4 Image guidance

Image-guided radiotherapy (IGRT) is the process of in-room imaging during radiotherapy, to reduce geometric uncertainty by more precise patient positioning (Sonke and Herk, 2010).

IGRT has increasingly replaced the alignment based on skin marks alone and is now in standard clinical use, with advancing technologies. It has been stated that to integrate IGRT in daily treatment delivery is one of the main ways to improve the cure rate by radiotherapy (Joiner and Kogel, 2009). This is based on the possibilities brought by resent technologies for better control with positioning, organ movement, and tissue- and tumor changes. By increasing control on these factors one may widen the therapeutic window by normal tissue sparing and dose-escalation. There are a range of different technologies, and the latest linear accelerators are typically equipped for 2D and 3D imaging.

1.1.3.5 Use of surrogates in image guidance

Despite improved quality of in-room images, it can still be a challenge to distinguish tumor from surrounding tissue. Often bony landmarks are used as surrogates for the tumor or treatment area, however this approach gives inherent uncertainties as the CTV can move independent of bone. One successful approach in certain tumor sites, like for instance prostate, has been to implant fiducial markers in or near the tumor, and thus help to determine the target in the images (Zelefsky et al., 2012). Other examples are the use of lipoidol in bladder cancer patients (Sondergaard et al., 2010), a polymeric marker in cervical cancer patients (Langerak et al., 2015) and real-time tumor tracking on gold markers in lung cancer patients (Takao et al., 2016). The markers are more visual in radiographs than soft tissue because they consist of high-density material, like gold, metal clips or radiopaque fluids, in the same way that the higher density of bone makes it more visual than soft tissue.

1.1.4 Treatment morbidity

The longitudinal shape of the esophagus through the thorax raises various challenges when radiotherapy is administered. The organs at risk, that appears to be critical and potential dose-limiting, vary according to tumor localization. Furthermore, organ and tumor motion is more pronounced distally, because of respiration and peristalsis (Jin et al., 2015).

Morbidity during and after radiotherapy for esophageal cancer is related to

dose, radiated volume, anatomical location, co-morbidity and concomitant treatment, and is divided into acute and late effects (Table 1-I). Acute morbidities are side effects that occur during and in the first three months after radiotherapy. They are caused by the immediate effects of radiation exposure, and occur in tissues with fast cell proliferation, like skin, bone marrow and mucosa. Radiation reduces the cell production from stem cells, while the normal cell loss continues as usual, with a consequence of increasing cell depletion. This effect is often followed by inflammatory reaction. There is also a vascular effect, which can be observed as erythema (Joiner and Kogel, 2009).

Late side effects appear after a period of latency. This period may last from months to years after treatment and may often be irreversible, progressive and may occur in any organ (Joiner and Kogel, 2009). The pathogenetic process of late effects is more complex than for the acute reactions, and affects organ parenchyma, connective- and vascular tissue.

Table 1-I: Acute and late normal tissue reactions in cervical/thoracal/abdominal organs, relevant to radiotherapy for esophageal cancer.

Organ	*Acute*	*Late*
Lung	Pneumonitis	Fibrosis, pneumopathy
Heart	Arrhythmias, ECG-changes	Pericard effusion, cardiomyopathy, pericarditis, heart valve damages, coronary artery damages
Spinal cord	Lhermittes syndrome	Myelopathy Vasculopathy
Kidney		Myelopathy Vasculopathy
Esophagus	Esophagitis, dysphagia, Reflux, mucositis, erythema	Stricture, dysphagia, fistula, ulceration
Stomach	Atony	Ulceration

Data collected from: Quantec papers (Werner-Wasik et al., 2010), (Marks et al., 2010) and Basical Clinical Radiobiology (Joiner and Kogel, 2009).

Earlier attempts to escalate the dose in radiotherapy in esophageal cancer to achieve better treatment results, have so far been hampered by unacceptable morbidity (Hawkins and Aitken, 2012). Refining local treatment delivery is

needed to enable dose escalation, since radiation dose is essential to treatment response and adverse effects.

Eastern Cooperative Oncology Group/World Health Organization's (ECOG/WHO) scale on performance status is used in health care and research to assess how a disease is progressing and how it affects daily living for patients, and also aids decisions concerning appropriate treatment and prognosis (National Cancer Institute, 2008).The scale reaches from 0-5, were 0 is a fully active condition without restriction, gradually worsening and in more need of assistance with increasing number, ending at death at value 5.

1.1.5 Coordinate systems

Different coordinate systems are defined to relate the treatment volume within the patient to the physical environment of both imaging- and treatment modalities. When different measurements are done it is important to specify which coordinate system it refers to. In this project the planning coordinate system is used and is briefly described below.

The planning coordinate system is by default set to conform the standard coordinate system, in which the Z-axis points towards the gantry of the treatment machine, the X-axis points to the right when facing the gantry, and the Y-axis points towards the floor (Figure 1-7) (Varian Medical Systems, 2016). The origo of the coordinate system (0, 0, 0) is set as a user origin, usually in the intersection of lines drawn between the led pellets placed on patients' skin marks during CT scan.

The standard position for a patient is supine on the table with head towards the machine gantry. Thus, the x-direction of the coordinate system is in the lateral direction (pointing from the right towards the left of the patient), the y-direction is in the ventral direction (pointing from the anterior side to the posterior of the patient) and the z-direction is in the longitudinal direction (pointing from the caudal end towards the cranial end) in the patient.

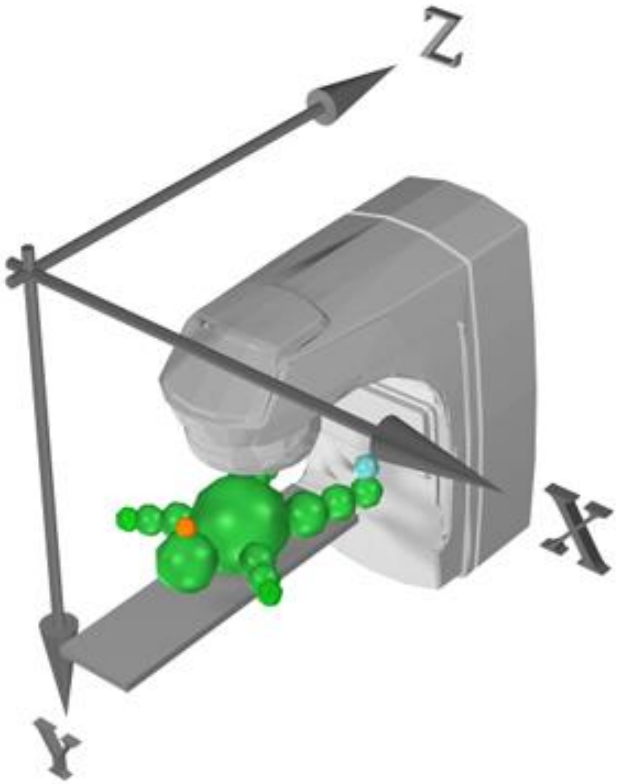

Figure 1-7: Planning Coordinate System in External Beam Planning. The patient is here positioned feet first supine, but this will not affect the coordinate system. When making adjustments on basis of online in-room imaging correct patient orientation is mandatory.

1.1.6 Volumes and margins

A careful definition of the treatment volume is central to achieve the optimal treatment result, and is dependent on extensive diagnostic imaging and a highly competent oncologist. In modern radiotherapy definition of treatment volume is one of the large contributors to uncertainties (Van Dyk et al., 2013). Volumes in radiotherapy are defined according to guidelines, like the ones given by International Commission on Radiation Units & Measurements (ICRU), (International Commission on Radiation Units & Measurements, 2016). In Norway the recommendations are given by the KVIST-group (KValitet I STråleterapi) (Levernes, 2012), which is based on the ICRU guidelines.

The gross tumor volume (GTV) is the visible tumor on diagnostic images or tumor that is palpable. This could be primary tumor, lymph nodes, distant metastases or tumor relapse (Figure 1-8). The area surrounding the tumor has a certain probability of housing microscopic spread. A margin is thus added to

cover this area, which gives the clinical target volume (CTV). In esophageal cancer there is a high risk of sub-mucosal spread along the esophagus, and the treatment volume is therefore expanded several centimeters in the longitudinal direction (Chang et al., 2010).

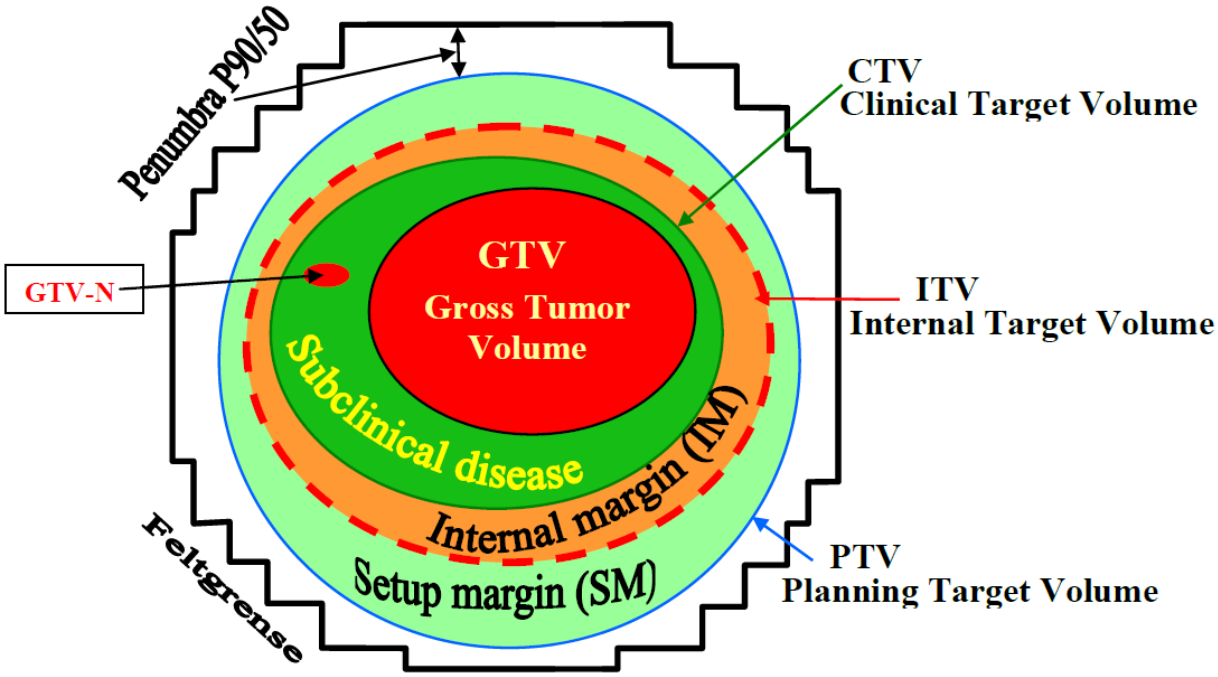

Figure 1-8: A schematic illustration of volumes and margins in radiotherapy (Levernes, 2012)

The planning target volume (PTV) is a geometrical volume where margins is added to ensure that the prescribed dose with an acceptable probability is given to the CTV, taking uncertainties into account (Figure 1-8). The addition of margins also contributes to increased dose to adjacent healthy tissue. Hence, balancing between these considerations is important, and caution must be taken when margins are calculated.

1.1.7 Uncertainties in radiotherapy

Treatment-related uncertainties are both of systematic and random character. A systematic error is a deviation in the same direction and of similar magnitude throughout the treatment course, and typically is initiated through the planning process. A random error is a deviation that can vary in direction and magnitude from fraction to fraction, and is an error in the execution of the planned

treatment at one fraction. Random errors are expected to blur the dose and thus make the gradients towards healthy tissue less steep, while systematic errors give a shift in the dose distribution.

Different formulas for calculation of margins have been suggested and are summarized in ICRU 83 (International Commission on Radiation Units and Measurements, 2010). The most common formula in use is Van Herk's margin formula (van Herk, 2004), where the CTV-PTV margin = $2{,}5\Sigma + 0{,}7\sigma$, where Σ is the systematic errors and σ is the random errors in a population of patients. This formula will estimate a margin that covers the CTV in 90% of patients with 95% of the prescribed dose. The principles of this formula have become a recognized standard in calculation of treatment margins in RT (International Commission on Radiation Units and Measurements, 2010).

1.2 Earlier research

The use of fiducial markers in patients with esophageal cancers has been investigated in some earlier studies (Table 1-II).

Table 1-II: Earlier research related to the topic of markers in radiotherapy for esophageal cancers.

Purpose	Study design	Number of participants (n)	Reference
Feasibility	Prospective, feasibility and comparative	30	(Machiels et al., 2015)
Feasibility	Retrospective small case series	30	(DiMaio et al., 2010)
Feasibility	Feasibility, phase II	26	(Chandran et al., 2016)
Quantify interfractional variation	Prospective	24	(Jin et al., 2015)
Quantify interfractional movement	Retrospective	44	(Fukada et al., 2013)
Report stability of fiducial markers	Retrospective review of records	60	(Fernandez et al., 2013)
Investigate 3D intrafractional movement of markers	Prospective	12	(Yamashita et al., 2011)
Compare CBCT with EPI	Prospective comparative	20	(Hawkins et al., 2011)

3D= three dimensional, CBCT= cone beam computed tomography, EPI= electronic portal imaging.

1.2.1 Feasibility

It has been demonstrated that the implantation of markers in patients with esophageal cancer is a safe and feasible procedure (DiMaio et al., 2010, Machiels et al., 2015), and that the markers aid the target delineation in radiotherapy treatment planning (Chandran et al., 2016, Machiels et al., 2015).

1.2.2 Visibility and loss of markers

Different types of markers have been evaluated with regards of visibility during radiotherapy, Table 1-III.

In a study of 30 patients with esophageal cancer the visibility of three different

marker types were investigated (Machiels et al., 2015). It was found that the main reason for non-visible markers were detachment/loss of markers. Other reasons were size of the markers (four makers were too small to be visible on the CBCT) and migration (one marker migrated to the lung). Of 101 implanted markers 94 were visible at the planning CT and 67 at the first CBCT at start of radiotherapy. The median (range) time from implantation to radiotherapy start was 13.5 days (7-21 days). At end of radiotherapy 63 of the markers were still visible; 63% of the solid makers, 80% of the flexible markers and 22% of the hydro gel markers. The hydro gel markers seemed to be absorbed gradually, and already at radiotherapy start the density were considered too low for clinical use.

A 10 mm long cylindrical gold marker with varying diameters was evaluated in a retrospective review of records of 60 patients; ten markers had 0.35 mm, one had 0.5 mm and 94 had 0.75 mm diameter (Fernandez et al., 2013). Forty-two of the patients were treated with IGRT and different imaging modalities were used; kV CBCT in 31 patients, daily 2D kV imaging and weekly kV CBCT in eight patients, daily helical Megavolt CBCT in two patients and daily 2D kV imaging in one patient. All the visible markers were also well visualized on kV CBCT and the Megavolt CT. In planar imaging markers with a diameter of 0.75 mm were visualized superiorly compared to smaller markers.

Out of 83 implanted metal clip markers in a retrospective study, two markers were lost after planning CT, five were lost by week two of radiotherapy and additional seven were lost by week five (Fukada et al., 2013). Orthogonal kV images were used for setup verification; daily for the first week and weekly thereafter. In lateral images it was not possible to identify thirteen of the markers due to overlap with bone. In addition, the time-difference between the lateral and front projection caused the markers to be in different position in the two projections of the image pair.

Summarized, the type and the size of the markers mattered when visibility was evaluated; length exceeding 5 mm, diameter over 0.75 mm and metal marker

was superior. The shape of the maker may also affect if the markers stayed attached.

Table 1-III: Visibility of different types of markers assessed by different imaging modalities and frequencies.

Marker type	N patients	N_m markers	Marker size [mm]	Visbility RT_e [%]	IGRT maging modality	Imaging frequency	Reference
Flexible gold marker	14	51	2-10	80	kV CBCT	Weekly	(Machiels et al., 2015)
Hydro gel	5	18	0,4 ml	11	kV CBCT	Weekly	
Solid gold marker	11	32	5	63	kV CBCT	Weekly	
Cylindrical gold marker	58	100	0,35-0,75 *10	88	kV CBCT kV CBCT + kV XR MV CBCT kV XR	Daily Weekly/ daily Daily Daily	(Fernandez et al., 2013)
Metallic clip			10	88	kV orthogonal	Daily 1st week, then weekly	(Fukada et al., 2013)
Metallic clip	12	22	2 * 10	Not reported	Not reported	Not reported	(Yamashita et al., 2011)

N= number of patients. N_m= number of markers. RT_e=end of radiotherapy. IGRT = image guided radiotherapy, kV= kilovoltage, CBCT= cone beam computed tomography, XR= x-ray.

1.2.3 Interfractional variation

The motion of esophagus has been investigated with different approaches. The interfractional position variation of markers relative to bony anatomy were assessed for 30 patients with esophageal cancer (Jin et al., 2015), and large systematic and random errors were mainly in the longitudinal direction and in the proximal stomach. Further, it was found that 12% of all 3D vector displacement was larger than 10 mm and 49% were larger than 5 mm. The absolute systematic errors and standard deviations of random errors were significantly larger in the longitudinal direction for all markers and for the subgroup of makers located in the distal esophagus. It was reported that in five of the patients there were no detectable markers on any of the CBCT scans. Three different marker types were used, and all of the types were represented

in the group with non-detectable markers. The pairwise distance between the markers was found to fluctuate over the treatment course, probably due to tumor deformations. After setup correction based on bony landmarks the markers were found inside the GTV, CTV and PTV in 69%, 95% and 100% of the cases, respectively. This study also demonstrates the need to distinguish between the different tumor-sites, due to marked displacement differences for the different anatomical sites. It was stated that marker-based image registration for esophageal cancers has to be further investigated.

A retrospective study of orthogonal 2D images in 44 esophageal cancer patients with endoscopic placed metallic clips, it was found that the displacement of the markers were significantly larger in the longitudinal direction than in the ventral direction and the lateral direction (Fukada et al., 2013). Further they found that the displacement of the distal placed markers were significantly larger than in the middle and the proximal esophagus. They analyzed the frontal and the lateral x-rays separately and found a difference caused by respiratory motion in the timespan between the two projections. They assumed the difference were in the longitudinal direction only and reported longitudinal measurements for front and lateral projections separately.

1.2.4 Intrafractional variation

The three-dimensional movement of markers was investigated in 12 patients with esophageal cancer using volumetric scan CT for 20 seconds, and there was found a strong correlation between respiration- and marker movement, especially in the longitudinal direction as demonstrated in 73% of the markers (Yamashita et al., 2011). They found that distal tumors had a greater respiratory motion than upper- or middle esophageal tumors, and that the motion was larges in the longitudinal direction.

In a retrospective study the respiratory motion was evaluated in 30 esophageal cancer patients, using a 4DCT scan (Patel et al., 2009). The measurements were performed on basis of the delineated structures and grouped according to the location of the bulky tumor. It was estimated that the mean displacements of tumors were 0.22 cm, 0.28 cm and 0.80 cm in the lateral-, ventral- and

longitudinal directions, respectively. For the celiac lymph nodes the displacements were 0.19 cm, 0.46 cm and 0.92 cm in the lateral-, ventral- and longitudinal directions, respectively.

The correlation between a pre-treatment 4DCT scan and real time fiducial-based motion tracking was studied in 14 patients with upper GI malignancies (Lischalk et al., 2016) and it was found that mean fiducial displacements were larger than the 4DCT in 39%, 22% and 25% of the fractions in the longitudinal, ventral and lateral directions.

1.2.5 Image-guided radiotherapy

Automated marker-based registration was explored as part of a study on esophageal markers, but was found that it only was feasible in 21 of 613 CBCT scans (Jin et al., 2015). Manual marker-based registration was also attempted, but was found not feasible because it was time-demanding and difficult to evaluate because of deformation of the volume.

Electronic portal imaging and CBCT for image-guided radiotherapy was compared regarding set-up variations, and it was found that discrepancies were more than three mm in 31.7% of the evaluated image pairs and exceeding five mm in 12.5% (Hawkins et al., 2011). CBCT was also able to identify rotations exceeding 3° in 44 of 207 images. They considered CBCT to be superior due to 3D images with adequate image quality.

Utilizing CBCT for patient set-up verification different registration methods can be chosen. In a retrospective study, comparing different registration methods in 50 esophageal cancer patients by evaluation set-up margins and number of corrections, it was found that CBCT based position verification gave a more consistent IGRT method than electronic portal imaging (van Nunen et al., 2017). Soft tissue registration gave smaller set-up corrections than registration on bone, but they were unable to conclude which method was better due to lack of a gold standard. Different observed soft-tissue changes were also registered, and the most frequent observed changes were reduction in GTV volume, heart volume reduction and changes in diaphragm position.

1.2.6 Other issues

Tumor volume and motion during radiotherapy in 22 esophageal cancer patients was studied using weekly 4DCT scans (Wang et al., 2015). The volumetric change in GTV volume was found to be declining over the radiotherapy course, mean decline of 10% at fraction number ten and 25% at fraction number 20. This might be a plausible explanation of the challenges Jin et al. experienced with marker based image registration, where automated registration only was possible in a few CBCT scan and manual registrations were found to be difficult and consuming (Jin et al., 2015).

