Master's thesis

Master's programme in Biomedicine

May 2021

Deep inspiration breath-hold in stereotactic and conventional fractionated radiotherapy of lesions in the lung

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MABIO5900

60Credits

Department of Life Sciences and Health

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OSLO METROPOLITAN UNIVERSITY
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Master's thesis

60 ECTS

Conducted at the Department of Oncology and Rehabilitation, Møre & Romsdal Hospital Trust, Ålesund Hospital, Ålesund, Norway

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Acknowledgements

The work presented in this master's thesis was carried out at the Department of Oncology and Rehabilitation at Ålesund Hospital and supported by the Møre & Romsdal Hospital Trust. The project was initiated for the master's programme in biomedicine at Oslo Metropolitan University.

I would like to express my sincere gratitude to my supervisor Christer André Jensen who has been encouraging and thorough and shared his knowledge throughout the process. He has been dedicated to my work and preformed well-appreciated supervision. A special thanks to my co-supervisor and colleague, Christoffer Lervåg, for all the scientific discussions on the subject and having an open door to his office.

I would like to thank all my colleagues who contributed at CT, delineation, treatment planning and treatment delivery for all their patience and support.

Finally, I would like to thank my family and friends for supporting me during this work. A special thanks to my children who had me focused on trains and cars in between working hours.

Ålesund, May 2021

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Abstract

The purpose of the clinical study was to evaluate lung cancer patients' ability to perform deep inspiration breath-hold (DIBH) during CT simulation and throughout the treatment course of radiation therapy (RT). In addition, we evaluated target sizes, organs at risk sizes and doses to the respective volumes in volumetric modulated arc therapy RT plans in free breathing (FB) and DIBH. Twenty-one patients with a peripheral lesion in the lung where RT was prescribed were included. All patients underwent breath-hold training at CT and if they complied with the requirements, a CT in DIBH, in addition to CT and 4DCT in FB, were obtained. Treatment plans in FB and DIBH were generated, and dose parameters as well as volume sizes were compared. The endpoints for evaluation were patient compliance, target dose coverages and doses to the organs-at-risk. Nineteen out of 21 patients completed treatment in DIBH. This clinical study found high patient DIBH compliance in both CT simulation and treatment for lung cancer patients. A significant reduction was found in target sizes overall and for stereotactic body radiation therapy in DIBH, as well as significantly decreased doses to heart, chest wall and lungs. DIBH in RT of lung lesions is feasible, and a routine to manage intra-fractional deviation should be established upon implementation.

Sammendrag

Målet med denne kliniske studien var å evaluere lungekreftpasienters evne til å holde pusten i dyp innpust under CT og strålebehandling. Vi evaluerte også størrelsen på målvolumet, risikoorganers størrelse og doser til de respektive volumene i volummodulert rotasjonsstråleterapi doseplaner i fri pust og i dyp inspirasjon. Tjueen pasienter med perifere lungelesjoner ble inkludert. Alle pasienter gjennomgikk pustetrening ved CT og om de bestod kravene gjennomgikk de tre CT 'er; en CT i dyp innpust, en CT i fri pust og en firedimensjonal CT i fri pust. Doseplaner i fri pust og dyp innpust ble utformet og volumstørrelser og dosestørrelser ble sammenlignet mellom fri pust og dyp inspirasjon. Endepunktene for evalueringen var pasientenes etterlevelse, dosedekning til målvolum, og doser til risikoorganer. Nitten av 21 pasienter fullførte behandling i dyp innpust. Denne studien fant en høy etterlevelse blant pasientene både under CT og i løpet av strålebehandlingen. Studien viste signifikant reduksjon i størrelsen på målvolumene totalt og for stereotaksi i dyp innpust, samt signifikant reduksjon av dosen til hjerte, brystvegg og lunger. Strålebehandling i dyp innpust er dermed gjennomførbart for pasienter med lesjoner i lunge og en rutine for håndtering av intrafraksjonell variasjon må etableres før man implementerer denne teknikken i behandlingen av lesjoner i lunge.

Abbreviations

3DCRT	Three-dimensional conformal radiotherapy
4DCT	Four-dimensional computed tomography
AC	Adenocarcinoma
AIP	Average intensity projection
BED	Biological effective dose
BPM	Breaths per minute
CBCT	Cone beam computer tomography
CI	Conformity index
CT	Computed tomography
CTV	Clinical target volume
COPD	Chronic Obstructive Pulmonary Disease
DIBH	Deep inspiration breath-hold
DSA	Norwegian Radiation and Nuclear Safety Authority
FB	Free breathing
FFF	Flattening filter free
FSU	Functional sub-units
ECOG	Eastern Cooperative Oncology Group
ED	Extended disease
EQD2	Equivalent dose in 2 Gy per fraction
GTV	Gross tumor volume
HU	Hounsfield units
IGRT	Image guided radiation therapy
IM	Internal margin
IMRT	Intensity modulated radiation therapy
ITV	Internal target volume
LCC	Large cell carcinoma
LD	Limited disease
MIP	Maximum intensity projection
MLC	Multi leaf collimator

MLD	Mean lung dose
NSCLC	Non-small cell lung cancer
OAR	Organs at risk
PET	Positron emission tomography
PTV	Planning target volume
RP	Radiation pneumonitis
RT	Radiation therapy
SCC	Squamous cell carcinoma
SCLC	Small cell lung cancer
SCLC-LD	Small cell lung cancer limited disease
SCLC-ED	Small cell lung cancer extended disease
SM	Setup margin
TNM	Tumor Node Metastases
VMAT	Volumetric modulated arc therapy

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1. Introduction

In 2019, the Cancer Registry of Norway recorded 34 979 new cases of cancer, with cancer of the lung being the second most common in both men and women. The incidence rate for men has, from 2015 to 2019, been reduced by 6,9% while it has increased by 8,6% for women over the same period. Smoking is the main cause of lung cancer and the difference between gender can be explained by the smoking habits of women and men varying over time.[1] For women under the age of 70 the incidence of lung cancer is decreasing, but for older women the incidence is still increasing. Not only is lung cancer common, but 19% of all deaths related to cancer in 2019 were caused by lung cancer. Lung cancer has a poor 5-year relative survival rate for regional disease of approximately 30% and survival rates in localized disease of 60% and 70% for men and women, respectively, however, the survival rate is increasing in both genders.[1] Most long-term survivals underwent surgery, but a high survival rate can also be expected after stereotactic body radiotherapy (SBRT).[2] The increased survival rate the last two decades could possibly be due to improved lung cancer treatment. [1] These trends in incidence, mortality and survival in Norway is displayed in figure 1.

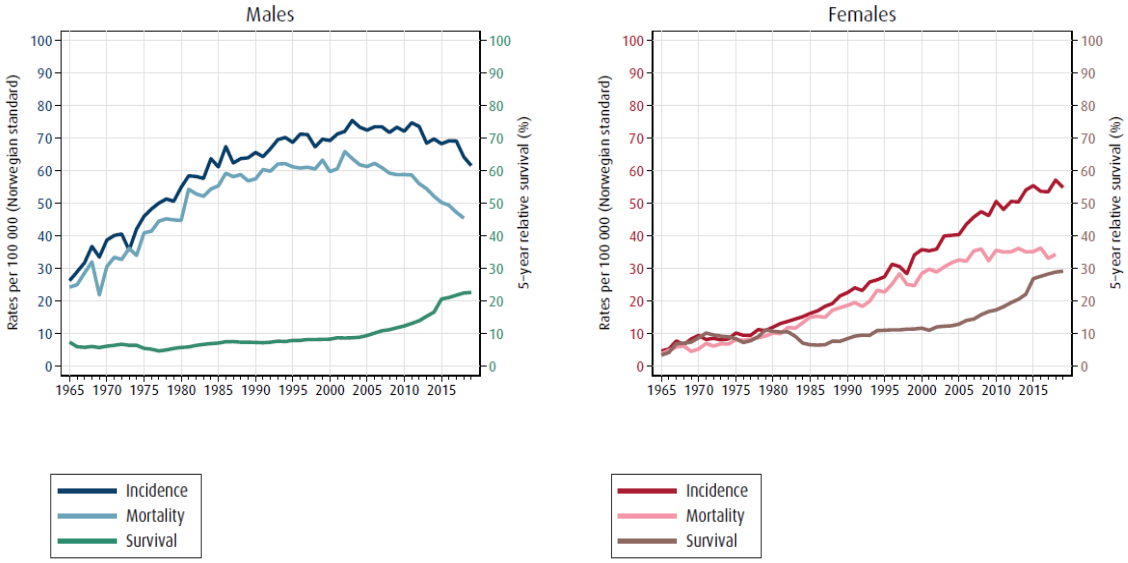

Figure 1 Trends in incidence and mortality rates and 5-year relative survival proportions [1]

1.1 Lung cancer

A patient presenting symptoms of lung cancer should be examined carefully. When lung cancer is indicated the examinations of the patient should result in information including histology, stage, extent of disease, and the patient's general health. Histological or cytological

diagnosis can determine the choice of treatment together with the patient's health in general. Computed tomography (CT) is always performed when suspicion is present, and positron emission tomography-CT (PET-CT) is done when curation is indicated. Scintigraph and magnetic resonance imaging is performed in some cases, and tissue should preferably be biopsied.[2] If lung cancer is left untreated it will eventually spread by growth into lymph or blood vessels. [2]

There are two main types of lung cancer, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). About 85% of lung cancers are NSCLC and can be divided into three subtypes: adenocarcinoma (AC), squamous cell carcinoma (SCC) and large cell carcinoma (LCC). The most common NSCLC is the AC, and these lesions are usually located peripherally in the lung. SCC is located near the large bronchiastinal branches and its origin is skin and mucous membrane. LCC does not have any microscopically features, other than being large.[2]

SCLC is the most aggressive type of lung cancer, usually located in the center of the lung. The cells are small and divide rapidly. Distant metastases have an early onset for this group of patients and SCLC is most often considered a systemic disease at onset. Local disease (LD) and extended disease (ED) is often used to describe the extent of the disease.[2] Some rare cases of cancer in the lung are neuroendocrine tumors and cancer in the mesothelium, mesothelioma.[2]

1.1.2 Classifying lung cancer

Since lung cancer can be diagnosed in different histology and stages [3], there are several guidelines to consider when diagnosing and classifying lung cancer. Tumor node metastases (TNM)-classification is a system that describes the anatomic extent of a lesion. The three letters T, N and M represents the extent of the primary tumor, lymph node involvement and distant metastases, respectively. T, N and M are divided into several subgroups and the combinations of these three categories define the patient's stage group. The group of T depends on tumor size and level of invasion in adjacent structures. The location of involved lymph nodes determines the N, and M is classified by either intrathoracic dissemination, extra thoracic metastasis or multiple metastases.[3]

Defining the clinical stages of a patient consists of gathering and evaluating all information available. The clinical stage is determined before treatment and includes physical signs, imaging, procedures, biopsies, and the patient's symptoms. The stages range from 0 to

IVB, IVB being the stage where the disease has developed into multiple metastases, usually in brain, liver, adrenal glands and/or bone. The lesion's grade of resection is also a part of classifying lesions post-surgery and is defined as the patient's pathological stage combined with clinical staging.[3]

Comorbidity and performance status must supply the stage of disease when choosing treatment. Chronic obstructive pulmonary disease (COPD) and coronary illness, among others, as well as performance status play a part in deciding risk of complication during and after surgery and level of lung capacity post-surgery.[2] The Eastern Cooperative Oncology Group (ECOG) has developed a scale to grade patient's performance status by six levels, as presented in table 1. The level of performance status can determine the choice of treatment.[4]

Table 1 Eastern Cooperative Oncology Group Performance status [4]

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

1.2 Lung cancer treatment

There is a wide range in overall survival and treatment options for lung cancer, all depending on type and stage. Lung cancer treatment consists of several modalities such as surgery, radiation therapy (RT), systemic medicine, or a combination of these. Surgery or RT can cure NSCLC in stage I-III and surgery is the method of choice if the illness is in early stage and surgery is possible, both medically and technically. If not, RT is an alternative. Chemotherapy cannot cure this disease alone, but it can improve treatment result if combined with surgery or RT in some cases.[2] In curative position, a patient in stadium III can receive immune therapy with Durvalumab for a year after chemoradiotherapy if the disease is not progressing and the PD-L1 expression is $\geq 1\%$.[2]

When curation is not possible, systemic treatment with chemotherapy, targeted therapy or immunotherapy can improve quality of life and prolong life for patients having NSCLC. If the patient is to receive tumor targeted treatment, prognosis, quality of life, comorbidity, age, and the patient's ECOG-status is essential considerations. The patient's wishes must also be taken into account.[2] Palliative treatment aims to prolong life, prevent symptoms and/or symptom relieving. Both RT and systemic treatment can contribute to non-curative treatment. Systemic treatment can be immune therapy, targeted therapy and/or conventional chemotherapy. Patients with AC or SCC without EGFR-, ALK-, ROS1-mutations and PD-L1 expression are considered for a combination of chemotherapy and immunotherapy. With a PD-L1 expression above 50%, immune therapy can be considered as monotherapy and AC with mutation are considered for targeted therapy. If the patient has oligo metastases, more aggressive treatment may be the treatment of choice. When mutations are present, the targeted therapy is preferred.[2]

For SCLC limited disease (SCLC-LD), chemotherapy is an important part of treatment.[2] Patients having SCLC-LD are treated with a combination of chemotherapy and RT. The second or third round of chemotherapy is usually administrated during the treatment period of RT. Based on recent studies, the guideline[2] in Norway recommends hyper fractionated scheme 1,5 Gy x 2 x 15. At least 6 hours between fractions is necessary and 8 hours is recommended when applicable. As an alternative, fractionation of 2,8 Gy x 15 is applicable when two fractions a day is not suitable.[5] For SCLC extended disease (SCLC-ED), RT of the lesion is not a part of the treatment recommendations.[2]

1.3 Radiation therapy in lung cancer

During the treatment course of lung cancer, 61% of the patients will receive RT.[6] RT of lesions in the lung is done by external beam therapy by a linear accelerator and even with lower life expectancy than after surgery, RT plays an important part in lung cancer treatment when surgery is not possible.[7] RT in the lung consists of either conventional fractionated treatment or SBRT. Today, most patients are treated with SBRT and Baumann et al.[8] showed a local control of 92 % in their Kaplan-Meier estimation three years post 45 Gy in three fractions.

