RIBI (Radiotherapy Induced Bone Injury) as a Late Side effect in Patients treated with Stereotactic Lung Radiotherapy

by

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A thesis submitted in conformity with the requirements for the degree of Masters of Science
Institute of Medical Sciences
University of Toronto

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2015

Abstract

The standard treatment for patients with early stage non-small cell lung cancer is a surgical approach; however inoperable patients may be treated with stereotactic body radiotherapy (SBRT) with an excellent local control rate of 80 to 90%. Although the majority of patients tolerate this treatment reasonably well, some may experience side effects such as chest wall pain and rib fracture. In this study several potential dosimetric and clinical factors related with rib fracture were evaluated and a nomogram estimating the risk of rib fracture based on the most relevant risk factors was created. Our study supported the relationship between dosimetric-clinical factors and rib fractures in patients with lung cancer treated with stereotactic radiotherapy. Based on our findings and supported published data, we have modified our radiotherapy dose in high risk patients for rib fracture.
Acknowledgments

I wish to thank my co-supervisor Dr. Andrew Hope for his generous time, advice and mentorship throughout my research work.

Thanks to Dr. Patricia Lindsay, Dr. Laura Dawson, Dr. David Jaffray, Sharon Fung, and my thesis supervisor; Dr. Andrea Bezjak for sharing their knowledge, experience, time and wisdom.
Contributions

Drs. Dawson, Hope, Jaffray, and Lindsay: Participation in the PAC meetings, project development, reviewing the thesis and RIBI paper.

Dr. Lindsay: obtaining dose volume histogram information from pinnacle system, formatting it into MatLab, and CERR data base; her work contributes to Figures 4-4, 4.a-5, 4.b-5, and appendices 2 to 7.

Ms. Fung: statistical analysis of the data, help to create dose/toxicity diagram and nomogram. Her work contributes to figures 4-2, 4-5 and 4-6.

Dr. Bezjak: supervisor, course selection, project development, weekly meetings to review the progress, help to identify and improve the weakness, reviewing the thesis and paper, participation in PAC meetings.

With the special thanks to the on line educational sites: edoctoronline.com; www.cancer.gov; webofknowledge.com; IASLC (International Association for the Study of Lung Cancer); for the general information used in chapter one and figures 1-1 to 1-4, and table 1-1 (printed with permission).

Dedication

For my wonderful mother and my dear son, thank you for all of your love, support and encouragement.
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LIST OF ABBREVIATIONS

AUC: area under the curve
BED: biologic effective dose
BMD: bone mineral density
CBCT: cone-beam computed tomography
CCS: cause specific survival
CERR: computational environment for radiotherapy research
CHART: continuous hyperfractionated accelerated radiotherapy
CI: confidence interval
cm: centimeter
COPD: chronic obstructive pulmonary disease
CR: complete response
CRA: clinical research associate
CT: computed tomography
CTCAE: common terminology for adverse events
CTV: clinical target volume
CW: chest wall
CWP: chest wall pain
DF: distant failure
DM: Diabetes Mellitus
DVH: dose volume histogram
ECOG: eastern cooperative oncology group
FDG-PET scan: fluorodeoxyglucose-positron emission tomography
4D-CT: four-dimensionnel computed tomography
fr: fraction
FU: follow up
Fx: fracture
GTV: gross tumor volume
Gy: gray (unit of radiotherapy dose)
IASLC: International Association for the Study of Lung cancer
IMRT: intensity modulated radiotherapy
ITV: irradiated target volume
L : left
LC : local control
LF: local failure
M: metastasis
MATLAB: matrix laboratory software package
Med: median
MIP: maximum intensity projection
MLL: maximum likelihood
mm: millimeter
MRI: magnetic resonance imaging
MSK: musculo-skeletal
N: node/nodes
NSCLC: non-small cell lung carcinoma
OAR: organ at risk
OP: osteoporosis
OS: overall survival
PD: progressive disease
PFS: progression free survival
PFT: pulmonary function test
PMH: Princess Margaret hospital
PR: partial response
Pt/Pts: patient/patients
PTV: planning target volume
QA: quality assurance
R: right
RC: regional control
REB: research ethics board
RECIST: response evaluation criteria in solid tumors
ROC: receiver operating characteristic
RF: regional failure
RIBI: radiotherapy induced bone injury
RTOG: Radiation Therapy Oncology Group
SAS: statistical analysis software
SBRT: stereotactic body radiotherapy
SD: stable disease
SUV: standardized uptake value
Sx: surgery
T: tumor
VATS: video assisted thoracic surgery
$V_D$: absolute volume receiving at least dose D
$D_V$: minimum absolute dose received by volume V
VMAT: volumetric modulated arc radiotherapy
Y: year
CHAPTER 1
LUNG CANCER - AN OVERVIEW

1.1 Anatomy of the Thorax
The thorax has two compartments: Chest wall and its contents (lungs, airways, heart, esophagus, nerves and vessels).