Hawkins compared set-up variations found at CBCT with automated soft tissue registration and planar megavolt imaging with manual registration on vertebras in 20 patients with esophageal cancer, regarding translations and rotations (Hawkins et al., 2011), and found poor correlation between the two modalities. It was found that 37.3% of the instances had more than 3 mm discordance and 12.5% had more than 5 mm, where registration on vertebras seemed to underestimate the set-up-errors.

Based on experiences from earlier studies it seems clear that there are variations in both intra- and interfractional motion in patients with esophageal cancer that needs to be taken into account. There also seem to be variations in motion in the different sub-divisions of esophagus. The method for calculating motion magnitude varies since the available hardware and software are utilized. There are several different technologies in imaging, and different types of markers to consider. The size of the markers needs to be of sufficient size to be well visualized. A novel type of marker was available for implantation in esophageal cancer patients in our clinic, and was primarily wanted to aid target delineation. Hence, we wanted to explore if the further use of this marker type was feasible in image guidance and to characterize organ motion in different time aspects.

2. Aim and Research questions

2.1 Purpose

The aim of this study is to investigate the potential for using a novel type fiducial marker in image-guided radiotherapy (IGRT) of esophageal cancer, by exploring marker attachment, coverage and motion during radiotherapy.

2.2 Research questions

A. What fraction of implanted fiducial markers stay attached during radiotherapy?
B. Do the planning target volume account for variation in marker position during a course of radiotherapy?
C. What is the interfractional variation in marker position?
D. What is the intrafractional variation in marker position?

3. Methods

3.1 Research design

This project was part of a study where the overall aim was to investigate the technical feasibility, the technical benefit and the safety of endoscopy/EUS guided placement of fiducial markers (or just markers) for radiotherapy of patients with esophageal cancer. Eligible patients with esophageal cancer were included prospectively and had fiducial markers implanted if consent was given by the patient. In this study the radiographic images taken during planning and execution of radiotherapy have been investigated to reveal how these markers behave during the treatment period. The study design was longitudinal as patients were enrolled prospectively and followed from marker implantation to completion of the radiotherapy.

A pilot study is often called a feasibility study as it is run to test the methods of a planned larger study. It is therefore run in a small scale and serves functions like evaluation of study procedures, appropriateness of measure instruments and to give preliminary evidence that may justify a larger study. It is also stated that pilot study plays an important role in studies on new interventions (Polit and Beck, 2012). As the use of fiducial markers in image guidance in esophageal cancer patients is a relatively new method it seems reasonable to consider this study a pilot study.

The study design was nonexperimental, using an observational descriptive approach attempting to characterize the phenomenon “implanted markers in patients with esophageal cancer”. In spite of that there was an intervention (the implantation of markers), the study did not seek to measure the effect of this intervention, because the marker itself will not be able to influence the effect of the treatment. When exploring how the markers behaved during treatment, it was done to reveal if and how they could possibly be feasible for use in image guidance. It was thus important to characterize if and how the markers move in different time aspects.

The correlation between time and markers are thus important, and gave the study an aspect of correlation design as well. Due to the limited number of patients included it was considered a pilot study with a case series design. This is because the study procedures were developed in the study and because there were few earlier studies to lean on.

The justification for the chosen study design was based on the limited knowledge of the value of fiducial markers in esophageal cancer treatment. According to Polit and Beck (Polit and Beck, 2012) an observational descriptive design is often suitable to use when the phenomenon are relatively unknown and there are limited earlier research to lean on.

3.2 Selection

Patients that were offered definitive, preoperative or palliative radiotherapy or chemo radiation at Haukeland University Hospital (HUH) were considered eligible for the study, until the number of participants reached 20. This was the estimated number of patients expected to be enrolled in the study in one year. The data collection started August 2016 and was finished in October 2017. The time restriction was decided due to the time schedule of the master thesis.

The inclusion criteria were:

- Age ≥18 years, both genders.
- Histological proven adenocarcinoma or squamous cell carcinoma of the esophagus or the gastric cardia Siewert type I and II.
- ECOG/WHO performance status 0-2 (National Cancer Institute, 2008).
- Radiotherapy had been proposed as neoadjuvant treatment before surgery, or as definitive- or palliative treatment by the multimodal/interdisciplinary team.
- The oncologist has considered the patient appropriate for participation in the study.

The exclusion criteria were:

- Major comorbidity, such as serious heart disease or lung disease that inhibited external radiotherapy.
- An endoscopic stent was placed in the patients' esophagus.
- Anatomical constraints in the esophagus hindered the implantations of the markers.
- Insufficient image quality as deemed by the candidate during data collection: if the position of a marker could not be ascertained, no data was collected for the affected marker at the present scan. This could be due to motion artefacts in the radiographic image or that the marker was not included in the image.
- Implanted markers that not were included in the treatment volume as defined by the oncologist.

3.3 Patient logistics and procedures

Visibility of the marker was assessed prior to patient inclusion; this was done by placing markers in a phantom and performing planar kV and 3D kV (CBCT) imaging of the marker (Figure 3-1). The markers were deemed clearly visible in both modalities.

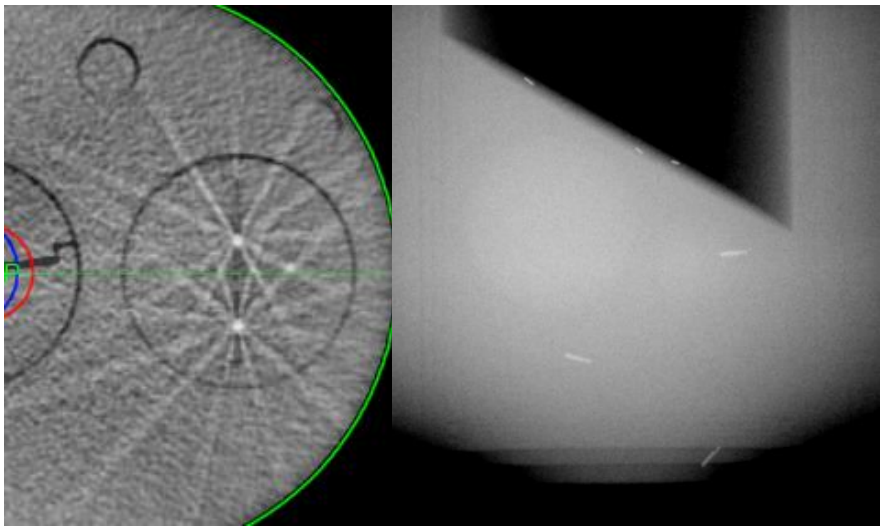

Figure 3-1: Test of marker visibility on cone beam computed tomography (CBCT) at the left and kilovoltage (kV) planar image at the right. The markers were clearly visible in both modalities.

After found eligible and given consent patients had markers implanted guided by endoscopic ultrasound (EUS). EUS is the use of high-frequency sound-

waves to create anatomic images trough body openings. In esophageal cancers EUS has a superior ability to demonstrate the exact extension of the tumor. The implantation procedure was performed by an experienced endoscopist in the Department of Internal Medicine at HUH, except for in one of the patients. For this patient the implantation was performed by another experienced endoscopist. The same type of markers where used in all patients. It was a solid gold marker 0.43-0.64 mm x 5 mm size, (Figure 3-2). A needle preloaded with four markers and designed to be used through an EUS device was used in the implantation of the markers. This product was not commercially available during the study. The markers were placed in the sub mucosal layer of the esophagus. It was placed just outside the tumor boarder, to prevent the marker to loosen in case of tumor shrinkage.

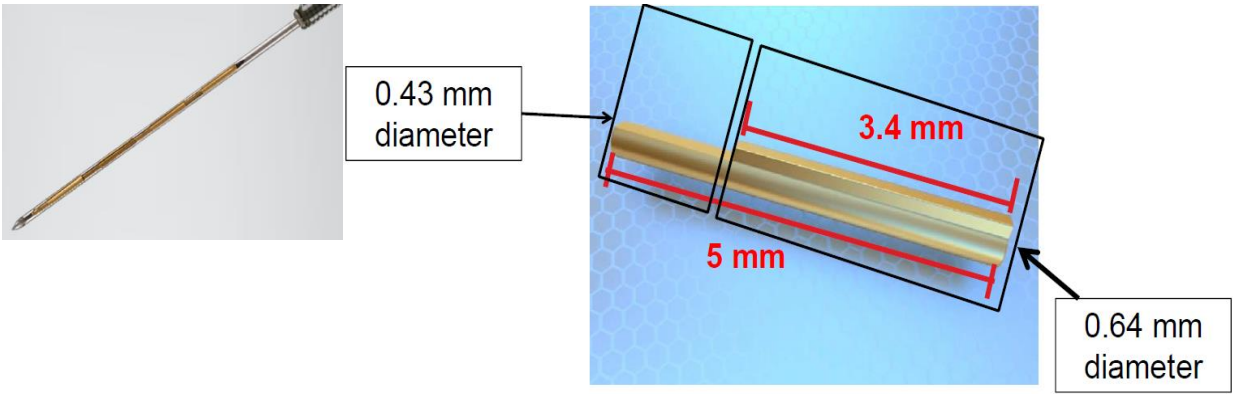

Figure 3-2: Gold markers were placed using a 22 gauge pre-loaded needle (EchoTip fiducial needle, Cook Medical, Ireland). Images from Cook medical.

The schematic plan for placing the markers was to place two markers at the cranial border and two at the caudal border of the tumor (Figure 3-3). In case of stenosis in esophagus that hindered the endoscope to pass, markers were placed at the cranial border only. Affected lymph nodes in close proximity to the esophagus and that were considered by the endoscopist to be difficult to detect with other diagnostic imaging modalities could also be marked by implanting a marker in the lymph node.

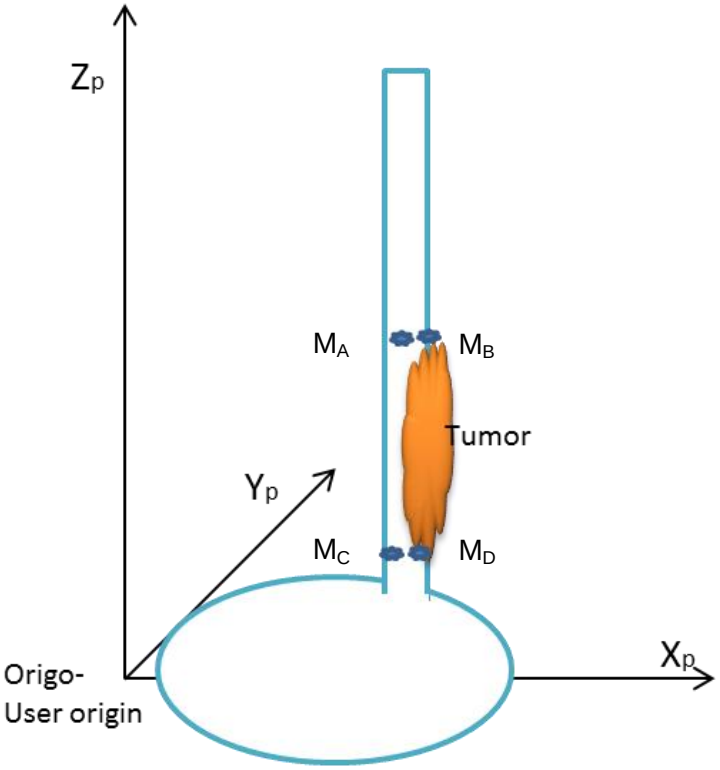

Figure 3-3: A schematic illustration of marker placement in the esophagus in the coronal plane, with the patient in a supine position with head towards the machine gantry. Markers (M_{A-D}) were named alphabetically from the most cranial and left marker, to the most caudal and right, as they appear in the axial CT images of each of the patients. The blue dots symbolize the markers. The directions x, y and z refers to the directions as described in section 1.1.5

A CT scan for radiotherapy planning (CT_p) purpose was performed as soon after implantation as possible, usually the next day. The patients underwent the scan in a head first supine position, in free breathing. They were immobilized with arms up in a Thorax-fix (CIVCO Medical Solutions, Rotterdam, The Netherlands), or with arms down in a thermoplastic mask with shoulder fixation (CIVCO Medical Solutions, Rotterdam, The Netherlands) and with a knee rest. Immobilization method was chosen according to tumor localization. The CT_p scan was performed by trained radiotherapists, according to a study protocol (Appendix C), on a Phillips Big Bore Brilliance multi-slice CT scanner (Philips, United Kingdoms). The protocol contained two series: a long scan with IV contrast media (if no contra-indications existed) and a 4DCT scan trough the

tumor area. The long scan were used for delineation and dose planning, the 4DCT scan were used to calculate a patient specific internal margin on base of actual organ motion. All planning scans were taken with 2 mm slice thickness.

Treatment volume delineation was performed by the responsible oncologists, who also approved the plan before treatment. Delineation was performed on basis on national guidelines (Frykholm et al., 2011) and was individualized by drawing a GTV structure from the 4DCT scan to account for intrafractional motion. Treatment planning was carried out by dedicated treatment planning experts (medical dosimetrist). The treatment fractions were delivered on weekdays until the prescribed number of treatment fractions was reached. Delineation of treatment volumes and treatment planning were performed according to clinical procedures at Department of Oncology and Medical Physics, HUH.

All treatment- and imaging procedures were performed by experienced radiotherapists (RTT), who were informed of the study procedures (Appendix C). The team of RTTs consisted of a team leader, which was responsible for training RTTs, and RTTs that roll over between the different treatment machines in four months intervals. The treatment machine used was a Varian TrueBeam linear accelerator with integrated OnBoard Imaging system (Varian Medical Systems, California USA). The images were obtained following study protocols which were developed for the purpose of this study by the candidate. All imaging methods and equipment used in this project were already implemented and in clinical use at HUH. Specific protocols for in-room imaging during treatment (Appendix D) were established. For the first four patients the procedure was to take four CBCT-scans and one pair of orthogonal images each week. During the treatment course for patient five this was adjusted to be daily CBCT-scans and additional weekly orthogonal images as the procedure is described in Appendix D. This procedure was used for all the following patients. A repeated CT (CT_r) scan was performed during the last week of radiotherapy, following the protocol for the CT_p scan, except that the use of IV contrast media not was indicated (Appendix C).

3.4 Data collection

To assess the images for data collection different applications in Aria Oncology Information Systems were used (Varian, California, USA). A specific study procedure was developed by the candidate to ensure consistency in the way the data collection was carried out (Appendix E). All data collection was performed by the candidate.

Demographic data of the included patients were collected from patient journals, including age, gender, diagnose code (International Classification of Diseases, ICD-10), treatment aim, tumor site and TNM-stage, as well as information about the EUS guided implantation of markers.

3.5 Variables and analysis

The data was analyzed in Excel 2010 (Microsoft, USA, version 14.1.7172.5000) and stored in a HUH server dedicated for research purpose. The project was assigned a server area, with access given to those who worked on this specific project, according to the research policy at HUH. The access to the research server was regulated after specific security procedures and all activity was logged. Variables and analysis are further described under each research question, as introduced in section 2.

General patient- and marker characteristics were collected, including demographic data (gender, age, ICD10 code, histology, tumor site, TNM stage), treatment information (number of treatment fraction and target dose) and information of the implanted markers (number and anatomical localization). Information about imaging was also collected, including modality and number of scans.

3.5.1 Research question A: What fraction of markers stay attached during radiotherapy?

For each patient the number of markers present at different time points were counted; at implantation, at planning CT (CT_p), start of treatment (RT_s) and end of treatment (RT_e). In case of marker loss at RT_s and RT_e, this was further explored by evaluation of daily CBCT and weekly planar images (Figure 3-4) to see if a more exact time point could be ascertained. The variables in research question A are shown in Table 3-I.

Table 3-I: Variables connected to research question A: What fraction of markers stay attached during radiotherapy?

Variabel	Symbol	Type	Measure level
Number of markers	$N_t^{markers}$	Dependent	Interval
Fraction of markers	$F_t^{markers}$	Dependent	Interval
Time point	t€ [CT_p, RT_s, RT_e]	Independent	Interval

$N_t^{markers}$ =number of markers at a given time point t. $F_t^{markers}$ = fraction of markers at a given time point t. CT_p=planning CT. RT_s= start of radiotherapy. RT_e =end of radiotherapy.

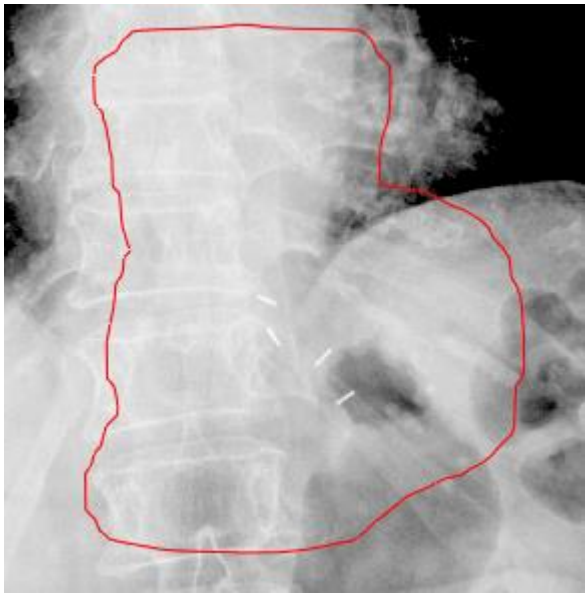

Figure 3-4: Planar image with four visible markers visualized inside the red line of the PTV structure. Image from an included patient.

The fraction (F) of markers present at time point t were given by

$$F_t^{markers} = \frac{\sum_{pat} N_t^{markers}}{\sum_{pat} N_{CT_p}^{markers}} \, x \, 100\%$$

3.5.2 Research question B: Do Planning Target Volume account for variation in marker position during a course of RT?

A marker was considered outside the PTV when the whole or a part of the marker was visualized outside the PTV in any part of the trajectory during the CBCT scan. To verify how well the applied margins covered the various positions of the markers, each marker was marked with a bulbous structure on each CBCT scan and then copied to the planning CT. The diameter of the bulbous structure was 5 mm, which is the same as the length of the marker. Thus, all marker positions were evaluated relative to the anatomy, the PTV and the marker-positions at the planning CT (Figure 3-5). The volumetric CT scan was checked in all three dimensions, and if a bulbous structure was discovered in close proximity to the PTV border the corresponding CBCT was reviewed to see if any part of the marker trajectory was outside the PTV.

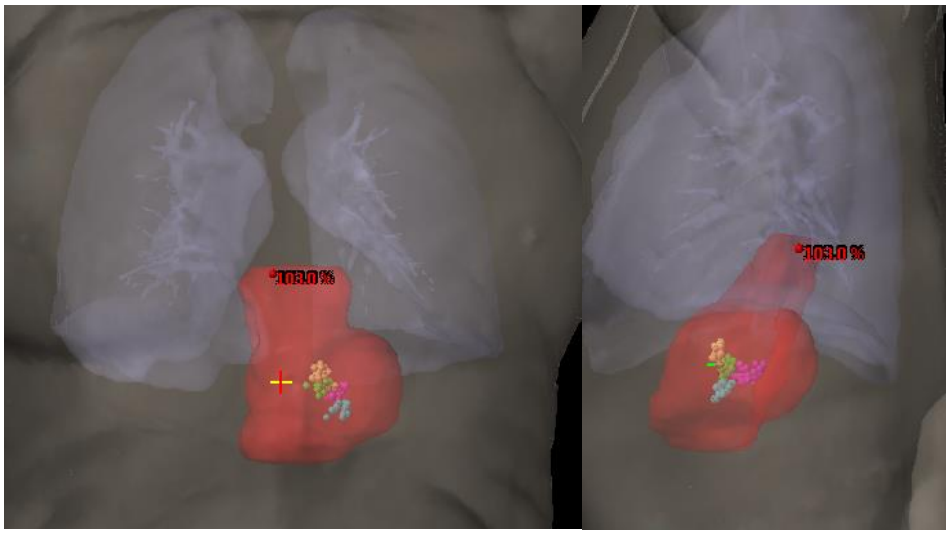

Figure 3-5: Front and lateral view of patient with the bulbous structures from all CBCT projected in the planning CT.

The number and percent of patients that had all markers inside the PTV in all treatment fractions, was calculated. Further, the percent of treatment fractions with markers inside PTV were calculated per patient and for all patients. The coverage was evaluated based on the principle for PTV coverage by van Herk and colleagues, i.e. the marker should stay within the PTV in more than 95% of

fractions for more than 90% of the patients (van Herk, 2004), The variables for this research question are shown in Table 3-II.

Table 3-II: Variables in research question B: Do planning Target volume account for variation in marker position during a course of radiotherapy?

Variable	Symbol	Type	Measure level
Number of patients with all markers inside PTV	Pt_i	Dependent	Interval
Number of fractions per patient with all markers inside PTV	Fr_i	Dependent	Interval
Total number of patients	Pt_{tot}	Independent	Interval
Total number of fractions	Fr_{tot}	Independent	Interval

PTV= planning target volume. Pt_i = number of patients with all markers inside PTV. Fr_i= Number of treatment fractions with all markers inside PTV. Pt_{tot}= total number of fractions. Fr_{tot}=total number of fractions.