RT in lung lesions differ from other RT due to the vast tissue density variations and extent of motion in the area being treated. As the lungs are responsible for the body's respiration, motion in the thoracic cavity is naturally occurring. A set of muscles in the thoracic cavity are active during inspiration and expiration, the diaphragm being the main

inspiratory muscle. The diaphragm separates the abdominal wall and the thoracic cavity[9] and Seppenwolde et al.[10] found that lesions in the lower lobe, close to the diaphragm, move 12±2 mm in cranio-caudal direction, in lateral and anterior-posterior directions, the movements of 2±1 mm had no correlation to its location. Peripheral tumors can have significant motion that must be considered when RT is indicated, in addition to natural motion; common diseases such as COPD, asthma and chronic bronchitis have an impact on a patient's breathing pattern.[9] The motion from the heart and large vessels are continuous during RT and their tolerance limits must be safeguarded.

1.3.1 Radiobiology

When RT was first brought to clinical use, it was given in one fraction and its effect and level of dose was evaluated based on skin reactions. In the 1960's, computer-based dose calculations were performed as the technology and knowledge on the subject evolved. Clinicians realized that the toxicity to healthy tissue caused by radiation could be decreased by lowering the dose.[11]

In RT, the aim is to achieve cell death while recovering as much healthy tissue as possible. The benefit of RT must be seen in relation to the costs that the healthy tissue, hence the patient, will suffer. In curative treatment, and where there is a high expected survival, the costs of radiation toxicity are of big importance as they may affect a patient's quality of life. The difference between the tumor control dose and the tolerance dose of healthy tissue is called the therapeutic window. Although cell death is more likely when exposed to higher radiation doses, the effects on healthy tissue will limit the options. Both the histology of tumor cells and the response in different tissues affect the choice of radiation dose as the response may differ in between various cell characteristics. The time from radiation exposure to the response highly depends on the tissue and the dose it has received. In the 1980's, the interest in fractionation started as the early and late responding tissues' different reaction to a change in dose was discovered. [12]

1.3.2 CT and simulation

Wilhelm Conrad Roentgen discovered the x-ray, as early as in 1895 and allowed for the world's first radiographs. Clinical radiographs first presented anatomic structures on film, and lately the digital radiographs have become the most frequently used. The images obtained are two-dimensional and has limitations as to which tissue densities are displayed, soft tissues are not displayed in detail and only the pattern of gray values are utilized when diagnosing.[13]

These radiographs were used to plan RT according to patients' anatomy in RT simulation and only a few clinics have simulators in use today.

In 1972, the first clinical computed tomography (CT) was acquired, and a new way of presenting anatomy was established. The CT allowed for a more detailed visualization of the anatomy due to advanced technology and slice imaging. CT images are displaying the patient's anatomy in slices, and when it first was introduced, the images were displayed as transverse slices. Today, the slices can be reconstructed in three directions; sagittal, coronal and the most frequently used, transverse. Although being severely time-consuming at first, the CT has developed over the years to become central in both diagnostic and therapeutic use with rapid scan times. In CT images, the intensity attenuated by an object is registered and attenuation values along each ray from the source is recorded by the detector. As attenuation is highly dependent on the photon energy applied, the computed attenuation coefficient is presented as CT-numbers. CT-values are presented relative to water attenuation and specified as Hounsfield Units (HU) with water, and water-equivalent tissue, having a HU of 0. As the body is composed by tissues with a highly variable density, the different tissues will be presented in a large specter of HU. Calcium has a high effective atom number and makes up the bony structures in the body, they have a high attenuation and can have CT numbers of 2000HU compared to low density tissues such as the lungs that will have a negative CT number. This wide range in tissue density makes up the contrast in CT images.[13]

CT was implemented in RT after Hounsfield won the Nobel Prize in 1979 due to his development of CT. CT became essential in treatment planning, as it is today.[14] CT technology has evolved over the years and today's modern CT has multi-row detectors and rapid rotations times, an acquisition is performed in seconds.[13]

Even with the rapid scan times, artefacts can cause poor image quality. Motion artefacts can cause streaking and enhancement of a structure due to the structure being present in several positions and voxels in the data set, affecting the calculated CT number in a displayed pixel. Motion can be caused by a patient moving during scan or internal organ motion. Motion from respiratory movement in the thoracic cavity can cause motion artefacts. The structures are blurred, streaking, or presented as shades.[13] A diagnostic thoracic CT is usually performed in breath-hold to limit artefacts and allow for more accurate measurements of structures. CT simulation performed prior to RT must be taken in free breathing (FB) if the patient is breathing freely during treatment, as the patient must be in treatment position when

planning. The organ motion makes target delineation and treatment planning difficult, especially with peripheral lesions.[7] As the target in RT is delineated based on radiological visible extent of the tumor, every position of the moving structure will be included, resulting in increased tumor volume compared to the measured tumor volume in diagnostic scans. Information about organ motion is essential in RT. Treatment plans must be based on a CT in treatment position when radical radiotherapy is indicated, and is the standard approach in all external beam treatments in Norway today.[7]

Four-dimensional computed tomography (4DCT) is an imaging-technique that take respiration into account. During acquisition, the patient is breathing normally, and external devices register the patient's respiratory curve. The 3D-images are combined with respiration-data as they are sorted in different phases of respiration and combined in a phase bin. Images can be sorted by either time or level of amplitude, phase- or amplitude binning. The application of 4DCT seems to reduce the volume of healthy lung tissue irradiated during treatment[15] while the target coverage is maintained. 4DCT provides information about the lesion's, and surrounding tissue's, motion and the margins can be defined accordingly.[16] To avoid artefacts from respiration in a 4DCT, the pitch value must be appropriate and based on each patient's breathing cycle, breaths per minute (BPM), and the detector configuration of the CT being used. The pitch is related to the maximum width of the detector and the frequency of the breathing. However, with low BPM the chances of artefacts are increased due to the prolonged scan time. The low BPM can also limit the scan length due to the x-ray tube's maximal beam on time.

The images are reconstructed into image set containing information about organ motion. The reconstructions most frequently used in RT is maximum intensity projection (MIP) and/or average intensity projection (AIP). These are used for target delineation. A MIP displays the area with the highest intensity in a volume by letting the highest intensity value found represent each pixel. MIP has proven to be a valuable tool in defining internal target volume (ITV) and AIP displays the average position of the lesion.[16]

During CT simulation, and RT, the patients are immobilized by a set of immobilization devices to ensure a reproducible setup as the patient will be in this position at every fraction. The choice of fixation devices and their location should be well documented at CT simulation. Markers are often used supplying tattooed reference points on the patient's skin.

1.3.3 Treatment planning

In treatment planning, the dose to the patient is calculated and the treatment target is covered by high energy x-ray fields surrounding the chosen isocenter. RT planning was at the beginning based on isodose charts and simulation of treatment fields in radiographs. Treatment planning techniques have evolved rapidly over the last decades and the implementation of CT simulation allowed for three-dimensional conformal radiotherapy (3D-CRT).[17,18] This treatment technique is based on anatomic information in 3D. The treatment fields are as conform as possible to the target. When implementing 3DCRT, the goal was to minimize the dose to surrounding tissue and still deliver an adequate dose to target.[18] Treatment planning systems, today, calculates a photons attenuation in the patient based on photon energy and tissue density, by CT images and CT numbers, in the treatment planning systems.

In the technique called intensity-modulated radiation therapy (IMRT), a nonuniform fluence is delivered as opposed to the uniform intensity across the field in 3DCRT. The fluence is delivered in any position of the treatment beam.[19] The intensity modulation allows superior dose conformity compared to conventional radiotherapy, such as 3DCRT. In IMRT planning, the operator determines the dose criteria and the optimal fluence is generated through inverse treatment planning. Beams are created and optimized based on the predefined dose criteria. The beams consist of several beamlets formed by multi leaf collimators (MLC) and the treatment is delivered in different angles. [19]

Due to the discovery that varying beam intensity by different gantry angles could result in superior dose distributions compared to static IMRT, the vendors presented a treatment delivery method where variable dose rates could be delivered while gantry rotated. The treatment with rotational cone beam, including variable shape and intensity, was named volumetric-modulated arc therapy (VMAT). This resulted in increased delivery efficiency, with the advantage of reduced treatment times and monitor units. Patient motion is limited to a minimum due to shortening of the delivery times.[20]

In traditional treatments, and in older linear accelerators, the photon fluence is filtered by a flattening filter to ensure a flat and even dose distribution. Recently, vendors have delivered linear accelerators with the possibility to not apply this filter during RT. Compared to conventional flattened beams, the flattening filter free (FFF) beams has an increased photon fluence rate resulting in decreased treatment times. [21]

1.3.4 Target delineation

Target delineation today is usually performed in treatment planning systems and in CT images obtained during CT simulation. Other modalities such as magnetic resonance imaging and positron emission tomography can contribute with extended information about the target.[14] During target delineation, a set of volumes and margins are delineated to define the target which is being radiated. Target delineations consist of defining gross tumor volume (GTV) which contains a palpable or radiological visible lesion. From GTV the clinical target volume (CTV) is defined by adding the area where there is a chance of subclinical, unknown, malignant cells relevant to ongoing treatment.[7] This margin has, for lung cancer, traditionally been 10 mm. Internal target volume (ITV) is CTV with an internal margin (IM) which correlate to internal motion and deformation of the CTV. This volume is only applicable if you can determine the internal movement at the area of interest. The planning target volume (PTV) takes IM and changes of the CTV into account. It also accounts for patient movement as well as patient and field setup variations, the setup margin (SM). PTV is important during treatment planning to ensure correct dose to CTV.[7]

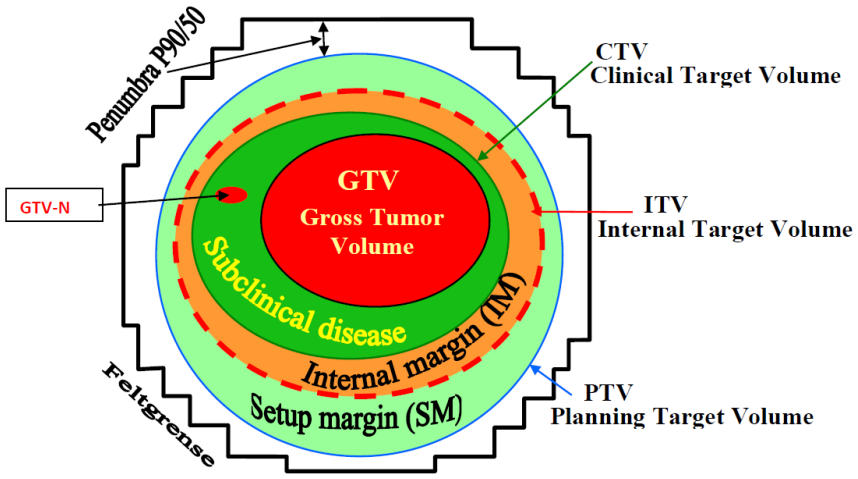

Figure 2 Volumes in treatment planning [7]

The chance of subclinical microscopic disease depends on the histology of the tumor. Giraud et al. [22] found that to ensure coverage in about 95% of all cases the adequate GTV-CTV margin for SCC and AC are 6 mm and 8 mm, respectively. Li et al. [23] found that the margins should be 5 mm and 7 mm, while Grills et al. [24] suggested a margin of 9 mm to ensure coverage of the microscopic disease in AC. If the treatment is conventionally fractionated, the GTV-CTV margin should be 5-10 mm.[7] In lung lesions, 4DCT is recommended treating both curative and palliative patients to provide information about the

lesion's internal movement. In cases where there are no information about the lesion motion from a 4DCT, the ITV-margin is based on research on lung lesion motion and their anatomical location in the lung. [7]The margins applied to targets in motion tend to be large to account for the variable lesion position.[25] If the lesion is located in the upper lobe, the margins necessary to account for motion will be smaller than for lesions located in the lower lobes due to lower lobe tumors larger extent of motion.[7]

If GTV is defined from 4DCT data, the GTV is called iGTV. If a CTV margin for the risk of microscopic disease is added to iGTV this new volume is called ITV.[7] When information about a lesions position during respiration is present, commonly from a 4DCT, the Norwegian Radiation and Nuclear Safety Authority (DSA) recommends a ITV-margin of 5-10 mm and PTV-margin of 5-10 mm in conventional fractionation to account for microscopic disease.