The skeleton component of the chest wall (Figure 1-1) is an osseo-cartilaginous cage, protecting the principal organs of respiration (lungs) and circulation (heart and vessels). The posterior surface is formed by twelve thoracic vertebrae and the posterior parts of the ribs. Anteriorly it is formed by sternum, costal cartilage and laterally by the ribs. It is covered by parietal pleura along the interior surface and by muscles and their serosa along the exterior surface. Inferiorly it is partially closed by the diaphragm and superiorly by the apex of the lungs.

Figure 1-1: Bony Anatomy of Thorax
Ribs are elastic arches of bone and there are twelve of them on each side. They are all connected to the individual vertebral bodies posteriorly. The first seven ribs, so called true ribs, are connected in front, through the individual costal cartilage to the sternum. The other ribs (8 to 12) are called false ribs. Ribs 8 to 10 are connected to the sternum through the cartilage of the 7th ribs. Ribs 11 and 12 are floating ribs as they are not connected to the sternum. The ribs vary in their direction and length. The upper ones being less oblique than the lower; the obliquity reaches its maximum at the ninth rib, and gradually decreases from that rib to the 12th. The ribs increase in length from the first to the 7th and then the length diminishes to the 12th rib.

Lungs are conical in shape and composed of lobes. There are three lobes on the right side separated by the oblique and horizontal fissures, and two lobes on the left side separated by the oblique fissure. The lungs are covered by a thin, transparent coat called visceral pleura which extends into the fissures separating the lobes.

The trachea (Figure 1-2) divides into two main bronchi, the left and the right, at the level of the sternal angle at the anatomical point known as the carina. The right main bronchus is wider, shorter, and more vertical than the left main bronchus. The right main bronchus subdivides into three lobar bronchi, while the left main bronchus divides into two. The lobar bronchi divide into tertiary bronchi.
Each of the tertiary (segmental) bronchi serves a specific broncho-pulmonary segment. These segments each have their own artery. Thus, each broncho-pulmonary segment is supplied by a bronchus, and two arteries, a pulmonary artery and a bronchial artery, which run together through the center of the segment. Veins and lymphatics drain along the edges.

There are 10 broncho-pulmonary segments in the right lung (3 in the superior lobe, 2 in the middle lobe, 5 in the inferior lobe) and 8-10 segments on the left (4-5 in the upper lobe, 4-5 in the lower lobe). The broncho-pulmonary segment is important because a surgeon can remove one segment, without seriously disrupting surrounding segments.
Two major types of cells compose the epithelium (Figure 1-3), thin epithelial cells: Type I pulmonary cells, (or Type I pneumocytes), across whose walls gas exchange takes place, and surfactant-producing cells (Type II pneumocytes). The pulmonary surfactant decreases the surface tension of the fluid on the alveolar surfaces by 5-10 folds. Without surfactant, the surface tension would require exhaustive muscular effort to overcome during inspiration.

1.2 INTRA-THORACIC LYMPH NODES

The lymph is drained from the lung tissue through subsegmental, segmental, lobar and interlobar lymph nodes to the hilar lymph nodes, which are located around the hilum of each lung. The lymph flows subsequently to the mediastinal lymph nodes.
Intra-thoracic lymph nodes consist of several lymph node groups, along the trachea, esophagus (e.g. a path of mediastinal structure), and between the lung and the diaphragm (Figure 1-4). In the mediastinal lymph nodes arises lymphatic ducts, which drains the lymph to the left subclavian vein (to the venous angle in the confluence of the subclavian and deep jugular veins).

Figure 1-4: Intra-thoracic Lymph Nodes

IASLC lymph node map 2009
The mediastinal lymph nodes along the esophagus are in tight connection with the abdominal lymph nodes along the esophagus and the stomach. Through the mediastinum, the main lymphatic drainage from the abdominal organs goes via the thoracic duct (ductus thoracicus), which drains the majority of the lymph from the abdomen to the above mentioned left venous angle.