The fraction of patients (F_p) where all markers were covered by the PTV was given by

$$F_p = \frac{\sum Pt_i}{\sum Pt_{tot}} * 100\%.$$

Likewise, the fraction of treatment fractions (F_{Fr}) with all markers inside the PTV margin was given by

$$F_{Fr} = \frac{\sum Fr_i}{\sum Fr_{tot}} * 100\%.$$

3.5.3 Research question C: What is the interfractional variation in marker position?

The 3D coordinates (x, y and z) of each marker were recorded for planning CT, repeated CT and for each CBCT scan. The markers appear smeared out on the CBCT. The 3D coordinates were therefore recorded at the visually central position of the smeared out trajectory of the marker visible on the CBCT scans. The interfractional variation in marker position was calculated by subtracting the marker coordinates at planning CT from the coordinates at each CBCT scan, using the planning coordinate system:

$$X_{rel} = X_{Frn} - X_{CTp},$$

were X_{rel} is the relative change in marker position from planning CT to a given treatment fraction, X_{Tr} is the marker position at treatment and X_{CTp} is the marker position at the planning CT, in the x-direction. Likewise for the y- and z-direction:

$$Y_{rel} = Y_{Frn} - Y_{CTp}$$

$$Z_{rel} = Z_{Frn} - Z_{CTp.}$$

The absolute change in marker position from position at planning CT to position at CBCT is calculated as a change vector length:

$$|\underset{v}{\rightarrow}| = \sqrt{(x)^2 + (y)^2 + (z)^2}$$

The variables for this research question are shown in Table 3-III.

Table 3-III: Variables in research question C: What is the interfractional variation in marker position?

Variable	Symbol	Type	Measure level
Treatment fraction number	Fr_n	Independent	Interval
Change in x, y and z direction [cm]	Xrel, Yrel, Zrel	Dependent	Interval
Change vector [cm]	$\vec{v}$	Dependent	Interval
Marker location	Loc ϵ[CE/UTE, MTE, LTE, EGJ]	Independent	Ordinal
Stenosis	S	Independent	Nominal
Group systematic error	M		Interval
Systematic error	∑		Interval
Random error	σ		Interval

Fr_n= treatment fraction number. X_{rel}=relative change in position in the x direction. Y_{rel}= relative change in position in the y direction. Z_{rel}=relative change in position in the z direction. CE/UTE= cervical esophagus/upper thoracic esophagus. MTE= middle thoracic esophagus. LTE= lower thoracic esophagus. EGJ= esophagogastric junction.

The position of markers located in lymph nodes may vary differently from the markers placed in the esophageal wall and are therefore excluded from the time trend analysis. Because of the small number it is not considered feasible to analyze those markers as a separate group. One marker was not accessible because of artefacts from other markers.

The group mean M, the systematic error ∑ and the random error σ was calculated according to methodology described by van Herk (van Herk, 2004).The M was the mean of the mean values per patient, the ∑ was the standard deviation of means per patient and the random error σ was the root mean squared of the standard deviation per patient.

3.5.4 Research question D: What is the intrafractional variation in marker position?

The exhale- and inhale position coordinates of the markers were defined as the end points of the marker trajectory which were visible as a continuous line, ellipse or irregular structure on the CT_p average reconstruction and on the CBCT scans, as demonstrated in Figure 3-6. The inhale position was always defined as the most caudal point of the marker trajectory and the exhale position was always defined as the most cranial point of the marker trajectory.

The difference in x, y and z-coordinates in the two outermost positions was calculated by subtracting the inhale position from the exhale position:

$$\Delta x = x_e - x_i$$

where x_i is the x-coordinate in inhale position and x_e is the x-coordinate in exhale position. Likewise were done for y- and z-coordinates.

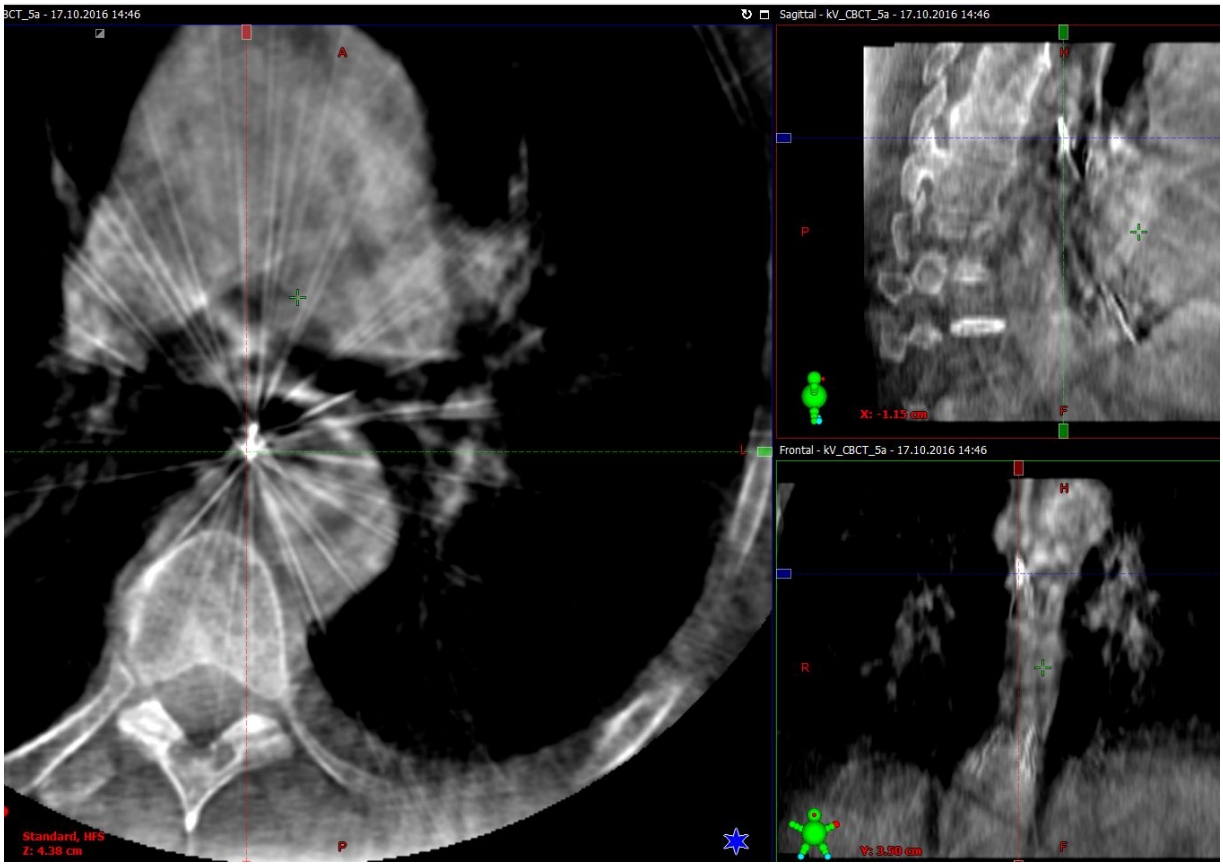

Figure 3-6: Demonstrates a marker (marker A in patient 1) in the intersection of the measuring lines (red and green dotted lines in the left image) and the given x, y and z coordinates of the center of the marker. The marker appears smeared-out due to breathing motion during the CBCT imaging.

Intrafractional variation in marker position was defined as the motion amplitude vector calculated by:

$$|\underset{\Delta v}{\rightarrow}| = \sqrt{(\Delta x)^2 + (\Delta y)^2 + (\Delta z)^2}$$

where [Δx, Δy, Δz] are the differences between exhale- and inhale position as previous described.

The 3D vector length at planning 4DCT (vCT_p) was considered to overestimate the breathing motion during treatment (v_{tr}) if the vCT_p > 3rd quartile of the v_{tr}. Likewise, the vector size at planning 4DCT was considered to underestimate the breathing motion during treatment if vCT_p<1st quartile of the v_{tr}.

The variables related to this research question are shown in Table 3-IV.

Table 3-IV: Variables in research question D: What is the intrafractional variation in marker position?

Variable	Symbol	Type	Measure level
Treatment fraction number	Fr_n	Independent	Interval
Change in x, y and z direction [cm]	$\Delta x, \Delta y, \Delta z$	Dependent	Interval
Motion amplitude[cm]	$\lvert \overrightarrow{\Delta v} \rvert$	Dependent	Interval
Marker location ϵ[CE/UTE, MTE, LTE, EGJ]	loc	Independent	Ordinal

Fr_n= Treatment fraction number. Δx= the difference between marker position in inhale and exhale position in the x direction, likewise for Δy and Δz. Δv= the 3D vector calculated from the marker position changes in x,y and z directions. CE/UTE= cervical esophagus/upper thoracic esophagus. MTE= middle thoracic esophagus. LTE= lower thoracic esophagus. EGJ= esophagogastric junction.

3.5.5 Statistics

Descriptive statistics were calculated for all research questions. The different datasets were tested for normality in SPSS (Shapiro-Wilk test), and measure of central tendency was chosen according to the result of the normality test.

Data of inter- and intra-fractional variation in marker position were grouped according to anatomical localization of the marker and per patient, and medians of interquartile ranges (IQR) were compared between the groups using a nonparametric test (Independent Samples Median test). Interfractional variations were also compared between the directions. The intrafractional 3D vector was compared to 3D vectors from the average reconstruction from the 4DCT at planning CT (CT_p) and the repeated CT (CT_r).

Data of interfractional variation were tested for time trends using the Data Analysis Tool in Microsoft Excel 2010 (test: Regression). The test returns among others the correlation coefficient r and the coefficient of determination r^2. The correlation coefficient tells us how well the linear relationship is; value 1 means a perfect relationship and 0 means no relationship at all. Next, the test returns more information on the data which is analyzed; particularly the p-value of the slope of the trend line. If the slope of the trend line was significant different from zero, the data was considered to have a time trend. The

interfractional motion data were also analyzed concerning distribution of time trend on anatomical localization and directions.

3.6 Ethical considerations

3.6.1 Approval

The study has been approved by the Regional Ethics Committee in Western Norway, reference number 2016/268 (Appendix A). The patients received oral and written information of the study (Appendix B), included potential harms and benefits before they were asked to give informed consent.

3.6.2 Safety

In this sub-project the major concern has been the additional radiation dose in connection with supplementary imaging during radiotherapy. The standard imaging protocol in clinical use in HUS was daily 2D-2D kV and gave an estimated dose of 20 mGy. The additional imaging in this protocol has given an estimated radiation dose of 183 mGy that is 163 mGy more than the standard imaging protocol. This will correspond to approximately 0.3 % of a total treatment dose of 50.4 Gy. Regarding the potential benefit of increased accuracy in the treatment delivery, this dose may be considered neglectable. Still it was important that the oncologist and dose planner were aware of this additional dose that the study participants received, especially in dose plans where dose to organs at risk approaches limit values.

Table 3-V: Imaging and estimated dose contribution from the different modalities.

Modality	Dose contribution	Frequency	Sum
CBCT	4.7 mGy	Daily (25 fractions)	118 mGy
Planar kV	0,09 mGy x 2	Weekly	1 mGy
4DCT	53 mGy ($CTDI_{vol}$)	Last week of RT	53 mGy
CT_r	11 mGy	Last week of RT	11 mGy
			= 183 mGy

CBCT= cone beam computed tomography, kV= kilo voltage, 4DCT= four dimensional computed tomography, CTr= repeated computed tomography, mGy= milli-gray, CTDIvol = volume CT dose index, RT= radiotherapy

The use of IV contrast is standard procedure unless it is contraindicated. At the repeated CT scan the use of IV contrast was not indicated.

The imaging procedures may be more time consuming than standard imaging procedures and this may be experienced as an extra load for the patients, who may be in a poor physical condition. The radiotherapists were instructed to let the patient safety and coping with the imaging be prior to study protocols. In some occasions the radiotherapists chose to reduce the extent of imaging or used standard procedure with only orthogonal images for patient reasons.

The potential risks and benefits regarding implantation of the markers and the treatment volume delineation are not described in this thesis, but will be treated in the other parts of the study.

4 Results

4.5 Patient characteristics

Twelve patients with esophageal cancer were included from august 2016 to September 2017. Patient- and treatment characteristics are summarized in Table 4-I. There was one female, and the age of the participants were between 61 and 84 years.

Table 4-I: information of the included patients disease and treatment.

P	ICD10 code	Histologic type	Tumor site	T	N	M	Fr	Target dose [Gy]
1	C15.5	AC	LP	1-2			23	41.4
2	C15.5	SCC	LP	3-4			23	41.4
3	C15.5	SCC	LP/C	2	1		23	41.4
4	C15.4	SCC	MP	3	1		33	66.0
5	C16.0	AC	LP/C	3	2	1	28	56.0
6	C15.5	SCC	LP	3	1	1	28	56.0
7	C15.4	SCC	MP	1-2	1		28	56.0
8	C15.5	AC	LP	2-3	1		25	50.0
9	C15.5	AC	LP	3	1-2		25	50.0
10	C15.3	SCC	UP	1-2			33	66.0
11	C15.5	AC	LP	3	1-2		25	50.0
12	C15.5	AC	LP	3-4	1	1	28	50.4

P=patient number. ICD10 code= International classification of diseases, version 10. Histological type, AC= adeno carcinoma, SCC= Squamous cell carcinoma. Tumor site; LP= lower part of thoracic esophagus, LP/C= Lower part of esophagus/cardia, MP= middle part of esophagus, UP= upper part of esophagus. T, N, M= Tumor-, lymph node-, metastases- stadium. Fr= number of treatment fractions. Gy= Gray (Joule/kilo).

The patients had median (range) 4 (1 to 6) visible markers at planning CT; 1(1 to 2) markers were placed at the upper tumor border, 1(0 to 4) markers at the distal tumor border and 0 (0 to 2) markers were located in lymph nodes. All patients had one or two markers at upper tumor border, and nine patients had one or two markers at lower tumor border. The three patients with no markers at lower tumor border had stenosis prior to treatment that hindered implantation. Five patients had one or two markers in lymph nodes. Anatomically, markers were distributed with two markers in the cervical esophagus; two in the upper thoracic esophagus, nine in the middle thoracic esophagus, fifteen in the lower

thoracic esophagus and eleven in the esophagogastric junction (Figure 4-1). Patient 1 had six visible markers, but the three most caudal markers were not accessible for motion analysis because the markers were placed so close together that is was difficult to separate them due to the image artefacts. They were still countable in a planar kV image.

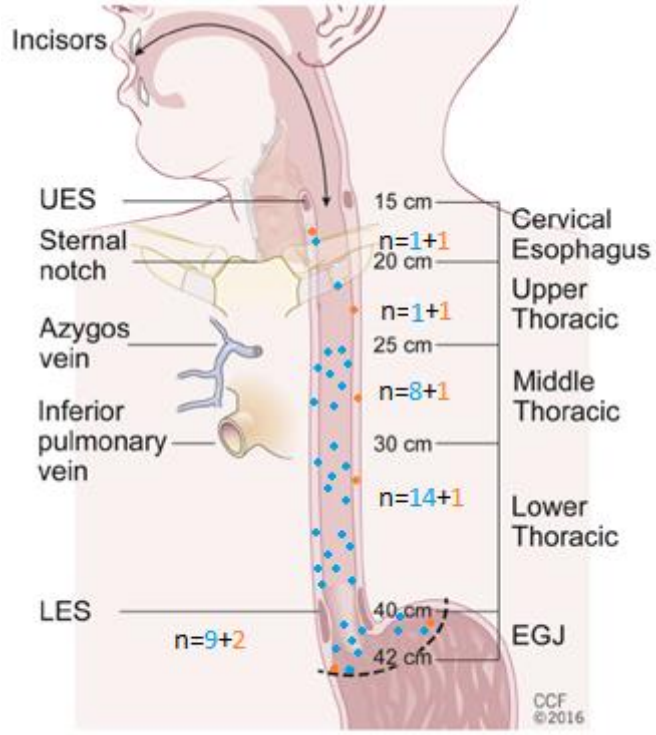

Figure 4-1: Illustration of all markers according to anatomical location. Blue dots are markers located at tumor boarder, orange dots are markers located in lymph nodes.(Rice et al., 2017).

The mean number of days from implantation to start of treatment were 12 (range 8 - 25), and 50 days (range 41 - 57) to end of treatment. The treatment fractions were delivered on weekdays until the prescribed number of treatment fractions was reached. Mean number of treatment fractions were 27(range 23 - 33). One of the patients had two treatment fractions in one day, to finish treatment before the last weekend. The patients received a median dose of 50.2 Gy, ranging from 41.1 - 66 Gy (Table 4-I). The three patients who had a target dose of 41.4 Gy had surgery after completed RT. The tumor site was in the lower part of the esophagus in nine of the cases, of which two reached into the cardia. Of the remaining, two were in the middle part and one in the upper part of the esophagus.

4.6 Imaging

The number of images per imaging modality per patient is listed in Table 4-II. The number of CBCTs and orthogonal images vary because of varying number of treatment fractions (Table 4-I), change in protocol, patient related reasons and misunderstanding of the protocol. Patient related reasons could be various medical reasons that affected the ability to comply to the imaging protocol. A total of 24 CT scans, 302 CBCT scans and 61 pairs of planar images were acquired and analyzed.

Table 4-II: Number of images/scans per modality for each patient.

P	CT	4DCT	CBCT	Orthogonal kV
1	2	2	20	3
2	2	2	21	3
3	2	2	20	4
4	2	2	25	8
5	2	2	25	6
6	2	2	28	5
7	2	2	28	5
8	2	2	25	5
9	2	2	25	5
10	2	2	33	6
11	2	2	25	6
12	2	2	27	5
Total	24	24	302	61

P= patient number CT= computed tomography, 4DCT= four dimensional computed tomography, CBCT= cone beam computed tomography, kV=kilo voltage.

4.7 What fraction of implanted markers stay attached during radiotherapy?

There were 42 visible markers at the planning CT scan. Three of these markers were not included in the PTV, which gave 39 markers. One marker detached between planning CT and RT start, so that 38 (97%) markers were present at start of RT. In total 36 (92%) markers were still present at end of treatment; in Patient 9 one marker was lost at fraction 7/ day 17 and one at fraction 19/day 35. The number of markers at different time points per patient is shown in Table 4-III.

Table 4-III: Number of markers present at different time points for each patient.

Patient	CT_p	RT_s	RT_e
1	6	6	6
2	2	2	2
3	4	4	4
4	4	4	4
5	1	1	1
6	2	2	2
7	3	3	3
8	4	4	4
9	3	3	1
10	3	2	2
11	4	3	3
12	4	4	4
Median (range)	3.5(1-6)	3(1-6)	3(1-6)
$N_t^{markers}$ (#)	39	38	36
$F_t^{markers}$ (%)	100	97	92

Time points t given by: CT_p = planning CT scan, RT_s = start of radiotherapy and RT_e = end of radiotherapy. $N_t^{markers}$ = number of markers at time point t. $F_t^{markers}$ = fraction of markers at time point t.

The three most caudal markers in patient 1 were implanted relatively close together; something which caused increased image artefacts on the CBCT images. The position of the markers were difficult to determinate with certainty, hence the markers were excluded from the analysis of position variation. The markers were still present and countable on planar images.

4.8 Do the planning target volume account for variation in marker position during a course of radiotherapy?

PTV covered all of the markers in all treatment fractions for ten out of 12 patients.

Patient 12 had one marker that was observed partially outside PTV in one treatment fraction, still all markers were covered in 96% of the treatment fractions for this patient.

For the two caudal markers in Patient 8 the PTV margin was not sufficient (Figure 4-2). One was totally outside the PTV in 8% of the treatment fractions, partially outside in 29% and inside PTV in 63% of the treatment fractions. The other was outside PTV, partially outside PTV and inside PTV in 38%, 38% and 25% of the treatment fractions, respectively. Hence, for Patient 8 all markers were covered in 25% of the fractions, and hereby failed to meet the criteria of PTV coverage >95% of the treatment fractions.

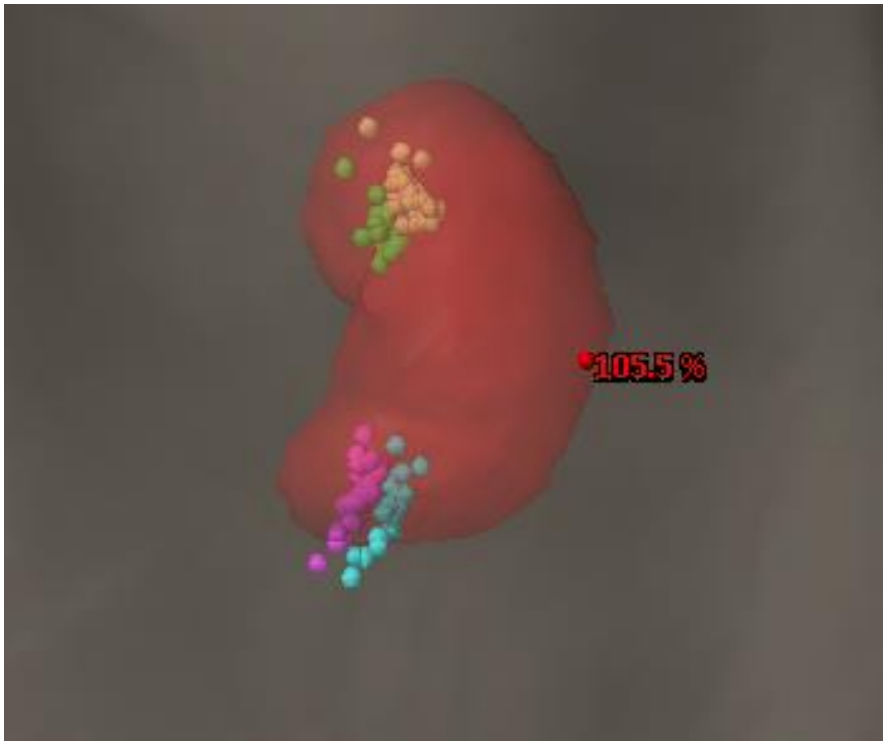

Figure 4-2: Lateral view of the planning target volume (red structure) with all marker centroid positions in patient 8.