In SBRT, the iGTV is often delineated based on mid-ventilation, the AIP reconstruction. The tumor motion is accounted for in the delineation of iGTV. Margins to assure sufficient coverage based on microscopic disease are added to this volume. The margins recommended by DSA are 0-5 mm and 3-5 mm to ITV and PTV, respectively.[7] In Guckenberger et al.[26] consensus guideline on SBRT in peripheral NSCLC, the 4DCT was mandatory in most clinics with a GTV-CTV margin of 0mm and a minimum CTV-PTV margin ranging from 3-7 mm. When reducing the margins, a possibly decrease in dose to surrounding tissue will follow.[27] Treating a patient while the patient is in deep inspiration breath-hold (DIBH) allows for the margins to be reduced even further.[7]

1.3.5 Conventional fractionated treatment

Traditionally, most RT was given in 2 Gy fractions. Today the fractionation schemes vary depending on several factors: tissue characteristics, location, patient performance status, among others. When the dose increases above 2 Gy per fraction it is called a hypo fractionated treatment while a decrease is called hyper fractionated.[28] Patients who cannot be cured from their disease but need treatment to relieve symptoms usually receive a fractionation that differs from the curative treatments. If the aim of treatment is to relieve symptoms as soon as possible, high doses can be given in few fractions such as 8,5 Gy x 2. As an alternative, other palliative fractionations can be applied, as described in table 2. The patient's prognostic factors are essential when deciding treatment and fractionation in lung cancer.[29]

Table 2 Fractionation in conventional radiation therapy[7]

Indication		Fractionation
Curative primary treatment in NSCLC	Inoperable stages I-III	2 Gy x 33 - 35 = 66 – 70 Gy
		2 Gy x 30 - 33 = 60 – 66 Gy Concomitant chemoradiotherapy

Abbreviations: NSCLC, non-small cell lung cancer.

Table 3 Fractionation in palliative radiation therapy[7]

Indication	Fractionation
Thoracic radiation therapy	2,8 Gy x 15 = 42 Gy
	3 Gy x 10 - 13 = 30 - 39 Gy
	8,5 Gy x 2 = 17 Gy with 1 week in between fractions
Pancoast tumor	3 Gy x 16 = 48 Gy
	2 Gy x 25 = 50 Gy

1.3.6 Stereotactic body radiotherapy

SBRT was developed in the 1990's. The technique allows for treating patients with high doses while maintaining the dose to surrounding tissue at an acceptable level. This can be done due to advanced technique and equipment, the patients are receiving doses from several angles resulting in conform dose, sparing surrounding tissue.[2] SBRT is an extremely hypo fractionated treatment, with fractionation of few fractions by 15-20 Gy each being the most common, allowing a decrease in patient appearances. SBRT is superior to the conventional approach in stage I NSCLC.[7] Biological effective dose (BED) is the biological dose that is delivered by a certain fractionation, total- and fraction-dose, according to the tissue irradiated and its sensitivity to radiation.[30] SBRT has a great advantage, delivering a biological effective dose above 100 Gy.[2] compared to the conventional treatments' BED of 70-80 Gy, considering the tumor has a α/β of 10.[7] Although SBRT has existed for quite some time now its use has just recently increased.[31]

SBRT is applicable when the patient is inoperable in stage I to T3N0, and it is the treatment of choice for inoperable stage I in NSCLC.[2] Different fractionation approaches are in clinical use, the most frequently used are listed in table 3. When choosing this technique,

lesions have to be < 6 cm and if they are located near central structures the fractionation must be adjusted accordingly, as presented in table 3. [2] The inhomogeneous dose distribution and small targets allow a reduction in toxicity to healthy tissue while escalating the dose to target. The high precision allows for smaller margins.[7]

Table 4 Fractionation options in stereotactic body radiotherapy[7]

	Peripheral tumor	Peripheral tumor close to the chest wall	Tumor < 1 cm from lobar bronchus or other critical structures
Fractionation	15 – 18 Gy x 3	11 Gy x 5	7 Gy x 8

1.3.7 Target coverage

Target coverage, or sufficient radiation effects in the predefined target of cancerous cells, is the primarily endpoint during treatment planning and RT. In RT planning, the main goal is to ensure sufficient dose to target to allow for the effect of the prescribed dose to be fulfilled. To reach this goal, a target volume must be chosen for the prescription volume. The generally adapted prescription is the median dose, $D_{50\%}$, to target being at 100% of prescribed dose, with the target volume being PTV. In lung cancer treatment, the vast difference in tissue density between lung and tumor is known to make the dose coverage by this approach difficult to achieve during treatment planning due to the insufficient dose build-up in lung tissue. The median dose to ITV/CTV or the mean dose to GTV is a better choice in lung cancer RT and is the preferred choice. However, in SBRT, prescribing the dose to the peripheral part of PTV has shown effective, maximum dose in central GTV could preferably be 120-150% in SBRT.[7]

In conventional RT, the $D_{98\%}$ of the prescription dose is generally recommended not to cover less than 95% of the prescription volume, but due to the previously mentioned density variations in the lung, a 90% coverage is often set as a criterion in the treatment of lung lesions. While achieving the best possible dose distribution to target, the organs at risk (OAR) and their dose limitations based on clinical endpoints must be considered.[7]

Treatment planning in lung cancer can be complex and clinical goals must be evaluated upon approval. In addition to evaluation of sufficient target coverage, the dose distributions conformity is of importance, especially in SBRT with high fraction doses.

Conformity index is the relationship between treated volume[7] and the target, and explains the conformity of the treatment.

1.3.8 Dose limitations to organs at risk

OAR or healthy tissue should always be spared as much as possible while maintaining the prescribed dose to target, and in some cases, OARs can limit target coverage. When considering the dose limitations of OAR's, the clinical outcome at a certain dose and the structure of the organ must be evaluated. Adverse effects after RT are commonly due to cell death. Cell death usually happens when the cells divide and fails due to defects. In tissues that has a high turnover, where the cells divide rapidly, the effects are often early or acute. Late responding tissue has cells that divide rarely and the effect from radiation expresses itself after months or years, and the tissue may never be repaired. The early and late responding tissue has different α/β ratios, explaining their different dose response relations.[7,32] The organization of functional subunits (FSU) decides the tissue's sensitivity to radiation. A tissue that has FSU in serial structure is dependent on each FSU to maintain function, and the maximum dose to any of these FSUs must be limited. Parallel tissue can function even if a part of its structure is radiated and the proportion of volume that is irradiated must be taken into account.[32] Other than the technical operations to ensure dose coverage and limiting doses to OAR, it is essential that the patients stop smoking before treatment start. Smoking reduces the effect of RT and causes a higher rate of complications.[2]

Traditional fraction dose is 2 Gy and most dose limitations come from research related to this fraction dose. The fractionation scheme has an impact on the organs at risk and the dose limitations must be set according to this. It is common to convert the dose limitations into what would be an equivalent to 2 Gy per fraction (EQD2) that would result in the same biological effect.[28] The conversion of doses by α/β values is being questioned for the high level of hypo fractionation in SBRT, due to the uncertainties in converting doses into EQD2 in high doses. Conventional and stereotactic fractionation use different doses and clinical goals in the planning and evaluation, and SBRT dose limits are based on research concerning high fraction doses and following endpoints. SBRT dose limitations to OAR are commonly presented as limits to dose per fraction.[7]

1.3.8.1 Heart

The heart is an organ that rarely has been reported to cause side effects from RT of lesions in the lungs. This is mainly due to the short overall survival of this group of patients, but also that a decrease in heart function often is described as a progression of disease and not as a

side effect. Symptoms are rarely seen until decades after radiotherapy. However, the heart is a vital organ and dose limitations must be followed as overall survival increases. Pericarditis, cardiomyopathy, damage to coronary arteries, valve damage and arrhythmia are adverse effects seen with total doses from 30 Gy and above 40 Gy. [33] According to DSA the mean heart dose should preferably be < 35 Gy and always below 46 Gy in conventional treatments.[7]

In SBRT, the maximum dose is a common parameter to evaluate with the endpoint being pericarditis. The maximum dose should be less than 10 Gy per fraction when RT fractionation is 15 Gy x 3, a total of 30 Gy.[7,34]

1.3.8.2 Lungs

Adverse effects of RT include acute or early occurring events as well as late adverse effects. Radiation pneumonitis (RP) being acute and radiation induced fibrosis occurring later, after 6 months from time of treatment. [35] A high proportion of patients being treated with RT for lung lesions get RP with traditional fractionation schemes. Therefor it is known as a common outcome in this group of patients. [36]

There can be some variations when delineating the lung volume. This could be due to the individual who is defining it, the chosen contrast in the CT images, and uncertainties in which structures is to be included as healthy lung tissue.[36] When reporting and optimizing doses to the healthy lung tissue it is common to generate a volume consisting of lungs excluding GTV (lungs-GTV). The GTV tends to deform during treatment, the lesion being replaced by healthy tissue, and the actual volume of healthy tissue being exposed to radiation may vary from the original plan. [36]

Elderly patients have a higher risk of getting RP than younger patients, assuming young patients are under the age of 60 or 70 years.[36] Lung capacity can permanently be reduced if healthy lung tissue is irradiated with more than 20 Gy. The amount of lung tissue receiving 20 Gy should be held to a minimum, at least below 35%. [2] Some chemotherapy agents are also associated with RP and in combination with RT the risk is increased.[7] For the union of lungs with GTV subtracted, the DSA[7] recommends a mean lung dose (MLD) < 20 Gy and that V_{20Gy} < 35 % and the V_{5Gy} < 65 %. All dose limitations when receiving 2 Gy per fraction.[7]

RP is uncommon in SBRT, however adverse effects such as bronchial injury has been reported in SBRT.[36] Chun et al. [37] found that being treated with IMRT or SBRT decreases the

risk of pneumonitis. According to the results, patients treated with the older technique, 3DCRT, had higher rates of severe pneumonitis than patients treated with IMRT. Modulated treatment is recommended when treating NSCLC due to its increased dose distribution conformity.[37] The lung volume commonly adapted when evaluating lung doses in SBRT is a union of both lungs with GTV subtracted. The DSA recommends that the volume that receives 10 Gy to be held below 40%.[7] Ong et al.[38] recommends keeping the V_{5Gy} to contralateral lung below 26% to avoid pneumonitis.

1.3.8.3 Spinal cord

Radiation induced chronic myelopathy usually occurs more than a year post radiation. The first peak at 13 months is most likely due to white substance damage and the second peak, at 29 months, is from vascular damage.[39] As the spinal cord is considered a serial organ, the maximum dose is important, D_{max} is reported.[40] Maximum dose to the spinal canal in EQD2 is 50 Gy according to the DSA, when hyper fractionated scheme is applied the equivalent value is 54 Gy.[5] $D_{0,35cc} < 6$ Gy and maximum point dose < 7,33 Gy are dose limitations in SBRT to avoid myelopathy, according to Timmermann [34] and Benedict et al. [41].

1.3.8.4 Esophagus

When treating a lesion close to the esophagus, the patient may experience a set of adverse effects during or immediately after the treatment period. These effects are mostly difficulty swallowing and/or pain. A late effect of radiation to the esophagus is fibrosis. The area (cm^2) receiving 55 Gy or more and the volume receiving 60 Gy or more has a correlation to esophagitis.[7] The DSA recommends a mean esophageal dose of < 34 Gy.[5] In SBRT, the maximum dose must be taken into account and $D_{5cc} < 7$ Gy and maximum point dose < 9 Gy are the dose parameters to evaluate as recommended by Timmermann [34] and Emami.[42]

1.3.8.5 Chest wall

Toxicity to the patients' chest wall following SBRT has an impact on patient's quality of life and therefor has a clinical meaning.[43,44] During treatment planning the chest wall should be listed as an organ at risk in SBRT. In a study to predict the risk of complications in chest wall after SBRT Dunlap et al. [43] showed that for treatments given in three to five fractions the volume of chest wall receiving 30 Gy, or more, should be less than 30 cm^3. In the same study, they suggested alternating the treatment by re-planning, increase the number of fractions or lowering prescription dose if the V_{30Gy} could not be managed.

Stam et al. [45] showed that when evaluating the risk of rib fracture, the D_{max} is the main predicting factor. A D_{max} below 225 Gy, corrected for EQD2, resulted in under 5% chance of

symptomatic rib fracture.[45] Maximal fraction dose, D_{2cc}, to rib is recommended to be below 9 Gy.[7]

1.3.9 Approaches to manage tumor and organ motion

Today, patients having RT, due to a lesion in the lung, are breathing freely and at their own pace during RT. Tumor motion is significant in lung lesions[10]. Motion of lesions in the lung can be managed by a set of approaches.[46] Traditionally, large margins have been applied to account for lesion motion. In recent years, the adaptation of four-dimensional computed tomography (4DCT) has improved target delineation with its ability to provide information on lesion movement.[16] 4DCT in FB is now the most frequently used approach and ensures coverage of the whole tumor in each position during the breathing cycle. To avoid underdosing the target, the margins applied are still large according to the variation in lesion position. Gating can manage and reduce respiration-related motion, either computer based or by voluntary breath-hold. Approaches such as mechanical compression of the upper abdomen can manage motion in lower lobes to some extent.[47,48]

Deep inspiration breath-hold (DIBH) treatment was introduced for left sided breast cancer the last decade and the technique is described as beneficial in breast cancer RT.[49] Previous research has shown that gated treatment with DIBH has several advantages for RT in lung lesions with conventional fractionation. It can reduce doses to healthy tissue [50-52], improve image quality [53] and increase dose conformity. [52] The research on lung cancer RT is mainly based on older techniques and fractionation, where patients were generally treated in FB. Even though research has shown advantages, DIBH is not the preferred technique for treating lung cancer today and little research exists on DIBH for stereotactic body radiation therapy (SBRT).[7]

Treatment equipment and techniques have evolved recently, resulting in shorter beam-on-time and more conform dose distributions. With today's modern linear accelerators equipped with flattening filter free (FFF)[21] delivery and treatment techniques such as volumetric modulated arc therapy (VMAT), treatment times have shortened considerably.[20] SBRT has the advantage of only a few fractions combined with superior local control and toxicity rates.[54] It has become the treatment technique of choice when treating smaller lesions in the lungs. These new techniques, adapted in modern RT, may contribute to a tolerable breath-hold treatment, also for this group of patients.

1.3.10 Image guided radiation therapy

In addition to applicable margins to ensure coverage of the target, the exact location of the lesion, OAR and patient position should be confirmed before treatment delivery. This assurance is done by image guided radiation therapy (IGRT). It can detect inter- and intra-fractional differences in anatomy or in the patient set-up. When performing IGRT, the use of cone beam computed tomography (CBCT) is mandatory. While the CT has circular detectors on the opposite side of the x-ray tube, the detectors in CBCT are imbedded in a flat panel with an x-ray tube opposite of it.[55] CBCT is done either when the patients are breathing naturally or in DIBH, when indicated. The same motion artefacts that occur in CT can distort the reconstruction in CBCT. Hence, the image quality of the IGRT can be enhanced by breath hold.[53]

Aim of Study

Treating a moving target can be challenging. The standard treatment in Norway today is treating lung lesions while the patient is breathing freely; the target is moving during treatment. The treatment machines and techniques have evolved recently, resulting in shorter beam on time and more conform treatments. Left sided breast cancer is treated in deep inspiration as a gold standard today, but the reduced lung capacity of lung cancer patients has been known to make breath-hold treatment difficult for this group of patients. Shorter treatment times can pave way for treating lung cancer patients with the breath hold technique. The aim of this study was to evaluate if lung cancer patients, being treated for a lesion in the lung, can hold their breath during the treatment course. In addition to the capability of these patients to hold their breath, doses to the targets and organs at risk were evaluated in silico. The research questions are:

1. Can lung cancer patients hold their breath during CT simulation and throughout the course of treatment?
2. Does the target and organs at risk volumes and the dose to surrounding tissue decrease when applying a breath hold treatment for lung cancer patients?

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96966 Pustestyrt strålebehandling av lesjoner i lunge (PUST)

Forskningsansvarlig: Helse Møre og Romsdal HF

Søker: Christer André Jensen

Søkers beskrivelse av formål:

En utfordring ved strålebehandling av lesjoner i lunge er at disse beveger seg gjennom pustesyklusen. Dette har tradisjonelt blitt løst enten ved å legge på store marginer rundt målvolumet som tar høyde for denne pustebevegelsen, eller å måle pustebevegelsen med multiple CT-opptak. Begge disse metodene innebærer imidlertid at målvolumet man strålebehandler blir betydelig større enn det ville vært uten pustebevegelse, og at omkringliggende organer som hjerte og lunge også får høyere stråledoser. I dette prosjektet vil vi teste om pasientene klarer å gjennomføre bildeopptak i dy innpust. De som klarer dette vil få gjennomført strålebehandling i dyp innpust istedenfor standard teknikk. For disse pasientene vil det bli laget to sett med behandlingsplaner (standard teknikk og dyp innpust), og doseparametre vil bli sammenlignet for å se om dyp innpust har dosimetriske fordeler sammenlignet med standardteknikken.

REKs vurdering

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional

komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst D) i møtet 12.02.2020. Vurderingen er gjort med hjemmel i helseforskningsloven § 10.

Dyp innpust er allerede standard teknikk ved bestråling av venstresidig brystkreft i Norge fordi det gir dosimetriske fordeler i form av lavere hjertedose. I dette prosjektet skal det undersøkes om pasienter med lungekreft, som ofte har dårligere lungefunksjon enn brystkreftpasienter, klarer å gjennomføre bildeopptak i dyp innpust. Det skal også undersøkes om denne metoden gir dosimetriske fordeler sammenlignet med standardteknikken.

Det skal inkluderes 21 pasienter over 18 år som har indikasjon for strålebehandling mot lesjon i lunge. Pasientene vil gjennomgå pustetrening og pustetest, og de som klarer pustetreningen vil få ekstra CT-bildeopptak. Det skal innhentes opplysninger om stråledoser fra gjennomført strålebehandling, samt stråledoser fra behandling planlagt med tradisjone metode, fra pasientjournal.

Etter komiteens syn er dette et nyttig prosjekt. Det kan være krevende for pasientene å gjennomføre pustetrening og pustetest, men pasientene følges tett og de kan når som helst velge å avbryte behandling i dyp innpust. Det ekstra CT-bildeopptaket som skal gjøres, vil medføre en ekstra stråledose, men det forventes samtidig at disse pasientene vil få reduserte stråledoser i gjennomføringen av strålebehandlingen. På bakgrunn av dette vurderer komiteen at det er liten risiko forbundet med deltagelse, og at nytten overstiger ulempene. Komiteen anser det dermed forsvarlig å gjennomfør prosjektet som beskrevet i søknad og protokoll.

Komiteen har imidlertid en merknad til informasjonsskrivet:

- Det oppgis at formålet med studien er å få kunnskap som kan bidra til å øke kvaliteten på strålebehandling av lungelesjoner. Etter komiteens syn er dette for lite presist. Det må fremkomme tydeligere at man skal undersøke om de å holde pusten under strålebehandling, gjør at lungelesjonene beveger seg mindre slik at man kan bestråle et mindre område og dermed redusere stråledoser til omkringliggende organer. Det kan også vises til at denne metoden allerede er vist å være en fordel ved bestråling av venstresidig brystkreft.

På denne bakgrunn setter komiteen som vilkår for godkjenning at informasjonsskrivet revideres i tråd med komiteens merknad. Revidert informasjonsskriv bes innsendes REK som svar på oppgave som prosjektleder finner under fanen «OPPGAVER» når innlogget i REK-portalen: https://rekportalen.no.

Vedtak

Godkjent med vilkår

REK har gjort en helhetlig forskningsetisk vurdering av alle prosjektets sider. Prosjektet godkjennes med hjemmel i helseforskningsloven § 10, under forutsetning av at ovennevnte vilkår er oppfylt.

Vi gjør samtidig oppmerksom på at etter ny personopplysningslov må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Det må forankres i egen institusjon.

I tillegg til vilkår som fremgår av dette vedtaket, er godkjenningen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad og protokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 31.12.2022. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 31.12.2027. Forskningsfilen skal oppbevares atskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse og omsorgssektoren»

Komiteens avgjørelse var enstemmig.

Med vennlig hilsen

Finn Wisløff
Professor em. dr. med.
Leder

Silje U. Lauvrak
Seniorrådgiver

Kopi: Helse Møre og Romsdal HF: postmottak@helse-mr.no

Sluttmelding
Søker skal sende sluttmelding til REK sør-øst D på eget skjema senest seks måneder etter godkjenningsperioden er utløpt, jf. hfl. § 12.

Søknad om å foreta vesentlige endringer
Dersom man ønsker å foreta vesentlige endringer i forhold til formål, metode, tidsløp eller organisering, skal søknad sendes til den regionale komiteen for medisinsk og helsefaglig forskningsetikk som har gitt forhåndsgodkjenning. Søknaden skal beskrive hvilke endringer som ønskes foretatt og begrunnelsen for disse, jf. hfl. § 11.

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

Vedlegg-1583316492958.pdf

@ Mottaksbekreftelse REK ▶ Christer André Jen

@ Pustestyrt strålebehandling av lesjoner i lunge (PUST) Christer André Jensen ▶ Ad Mini Str

Oppfølging av vilkår

Tilordnet : Christer André Jensen

Melding/instruks

Hei, Vi viser til vedtak datert 04.03.2020. Her skal informasjon legges til og sendes inn i henhold til vedtaket. Med vennlig hilsen, Marianne Carson, REK sør-øst D

164/1024

Tilleggsinformasjon (tekst)

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Tilleggsinformasjon (vedlegg)

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Tilbake til startside

Deep inspiration breath-hold in stereotactic and conventional fractionated radiotherapy for lesions in the lung

By Siri Tessem Mørkeset

Journal of Applied Clinical Medical Physics:
https://aapm.onlinelibrary.wiley.com/journal/15269914

Figures and tables are presented in the running text to increase readability.

Deep inspiration breath-hold in stereotactic and conventional fractionated radiotherapy of lesions in the lung

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Running title: Deep inspiration breath-hold in stereotactic and conventional fractionated radiotherapy of lesions in the lung

Deep inspiration breath-hold in stereotactic and conventional fractionated radiotherapy of lesions in the lung

ABSTRACT

The purpose of the clinical study was to evaluate lung cancer patients' ability to perform deep inspiration breath-hold (DIBH) during CT simulation and throughout the treatment course of radiation therapy (RT). In addition, we evaluated target sizes, organs at risk (OAR) sizes and doses to the respective volumes in volumetric modulated arc therapy RT plans in free breathing (FB) and DIBH. Twenty-one patients with a peripheral lesion were included. All patients underwent breath-hold training at CT and if they complied with the requirements, 3 CTs were obtained; a CT in DIBH, a CT in FB and a 4DCT in FB. Treatment plans in FB and DIBH were generated, and dose parameters as well as volume sizes were compared. The endpoints for evaluation were patient compliance, target dose coverages and doses to the OAR. This clinical study found high patient DIBH compliance in both CT simulation and treatment for lung cancer patients. A significant reduction was found in target sizes overall and for stereotactic body radiation therapy in DIBH, as well as significantly decreased doses to heart, chest wall and lungs. DIBH in RT of lung lesions is feasible, and a routine to manage intra-fractional deviation should be established upon implementation.

Keywords: DIBH, deep inspiration breath-hold, SBRT, stereotactic body radiotherapy, RT, radiation therapy, radiotherapy, free breathing, lung

INTRODUCTION

Cancer of the lung was the second most common cancer in both genders in Norway in 2019 and caused 19% of all deaths related to cancer the same year. Lung cancer has a poor 5-year relative survival rate for regional disease of approximately 30% and survival rates in localized disease of 60% and 70% for men and women, respectively.[1] This shows the importance of improving treatment options for this group of patients. As lung cancer is divided into several subgroups, based on both morphology and extent of disease, the prognosis and treatment of choice may differ. Improvements in lung cancer treatment during the past two decades may have contributed the recent increase in survival rate.[1] Non-small cell lung cancer (NSCLC), with its aggressive biology[2], accounts for approximately 85% of all lung cancer.[3] The increase in survival rate is especially seen in patients having this subtype. Treatment can be multimodal, but surgery is the method of choice when possible. As radiation therapy (RT) has rapidly evolved, patients are now receiving RT with a curative intent in stages I-III.[3]

During the course of lung cancer disease, RT will be indicated in 61% of the patients.[4] The standard RT technique today is treating lung lesions while the patient is breathing freely; the target is moving during treatment. Seppenwolde et al.[5] found that lesions in the lower lobe, close to the diaphragm, move 12±2 mm in cranio-caudal direction. In lateral and anterior-posterior directions, the movement of 2±1 mm had no correlation to its location. This motion, caused by natural respiratory action, causes geometrical distortion in the computed tomography (CT) images which treatment planning is based on.[6] Treating a moving target can be challenging and the motion must be managed to ensure sufficient dose to the target volume.