The PTV thus accounted for variation in marker positions for more than 95 % of treatment fractions for 92 % (11/12) of the patients and was therefore considered sufficiently robust.

4.9 What is the interfractional variation in marker position?

Thirty-five markers were included in the analysis of interfractional position variation.

The frequency distribution of interfractional position variations in the lateral-, ventral- and longitudinal directions for all markers are shown in Figure 4-3. The frequency distributions had median values of -0.06 cm, -0.11 cm and -0.20 cm in the lateral-, ventral- and longitudinal directions, respectively (Table 4-IV). The width of the frequency distribution characterized by the interquartile range (IQR) was 0.41 cm, 0.47 cm and 0.80 cm in the lateral-, ventral and longitudinal directions, respectively (Table 4-IV). In other words, 50% of the markers were at treatment located within 3 mm to the right, 1 mm to the left, 3 mm anterior, 1 mm posterior, 2 mm cranial and 6 mm caudal to the position at planning CT. However, the frequency distributions in Figure 4-3 have long tails, meaning that some of the markers were at treatment located quite far from the position at planning. All markers were at treatment located within 1.86 cm to the right, 1.90 cm to the left, 1.94 cm anterior, 1.10 cm posterior, 2.40 cm caudal and 1.00 cm cranial (Table 4-IV). A few markers had a systematic shift (median marker displacement) ≥1 cm; one in the left direction and four in the caudal. In the longitudinal direction there were also 10 markers which had a systematic shift ≥ 0.5 cm in the caudal direction, about twice as many as in the ventral and right directions.

To investigate if there was a significant difference in motion directions, the median of patient-specific IQR was compared between the lateral-, ventral- and longitudinal directions (Independent Samples Median Test) and it showed that the median of the IQR was significantly different between the directions ($p<0.05$). The pairwise test showed that it was the longitudinal direction that differed from the lateral- and ventral directions. Hence, the motion was significantly larger in the longitudinal direction compare to the lateral and ventral directions.

The influence of anatomical region of the esophagus where the individual marker was located on interfractional variation in marker position is shown in Table 4-IV. In order to investigate if the interfractional variation in marker position was different between groups of anatomic location, the marker position data was initially tested for normality (Shapiro-Wilk test) and was found not normally distributed. Nonparametric tests (Independent Samples Median test) showed significant differences in medians between markers located in cervical-/upper thoracic esophagus and all other sub-groups and between middle thoracic esophagus and esophagogastric junction/lower thoracic esophagus in the longitudinal direction. In the lateral direction there were significant different medians in all sub groups except for markers located in middle- and lower thoracic esophagus. Likewise, in the ventral direction there were significant different medians in all sub groups except for markers located in lower thoracic esophagus and esophagogastic junction. Testing all variations in marker position regardless of direction, the differences in medians are significant between all anatomical sub-groups, except between middle- and lower thoracic esophagus. Finally, testing medians of IQR between markers in the anatomical sub divisions (Independent Samples Median test) the only significant difference was between esophagogastric junction and middle thoracic esophagus in the longitudinal direction.

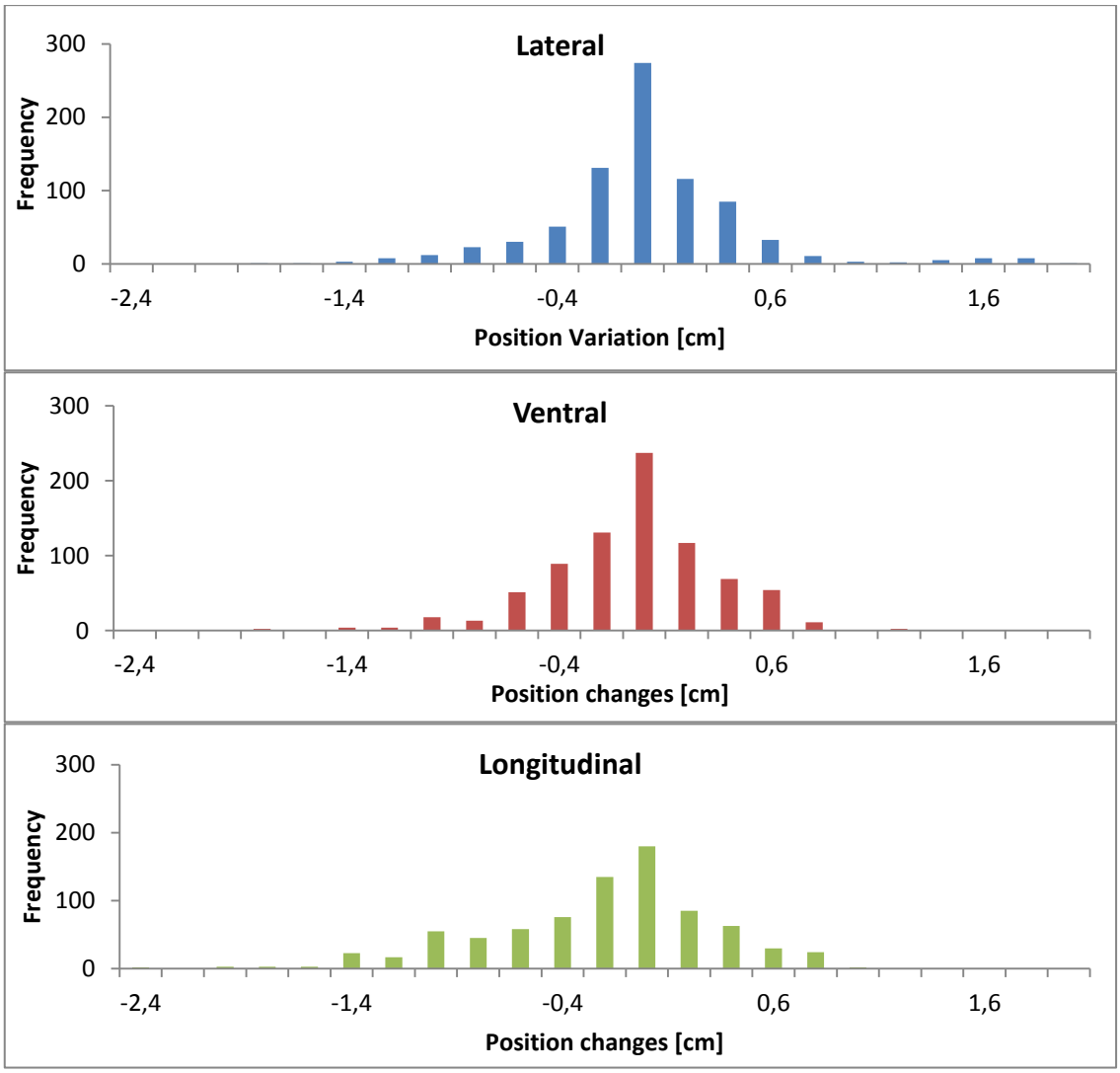

Figure 4-3: Frequency distribution of variation in marker position relative to position at planning CT in the three directions; lateral, anterior–posterior and longitudinal.

Table 4-IV: Median, range and interquartile range of changes in position of the markers relative to position on the planning CT per anatomical region of esophagus.

Direction / *Location*	*Lateral*	*Ventral*	*Longitudinal*
	Median (range) IQR	Median (range) IQR	Median (range) IQR
	[cm]	[cm]	[cm]
CE/UTE	-0.02 (-0.81 - 0.27) 0.13	0.13 (-0.45 - 0.66) 0.38	0.20 (-0.20 - 0.40) 0.20
MTE	0.00 (-0.45 - 1.33) 0.36	0.00 (-1.25 - 0.78) 0.40	-0.40 (-1.80 - 1.00) 0.80
LTE	0.00 (-0.80 - 1.90) 0.41	-0.27 (-1.24 - 0.57) 0.36	-0.40 (-2.40 - 1.00) 0,80
EGJ	-0.39 (-1.86 - 0.83) 0.70	-0.12 (-1.94 - 1.10) 0.51	-0.20 (-1.87 - 0.80) 0,67
OVERALL	-0.06 (-1.86 - 1.90) 0.41	-0.11 (-1.94 - 1.10) 0.47	-0.20 (-2.40 - 1.00) 0.80

IQR= interquartile range, CE= cervical esophagus, UTE= upper thoracic esophagus, MTE=Middle thoracic esophagus, LTE= lower thoracic esophagus and EGJ= esophagogastric junction.

The 3D vector length of the positional changes (i.e. the *change vector*) demonstrated the total length of the change in marker position relative to the planning CT position. The frequency distribution of the length of the change vector for all markers and per anatomical location is shown in Figure 4-4. Of all position change vectors, 23% had a length of more than 1 cm and 58% had a length of more than 0.5 cm (Table 4-V). The long tail of the frequency distribution is noticeable, showing vector lengths of more than 2.5 cm. The median and range of the change vector length per marker, grouped for each patient, is presented in Figure 4-5. There is a notable difference in interfractional position variation not only between patients, but also between markers at different locations within the patient, as shown in Figure 4-6.

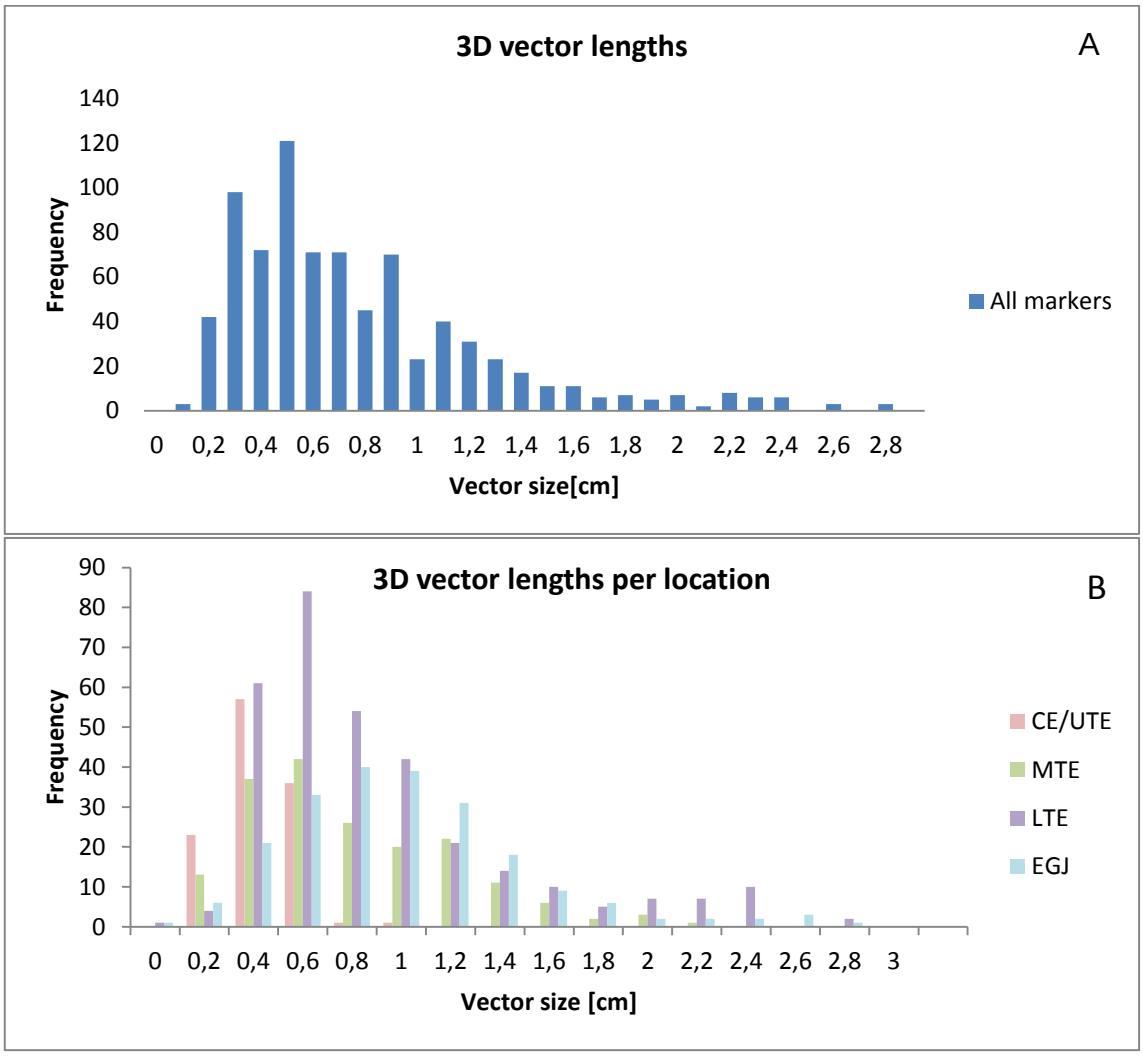

Figure 4-4: Distribution of 3D change vector lengths $|\vec{v}|$ for all markers (A) and per anatomical location of the markers (B); cervical esophagus/upper thoracic esophagus (CE/UTE), middle thoracic esophagus (MTE), lower thoracic esophagus (LTE) and esophagogastic junction (EGJ). The vector $\vec{v}$ represents the change in position of the marker from planning CT to CBCT.

Table 4-V: Distribution by percentage per anatomical location of the 3D position changes $|\vec{v}|$ exceeding 0.5 cm and 1.0 cm.

Anatomical location of marker	$\|\vec{v}\|$ > *0.5 cm [%]*	$\|\vec{v}\|$ > *1 cm[%]*
CE/UTE	11	0.0
MTE	56	25
LTE	64	23
EGJ	77	34
Overall	58	23

$|\vec{v}|$= 3D change vector length. CE/UTE= cervical esophagus/upper thoracic esophagus, MTE= middle thoracic esophagus, LTE= lower thoracic esophagus and EGJ= esophagogastric junction.

The influence of anatomical location on the 3D change vector length was noticeable in Figure 4-4 B, and in Table 4-V. The percentage of change vectors exceeding 0.5 cm and 1 cm per anatomical location were smallest for markers located in cervical esophagus/upper thoracic esophagus and largest for markers located at the esophagogastric junction. The median and range of the change vector length per marker, grouped per anatomical location, is presented in Figure 4-6. The IQR per anatomical location were 0.19 cm, 0.60 cm, 0.50 cm and 0.56 cm for the cervical- and upper thoracic esophagus, middle thoracic esophagus, lower thoracic esophagus and esophagogastric junction, respectively. There is a notable difference between the markers located in the cervical esophagus/upper thoracic esophagus both in median values and variation in interquartile range compare to the other anatomical regions. For the other anatomical regions, there are notable variations in both median values and IQR of the change vector length between markers belonging to the same anatomical region.

The change vector data grouped according to anatomical location of the markers were not normally distributed. Nonparametric test (Independent Samples Median Test) were performed to compare medians between the anatomical groups, and the medians were found to be significantly different across the groups (p=0.00). The pairwise tests showed no significant different in median between markers located in middle- and lower thoracic esophagus. Otherwise, the differences in medians were significant.

Three of the patients had a stenosis at acquisition of the planning CT. During the treatment, the stenosis resolved in all three patients. To investigate the influence of stenosis on interfractional marker position variation, we compared groups of patients with (n=3) and without (n=9) stenosis. A significant difference ($p<0.05$) in median values of the interfractional marker position variation of 0.20 cm, -0,21 cm and -0,40 cm in the lateral, ventral and longitudinal directions for patients with stenosis versus -0.11 cm, -0.10 cm and 0.80 cm in the lateral, ventral and longitudinal directions for patients without stenosis was found (Independent Samples Median Test). Interquartile ranges of the marker positions were 0.74 cm for patients with stenosis vs 0.38 cm for patients without stenosis, which was also significant. It was however notable that interfractional median variation was larger in the ventral and lateral directions for patients with stenosis, while patients without stenosis had larger median variation in the longitudinal direction.

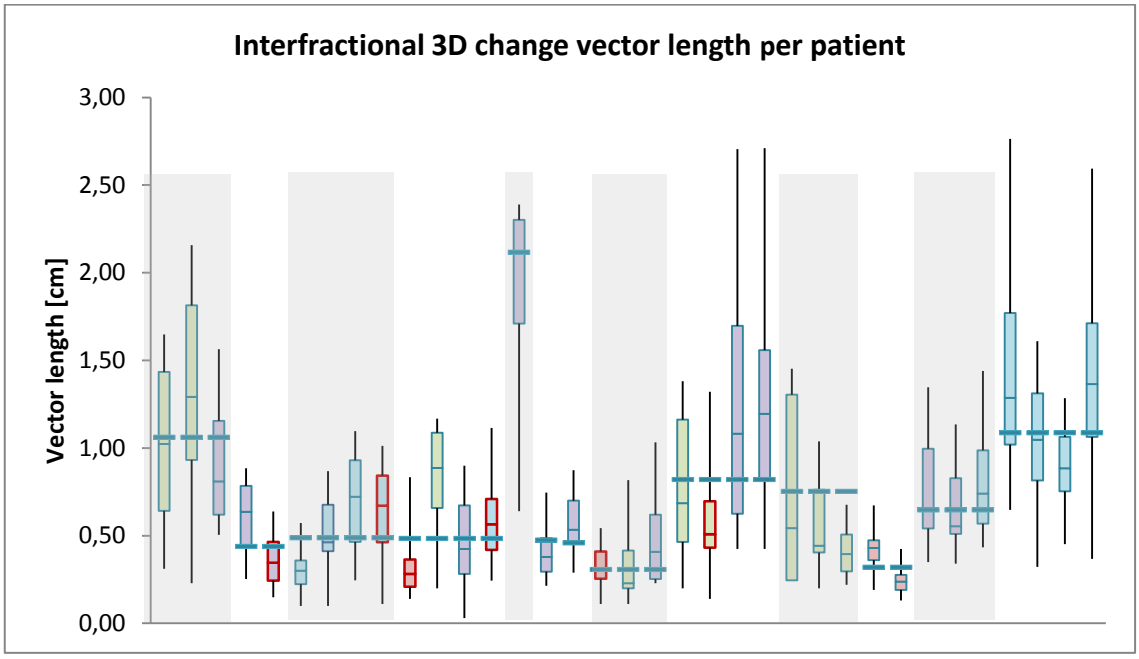

Figure 4-5: The markers are grouped per patient; patient 1 at the left with three markers in the area with a grey background, patient 2 next with two markers in the area with white background, etc. The stapled line across each group shows the patient median. Each single marker is colored according to anatomical location, as in Figure 4-5. Markers with red boarder line were located in lymph nodes.

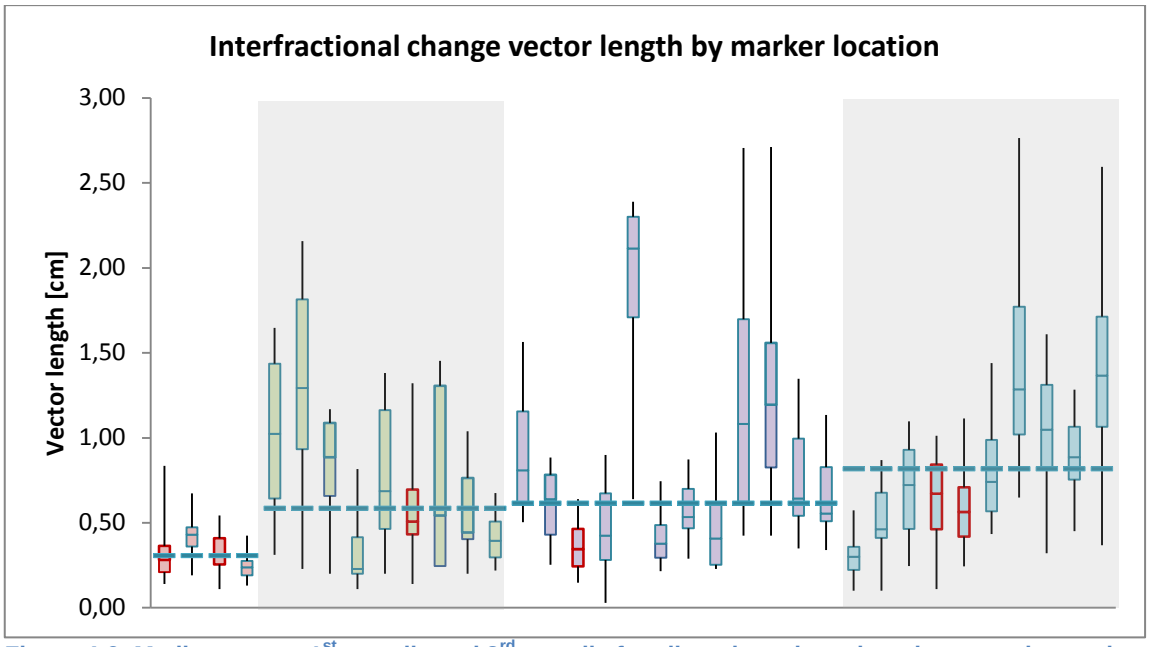

Figure 4-6: Median, range, 1st quartile and 3rd quartile for all markers, based on the same data as in Figure 4. The markers are grouped per anatomical localization; cervical esophagus/upper thoracic esophagus (CE/UTE, red), middle thoracic esophagus (MTE, green), lower thoracic esophagus (LTE, purple) and esophagogastric junction (EGJ, blue). The horizontal streak at the right side of each group is the group mean, and is sized according to the scale on the right side axis.