Motion of lesions in the lung can be managed by a set of approaches.[7] Traditionally, large margins have been applied to account for lesion motion. In recent years, the adaptation of four-dimensional computed tomography (4DCT) has improved target delineation with its ability to provide information on lesion movement.[8] 4DCT in free breathing (FB) is now the most frequently used approach and

ensures coverage of the whole tumor in each position during the breathing cycle. To avoid underdosing the target, the margins applied are still large according to the variation in lesion position. Gating can manage and reduce respiration-related motion, either computer based or by voluntary breath-hold. Approaches such as mechanical compression of the upper abdomen can manage motion in lower lobes to some extent.[6,9]

Deep inspiration breath-hold (DIBH) treatment was introduced for left sided breast cancer the last decade and the technique is described as beneficial in breast cancer RT.[10] Previous research has shown that gated treatment with DIBH has several advantages for RT in lung lesions with conventional fractionation. It can reduce doses to healthy tissue [11-13], improve image quality [14] and increase dose conformity. [13] The research on lung cancer RT is mainly based on older techniques and fractionation, where patients were generally treated in free breathing (FB). Even though research has shown advantages, DIBH is not the preferred technique for treating lung cancer today and little research exists on DIBH for stereotactic body radiation therapy (SBRT).[2]

Treatment equipment and techniques have evolved recently, resulting in shorter beam-on-time and more conform dose distributions. With today's modern linear accelerators equipped with flattening filter free (FFF)[15] delivery and treatment techniques such as volumetric modulated arc therapy (VMAT), treatment times have shortened considerably.[16] SBRT has the advantage of only a few fractions combined with superior local control and toxicity rates.[17] It has become the treatment technique of choice when treating smaller lesions in the lungs. These new techniques, adapted in modern RT, may contribute to a tolerable breath-hold treatment, also for this group of patients.

The purpose of this study was to evaluate if lung cancer patients, being treated for a lesion in the lung, could tolerate DIBH during CT training and throughout the treatment course. In addition to the

capability of these patients to hold their breath, this research aimed to evaluate sizes and doses to the targets and organs at risk by comparing treatment plans in FB and DIBH.

METHODS

A. Patient selection and training

The study was performed at Ålesund Hospital between 2020-04 and 2021-02. Written consent was obtained from 21 participants; 18 patients diagnosed with NSCLC and three having lung metastases from other origins. The study was approved by the Regional Ethics Committee (ref. 96966). All patients had ECOG performance status ≤ 2.[18] Median age was 74 years (range 56-88).

The patients were immobilized by WingSTEP (IT-V, Innsbruck, Austria) and ProSTEP (Elekta, Stockholm, Sweden). CT imaging was performed with a Brilliance Big Bore Oncology (Philips, Amsterdam, Netherlands) and breathing was registered by Sentinel (C-RAD, Uppsala, Sweden). All patients underwent breath-hold training, including taking deep breaths to find their maximum amplitude level. The level of amplitude was established at minimum 80% of the maximum inhale and the window of amplitude was set to 3 mm. The patients had to hold their breath for 180 s in total, each breath-hold lasting a minimum of 20 s. The patients who complied with these requirements underwent CT in DIBH, in addition to FB in a conventional scan and 4DCT. Slice thickness was 3 mm and 2 mm depending on treatment technique, SBRT demanding smaller slice thickness than conventional fractionation. There were 20 patients that complied with the training, resulting in treatment plans in DIBH and FB for 20 patients; three had two separate lesions, resulting in 23 different targets.

B. Target and OARs delineation

Target and OAR delineation was performed in RayStation version 9A (RaySearch Laboratories, Stockholm, Sweden). The oncologists delineated the gross tumor volume (GTV)[2], heart and esophagus. GTV in FB was delineated based on the reconstruction maximum intensity projection (MIP) and average intensity projection (AIP). Clinical target volume (CTV)[2] was derived as an extension of 0-5 mm from GTV in all directions at the oncologist's discretion. Planning target volume (PTV) was derived from CTV with an extension of 5 mm in all directions.[2] Radiation therapists ran a

delineation script for OARs and quality assured all generated volumes. The same individual delineated the volumes in both image sets for each patient, avoiding inter-observer variability.

C. Treatment planning

Treatment planning was performed in RayStation. The same radiation therapist planned both sets of plans for each patient. The modelled machine in RayStation was an Elekta VersaHD with 5 mm multi leaf collimators (MLC), and all treatment plans were generated with VMAT technique. An oncologist and a medical physicist approved all treatment plans. In conventional fractionation, the prescription dose was $D_{50\%}$ to CTV with all arcs being 6MV. In SBRT plans, the prescription dose was $D_{99\%}$ to PTV, utilizing only 6 MV flattening filter free (FFF) beam quality. Plan dose was calculated with a collapsed cone v5.1 algorithm, with a dose grid of 0.2x0.2x0.2 cm^3 in SBRT and 0.3x0.3x0.3 cm^3 in conventional fractionation.

An in-house protocol with the clinical goals listed in supplement 1 was used during treatment planning. All in-house dose limits were based on national guidelines[2,3] and the doses are presented as EQD2.[19] The clinical goals were recalculated depending on fractionation scheme with $\alpha/\beta = 2$ when calculating dose to spinal cord and $\alpha/\beta = 3$ in all other OARs. SBRT and conventional fractionation had different sets of goals, and SBRT dose limits are set based on previous research.[3,20] Patient specific quality assurance was performed for all clinical plans using an ArcCHECK phantom (Sun Nuclear Corp., Melbourne, FL). Gamma passing rate was 95% with a global dose difference threshold of 3% and a distance to agreement of 3 mm.

D. Treatment delivery

All patients were treated with Catalyst (C-RAD, Uppsala, Sweden) breathing control on VersaHD (Elekta, Stockholm, Sweden) machines. Positioning was verified with kV cone beam computed tomography (CBCT), every fraction. SBRT had two CBCTs before each fraction, both with dual registration[21] and action limits upon having to reposition the patient. The first CBCT had a limit of 5 mm difference in all directions and the second had a 3 mm limit. The tumor-match was always the

decisive factor and couch movements followed all CBCTs. The action limits were 10 mm in three directions for conventional fractionation with clip-box-matching. All XVIs had the limit of 3° rotational deviation.

E. Statistics

Wilcoxon signed rank test was performed for statistical analysis. The findings were considered significant when p was lower than 0.05. Analysis was performed in SPSS version 27 (IBM, Armonk, US).

Conformity index (CI) was calculated in RayStation and defined as the ratio between the ROI volume covered by the isodose and the total isodose volume.

RESULTS

In this study, 21 patients were included of which 20 patients were able to perform the DIBH procedure. The patient that were not able to perform DIBH during radiation therapy were treated in FB, 1 out of the 20 initially DIBH compliant patients. Thirteen patients had SBRT and 7 had conventional fractionation. Mean estimated delivery time, calculated in RayStation, for FB and DIBH was 150 and 144 seconds, respectively. All DIBH treatments had a 20-minute time slot, FB treatments had 10 minutes slots. Mean amplitude was 12 mm and mean maximum breath hold was 42 seconds. The lung volume was significantly larger in DIBH treatment plans, 55 % larger volume than in FB (Table 1). Lesions from all lung segments were included (Supplement 1).

A. Target size

There was a significant difference between FB and DIBH in target volumes overall as well as for volumes treated with SBRT, DIBH having smaller targets. There was no significant difference between FB and DIBH for volumes treated with conventional fractionation. (Figure 1).

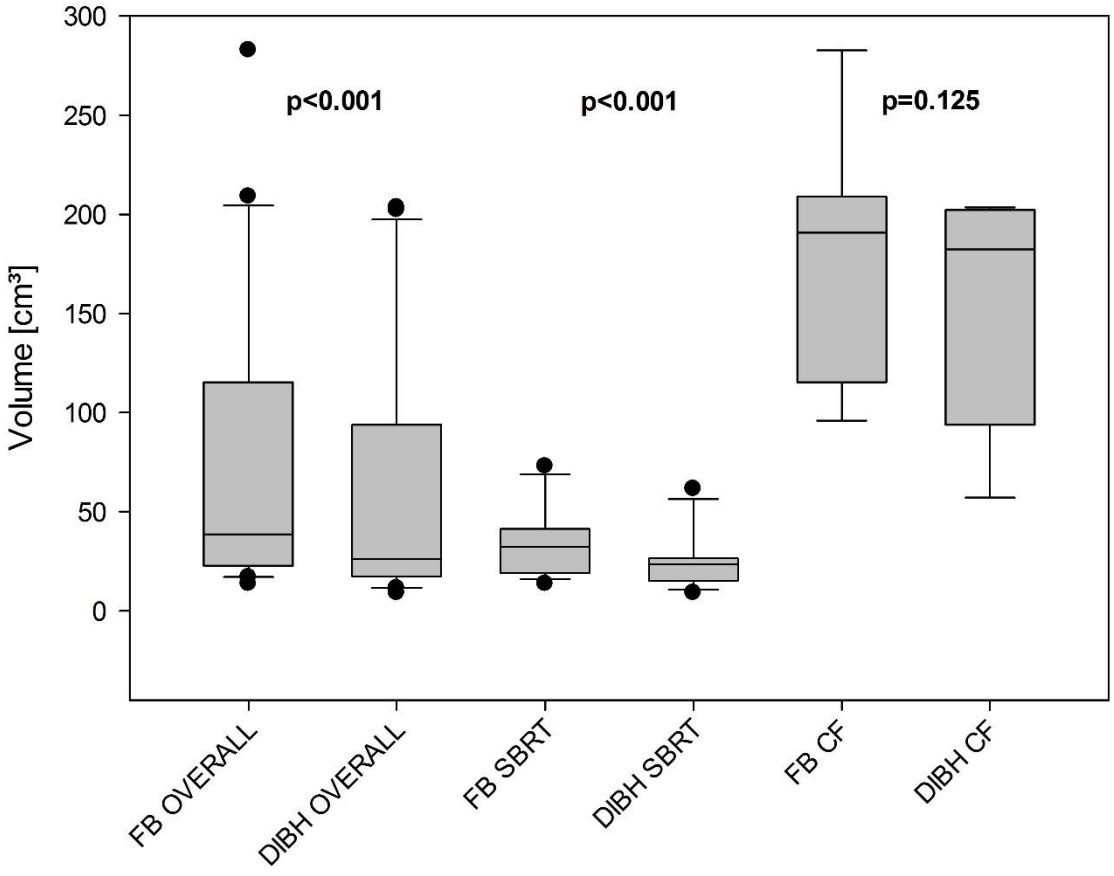
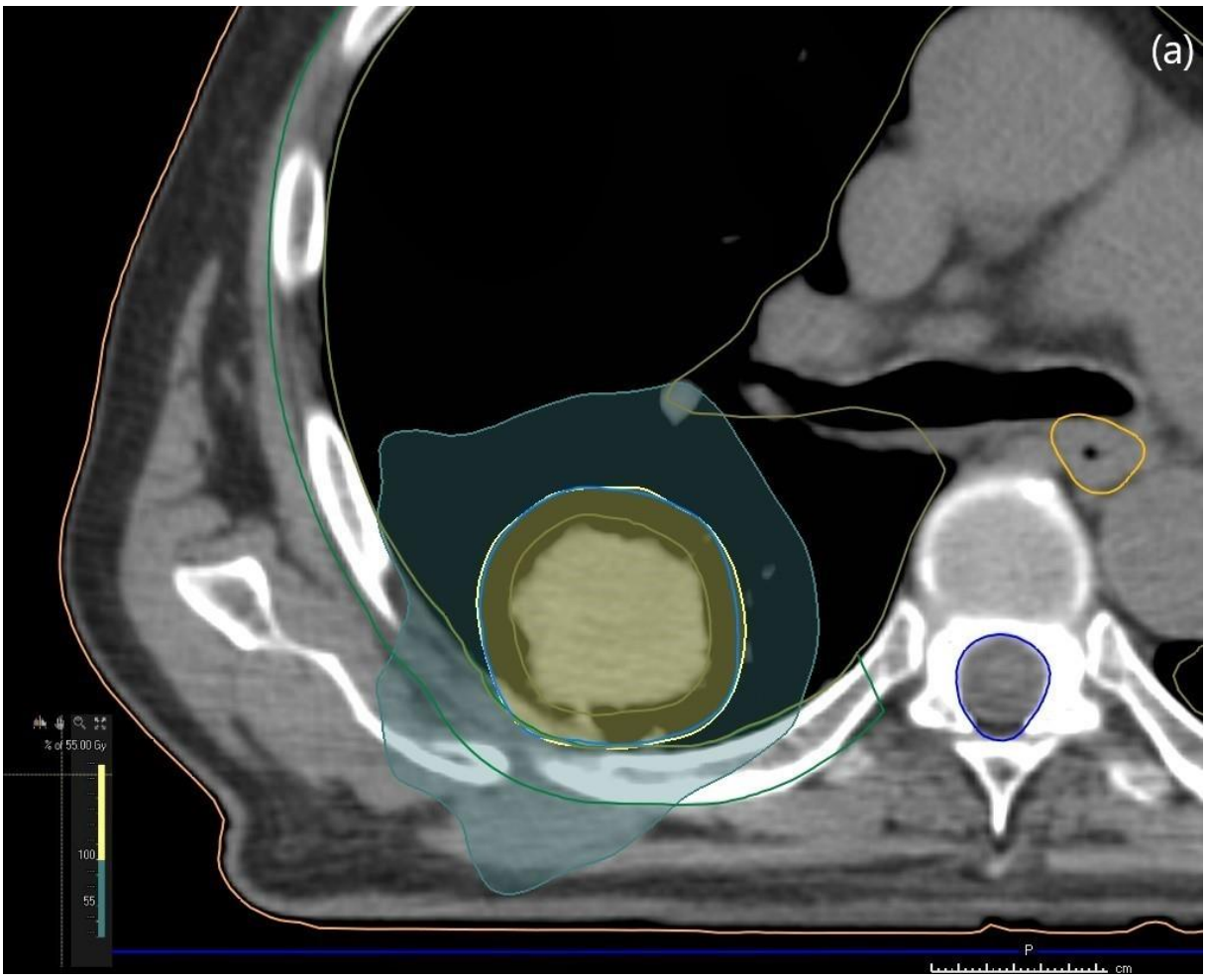


Fig. 1. PTV Volume in free breathing (FB) and deep inspiration breath-hold (DIBH) overall, stereotactic body radiotherapy (SBRT) and conventional fractionation (CF). Boxes extending from 25th to 75th percentiles. The whiskers represent 10th and 90th percentiles, and all outliers are displayed.

B. Dosimetric parameters

No significant differences were found in target coverage between DIBH and FB plans when considering $D_{98\%}$ to CTV and PTV (Table 1 and Figure 3). The clinical maximum dose did not differ significantly between the two breathing techniques, but in the dosimetric comparison of DIBH and FB, DIBH showed significantly lower doses in all measured volumes except $D_{2\%}$ to the spinal cord and

$D_{0.00cc}$ to the esophagus (Table 1). The chest wall volume receiving > 30 Gy is significantly lower in DIBH compared to FB. Chest wall and target for patient 6 is shown in figure 2.



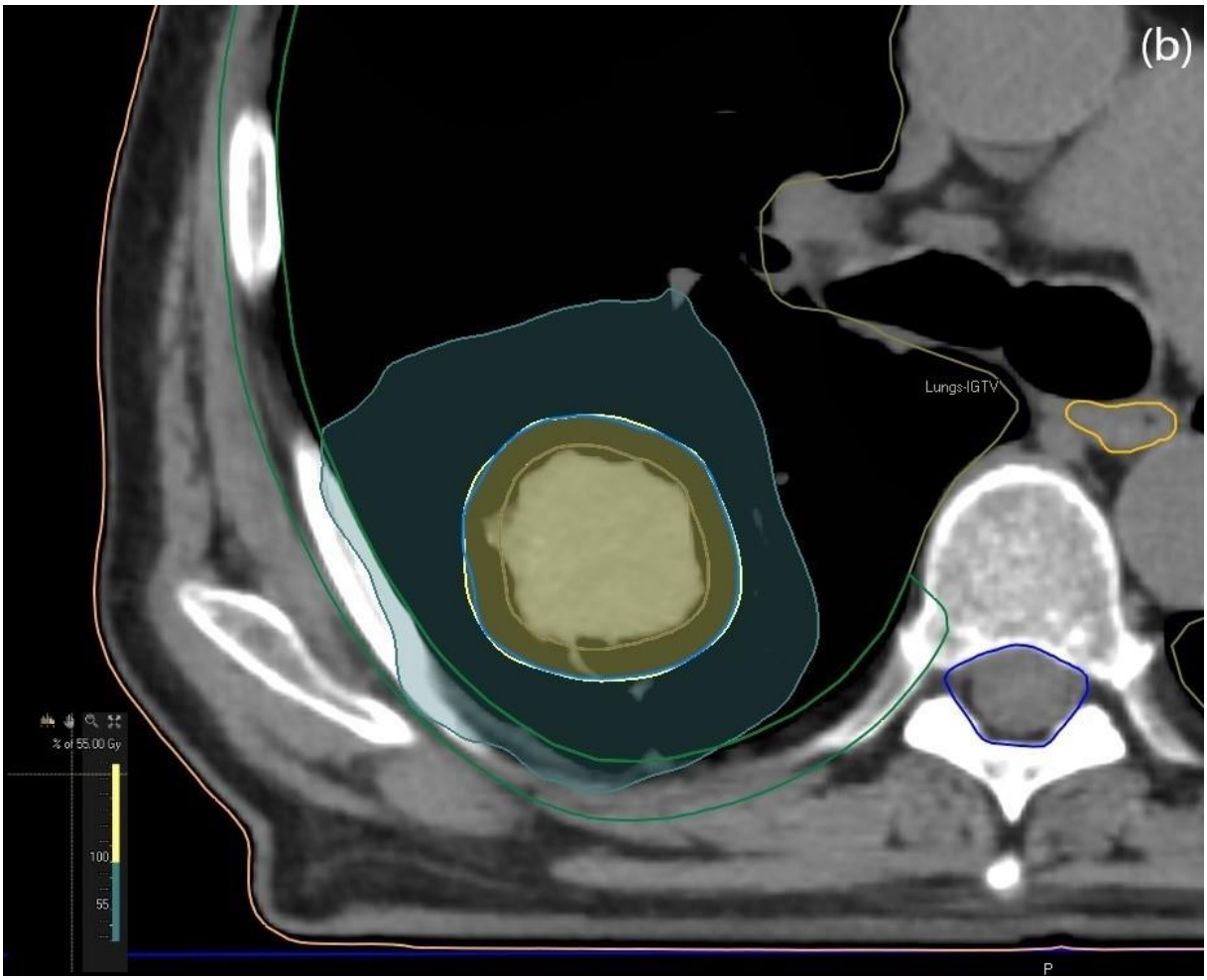


Fig. 2. Dose distribution to dorsal target in free breathing (a) and deep inspiration breath-hold (b) for patient 6. Green isodose at 30Gy.

Table 1 Dosimetric and volume size comparison of free breathing and deep inspiration breath-hold in volumetric modulated arc therapy-plans.

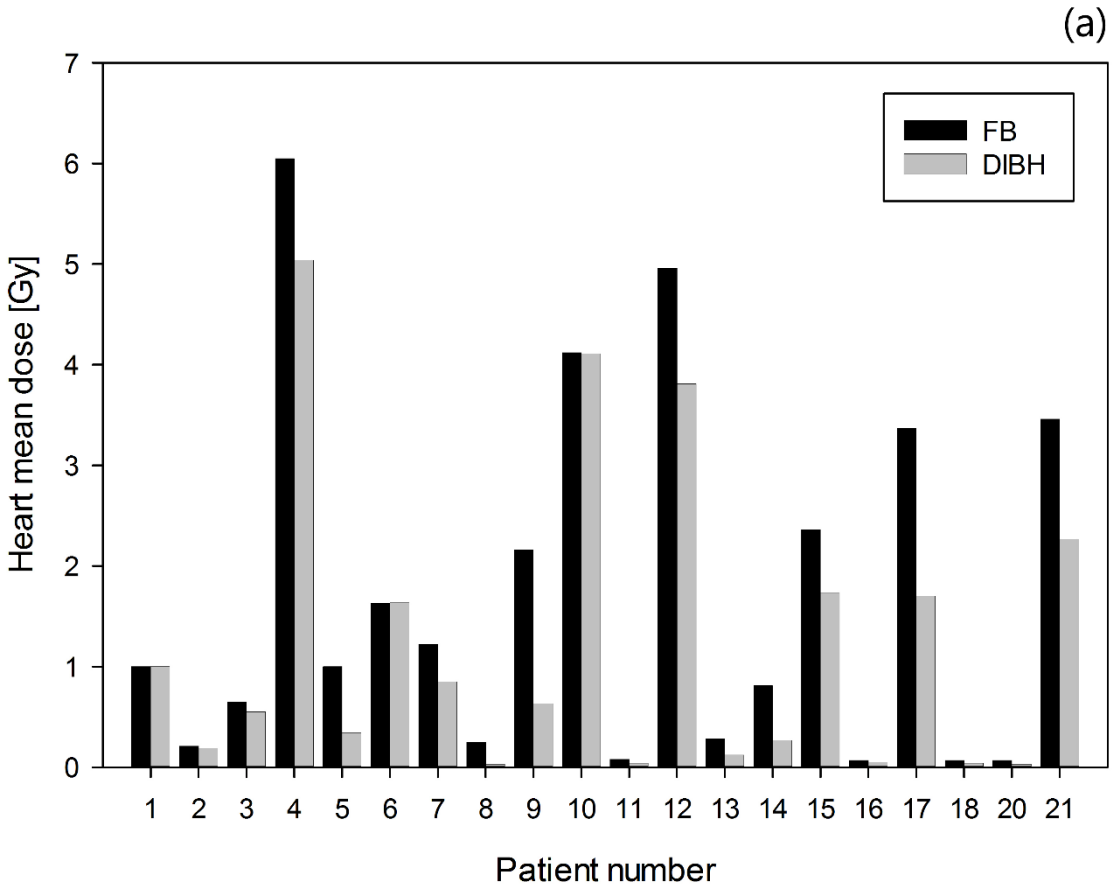
Parameter	FB		DIBH			
	Median	(Range)	Median	(Range)	Number of volumes	p-value
Target						

PTV [cm^3]	38.59	(13.64-282.66)	26.13	(9.06-203.52)	23	<0.01
PTV $D_{98\%}$ [Gy]	45.68	(27.96-62.15)	45.62	(28.31-61.52)	23	0.39
CTV $D_{98\%}$ [Gy]	52.62	(29.44-66.35)	52.33	(29.58-66.00)	23	0.93
Conformity index	0.90	0.85-0.99	0.88	0.85-0.96	20	0.02
OAR						
Clinical maximum dose [Gy]	60.55	30.83-76.24	61.42	30.56-76.69	20	0.82
Lungs-GTV [cm^3]	3746.45	(2331.17-7656.70)	5828.86	(3750.31-9911.26)	20	<0.01
Lungs-GTV mean [Gy]	4.19	0.66-8.11	3.02	0.49-7.71	20	<0.01
Lungs-GTV V_{20Gy} [%]	4.71	0.47-17.22	3.43	0.45-15.87	20	0.02
Heart mean [Gy]	1.00	0.07-6.05	0.59	0.03-5.04	20	<0.01
Heart $D_{2\%}$ [Gy]	6.75	0.32-29.99	4.26	0.12-27.34	20	<0.01
Spinal canal $D_{2\%}$ [Gy]	8.07	2.33-25.47	8.34	3.00-24.95	20	0.68
Esophagus D_{5cc} [Gy]	6.64	0.81-16.29	5.55	0.12-17.69	20	0.02
Esophagus $D_{0,00cc}$ [Gy]	12.43	3.50-40.70	10.71	0.22-45.50	20	0.08