Tumor regression is another factor that could affect the marker position changes. Figure 4-7 shows an example of tumor regression during radiotherapy in Patient 9. Depending on where in the circumference of the esophageal wall a marker is implanted it may affect the measured change in position considerably. The visible marker in Figure 4-7 C (at the intersection of the green and blue lines) has a changed position at the repeated CT scan, Figure 4-7 D, where it has moved away from the intersection.

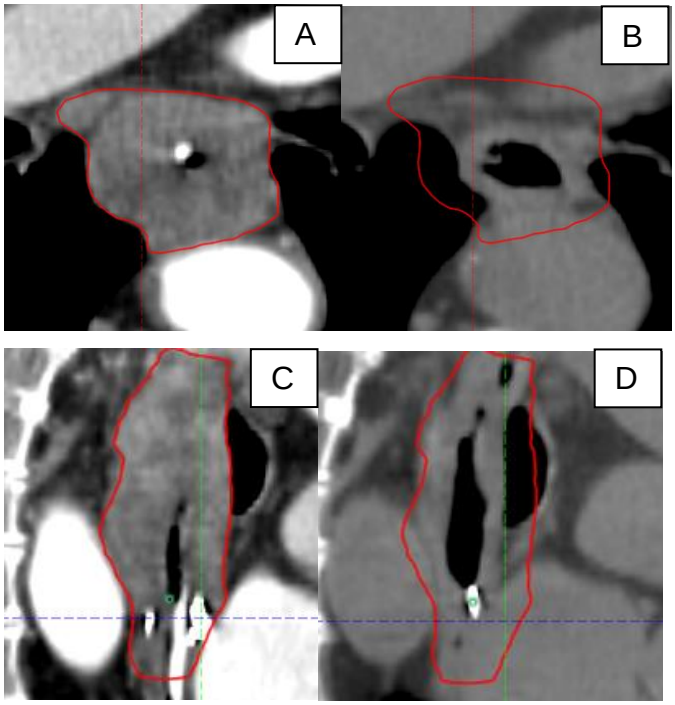

Figure 4-7: Patient 9: an example of tumor regression. A: Transversal view of esophageal diameter at the planning CT. B: Transversal view from the repeated CT scan at the last treatment day. C: Sagittal view from the planning CT. D: Sagittal view from the repeated CT scan.

Interfractional marker position variation is usually divided into systematic and random uncertainties. This methodology assumes that the data is normally distributed. The position variation for each marker was therefore tested for normality (Shapiro-Wilk test) per direction, and the test showed that the interfractional marker position variations were normally distributed for some of the markers in some of the directions. In spite of that, the margins were calculated with the purpose to compare our data with other studies that have used this methodology in margin estimation. The data were used to calculate the group mean (M), standard deviation of systematic errors (Σ) and the root mean square of standard deviations of random errors (σ), and finally to estimate the required margin (Table 4-VI).

Table 4-VI: Based on the data on variation in marker position from this sample of patients the required margins are estimated.

Anatomical site of the marker		Lateral [cm]	Ventral [cm]	Longitudinal [cm]
Cervical-/upper thoracic esophagus (n=4)				
	M	-0.1	0.1	0.1
	Σ	0.1	0.0	0.1
	σ	0.1	0.1	0.1
	2.5Σ+0.7σ	0.3	0.2	0.2
Middle thoracic esophagus (n=9)				
	M	0.1	-0.0	-0.4
	Σ	0.3	0.3	0.4
	σ	0.2	0.3	0.4
	2.5Σ+0.7σ	0.9	1.0	1.2
Lower thoracic esophagus (n=12)				
	M	0.1	-0.3	-0.4
	Σ	0.5	0.1	0.2
	σ	0.2	0.2	0.4
	2.5Σ+0.7σ	1.4	0.4	0.7
Esophagogastric junction (n=10)				
	M	-0.4	-0.3	-0.2
	Σ	0.4	0.3	0.5
	σ	0.3	0.4	0.3
	2.5Σ+0.7σ	1.1	1.0	1.4
Overall (N=35)				
	M	-0.1	-0.2	-0.3
	Σ	0.5	0.3	0.4
	σ	0.3	0.3	0.4
	2.5Σ+0.7σ	1.3	0.9	1.3

M= group mean, Σ= standard deviation of systematic errors, σ= (Σ) and root mean square of standard deviations of random errors. Caution: Margins are estimated for a small sample of patients on data that only were partially normally distributed and should not be applied in patients.

A possible time trend in the interfractional position variation could explain the deviations from normality. When testing (Regression, Data Analysis tool in Excel) for time trend per marker and per direction, it was found that 44% had a regression line that was significant different from zero, i.e. the changes in

position are likely to have a time-trend for these markers in the given directions. The cases of significant changes were equally distributed over the lateral-, ventral- and longitudinal directions. There were respectively 33%, 51%, 41% and 45% significant changes over time in the cervical esophagus/upper thoracic esophagus, middle thoracic esophagus, lower thoracic esophagus and the esophagogastric junction. Eighty percent of the markers had a trend line-slope significant different from zero in one or more directions. The trend analysis performed for all data from all twelve patients and sorted per direction, showed that the slope of the trend line were significant different from zero in the lateral- ($p=0.04$) and ventral ($p=0.00$) direction. The estimated change in position during a treatment course with 25 treatment fractions, done by multiplying the slope of the regression line by 25 treatment fractions, was respectively 1 mm, 3 mm and 0.4 mm in the ventral-, lateral- and longitudinal directions on a group level. For a few markers with the steepest slope the estimated position change exceeded 1 cm in 25 fractions.

4.10 What is the intrafractional variation in marker position?

The frequency distributions of intrafractional change in marker position (e.g. due to breathing motion) in lateral (Δx), ventral (Δy) and longitudinal (Δz) directions are shown in Figure 4-8 A-C. Note that Δx and Δy can take both positive and negative values, while Δz can take only positive values due to the definition of the exhale position being the most cranial point of the marker trajectory as seen on CBCT. The frequency distributions were tested for normality (Shapiro-Wilk test) and were found not normally distributed. They are therefore characterized by median, range and interquartile range (IQR) in Table 4-VII.

Overall, intrafractional changes were largest in the longitudinal direction where 50% of the changes were between 1.00 cm and 1.40 cm. Some intrafractional change was also found in the ventral direction, but here 50% of the changes were between 1 mm and 3 mm. Very small changes were found in lateral direction (Table 4-VII and Figure 4-9). The distributions in ventral and longitudinal direction have narrow tails because of a few outliers. The medians of interquartile ranges (IQR) were tested across the three directions (Independent Samples Median Tests), but there was no significant difference between any of the directions ($p=0.21$).

For the markers located in lymph nodes the median (IQR) overall displacement of the markers were respectively 0.00 cm (0.23 cm), 0.00 cm (0.35 cm) and 1.00 cm (0.40 cm) in the lateral, ventral and longitudinal directions. To explore if there were significant differences between markers located in lymph nodes and markers located in the esophageal wall concerning median displacement and median IQR, a nonparametric test (Independent Samples Median Test) were performed. There were no significant difference in median ($p=0.83$) or median IQR's ($p=0.65$) between markers located in lymph nodes and markers located in the esophageal wall.

The influence of anatomical region of the esophagus where the individual marker was located on intrafractional variation in marker position is shown in Table 4-VII. In the longitudinal direction IQR was increasing as the markers are

more caudally located. The same trend was observed in the ventral direction, even though the size of the variation was less pronounced. In the ventral direction the IQR was increasing from 0.23 cm in the cervical- and upper thoracic esophagus to 0.41 cm in the esophagogastric junction, compared to 0.20 cm increasing to 0.80 cm in the longitudinal direction. To investigate if the differences were significant, the distribution of marker-specific IQR was compared between the anatomical sub-divisions of the esophagus (Independent Samples Median Test) and is showed a significant difference between markers located in cervical esophagus/upper thoracic esophagus and markers located in esophagogastric junction.

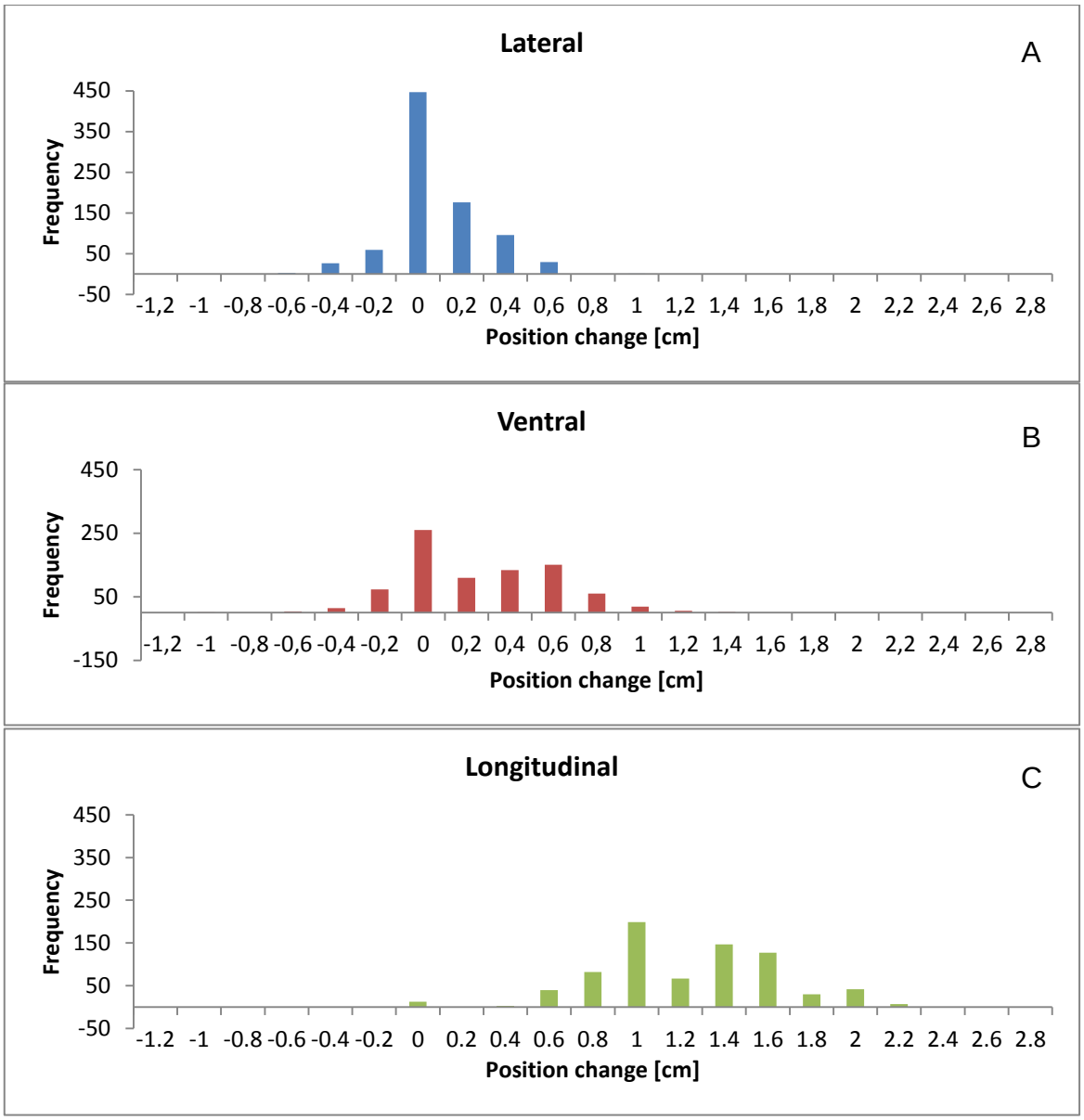

Figure 4-8: Frequency distribution of intrafractional position changes in marker position in A lateral-, B ventral- and C longitudinal direction.

Table 4-VII: Median, range and interquartile range for intrafractional changes per direction of the markers for each anatomical region of esophagus.

Direction / *Location*	*Lateral*	*Ventral*	*Longitudinal*
	Median (range) IQR [cm]	Median (range) IQR [cm]	Median (range) IQR [cm]
CE/UTE	0.00 (-0.14 - 0.34) 0.13	0.14 (-0.41 - 0.55) 0.23	0,80 (0.0 - 1,20) 0.20
MTE	0,00 (-0.68 - 0,44) 0.25	0.11 (-1.13 - 0.92) 0.33	1.20 (0.60 - 2.20) 0.20
LTE	0,00 (-0.58 - 0.45) 0.00	0.22 (-0.66 - 1.30) 0.41	1.20 (0.00 - 2.20) 0.40
EGJ	0,10 (-0.77 - 0.86) 0.30	0.31 (-0,67 - 1.04) 0.41	1.20 (0.00 - 2.80) 0.80
OVERALL	0.00 (-0.77 - 0.86) 0.12	0.12 (-1.13 - 1.30) 0.41	1.20 (0.00 - 2.80) 0.40

IQR= interquartile range, CE= cervical esophagus, UTE= upper thoracic esophagus, MTE=Middle thoracic esophagus, LTE= lower thoracic esophagus and EGJ= esophagogastric junction

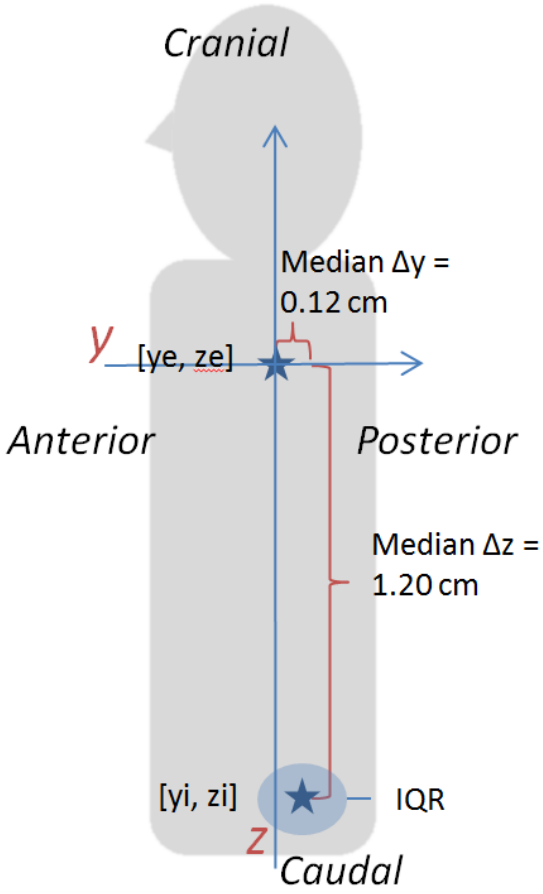

Figure 4-9: Illustration of the overall intrafractional variation, Table 4-IIV. $\Delta y=y_e-y_i$, $\Delta z=z_e-z_i$, where i = position at inspiration and e = position at expiration. IQR= inter quartile range.

The median length of the 3D intrafractional change vector **Δv**, which can be interpreted as the median 3D breathing amplitude, was 1.22 cm (range: 0.40 to 2.97 cm). The IQR was 0.41 cm, hence 50% of the vectors were between 1.02 to 1.43 cm long. The length of the marker was not subtracted from the vector, and therefore contributed with 0.64 to 5 mm to the amplitude, according to the markers orientation. Excluding the markers located in lymph nodes gave the same 3D amplitude (median of 1.22 cm, range: 0.4 to 2.97 cm). For the six markers located in lymph nodes the median amplitude was 1.11 cm (range: 0.60 to 2.02 cm).

The size and variation of the 3D intrafractional motion amplitudes per marker and patient are shown in Figure 4-10. As to influence of anatomical location of

the marker on the 3D vector length, variation in amplitude per marker and sorted on anatomical location, is shown in Figure 4-11. In order to investigate if there was a significant difference according to were the markers were located, the distribution of vector length were compared between the anatomical locations of the markers. Nonparametric test (Independent Samples Median Test) showed a significant difference between the locations, except between middle thoracic esophagus and both lower thoracic esophagus and esophagogastric junction. The variation between the patients was noteworthy as the median 3D vector per patient varied between1.00 to 1.53 cm, while it was 1.00 to 1.31 cm among the groups of markers per anatomical location. Likewise, the variation in IQR was 0.15 to 0.92 cm between the per-patient-grouped markers, while it was 0.21 to 0.67 cm between the anatomical groups. Though there was a visual trend for the median value in Figure 4-11, with increasing median value for markers located more caudally, there was considerable variation per marker for some markers and between the markers as such. There was a marked less median and variation in markers in the cervical- and upper thoracic esophagus than for the other locations.

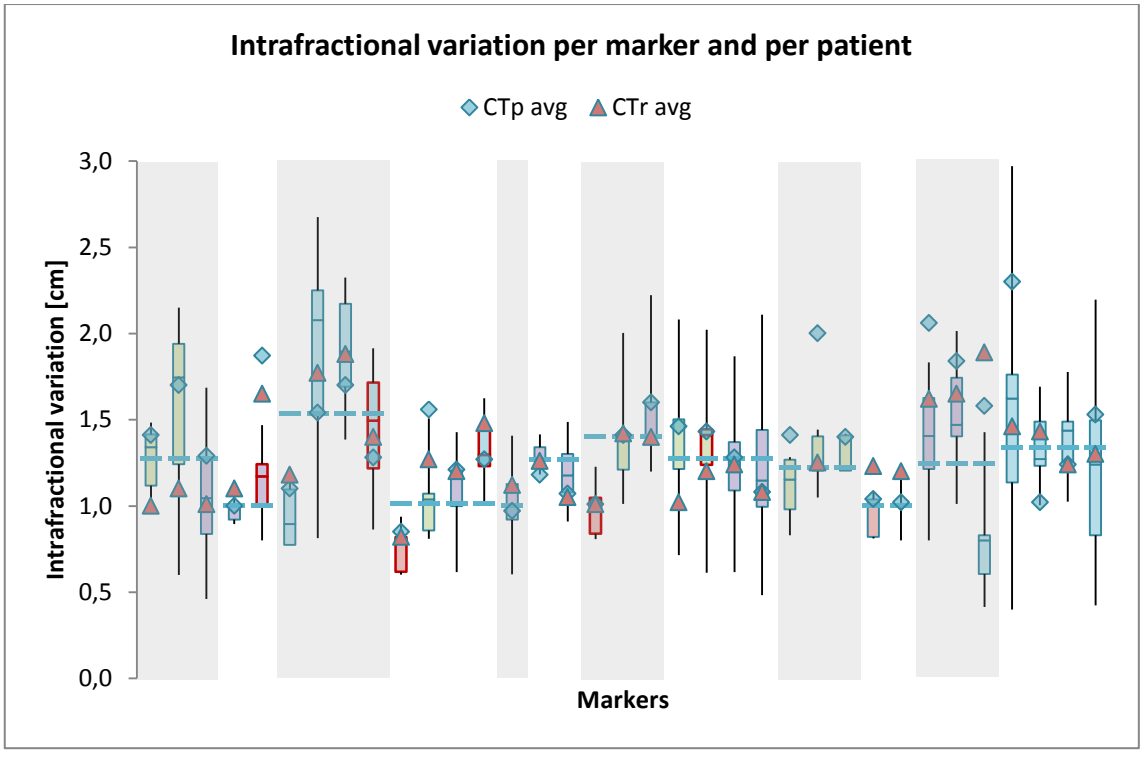

Figure 4-10: Variations in intrafractional motion per marker. The markers are sorted per patient. The stapled line across each patient is the group medians. Further description as in Figure 4-11.

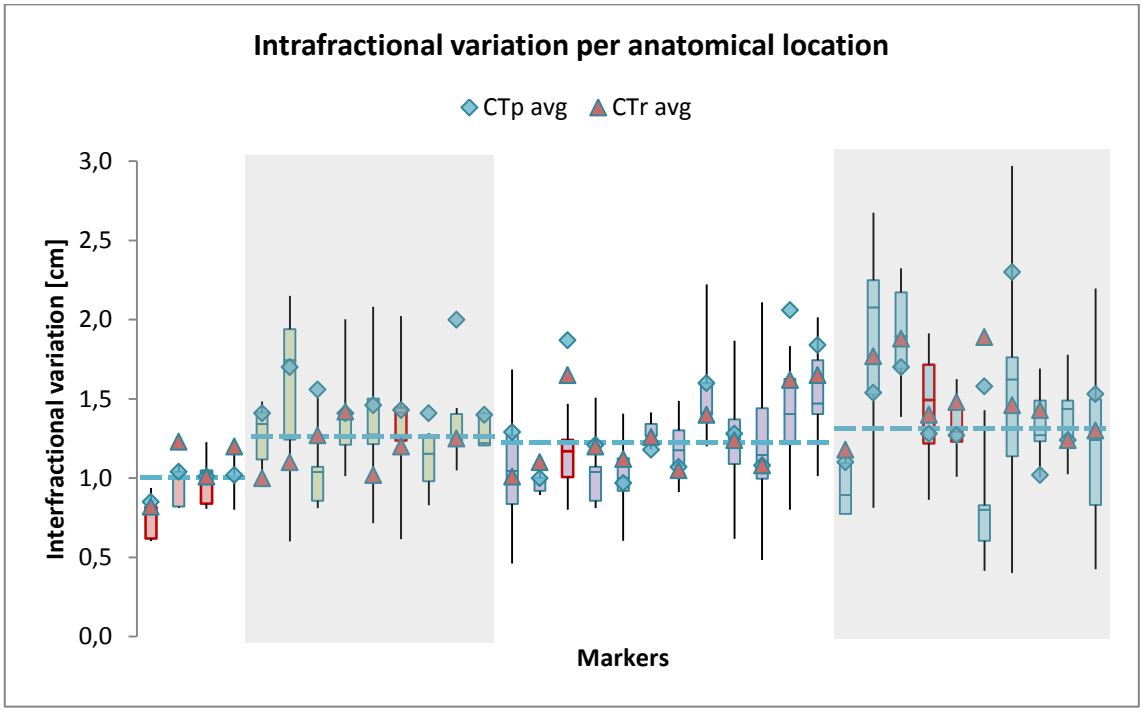

Figure 4-11: Variations in intrafractional motion per marker. The markers are sorted per anatomical location. The markers are colored according to anatomical location; markers located in cervical esophagus/upper thoracic esophagus are red, middle thoracic esophagus are green, lower thoracic esophagus are purple and esophagogastric junction are blue. Markers located in lymph nodes have a red boarder line. The stapled line across each anatomical group is the group medians. The diamond and the triangle are the intrafractional variations from the average reconstruction of planning CT scan and the repeated CT scan.

Sorted anatomically, the ranges for the vector length were respectively 0.60 to 1.23 cm, 0.60 to 2.15 cm, 0.46 to 2.22 cm and 0.40 to 2.97 cm in the cervical- and upper thoracic esophagus, middle thoracic esophagus, lower thoracic esophagus and the esophagogastric junction. Hence the minimum vector length decreases slightly, while the maximum length increases with more caudal localization. This is shown in Figure 4-10 B. The marker with the widest range was located in the gastroesophageal junction and about 7 cm lateral to the midline of the patient (Figure 4-12).

The variation in marker breathing amplitudes for planning CT (CT_p), repeated CT (CT_r) and CBCT, characterized by median, range and IQR is shown in Table 4-VIII. The median vector of treatments (M_{tr}) for each marker was from 0.54 cm less than CT_p to 0.78 cm larger than CT_p. The difference in vector size between the CT_p and CT_r was from -0.41 to 0.84 cm. For the markers located in lymph nodes the difference between the CT_p and M_{tr} vary from -0.03 to 0.66 cm, and

the difference between the CT_p- and the CT_r -vector size varied from -0.21 to 0.23 cm.

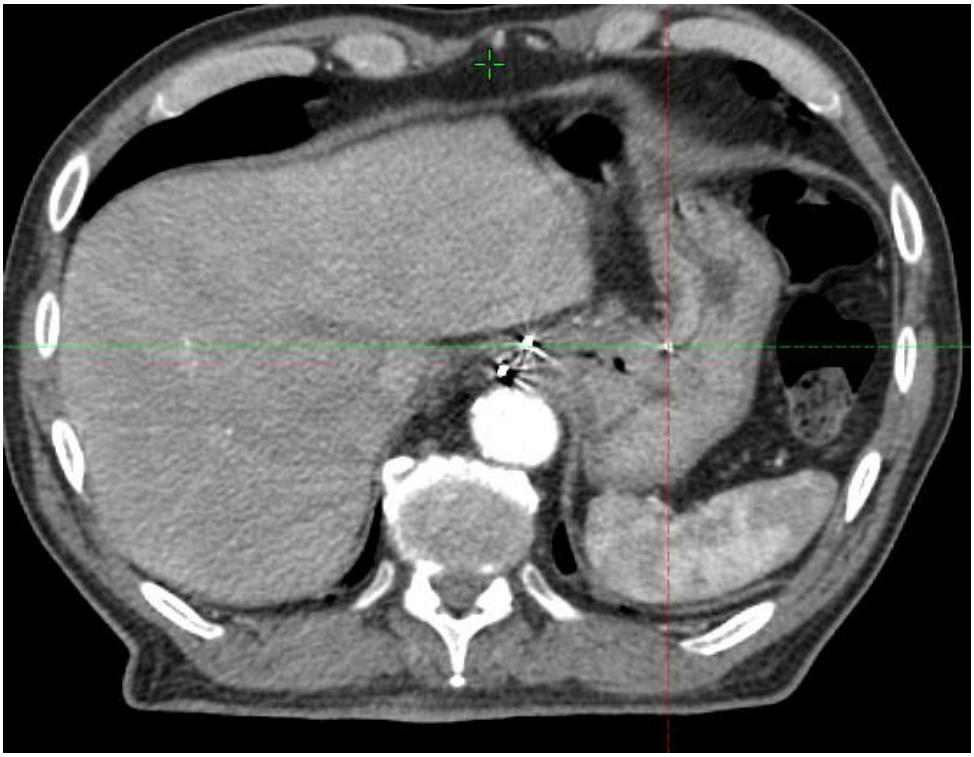

Figure 4-12: The marker at the intersection between the red and the green line was located about 7 cm laterally to the patient mid line in this transversal view from the planning CT scan.

Table 4-VIII: Breathing motion on the average reconstruction of the 4DCT scan at CT_p and CT_r compared to breathing motion on pre-treatment CBCT.

	Median[cm]	Range [cm]	IQR [cm]
CT_p	1.40	1.08 – 1.58	0.50
CT_r	1.24	1.10 – 1.45	0.35
$Overall_{tr}$	1.22	0.40 – 2.97	0.41

CTp= planning CT, CTr= repeated CT scan, $Overall_{tr}$= overall treatment

The overall IQR for CBCT vectors were 0.41 cm, hence 50% of the vectors were from 1.02 to 1.43 cm. Out of 821 vectors from CBCTs, 128 (16%) were larger than the maximum vector at the corresponding planning 4DCT, and 178 (22%) vectors were larger than the maximum vector at the corresponding repeated 4DCT scan. It is also noteworthy in Figure 4-10 that for five markers the vector length at planning CT was larger than the maximum vector length at treatment, likewise for the repeated CT scan for four of the markers. For two

markers both the planning CT- and the repeated CT scan had a larger vector size. Since the intrafractional variation at planning 4DCT is essential to determination of patient specific internal margin (IM, Figure 1-8) the IM could possibly be overestimated in these cases. The vector length at planning- or repeated 4DCT scan was never less than the minimum vector length at treatment, yet vector length at planning 4DCT was less than the 1st quartile for four markers and repeated 4DCT was less than 1st quartile in seven markers, and hence was less than the central 50% of the vectors.

Out of 35 markers 15 had an overestimated size of the breathing motion at the planning 4DCT. The breathing motion was overestimated for all markers in one patient (Patient 11). The breathing motion was underestimated for three markers, of which two were in the same patient.

Sorted on anatomical site of the markers, the difference in vector size between CT_p and M_{tr} was largest in the middle esophagus with -1.12 to1.02 cm, followed by esophagogastric junction with -0.54 to 0.77 cm and lower thoracic esophagus with -0.15 to 0.73 cm. There was practically no difference for markers in the cervical- and upper thoracic esophagus with 0.00 to 0.05 cm, Figure 4-10. Likewise, the difference between CT_p and CT_r was largest in the esophagogastric junction with -0.84 to 0.84 cm, followed by middle- and lower thoracic esophagus with -0.48 to 0.75 cm and -0.15 to 0.81 cm, respectively. The differences were small in the cervical- and upper thoracic esophagus with -0.20 to 0.03 cm.

As margins in HUH were defined per patient, the median vector size from average reconstructions of all 4DCTs for each patient was compared to the median, 1st quartile, 3rd quartile and range for all vectors per patient during treatment, Figure 4-13. Analyzed per patient the breathing motion was overestimated in three patients and underestimated in one patient.

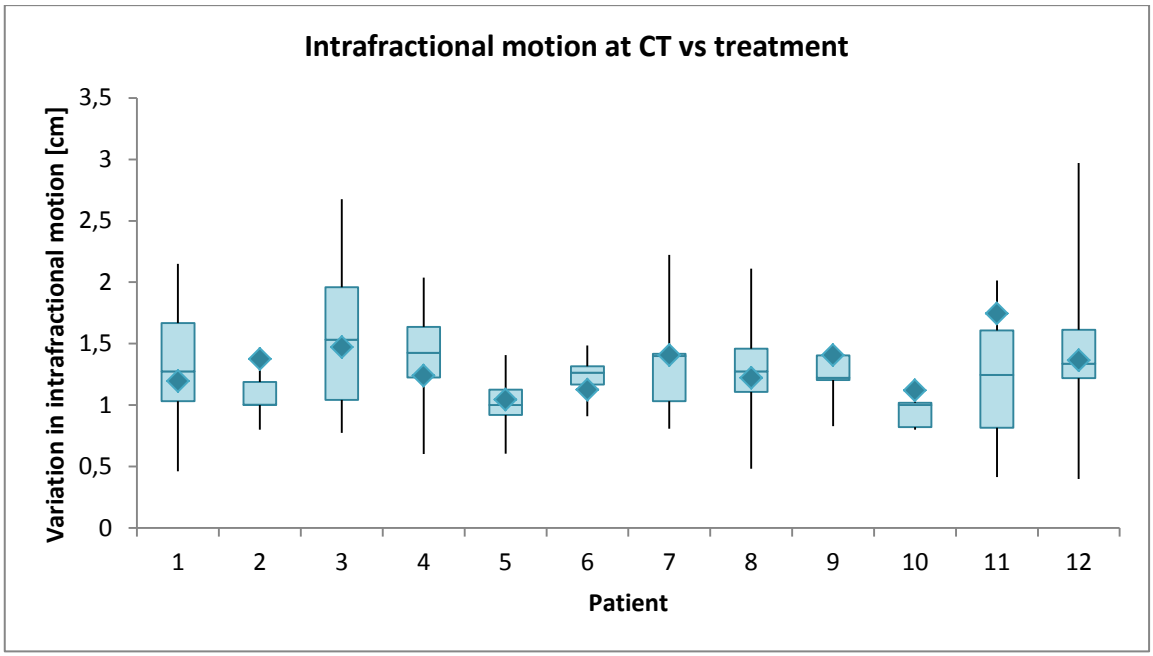

Figure 4-13: The diamond shows the median 3D vector from the average reconstruction of the CTs (planning CT and repeated CT) for each patient, together with the median, 1st quartile, 3rd quartile and range of all 3D vectors for all markers per patient.

5 Discussion

In this study the potential for using implanted fiducial markers in image guided radiotherapy for esophageal cancer patients was investigated, by addressing whether the markers stayed in place and were covered by the PTV, and by characterizing the different aspects of motion in esophageal cancers.

5.1 Result discussion

5.1.1 What fraction of implanted markers stay attached during radiotherapy?

It is an important prerequisite for marker based image guidance that the implanted markers are present and in place during the whole treatment course. In the present study, 92% of the markers stayed attached from planning CT to end of radiotherapy. Machiels et al. (2015) used three different types of markers; solid markers, flexible markers and hydrogel markers. The solid marker was likely of the same type as the one that was used in the present study. It was reported that 71% of the solid markers present at planning CT still were visible at the end of radiotherapy. Our result of 92% is an even better result than the flexible marker Machiels considered superior to the solid marker. The difference may be explained by that continuous clear visibility of the marker was the endpoint in Machiels' study, and that some of the flexible markers were cut too short to be visible at the CBCT scan, while still being visible at planar imaging. Hence these short markers were not counted as having "clear visibility", but were still present. All of the markers in the present study were visible in CBCT scans during RT. Fernandez et al. reported that in their 60 patients 93% of the markers (cylindrical fiducial marker, 0,35 -0.75 mm x 10 mm) that were visible at the planning CT still were present at a post treatment CT scan (Fernandez et al., 2013).

The findings from these studies, including ours, support that over 90% of markers stay attached during radiotherapy. In other words, we recommend having enough markers at planning CT to withstand a 10% marker loss during therapy on a population level. The exact number of implanted markers was

difficult to assess in the present study, as no image verification was employed, and journal descriptions sometimes were inaccurate. The number of implanted markers may therefore have to be even higher, as some marker loss from implantation to planning CT may occur. Machiels et al. (2015) and Fernandez et al. (2013) reported that respectively 87.5% to 98%, depending on marker type in Machiels' study, and 94% of the implanted markers were visible at planning CT.

As mentioned, the endpoint in Machiels' study was continuous visibility of the markers (Machiels et al., 2015). This is important when comparing different types of markers. In our study, we tested the visibility of the marker in planar images and CT- and CBCT scans prior to patient inclusion. Different types of artefacts may hamper the visibility of the markers. Marker material and size may affect the visibility as well, as materials of higher density (as metal) is used to give sufficient contrast compared to body tissue, still it is also known to give metal artefacts. On the other hand, lower density material in the marker makes it hard to separate from soft tissue. Too small markers and too low density hampered visibility in some of the markers in Machiels' study. Further, a CBCT scan is exposed to motion artefacts, as the scan is performed over several breathing cycles. This study benefited from this fact as it was used as a measure of intrafractional motion, which is discussed in Section 5.4. A planar image may visualize a maker clearly, but also fails to visualize the actual motion that occurs in the treatment volume.

5.1.2 Do the planning target volume account for variation in marker position during a course of radiotherapy?

Even if the CTV-PTV margin was considered sufficient on a sample level in the present study, the PTV did not cover the markers in 100% of cases, as in Jin's study (Jin et al., 2015). This may be explained by the chosen margin in Patient 8, which was only 1 cm isotropic margin from GTV to PTV. The number of acquired CBCT scans in Jin's study was on average 11 CBCT scans per patient, versus 20-33 in the present study. One could expect an increased possibility to observe random makers outside PTV with more frequent imaging, as exemplified in Patient 12 in our study, were we observed one marker outside PTV in one fraction only. However, the consequences for the dose delivery in such a case would be limited. In Patient 8 on the other hand, where two markers were observed outside the PTV in a larger part of the treatment fractions, the lack of coverage would probably also be discovered, even with a less frequent imaging than in our study. However, with narrower margins than employed in our clinical practice, frequent imaging to assure PTV coverage at all times should be considered.

In image guidance evaluation of whether the markers are inside the PTV or not could be used as a part of a decision support protocol. A lack of dose-coverage to CTV in Patient 8 was discovered in clinical practice due to the implanted markers of the current study, and measures were taken to ensure sufficient coverage for the remaining treatments, by adapting the set-up protocol to include the markers. The cases when a marker is visualized partly outside the PTV during a CBCT at random treatment fractions may not be clinical relevant, as the dose coverage would be less affected. This should be reflected in the protocol with different action levels, as described in a study where a decision support system for lung cancer IGRT was established (Kwint et al., 2014) .

The van Herk margin formula has been frequently used for margin estimation in previous studies of radiotherapy in esophageal cancer (van Herk, 2004). The formula was originally developed for use in prostate radiotherapy with the aim of estimating an isotropic margin around a spherical structure. As opposed to the close to spherical prostate target, the treatment volume in esophageal cancer

patients is usual longitudinal in shape and vary a lot in size and shape between the patients. Elongated volumes are shown to be more exposed for rotational variations (Guckenberger et al., 2006).

5.1.3 What is the interfractional variation in marker position?

Overall and directional position variation

The overall median interfractional position changes of the fiducial markers for this sample of twelve patients of the current study were relatively modest. The range was large in all three directions, due to a few measurements with offsets close to 2 cm. This is in line with findings from other studies. Fukada et al. reported that the absolute mean displacement were similar in all directions, and close to zero (Fukada et al., 2013). It is noteworthy that the only displacement exceeding 2 cm was in the longitudinal direction in Fukada's study, like in our study, while Jin et al. (2017) found that the only displacement exceeding 2 cm was in the lateral direction. Hawkins et al.(2011) reported no values exceeding 2 cm, but the maximum value of 1.9 cm was found in the longitudinal direction. Hawkins did however not study implanted markers, but calculated the displacement based on automated soft tissue registration. It is important to be aware of the possibility of such large random displacements in esophageal cancer patients, and that these are occasional in nature.

In the present study we found a significantly higher inter quartile range in the longitudinal direction as compared to lateral and ventral directions. While Fukada et al. (2013) reported similar standard deviation (SD) in all three directions, Jin et al. (2015) reported that the absolute systematic errors were significantly larger in the longitudinal direction. Wang et al. (2013) used repeated 4DCT scans to detect interfractional displacement of the centroid GTV in 32 thoracic esophageal cancer patients and also reported slightly larger displacement in longitudinal direction. Hence, our results are in line with the findings of two earlier studies when it comes to larger displacements in the longitudinal direction.

The proximity to the diaphragm suggests that respiratory motion is the main contributor to this variation. In our study we used the central position of the smeared out trajectory of the marker as a measure of the position at each CBCT scan, and hence tempted to eliminate the momentary respiration motion. The Norwegian guideline (Frykholm et al., 2011) suggests that a somewhat larger margin is to be used in the longitudinal direction to include the variation

caused by organ motion ,and emphasizes the use of 4DCT to calculate individual margins.

3D vector length

Compared to Jin et al. (2015) there were a higher percentage of 3D vectors exceeding 0.5 cm and 1 cm in the present study; 59% vs 49% and 24% vs 12% respectively. This may be explained by a small sample size and that with a sufficient large sample these differences may have been leveled out. Another explanation could be the influence by the artefacts in the CBCT scan and how the centroid position of each marker was determined. Jin's study had more patients, but less data points per patient, which also may give a more robust estimate. This may be due to that esophageal cancer patient are an inhomogeneous group, with varying treatment sites and volumes.

Anatomical regions

In our data we found that medians and IQR for variation per direction were significantly different between the markers grouped according to anatomical location, with increasing IQRs for markers located more caudally. Jin et al similarly found significantly larger random and systematic variations in the longitudinal direction in markers in the distal esophagus, but not in the other locations (Jin et al., 2015). Likewise, Fukada et al. (2013) reported significantly larger absolute displacements in the longitudinal direction for markers located in the distal esophagus, which was 0.60 cm on frontal projection and 0.67 cm on the lateral projection. In our data there were wide ranges and IQRs for all anatomical regions, except for the cervical esophagus/upper thoracic esophagus.

In the present study we found significant differences in median 3D vector length between all the anatomical sub groups, except between markers in lower- and middle esophagus, while Jin only had significantly larger systematic errors and random errors in the proximal stomach. Because we could not assume our data to be normally distributed, median and IQR were tested, while Jin tested mean and SD, and therefore used tests that presupposes normal distribution. The

choice of measures of the central tendency and variation may have affected the results from the tests.

The anatomic location of the marker did not seem to fully explain the variation in interfractional variation. Patient 3 and Patient 12 had all markers located in the esophagogastric junction, still there were much wider ranges of vector lengths in Patient 12, and the median vector length was also larger. Patient 4 had four markers, all located in different anatomical regions. Still there was little variation between the vector lengths in this patient. Likewise for Patient 7, which had markers located in three different anatomical sub divisions and relatively modest range per marker.

Influence of stenosis and tumor regression

To our knowledge, it is not earlier described how the presence of an esophageal stenosis at planning CT affect the interfractional motion. We found that there were significant differences in median and distribution for the directional changes in marker position between the markers in patients with stenosis and those without. However, the variations were actually larger in the group without stenosis. We visually observed in one patient that a stenosis could cause a dilated esophagus and when the stenosis resolved during treatment it caused a shift in the marker position, especially in the lateral and longitudinal directions. The other two patients with stenosis did not have the same dramatic interfractional variation. Hence, on a group level patient with stenosis had a lower median IQR value than in patients without stenosis. This implies that to which degree a marker's position is affected by resolving of an esophageal stenosis depends on where in the circumference of esophagus the marker is located. Since the esophagus rest against the spine and the aorta posteriorly and at the left, the change would likely happen on the right side and anteriorly. This may increase the dose to the right lung and to the posterior parts of the heart, and should be considered. It is worth noting that stenosis is at risk of changes in the treatment area during RT. We experienced that a dilated esophagus was easy to discover in both the planning CT and in CBCT scans, even if there may be considerably motion artefacts. Hence, CBCT as part of the IGRT protocol may be valuable in discovering anatomical changes during

radiotherapy. However, there were only three patients with a stenosis in our small sample of esophageal cancer patients, therefore this issue should be further explored in a study with a larger sample of patients.

Systematic and random uncertainties

Van Herk's margin formula has been used for margin calculation in several studies. Generally, there were too few makers in each anatomical region to give a robust margin estimate in our data. As noted in the result section we could not find all data series to be normally distributed. Earlier studies had fewer measurements per patient, Jin et al (Jin et al., 2015) had on average 11 CBCT scans and Fukada et al. (2013) had on average 8 sets of orthogonal 2D images per patient.

In the cervical esophagus and upper thoracic esophagus our estimated margins were much smaller compared to earlier studies.. In the proximal esophagus Jin et al. (2015) estimated a margin 0.44 cm, 0.55 cm and 1.13 cm in the lateral, ventral and longitudinal directions, respectively. In the same area Fukada et al. (2013) estimated margins of 0.91 cm, 1.05 cm and 1.09 cm. Our margins were much smaller; 0.3 cm, 0.2 cm and 0.1 cm, respectively. There were only four markers in the upper part of esophagus in our study, and insufficient for margin calculation.