Chest wall V_{30Gy} [cm^3]	12.71	2.17-56.91	10.06	0.15-29.32	15	0.01

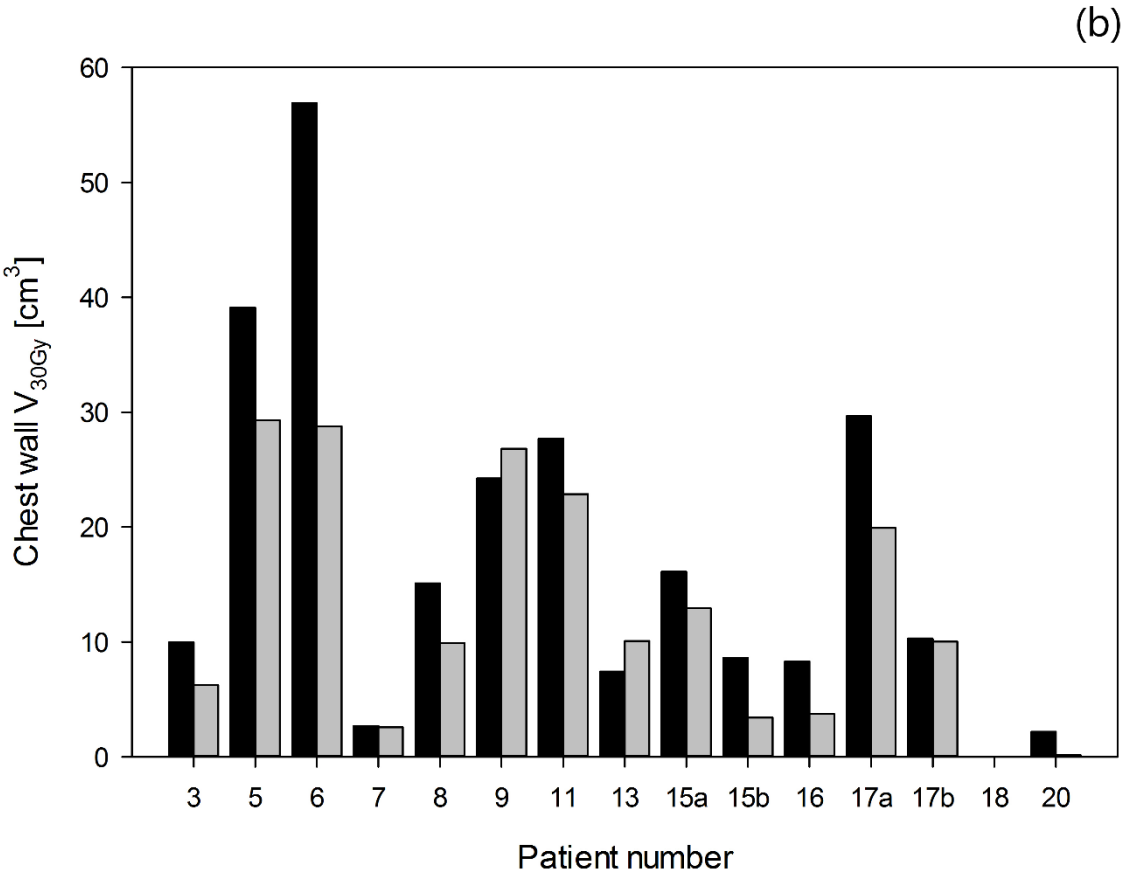
Abbrevations: CTV, clinical target volume; D_{2cc} , maximum dose administered to a 2 cm^3 volume; D_{5cc} , maximum dose administered to a 5 cm^3 volume; $D_{0,00cc}$, maximum dose administered to a 0,00cm^3 volume; $D_{2\%}$, maximum dose administered to 2% of volume; $D_{98\%}$, dose to 98% of the target volume; DIBH, deep inspiration breath-hold; FB, free breathing; GTV, gross tumor volume; OAR, organs at risk; PTV, planning target volume; VMAT, volumetric modulated arc therapy; V_{20Gy}, organ volume receiving > 20 Gy; V_{30Gy}, organ volume receiving > 30 Gy.

1

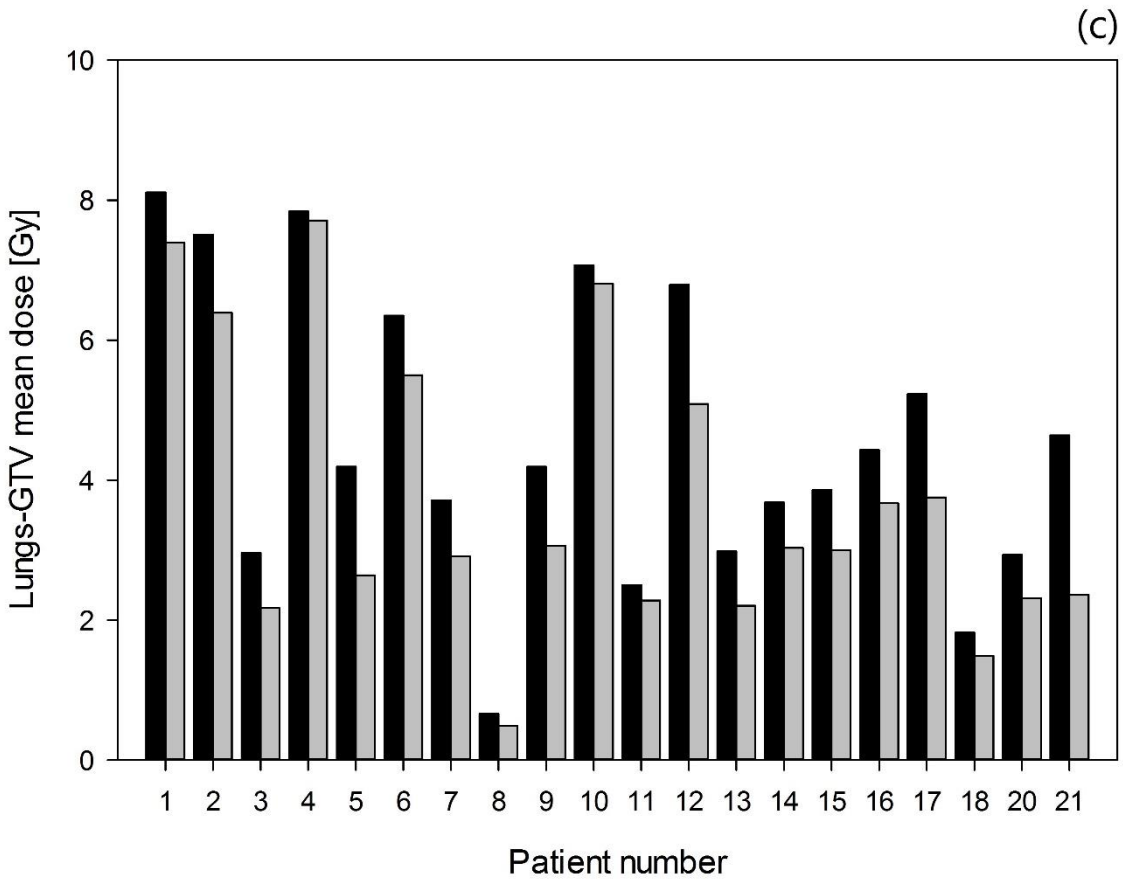

(a)
FB
DIBH
Heart mean dose [Gy]
0
1
2
3
4
5
6
7
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 20 21
Patient number

2

3


(b)
Chest wall V_{30Gy} [cm^3]
60
50
40
30
20
10
0
3
5
6
7
8
9
11
13
15a
15b
16
17a
17b
18
20
Patient number

1


(c)
Lungs-GTV mean dose [Gy]
0
2
4
6
8
10
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 20 21
Patient number

1

2

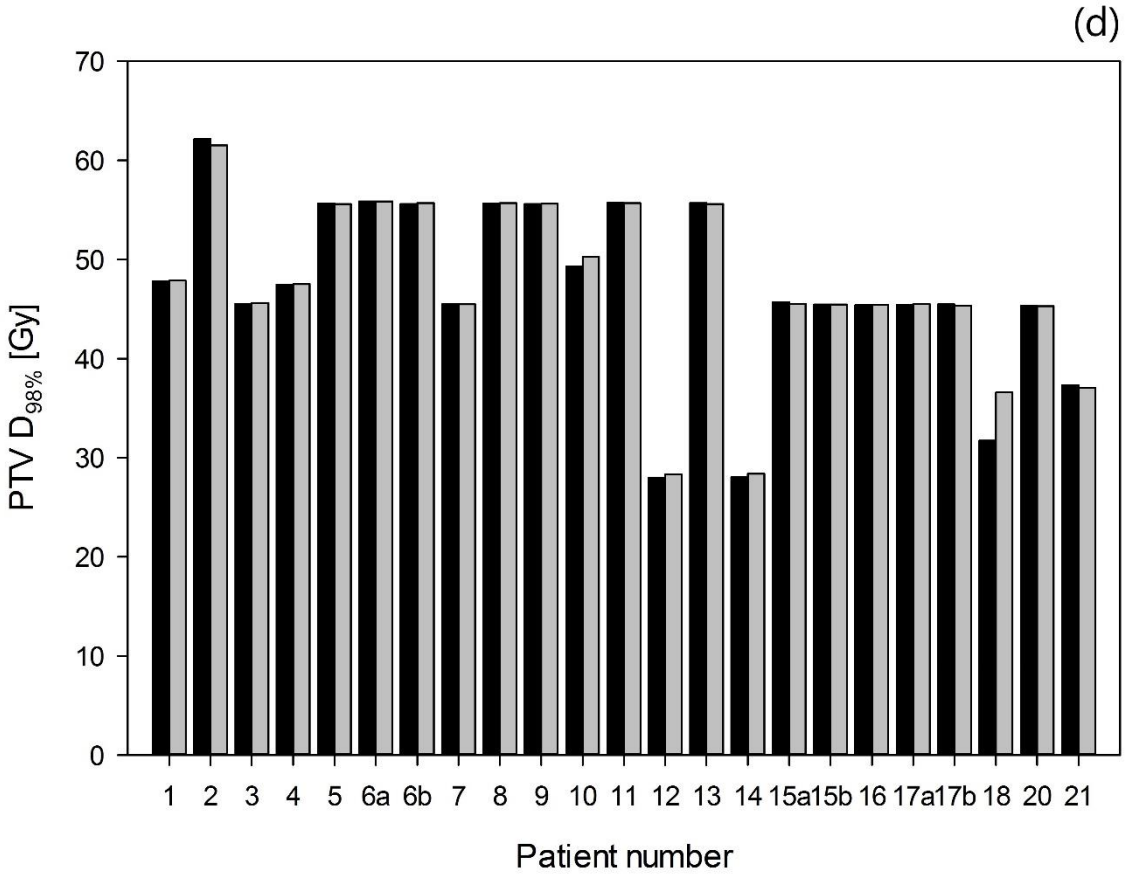


Fig. 3. Dosimetric comparison of free breathing (black bars) and deep inspiration breath-hold (gray bars) in heart (a), chest wall (b), lungs-GTV (c) and PTV (d). Patients 15 and 17 had doses to chest wall in both left and right lung due to them having targets in both lungs.

DISCUSSION

In this study, we evaluated the implementation of DIBH utilizing modern treatment techniques and equipment in lung cancer patients. Target coverage, as well as OAR doses, were assessed for both FB and DIBH plans.

Our clinical study found that 20 out of 21 patients were able to perform the respiratory training, and hence were eligible for DIBH. One patient was unable to hold their breath at all, and the training was terminated. DIBH in lung cancer treatment is feasible, but there are some issues to be addressed. One of the patients, initially eligible for DIBH RT, received treatment in FB due to technical challenges. For this patient, the Sentinel surface signal at the CT was weak due to an unfavorable sternum angle. To solve this challenge, a wedge was added underneath the Wingstep to improve the surface signal. The wedge, combined with a lesion located dorsally close to the diaphragm, resulted in the linear accelerator's gantry not being able to rotate without colliding with the patient's arms. Additionally, the gantry shadowed the gating point providing a further complication. A solution to detect and manage this challenge during CT simulation needs to be established.

Recent research indicates an ongoing development of the DIBH technique in lung cancer treatment. A study by Josipovic et al. [22] showed a high patient compliance in voluntary DIBH in both CT simulation and RT over 33 fractions. We present confirming results, also for SBRT. Naumann et al.[23] showed patient compliance in a small cohort of three lung cancer patients in SBRT. Several studies have shown DIBH-compliance in CT simulation, but the patients were treated in FB. [12,24]Other studies have shown similar results mainly based on assisted DIBH[13,25,26] and older treatment techniques.

Intra-fraction organ motion possibly contributed to a suboptimal match on IGRT in one patient which resulted in FB treatment. The lesion was located in the lower left lobe, and the stomach was considered too close to the target in repeated CBCTs. The fractionation was altered from 15 Gy x 3 to

4 Gy x 7 to spare the stomach from toxicity. The same patient was treated in DIBH for the second target, in the opposite lung, without challenges. This might indicate that the patient's compliance with the DIBH-technique was not the issue, but possibly involuntary intra-fractional organ motion. Fasting before treatment may have a positive impact in treating left sided lower lobe lung lesions, as it could cause the stomach to be smaller and less active. The relevance of fasting in RT of left lower lobe lung lesions need further investigation. In general, research has shown small intra-fractional deviations in tumor position for lung lesions[22,23,27,28], with some cases of larger variations. The uncertainty in intra-fractional motion must be included in PTV margins, and Josipovic et al. recommended consecutive CTs in DIBH to evaluate each lesion's positional variation in several breath-holds to avoid underdosage of the target, which we did not perform in this study.[22]

The lung volume in DIBH compared to FB increased by 55%. This is close to the increase our group has previously found in breast cancer patients[29], who are generally presumed to have superior lung capacity due to their disease not affecting the lungs. Patients included in this study had ECOG-status ≤ 2 and their performance status might have had a positive impact on their ability to hold their breath. Previous research has shown a comparable increase in lung volume treating NSCLC, showing that our results are representative for the patient group.[11,12] Giraud et al.[30] showed an increase in lung volume of only 26%, but a large proportion of the participants was gated with assisted breath-hold methods, shown to result in poorer lung volume increase than in voluntary DIBH.[31,32]

Mean estimated delivery time was reduced in DIBH compared to FB. However, the patients in this study required a time slot of 20 minutes for DIBH compared to 10 minutes in those who were treated in FB. Doubling the time slot will have an impact on the daily scheduling. An increase in delivery time, resulting in longer time slots, may be a highly relevant disadvantage in some larger clinics with a substantial number of patients. The economics of having modern equipment for tracking of respiratory

signal, treatment delivery and IGRT may affect an institution's ability to implement DIBH technique for lung cancer patients.