In the middle esophagus, the margins were more comparable between the studies. In the lateral direction our data gave a 0.9 cm margin, Jin had 0.89 cm and Fukada 1.18 cm. Ventrally, a 1.1 cm margin were calculated, Jin reported 0.96 cm and Fukada 0.84 cm. In the longitudinal direction however we found that a 1.2 cm margin, like Fukada, while Jin had a 0.86 cm margin

The values reported from different studies are not straight forward to compare and have some variations. This may be because esophageal cancer patients are an inhomogeneous group and the studies have relatively small number of included patients. A small sample from a patient group were large variations occur may turn out to have a larger share of the patients with the largest variations, and therefore not be representative. Because of the relatively few

new cases each year, with 397 new cases in Norway in 2015 (Frøland et al., 2016), it would be time consuming to include enough patients to have more robust values. The inhomogeneity of the group also indicates that the use of population based margins may not be suitable. The division of esophagus into anatomical sites have some discrepancies between the studies; cervical esophagus and upper thoracic esophagus are often called proximal esophagus and the lower limit for the middle esophagus vary from 30 to 35 cm from the incisors. Rice et al. (2017) published an updated staging guideline for esophageal cancer staging, which the present study has based the sub division of esophagus on. A sub division based on magnitude of motion would be more expedient in purpose of establishing treatment margins in radiotherapy, and should be subject to further research.

Another issue worth noting is that the van Herk formula presumes normally distributed data. Testing for normality, it was found that it varied between the markers and even between the measuring directions for one marker if the data were normally distributed. It is not explicitly noted that the formula is used on normally distributed data in the former studies, except in Hawkins' study (Hawkins et al., 2011). The lack of normality in the data may be caused by a possible time trend, as were shown in 80 percent of the markers. It was beyond the scope of this thesis to investigate this further.

Random displacements have a limited effect on the dose delivery in total, and have the effect that the dose gradients get less steep. Yet it is important to avoid even random errors. A systematic shift during a treatment course may be even more clinically important to discover. In our data there were some markers that had systematic shifts of 1 cm or more; four markers had a shift in the caudal direction and one towards the left. One of the markers had both in the left and caudal directions and this were observed in a patient with a resolving stenosis. Two of the others markers with caudal shifts were markers from the patient with not sufficient PTV coverage. Hence, marker displacements have the potential to aid detection of anatomical changes that might affect dose delivery accuracy. For the last marker with a shift of 1 cm the reason for marker

shift was not revealed. The interquartile range was significantly larger in the longitudinal direction.

Possible time trend

Except from Jin et al (2015), whom evaluated if there were a time trend in pairwise distances between markers, there are to our knowledge no other studies that consider a time trend. It was possible to do so in the present study because of the extensive imaging, that gave a visual impression that a time trend might be present in some of the markers. Anyhow, the possible time trend seems to be more complex than a linear model can describe fully, and should be further analyzed. However, that is beyond the scope of this thesis.

Tumor regression will probably appear gradually over time, as demonstrated in esophagogastric junction adenocarcinoma patients (Wang et al., 2012). The position of markers may therefore have a time trend. A minor time trend in pairwise distance between markers located in the upper and lower tumor boarder has also been described (Jin et al., 2015). In the present study we tested the position changes per direction on the directional data from all markers, and the position changes had a trend line significant different from zero in two directions. On a sample level the effect of the time trend was neglectable with median estimated changes ranging from 0.4 to 3 mm in the different directions, however in single markers the changes could exceed 1 cm during 25 fractions. Again, this point to that population based margins not may be suitable in radiotherapy of esophageal cancer.

It is also worthy to note that none of the markers in lymph nodes had a regression line significantly different from zero. This could indicate that lymph nodes may have a different pattern of motion than the esophagus. This is probably because effects related to anatomical changes in esophagus, like tumor regression and dissolving of stenosis, would not affect the position of lymph nodes.

5.1.4 What is the intrafractional variation in marker position?

Several studies have applied 4DCT scans to evaluate the intrafractional variation in marker position in upper gastrointestinal organs, some without implanted markers (Patel et al., 2009, Kobayashi et al., 2016) and some with implanted markers (Lischalk et al., 2016, Jin et al., 2016, Yaremko et al., 2008). In the current study we used the smeared out appearance of implanted markers in the CBCT images as a surrogate for intrafractional motion, and compared it to the 4CDT average reconstruction at two different time points. We found that the intrafractional changes were largest in the longitudinal direction; this is in line with earlier studies (Patel et al., 2009, Lischalk et al., 2016, Jin et al., 2016). Patel et al. (2009) reported the variations in the longitudinal direction to be median 0.75 cm and with a range from 0.25 to 2.38 cm, while Jin et al (2016) reported median and interquartile range (IQR) to be 0.54 cm and 0.42 cm. Kobayashi et al. (2016) evaluated esophageal motion according to tumor stage and found mean variation in the longitudinal direction above carina of 0.45 cm in T4 tumors and 0.68 cm for T1-3 tumors, and likewise for tumors below carina were 0.22 mm for T4 and 0.68 cm for T1-3. Lischalk et al. (2016) collected data from real time fiducial-based motion tracking in twelve pancreatic- and two hepatic cancer patients and found median longitudinal displacement of 0.32 cm, ranging from 0.02 to 1.03 cm. In our data the overall median variation in the longitudinal direction was median 1.20 cm, ranging from 0.00 to 2.80cm and with an IQR of 0.40 cm. Since all the other studies report a lower measure of central tendency (mean or median), varying from 0.22 to 0.75 cm, it may seem like our method tend to overestimate the variation. This may also be related to the sample of patients in our study; with large variations between patients the sample of patients should ideally be much larger. Anyhow, our overall IQR of 0.40 cm was comparable to the IQR of 0.42 cm in the study by Jin et al. (2016).

In the ventral direction the variations were more limited in our data, with a median (IQR) of 0.11 cm (0.41cm). Jin et al. (2016) reported median (IQR) of 0.32 cm (0.29 cm), which means 50% of the measured variation were between 2 to 5 mm, which is more comparable to our numbers (-2 mm to 3 mm). Lischalk et al. (2016) found a mean (SD) 0.13 cm (0.1 cm) in the ventral direction. Hence, our data were of similar magnitude as earlier studies and did

not overestimate the motion in the ventral direction. However, the range in in our data were substantial (-1.13 to 1.30 cm).

Finally, in the lateral direction there was very limited intrafractional motion in our study, with a median (IQR, range) of 0.00 cm (0.12 cm, -0.77 to 0.86). This corresponds well to the findings of Jin et al. (2016), with median and IQR of 0.24 cm and 0.19 cm, and second with Patel et al. (2009) with a mean (SD) of 0.22 cm (0.23 cm) and finally with Lischalk et al. (2016), who reported a mean (SD) range of 0.07 cm (0.05 cm) 0.00 to 0.20 cm on the lateral variation. We did however have a wider range for the lateral variation than Jin (0.00 to 1.1cm) and Lischalk (0.00 to 0.20 cm). It is also noteworthy that our method mainly captures the variations in the longitudinal direction as we registered the extreme positions in the longitudinal direction. It was observed during data collection that the smeared out trajectories of the markers had varying shape; elliptic, linear, bow-shape or irregular. Therefore the method may not capture all intrafractional variation in the ventral and lateral directions. The methodology used by Jin et al. (2016) managed to characterize these variations more completely as they registered each marker in each breathing phase to the planning CT.

Artefacts in the CBCT images, that sometimes made it challenging to determinate the exact endpoint of the trajectory of the marker, the fact that the length of the marker contributes with 0.64 to 5 mm, and our limited sample size could all contribute to the larger intrafractional variation in our study. In the ventral direction, with less variation no overestimation was seen. This may point to that our method tends to overestimate variation when there are large variations that cause motion artefacts. Further, the CT slice thickness of two mm causes the scrolling along the length axis of the patient to move in steps of two mm. Even if the true end of the marker was in the middle of a CT slice, it appears to be present in the whole slice (partial-volume effect). This was an issue that we were aware of during data collection, and attempted to minimize the effect of this by preventing the effect of the slice thickness to affect the length position in both ends of the marker. The impact of inter-observer variability in determining marker positions could with benefit have been assessed to validate the reproducibility of the method; however, this was

beyond the scope of this thesis. Considering the fact that a CBCT scan gives a much lower dose (less than 10%) to the patient than a 4DCT scan (Table 3-V) and that the modality have other advantages in in-room verification (like dealing with rotations and soft tissue changes) the method is worth further refinement and investigation.

Anatomical location

Concerning anatomical location of the markers, in the present study the variation was increasing for markers located caudally in the longitudinal- and ventral directions. Jin et al. (2016) found a similar trend, but the IQR were generally of less magnitude. Yaremko et al. (2008) investigated motion in the distal esophagus and found increasing displacement of the GTV centroid for more caudally tumors. Comparing tumors cranially and caudally of the diaphragm, significantly larger displacements were found caudally to the diaphragm in the longitudinal- and ventral directions, as well as for the 3D vector of displacement in their study. Jin et al. (2016) used similar anatomical sub groups as in the current study, but referred to an earlier version (7^{th} edition) of Rice et al.'s staging manual (Rice et al., 2010). Jin found significantly larger variation in the longitudinal direction for markers located in middle- and distal esophagus, and in the proximal stomach, but not in the proximal esophagus. Further, they found that the 3D motion were significantly larger in distal esophagus and proximal stomach than in the proximal- and middle esophagus. In tumors located in the esophagogastric junction distance from the midline may be an issue, as tumor located under the dome of the diaphragm are more exposed to the breathing motion, as exemplified by Figure 4-12.

Lymph nodes are often included in the treatment volume in esophageal cancer patients, due to the frequent nodal invasion at the time of diagnose. In lung cancer, nodes has been shown to move different from the tumor (Schaake et al., 2014). To ensure coverage of both tumor and nodes, the motion of the included lymph nodes need to be considered. Patel et al. (2009) reported the motion of twelve positive celiac nodes. The mean (SD) displacement was respectively 0.19 cm (0.26 cm), 0.46 cm (0.27 cm) and 0.92 cm (0.56 cm) in the lateral, ventral and longitudinal directions. Kobayashi et al. (2016) reported

nodal motion for metastatic nodes in twenty patients without implanted markers, eleven nodes were cervical/ thoracic and nine were abdominal. In the cervical and the thoracic nodes the mean (SD) intrafractional motion was 0.07 cm (0.06 cm), 0.06 cm (0.05 cm) and 0.12 cm (0.09 cm) in the lateral, ventral and the longitudinal directions, respectively. In the abdominal nodes the mean (SD) intrafractional motion was 0.15 cm (0.12 cm), 0.50 cm (0.27 cm) and 0.86 cm (0.33 cm) in the lateral, ventral and the longitudinal directions, respectively.

In our study, six of the markers were located in lymph nodes. The lymph nodes were spread over all the anatomical sub divisions; two in the cervical- and upper thoracic esophagus, one in the middle thoracic esophagus, two in the lower thoracic esophagus and one in the esophagogastric junction. In our data the overall 3D intrafractional motion for the markers located in lymph nodes was median (IQR) 1.11 cm (0.55 cm), and per direction it was 0.00 cm (0.23 cm), 0.00 cm (0.35 cm) and 1.00 cm (0.40 cm) in the lateral, vertical and longitudinal directions, respectively.

As to whether the planning 4DCT scan counts for the intrafractional variations, Lischalk et al. (2016) found that the 4DCT scan failed to account for interfractional variation in fractionated stereotactic body radiotherapy as the variation were underestimated by the 4DCT in nearly 40 % of fractions in the longitudinal direction, but also in lateral and ventral directions. Guckenberger investigated whether a single 4DCT scan was sufficient for treatment planning of stereotactic body radiotherapy in pulmonary tumors, using repeated 4DCT scans (2 to 4 scans per patient) over a 30 minutes period in 10 patients (Guckenberger et al., 2007). They found that planning on a single 4DCT scan was sufficient in the majority of patients. None of those two studies are directly comparable to esophageal cancer patients, but is valuable when addressing some important issues. The two studies come to different conclusions on whether a 4DCT was sufficient for planning. In our twelve esophageal cancer patients the 4DCT scan more often overestimated the intrafractional motion than underestimated; 15 out of 35 markers had a overestimated amplitude, while in three markers the motion were underestimated, per patient the motion were overestimated for three patients and underestimated for one. The median for all amplitudes at planning 4DCT was higher than for amplitudes from

CBCTs, but the range for the CBCTs were wider. It is important to keep in mind that the 4DCT acquired at the time of planning also is a snapshot, and that the scanning is performed at a moment when the patient is facing the new, and for some frightening, radiotherapy environment for the first time. Some patients also receive concomitant chemotherapy that often causes nausea. Hence, it may carry the potential to introduce systematic errors as respiration may be affected by anxiety, nausea and pain. Further, it is important to note that the PTV coverage only was compromised in one patient, and this was not the same patient where the intrafractional motion was underestimated. Hence, there were other reasons for the lack of coverage than intrafractional variation. This points to that when it comes to intrafractional motion there may be room for margin reduction as it was practiced in our clinic. Combined with techniques for respiratory motion reduction like respiratory gating or abdominal compression, or with careful surveillance through image-guidance procedures or surface monitoring system, sparing of healthy tissue should be within reach.

The intrafractional variation was substantial in this group of twelve patients. Respiratory gating or abdominal compression has been recommended when respiratory motion is found to excess 1 cm (Wu et al., 2015). In our group of patients the median intrafractional variation was 1 cm or more for all patients and they would be treated with such techniques, based on measures made on the amplitude from 4DCT average reconstruction at planning CT. According to post treatment evaluation 29 out of 35 patients had median amplitude larger than 1 cm and 76% of all amplitudes for all patients were over 1 cm.

Even though our data compared to other studies seemed to overestimate the intrafractional variations, we still can't find that the variation was overestimated compared to the 4DCT scan from the planning CT. We also find that the applied margins take both inter- and intrafractional motion into account in eleven of twelve patients.

5.2 Method discussion

Validity is a central concept in planning and performing a study, and is about whether the results is true for the studied sample and phenomenon (internal validity) and further if it is transferable to other samples and situations (external validity) (Polit and Beck, 2012). Sometimes one have to make trade-offs between the two as one may use different control mechanisms to strengthen the two types of validity. Some aspects of internal validity, e.g. measuring method for intrafractional variation and external validity, e.g. sample size, have already been discussed in the previous sections. Here, a few central issues are discussed.

The main limitation of the present study was the sample size. We aimed to include 20 patients, but had to stop at twelve included patients due to time restrictions of the master thesis. However, extensive and daily imaging gave a quite substantial amount of data, with 24 CT scans, 24 4DCT scans, 302 CBCT scans and 61 orthogonal 2D image pairs, and therefore was a major strength. This gave a fine-grained image of the variations that occurs in a patient during a course of radiotherapy, and also in the group of patients. Numerous measuring points per patient gave us the opportunity to reveal a possible time trend, which have been limited investigated in earlier studies with less extensive imaging. We also used the large set of data to explore both intra- and interfractional motion, which both is important in defining sufficient treatment margins, and thus was considered a strength.

The study protocol (Appendix E) was developed as a part of the study, and we explored a new method of measuring the intrafractional motion by using the CBCT scan that was acquired over several breathing cycles. It was a simple method that might need refinement and validation for further use, as it may tend to overestimate intrafractional variation in areas with much motion, compared to earlier studies. The simplicity of the method may however strengthen the external validity as it is easy to perform and only requires equipment that is standard in modern radiotherapy facilities, and no additional in-house solutions. The results using our method was compared to other studies and compared to

the clinically implemented method, i.e. 4DCT, for calculation intrafractional motion. We could not find the method to systematically overestimate motion compared to the 4DCT scan. All the data collection was performed by one person to assure consistency in the method, something that increases the internal validity. The method of measuring could with advantage have been validated by inter observer analysis; this could have strengthened the external validity of the study further. This was however beyond the scope of this study, but may be an issue for future research.

The group of patients was heterogeneous, with differing tumor sites and treatment volumes. This caused few markers in each group when comparing variation between sub groups. A homogenous sample would give better control with confounding factors. Tumors in the lower esophagus and the esophagogastric junction could be an interesting sub-group for further research, because adenocarcinomas are increasing and most often occurs in lower esophagus. It has also been shown to be larger motion in the lower part of esophagus. However, this was not possible in the current study, due to limited time to include patients. A larger study could be an alternative to assure the recruitment of enough participants, in a larger center or as a multicenter study.

5.3 Conclusion

The solid gold marker was feasible to use in image guidance as it was visible on planning CT, as well as CBCT and planar images. We found that 92% of the markers stayed attached from planning CT to end of radiotherapy. This was an important prerequisite to evaluate inter- and intrafractional motion and to consider the markers possible benefit in image-guided radiotherapy.

The CTV-PTV margin was considered sufficient on a sample level, as the markers were covered in more than 95% of the treatment fractions for more than 90% of the patients. However, in one patient the PTV coverage failed due to changes in the treatment volume. We were able to discover this due to the implanted markers, and this suggests markers have the potential to highlight lack of coverage of the CTV as part of an imaging protocol.

There were significantly larger interfractional displacements in the longitudinal direction compared to the lateral and ventral directions in our data. Though the interfractional variation in marker position was increasing as the markers were located more caudally, the sub division of the esophagus into anatomical regions could not explain all interfractional variation. Due to extensive imaging we were able to point to possible time trend that may be explained by e. g. tumor regression and resolving stenosis. However, to discover these changes on basis of implanted markers is sensible to where in the esophageal circumference the markers are located.

As to intrafractional variation, it was found to be largest in the longitudinal direction and like the interfractional variation it was more extensive as the markers were located more caudally. Our method of measuring intrafractional motion was simple and feasible, but should be validated concerning inter observer variation and compared to other techniques in a larger study. As a pilot study this work gives input to how future studies could be designed to address the complex issues of motion in different time aspects during radiotherapy of esophageal cancer patients.

The extensive variations in both inter- and intrafractional motion points to that personalized margins may be more suitable in esophageal cancer radiotherapy. If a reduction of the margins should be tempted to reduce dose to healthy tissue, it is crucial to follow up with an imaging protocol that facilitates the discovery of both large random errors and systematic errors. Implanted markers could be a valuable aid in discovering variations, together with the information from in-room 3D imaging about both anatomical changes and rotations.

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Appendix

Appendix A: Approval by the Regional Ethics Committee.

Appendix B: Patient Information sheet.

Appendix C: CT protocol.

Appendix D: Imaging protocol.

Appendix E: Prosedyre for avlesning av markører.

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Camilla Gjerstad	55978499	04.04.2016	2016/268/REK vest
			Deres dato:	
			16.02.2016	

Vår referanse må oppgis ved alle henvendelser

Nils Idar Glenjen
Avdeling for kreftbehandling og medisinsk fysikk

2016/268 Bruk av strålemarkører ved kreftsykdom i spiserøret

Forskningsansvarlig: Helse Bergen HF
Prosjektleder: Nils Idar Glenjen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK vest) i møtet 10.03.2016. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektomtale
I denne pilotstudien vil strålemarkører plasseres ved yttergrensene av kreftsvulster i spiserøret. Slike markører kan være til hjelp når målvolumet for strålebehandling skal defineres og når man skal kontrollere at strålefeltene treffer det ønskede målvolumet. Forskerne ønsker å undersøke om bruk av strålemarkører kan føre til at man trenger mindre sikkerhetsmargin fra kreftsvulstene til yttergrensene av strålefeltene. Dette kan gi mindre stråledoser mot nærliggende organer som lunge, hjerte, nyrer og ryggmarg og dermed redusere bivirkninger av strålebehandlingen. 20 pasienter med kreftsykdom i spiserøret eller i overgangen mellom spiserør og magesekk rekrutteres til studien.

Vurdering
Forsvarlighetsvurdering
Medisinsk og helsefaglig forskning skal organiseres og utøves forsvarlig, jf. helseforskningsloven § 5. Pasientene vil motta strålebehandling uavhengig av om de deltar i studien eller ikke. Deltakerne vil få implantert markører ved yttergrensene av svulsten der markørene kontrolleres hyppig for å se at de ligger innenfor strålefeltene. Deltakelsen innebærer en ekstra endoskopisk ultralydundersøkelse for å få implantert markørene. Komiteen finner at deltakerne er ivaretatt og at studien er forsvarlig å gjennomføre.

Informasjonsskriv
REK har følgende merknader til informasjonsskrivet som gis til deltakerne i studien:

- I presentasjonen av formålet må studien må det fremgå at dette er en pilotstudie for å undersøke om implantasjon av markører er teknisk mulig å gjennomføre.
- Informasjonen må være tydeligere på hva som er standardbehandling og hva som er tilleggsundersøkelse i studien, jf. «*Mulige fordeler og ulemper*».
- Skrivet må informere om at deltakerne er dekket av pasientskadeforsikringen.
- Henvisning til prøver (*Hva skjer med prøvene og informasjonen om deg*?) må fjernes ettersom biologiske prøver ikke samles i studien.
- Skrivet må merkes med samme prosjekttittel som i søknaden til REK samt REKnr. 2016/268.
- Informasjon om NSD må fjernes.

Besøksadresse:
Armauer Hansens Hus (AHH), Tverrfløy Nord, 2 etasje. Rom 281. Haukelandsveien 28

Telefon: 55975000
E-post: rek-vest@uib.no
Web: http://helseforskning.etikkom.no/

Rekruttering
Pasienter blir henvist fra gastrokirurgisk avdeling til kreftavdelingen. I forbindelse med kontroll ved kreftavdeling vil pasienter bli spurt om å delta i studien. REK gjør oppmerksom på at dersom pasienten kan anses å være i et avhengighetsforhold til den som ber om samtykke, skal samtykket innhentes av en annen som deltakeren ikke har slikt forhold til, jf. helseforskningsloven § 13.

Prosjektslutt
Oppgitt prosjektslutt i søknaden er 31.05.18. Det søkes om å lagre datamaterialet i 15 år etter prosjektslutt. Hovedregel er imidlertid at opplysningene ikke skal oppbevares lenger enn det som er nødvendig for å gjennomføre prosjektet. Dette innebærer at tillatelsen til å behandle data gjelder til prosjektslutt. REK aksepterer at opplysningene lagres i fem år etter prosjektslutt av hensyn til etterkontroll, jf. helseforskningsloven § 38. Dersom det viser seg å være behov for forlengelse av studien, må det sendes endringssøknad til REK før angitt prosjektslutt.

Vilkår

- Komiteen ber om at informasjonsskrivet revideres og sendes til REK vest.

Vedtak
REK vest godkjenner prosjektet på betingelse av at ovennevnte vilkår tas til følge.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK vest på eget skjema senest 30.11.2018, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK vest dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Ansgar Berg
Prof. Dr.med
Komitéleder

Camilla Gjerstad
rådgiver

Kopi til: postmottak@helse-bergen.no

Forespørsel om deltakelse i forskningsprosjektet

"Verdien av strålemarkører ved strålebehandling av kreftsykdom i spiserør og overgang spiserør - magesekk"

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i en forskningsstudie for å undersøke om det er fordelaktig å bruke strålemarkører ved strålebehandling av kreftsykdom i spiserør og overgang spiserør-magesekk.

Ved slik type kreftsykdom er strålebehandling ofte en viktig del av behandlingen, enten alene, eller kombinert med cellegift. Det er ofte vanskelig å avgrense svulster i spiserøret og øvre del av magesekken på vanlige røntgen og CT bilder. Når man utformer stråleplanen må man ta høyde for mulig vekst av kreftsykdom som strekker seg lengre utover i veggen av spiserøret eller magesekken enn hva man kan se på vanlige røntgen og CT bilder. Man må også ta høyde for geometrisk usikkerhet knyttet til organbevegelser/deformasjon av målvolumet for strålebehandlingen. Når man lager strålefeltene må man derfor legge til sikkerhetsmarginer rundt svulsten. Dette kan medføre uønsket strålebehandling av nærliggende organer som hjerte, lunger, nyrer og ryggmarg.

Ved endoskopisk ultralydundersøkelse (EUS) ser man ofte grensen mellom svulsten og det normale vevet klarere. Ved endoskopisk ultralyd kan man legge inn små, røntgentette gullmarkører ved yttergrensen av svulsten slik at den blir lettere å se på røntgen og CT bilder som man bruker for å definere målvolumet for strålebehandlingen. Man kan med lavdose røntgenkontroller før strålebehandling kontrollere at svulsten ligger innenfor strålefeltene som man gir. Da man på en bedre må kan se hvor svulsten ligger kan man trolig bruke mindre sikkerhetsmarginer rundt svulsten under strålebehandlingen og dermed redusere uønsket strålebehandling av nærliggende organer.

Hensikten med studien er å bedre treffsikkerheten av strålebehandlingen samtidig som uønskede bivirkninger av strålebehandlingen holdes på et så lavt nivå som mulig.

Du har fått påvist en kreftsvulst i spiserøret eller overgangen spiserør – magesekk. Av din behandlende lege har du allerede fått informasjon om de forskjellige aspekter omkring dette. Da du har en slike type kreftsykdom hvor vi ønsker å forske på verdien av strålemarkører ved strålebehandling av kreftsykdom i spiserør og overgang spiserør-magesekk forespørres du om du vil delta i denne undersøkelsen.

Studien gjennomføres ved Haukeland Universitetssjukehus i Bergen. Hovedansvarlig for studien er overlege Nils Glenjen ved Haukeland Universitetssjukehus.

Prosjektet er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk, Vest-Norge, og studien er meldt til Norsk Samfunnsvitenskapelig Datatjeneste.

Hva innebærer studien?
Studien tester nytten av strålemarkører ved strålebehandling av kreftsykdom i spiserøret eller overgang spiserør-magesekk. Dersom du ønsker å delta, vil du ved endoskopisk ultralyd (EUS) få lagt ned små, røntgentette gullmarkører ved svulstens yttergrenser. Disse brukes til å definere målvolumet for strålebehandlingen og til å kontrollere at strålefeltene dekker svulsten under strålebehandlingen.
Du vil før behandlingen igangsettes få anledning til å diskutere de forskjellige aspekter vedrørende behandlingsopplegget med onkolog (kreftlege).

Strålebehandlingen vil foregå i regi av kreftavdelingen i samsvar med nasjonale retningslinjer for hvordan slik behandling skal gis. Under strålebehandlingen vil du bli kontrollert ukentlig og man vil registrere komplikasjoner og bivirkninger til behandlingen. Etter strålebehandlingen vil du kontrolleres første gang 4-10 uker etter at strålebehandlingen ble avsluttet, deretter hver 3. til 6. måned i opptil 2 år. I

forbindelse med kontrollene vil du bli bedt om å fylle ut et spørreskjema med tanke på å evaluere din livskvalitet etter behandlingen.

Mulige fordeler og ulemper
Strålebehandling, eventuelt kombinert med cellegifter kan gi bivirkninger i form av kvalme, oppkast og redusert almentillstand. I tillegg kan dine blodverdier, hjerte-, lunge- og nyrefunksjon påvirkes. Disse forhold vil derfor bli nøye kontrollert i forløpet av studien. Skulle evt. bivirkningene bli for store vil strålebehandlingen avbrytes, eller strålefeltene justeres for å minske risikoen og ubehaget ved behandlingen.
Liknende studier, som andre har gjort tidligere, indikerer at pasienter som får strålemarkører har lite plager av selve markørene og at markørene er til hjelp i gjennomføringen av strålebehandlingen. Resultatene er imidlertid ikke slik at vi kan si at dette spørsmålet er endelig avklart. Det er nettopp dette spørsmålet denne studien skal forsøke å belyse bedre.

Hva skjer med prøvene og informasjonen om deg?
Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og personnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Opplysningene vil bli oppbevart i en database ved Kreftavdeling Haukeland Universitetssjukehus, Bergen. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres. Databasen vil bli oppbevart i 15 år etter at studien er avsluttet. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. For at vi alltid skal kunne være sikre på at riktige opplysninger registreres, vil en person fra Kreftavdeling ved Haukeland Universitetssjukehus regelmessig kontrollere at disse stemmer overens med de som finnes i din pasientjournal. Prosjektmedarbeiderne har taushetsplikt i henhold til Forvaltningslovens § 13 og Helsepersonellovens § 21. Alle persondata behandles konfidensielt og lagres i en database slik at pasientene kun er registrert med et løpenummer.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Frivillig deltakelse
Det er frivillig å delta i studien. Ønsker du ikke å være med vil du få tilbud om standard behandling. Blir du med, kan du likevel, når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta videre i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. På samme måte kan du når som helst kreve at oppbevarte vevsprøver skal destrueres. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte:

Overlege Nils Glenjen, kreftavdeling, Haukeland Universitetssjukehus, tlf 05300

Prosjektleder er:

……..
Overlege Nils Glenjen
Kreftavdeling. Haukeland Universitetssjukehus
Bergen
Tlf. 05300

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato) (Navn med blokkbokstaver)

Jeg bekrefter å ha gitt informasjon om studien

(Signert av prosjektlege, dato) (Navn med blokkbokstaver)

HELSE BERGEN	STUDIEPROTOKOLL: CT Ca oesofagus	
	Kategori: Forskning og utvikling	Gyldig fra: 28.06.2016
Organisatorisk plassering: - HVRHF - Helse Bergen HF - Avdeling for kreftbehandling og medisinsk fysikk - Stråleterapi		Versjon: 1.04 Standard
Dok. eier: Helga Gripsgård Appendix C	Dok. ansvarlig: Helga Gripsgård	

Pasientforberedelse	• Info om iv kontrast hvis dette er rekvirert • Info om faste hvis rekvirert
Fiksering	• Thorax fix, legge ve hånd underst / Lang maske, for tumor i øvre del av øsofagus, se rekv. • Madrass, 8
Leie	• Rygg • Taklaser gjennom neseskillevegg, jugulum, xiphoideus, midt i bekkenet og midt på pute 8.

Merknad og utstyr

- Kule på sternum ref
- 4D belte tas på etter 1. scan

Intravenøs kontrast

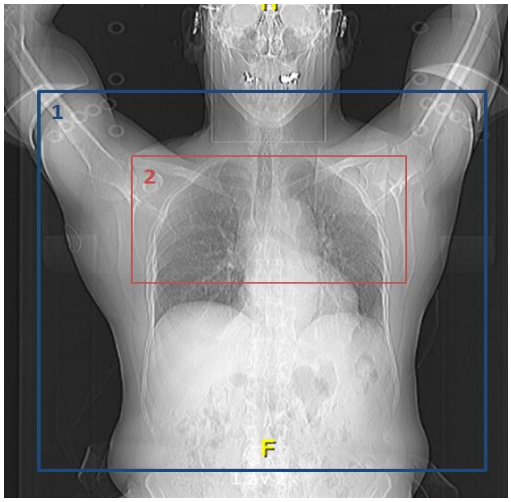
- Som rekvirert
- THORAX på trykksprøyten
- Veneflon fjernes 30 min etter injeksjon

Annet

- **Sjekk om pas skal faste** (på rekv eller i Dips).
- **Merk strålekort med «Protokoll øsofagusmarkører»**
- Bildene lagres på CT ved å låse seriene!
- **Dersom 4DCT scan går over i abdomen: endre til 1000 mAs**

Scanområde

1. Tungebein til crista iliaca
2. 4DCT, 4 cm under til 4 cm over omr med gullmarkører (se rekvisisjon)



Refpunkt på sternum m perle
Hjelpetato: tre tato caudalt i thoraxområdet

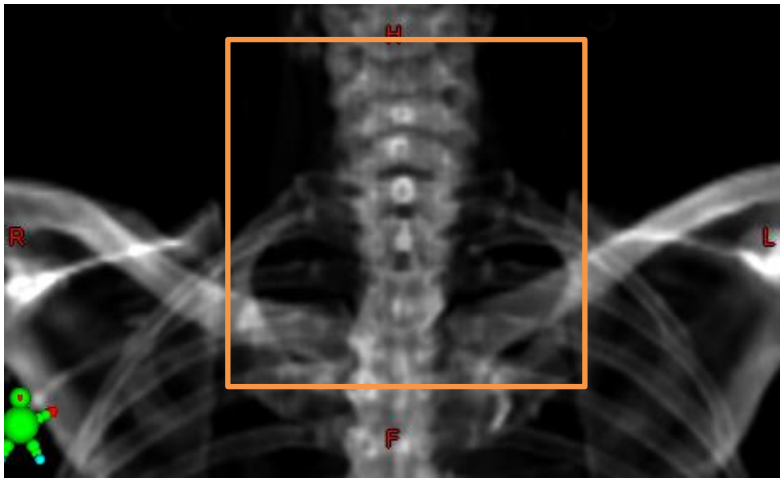
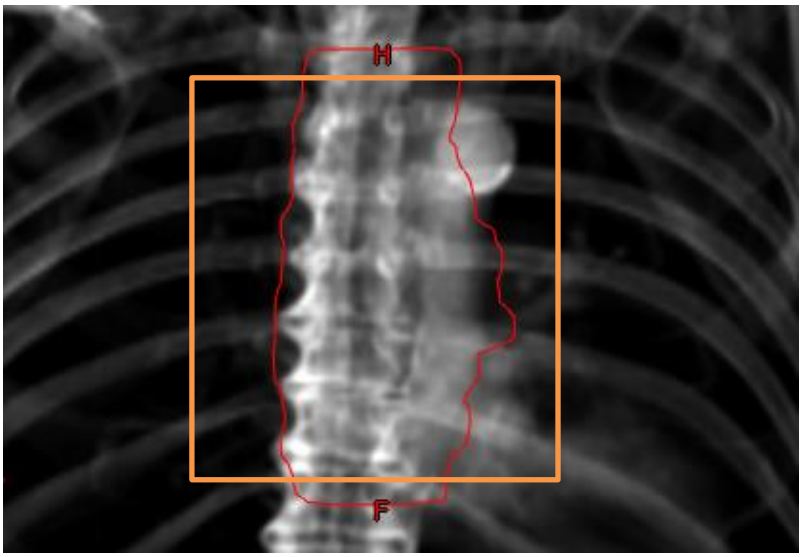
Protokoll: Thorax K+/- +4D

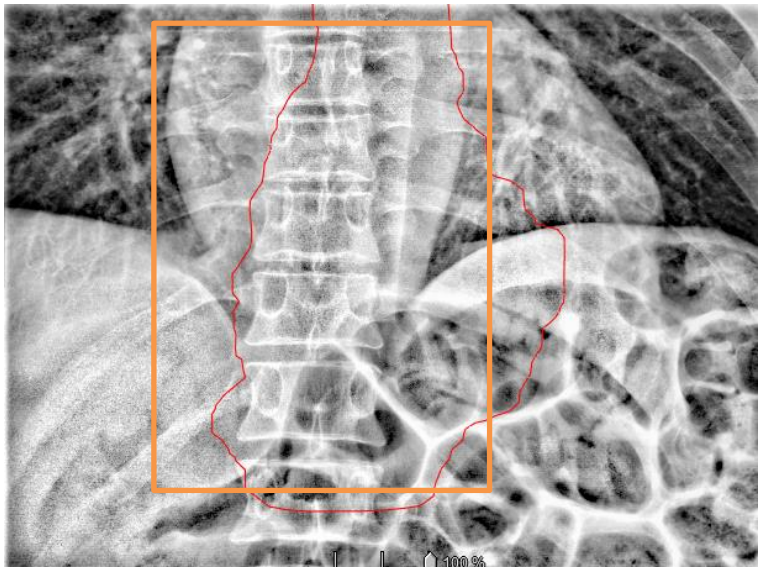
Iv kontrast	80 ml Iomeron 350 mgI/ml		
Flowrate	3.0 ml/s		
Startdelay	30 s		
Rekonstruksjoner	Eclipse	PACS	Kryssreferanser
3/3	X		02.3.7.3.2-01 Undersøkelser med kontrast 02.3.7.3.2-02 Bruk av trykksprøyte ved IV kontrast INFORMASJON OM STUDIEPROTOKOLL: øsofagusmarkører
5/5 +scout+doseinfo		X	

Appendix D

Studieprotokoll som brukes for pasienter som er inkludert i studie der man implanterer gullmarkører hos pasienter med spiserørskreft.

- Daglig CBCT m skjelettmatch
- Ukentlig Trigger avbilding

Protokoller	Daglig 3D med online skjelettmatch, ukentlig offline bløtvevsvurdering Ukentlig triggered imaging during treatment
3D: kV CBCT Skann: ***Bow-tie filter:*** *full-fan* ***CBCT mode:*** *Spotlight* ***Skann lengde:*** *17,5 cm, plasseres over området der markørene er.* Match: ***Registrering:*** *Thorax average* ***Parameter set:*** *Thorax* ***Metode:*** Online: Finn riktig nivå manuelt, deretter skjelett automatch med rektangulær VOI på strukturer i tilknytning til PTV Offline: manuell bløtvevsvurdering ***Strukturer:*** *PTV og evt OAR og markører** **markører skal være lagt inn som eget volum, navnet* GTV_{FM}	Scanområde Øvre del av øsofagus:  Midtre del av øsofagus:  Nedre del av esofagus:



Gjennomføring/kommentarer

Skann: Spotlight er et skann som kjøres 200° og gir derfor mindre bevegelsesfartefakter enn et fullt skann. Diameteren på FOW er 26 cm slik at ytterkonturen til pasienten ikke fremstilles.
Beinmatch**:** *VOI* skal dekke de omkringliggende benede strukturer til PTV og inkludere lengden av columna. Sjekk at man er i riktig nivå før automatch gjennomføres.

NB: Det er ikke forventet at markørene vil være synlige utenfor PTV. Dersom det mot formodning skulle forekomme, må overlege (Glenjen/Abelseth) konfereres.

Offline vurdering av CBCT bilder: Ved endringer av dosimetrisk betydning kontaktes rekvirent og evt. fysiker for å avgjøre om re-planlegging er nødvendig.

Vær oppmerksom på følgende endringer:
- Vokser/skrumper tumor?
- Kan det være forskjeller i anatomi som kan påvirke PTV og/eller dosefordelingen (for eksempel tumorskrumpning, atelektase).

Vær spesielt oppmerksom på medulla når denne ligger nær PTV.
Spesielle hensyn gjort ved doseplanlegging markeres i *Comment field* fra dpl.
Det er behandlede stråleterapeut som er ansvarlig for at CBCT også ses på i *Offline.*

Når CBCT er sett på og godkjent endres Status til *Approve* og hakes av som godkjent i strålekort.

Triggered:

Opptak:

Modalitet: *kV - During*

Imaging application:
Application settings: Trigger

Valg av trigger: *Tid*

Anatomi: *Thorax arms up/arms down*

Intervall: *4 sek*

Triggered imaging kan ikke bestilles på forhånd, men må legges til når aktuell plan behandles. Røntgenrør og bildeplate er ute under behandling. På behandlingsmaskinen:

- Åpne pasienten
- Velg et behandlingsfelt/bue og velg **ADD** i Treatment Application skjerm
- Kryss av for modalitet: **kV** og Execution phase: **During**, og trykk **OK**
- På statiske planer må dette gjøres på hvert felt
- Se vedlagt prosedyre for detaljer (ref 4)
- Anatomi: Thoraxfix: velg arms up. Maske: velg arms

	down.

Referanser

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2. Gripsgård H. *Project plan: Fiducial markers and image guided radiotherapy in esophageal cancer*. 2016
3. Varian Medical Systems, Inc. *TrueBeam Reference guide – Volume 2: Imaging*. Chapter 8: Image Acquisition Chapter 11: Motion managing. June 2013
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Apendix E

Prosedyre: avlesning av x, y, z verdier for hver markør

Interfraksjonell bevegelse: Avlesning av markørenes posisjon gjøres i Image Registration.

Avleste verdier registreres under aktuell pasient i Excel-arket C: FM position – relative values.

Markørenes posisjon på planleggings CT:

1. Dobbeltklikk på planleggings CT slik at bildene vises på skjermen i tre plan.
2. Les av markørene i samme rekkefølge som de er navngitt, dvs start kranielt og arbeid deg nedover.
3. Trådkrysset plasseres i senter av markøren (center of mass). Sjekk at krysset er plassert i senter i alle tre plan. Dersom markøren er utsmurt pga bevegelse/respirasjon, plasseres krysset i senter av den utsmurte markøren.

Markørenes posisjon på CT avg:

1. Ta opp både CT (som har user origin) og CT avg rekonstruksjonen. De har samme koordinatsystem, men det er ikke satt et user origo på CT avg. Ved å ta de opp samtidig kan man bruke user origo for planleggings CT'en. Dette gjøres ved først å ta opp Planleggings CT. Marker deretter den stiplete, oransje rammen rundt CT seriene som hører sammen. Denne blir da gul. Klikk deretter på CT avg, man får da opp begge CT seriene overprojisert.
2. Sett blenderen over på CT avg
3. Les av markørene i samme rekkefølge som de er navngitt, dvs start kranielt og arbeid deg nedover.
4. Trådkrysset plasseres i senter av markøren (center of mass). Sjekk at krysset er plassert i senter i alle tre plan. Dersom markøren er utsmurt pga bevegelse/respirasjon, plasseres krysset i senter av den utsmurte markøren.

Markørenes posisjon på CBCT:

1. Bruk den registreringen som er gjort online som utgangspunkt. Dvs at bildene er matchet på skjelett.
2. Marker den aktuelle registreringen mellom CT og CBCT
3. Vis CBCT på skjermen, dvs sett «blenderen» helt over på CBCT.
4. Les av markørene i samme rekkefølge som de er navngitt, dvs start kranielt og arbeid deg nedover.
5. Trådkrysset plasseres i senter av markøren (center of mass). Sjekk at krysset er plassert i senter i alle tre plan. Dersom markøren er utsmurt pga bevegelse/respirasjon, plasseres krysset i senter av den utsmurte markøren.

Markørenes posisjon på repetert CT skann:

1. Det er ikke definert user-origin på denne CT serien. Plaser først krysset i krysningspunktet mellom blykulene som ligger på hudtatoveringene på pasienten. Alternativt kan det gjøres en registrering på skjelett mellom Planleggings CT og

repetert CT. Når krysset er plassert i samme sted som user origin på planleggings CT: høyreklikk og velge set user origin.
2. Les av markørene i samme rekkefølge som de er navngitt, dvs start kranielt og arbeid deg nedover.
3. Trådkrysset plasseres i senter av markøren (center of mass). Sjekk at krysset er plassert i senter i alle tre plan. Dersom markøren er utsmurt pga bevegelse/respirasjon, plasseres krysset i senter av den utsmurte markøren.

Avlest posisjon for markørene skrives inn i exel- ark som heter «FM position», på den arkfanen for den aktuelle pasienten.

Intrafraksjonell bevegelse: Avlesning av markørenes ytterposisjon gjøres i Image Registration.

Bruk samme fremgangsmåte som for interfraksjonell bevegelse. I stedet for senterposisjon leses begge ytterposisjonene til hver enkelt markør av. Start med den mest kranielle posisjonen (ekshalasjon), deretter mest kaudale posisjon (inhalasjon). Alle verdier registreres under aktuell pasient i Excel-arket D: Movement Vectors.