We found a significant overall reduction in target size in favor of DIBH. When looking at the conventional fractionation separately, there were no significant difference between target sizes in FB and DIBH. The results may be due to the inclusion of only 7 patients with conventional fractionation. Reduction in target size is mainly due to motion artefacts not being present in DIBH CT images, hence a smaller GTV. Several studies have shown a reduction in target size when implementing DIBH, either voluntarily or assisted. [11,12,23,30,33] The target coverage was maintained as there were no significant difference in $D_{98\%}$ to CTV and PTV. These findings of similar dose coverage are consistent with previous research.[24] We found a significant reduction in CI in DIBH compared to FB. A possible explanation to these findings might be that the significant reduction in target sizes was followed by well-known difficulties of achieving optimal conformity due to small target volumes.[34] A MLC-size <5 mm could have resulted in more conform dose distributions.

The DIBH plans resulted in a significant reduction of dose to the chest wall. Chest wall pain and rib fractures are correlated to dose per fraction, hence an important part of SBRT.[35] We found a significant decrease of 20% in the dose to chest wall, by V_{30Gy}, when applying DIBH. Some of the patients in this study would have received 55 Gy in five fractions instead of 45 Gy in three fractions if they were to be treated in FB. These considerations were made to spare them from chest wall toxicity, having lesions in relation to the chest wall. This decrease in dose is thought to be due to the lesion separating from the chest wall when inflating the lungs. Previous research on RT in FB could not find significant correlation in distance from lesion to the chest wall and the patients having chest wall pain and/or rib fractures.[35,36] However, Jaccard et al.[37] found a reduction of the chest wall dose as the lesion separated from the chest wall in DIBH. The study included only four patients eligible for DIBH. Huang et al. found, in a treatment plan study, that a method where RT is given in a combination of

DIBH and expiration reduces the dose to the chest wall even further but included only four patients. However, little research exists on this topic and it should be investigated further.

Healthy lung tissue received a significantly lower dose in DIBH compared to FB. We showed a reduction of dose to mean lung dose (MLD) by 29% when applying DIBH. This is likely related to the significant increase in lung volume when inflating the lungs. In SBRT, high doses can be delivered to an even smaller target, sparing the healthy lung tissue. Josipovic et al.[11], Persson et al.[12] and Ottoson et al.[24] all found a reduction of approximately 20% in MLD when applying DIBH. Previous research has found that overall dose to healthy lung tissue decrease in DIBH in conventional fractionation, regardless of DIBH approach. [9,11,13,24,25,30] Mani et al.[38] did a retrospective comparison of lung dose between FB and DIBH in SBRT and found a reduction of mean dose to ipsi- and contralateral lung of 37% and 15%, respectively.

We found a significant reduction in mean and near maximum dose, $D_{2\%}$, to the heart by 40% and 35%, respectively. Giraud et al.[30] found a significant reduction in both mean and maximum doses to the heart. Several studies have shown decreased doses to the heart, implying that DIBH has superior OAR sparing compared to FB.[12] The patients included in our study had lung lesions located in lung tissue, and only one patient had lymph nodes as a part of their target. The dose to the heart might be dependent on the location of target, hence, location might have affected the results although Persson et al.[12] found no significant correlation between location and dose to OAR. Mani et al.[38] is the only published research, to our knowledge, on dosimetric comparison between FB and DIBH in SBRT, and they found that the mean dose to the heart was reduced by 12%.

A limitation of the study was the low number of conventional fractionated patients. Conventional and stereotactic fractionation use different doses and clinical goals in the planning and evaluation, and this is a challenge that is common in the clinic. Previous research has described limitations in the DIBH

treatment technique.[39] As Josipovic et al.[39] presents in their case report, multiple targets in the thorax may separate when inflating the lungs and cause increased doses to OARs due to an enlargement of the target. Our study included a patient with two separate lesions separating in deep inspiration. In this patient, there was no disadvantage observed. As the lesions was defined as two separate targets, the separation had no impact on the doses to surrounding tissue or target coverage. In the case report by Josipovic et al.[39], the target included parts of the mediastinum and not only lesions located in the lungs. This is likely the reason the target was enlarged and resulting in increased doses to surrounding tissue. DIBH may not be suitable for all RT in the thoracic region. In cases where lymph-nodes, or other structures with a different motion pattern and margins, are to be included as target, the effect of DIBH and way of treatment planning and IGRT technique needs further investigation.

CONCLUSION

The study shows that, with today's techniques and high-end equipment, the DIBH treatment is feasible with high patient compliance in lung cancer patients. The DIBH technique allows for a target size reduction while the target coverage is maintained. DIBH significantly reduces doses to heart, lungs, and chest wall in lung cancer RT. A routine to manage the intra-fractional deviation should be established.

ACKNOWLEDGEMENTS

Our work was supported by Møre og Romsdal Hospital Trust, Ålesund Hospital, Ålesund, Norway.

CONFLICT OF INTEREST

The author reports no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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SUPPLEMENTARY FILES

Table 1

Clinical goals in conventional treatment, 2Gy x 33

Structure	Clinical Goal	Priority
ICTV	$D_{98\%}$ > 95.0%	High
	$D_{2\%}$ < 107.0%	High
	$D_{50\%}$ > 99.5%	High
	$D_{50\%}$< 105.5%	High
PTV	$D_{98\%}$ > 90.0%	High
	$D_{2\%}$ < 107.0%	High
Spinal canal	$D_{2\%}$ < 54,7Gy	High
IGTV	$D_{98\%}$ > 98.0 %	Medium
Heart	D_{mean} < 20.0Gy	Medium
	V_{50Gy} < 25.0%	Medium
Esophagus	$D_{mean} \leq$ 34.0Gy	Medium
	V_{60} < 17.0%	Medium
Lungs-GTV	D_{mean} < 20.0Gy	Low
	V_{20Gy} < 30.0%	Low
Lung	V_{20Gy} < 30.0%	Low
External	$D_{2.00cc}$ < 105.0% of prescription dose	Low

Abbreviations: CTV, clinical target volume; $D_{2.00cc}$, maximum dose administered to a 2 cm^3 volume; $D_{2\%}$, maximum dose administered to 2% of volume; $D_{50\%}$, dose to 50% of the target volume; $D_{98\%}$, dose to 98% of the target volume; D_{mean}, mean dose, GTV, gross tumour volume; PTV, planning target volume; $V_{20Gy,}$ organ volume receiving > 20Gy; V_{50Gy}, organ volume receiving > 50Gy; V_{60Gy}, organ volume receiving > 60Gy.

Table 2

Clinical goals in stereotactic body radiotherapy, 15Gy x 3

Structure	Clinical Goal	Priority
PTV	$D_{99\%} > 45.0$ Gy	High
	CI > 0.88 at 45Gy	Low
Spinal canal	$D_{0.00cc} < 21,9$ Gy	High
	$D_{1.20cc} < 12.3$ Gy	High
Trachea	$D_{0.00cc} < 30.0$ Gy	High
	$D_{4,00cc} < 15.0$ Gy	High
Bronchus main	$D_{4,00cc} < 15.0$ Gy	High
	$D_{0.00cc} < 30.0$ Gy	High
Esophagus	$D_{0.00cc} < 25,2$ Gy	Medium
	$D_{5cc} < 17,7$ Gy	Medium
Great vessel	$D_{10,00cc} < 39.0$ Gy	Medium
	$D_{0.00cc} < 45.0$ Gy	Medium
Heart	$D_{0.00cc} < 30.0$ Gy	Medium
	$D_{15,00cc} < 24.0$ Gy	Medium
Chest wall	$V_{30Gy} < 30$ cm^3	Low
Contralateral lung	$V_{4,50Gy} < 26$ %	Low
	$D_{mean} < 3.6$	Low
External	$D_{2,00cc} < 63.0$ Gy	Low
	$D_{0.00cc} < 67.5$ Gy	Low
Ribs	$D_{2,00cc} < 27$ Gy	Low
	$D_{0.00cc} < 53.8$ Gy	Low

Skin	$D_{10,00cc}$ < 22.5 Gy $D_{0.00cc}$ < 24.0 Gy	Low Low

Abbreviations: CTV, clinical target volume; CI, Conformity index; D_{15cc}, maximum dose administered to a 15cm^3 volume; D_{5cc} , maximum dose administered to a 5 cm^3 volume; $D_{0,00cc}$, maximum dose administered to a 0,00cm^3 volume; $D_{1,20cc}$, maximum dose administered to a 1,20cm^3 volume; $D_{4,00cc}$, maximum dose administered to a 4,00cm^3 volume; $D_{5,00cc}$, maximum dose administered to a 5,00cm^3 volume; $D_{10,00cc}$, maximum dose administered to a 10,00cm^3 volume; $D_{15,00cc}$, maximum dose administered to a 15,00cm^3 volume; $D_{2\%}$, maximum dose administered to 2% of volume; $D_{99\%}$, dose to 99% of the target volume; D_{mean}, mean dose, GTV, gross tumour volume; PTV, planning target volume; V_{20Gy}, organ volume receiving > 20 Gy; V_{30Gy}, organ volume receiving > 30 Gy; $V_{4.5Gy}$, organ volume receiving > 4.5 Gy.

Table 3 Lesion location

Lesion location	Number
Right upper lobe	9
Right middle lobe	6
Right lower lobe	2
Left upper lobe	4
Left lower lobe	3

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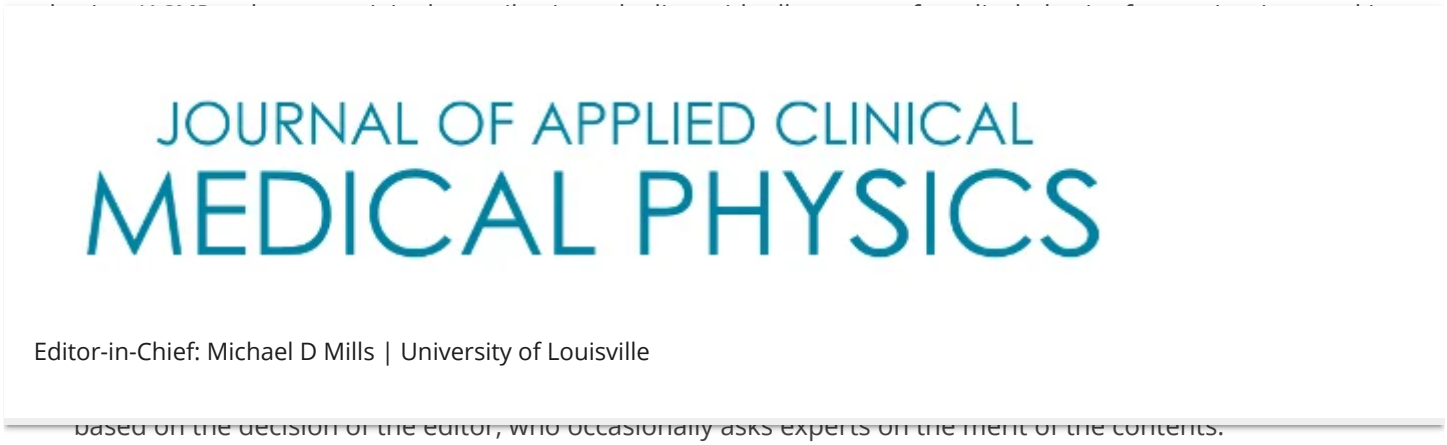

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  1. Centers for Disease Control and Prevention (CDC). Licensure of a meningococcal conjugate vaccine (Menveo) and guidance for use--Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Morb Mortal Wkly Rep*. 2010;59(9):273.

- Electronic Journal article:

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    1. Aggleton JP. Understanding anterograde amnesia: disconnections and hidden lesions. *Q J Exp Psychol*. 2008;61(10):1441-1471. http://search.ebscohost.com/login.aspx?direct=true&db=pbh&AN=34168185&site=ehost-live Accessed March 18, 2010.

- Journal article published online ahead of print:
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