In 2009 a new lung cancer lymph node map (Table 1-1) was proposed by the International Association for the Study of Lung Cancer (IASLC), (Irion, Fewins et al. 2009).
### Table 1-1: Intra-thoracic LN as proposed by International Association for the Study of Lung Cancer

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Highest mediastinal</td>
</tr>
<tr>
<td>2R / 2L</td>
<td>Upper Paratracheal</td>
<td>Right - Bounded superiorly by the apex of the lung, laterally by the pleura, medially by the trachea, inferiorly by the intersection of the caudal border of the brachiocephalic artery and trachea. Left - As for right, except the inferior boundary is formed by the superior part of the arch of aorta</td>
</tr>
<tr>
<td>3A</td>
<td>Pre-vascular</td>
<td>Superior border: superior border of manubrium Inferior border: Carina Anterior border: Posterior aspect of the sternum Posterior border: anterior border of the SVC (rt) and common carotid artery (Lt)</td>
</tr>
<tr>
<td>3P</td>
<td>Pre-vertebral</td>
<td>Superior border: Apex of chest Inferior border: Carina Anterior border: Posterior aspect of the trachea Posterior border: vertebral body</td>
</tr>
<tr>
<td>4R / 4L</td>
<td>Lower Paratracheal</td>
<td>Right – Bounded above by station 2R, inferiorly by the caudal margin of the azygos vein. Left – Bounded superiorly by station 2L, laterally by the ligamentum arteriosum, and inferiorly by the carina</td>
</tr>
<tr>
<td>5</td>
<td>Aortopulmonary</td>
<td>Located lateral to the ligamentum arteriosum and above the pulmonary artery / trunk</td>
</tr>
<tr>
<td>6</td>
<td>Anterior mediastinum</td>
<td>The space located anterior to the trachea, pulmonary arteries, aorta and ligamentum arteriosum</td>
</tr>
<tr>
<td>7</td>
<td>Subcarinal</td>
<td>The mediastinum beneath the carina, medial to station 9</td>
</tr>
<tr>
<td>8</td>
<td>Paraoesophageal</td>
<td>The mediastinum posterior to the trachea, on either side of the oesophagus</td>
</tr>
<tr>
<td>9R / 9L</td>
<td>Pulmonary Ligament</td>
<td>Located within the pulmonary ligament, inferior to the root of the lung</td>
</tr>
<tr>
<td>10R / 10L</td>
<td>Tracheobronchial</td>
<td>Right - Superior to the carina / right main bronchus, medial to the origin of the right upper lobe bronchus, and inferior to station 4R. Left – Lateral and superior to the carina / left main bronchus, medial to the origin of the left upper lobe bronchus, and inferior to station 4L</td>
</tr>
<tr>
<td>11R / 11L</td>
<td>Interlobar</td>
<td>Located between the junction of the lobar bronchi</td>
</tr>
<tr>
<td>12R / 12L</td>
<td>Lobar</td>
<td>Located along the lobar bronchi</td>
</tr>
<tr>
<td>13R / 13L</td>
<td>Segmental</td>
<td>Located along segmental bronchi</td>
</tr>
<tr>
<td>14R / 14L</td>
<td>Subsegmental</td>
<td>Located along subsegmental bronchi</td>
</tr>
</tbody>
</table>
1.3 **Lung Cancer; Epidemiology**

Lung cancer is the most common cancer in the world with approximately 13% of newly diagnosed cases in each year (Hoggart, Brennan et al. 2012). It is the second most commonly diagnosed cancer in North America (behind prostate cancer in men and breast cancer in women). Lung cancer is the leading cause of cancer death in North America accounting for 28% of all cancer deaths. Smoking is the primary risk factor (Iyen-Omofoman, Hubbard et al. 2012). Patients with a history of lung cancer are at increased risk for a second lung cancer with a rate of 1 to 2% per year. The other risk factors include exposure to asbestos, coal tar fumes, nickel, chromium, arsenic, diesel exhaust, indoor radon, and radioactive materials.

1.4 **Pathologic Classification of Lung Cancers**

The World Health Organization (WHO) pathological classification includes nine main groupings of malignant lung tumors: squamous cell carcinoma, adenocarcinoma, large cell carcinoma, adenosquamous cell carcinoma, small cell lung carcinoma (SCLC), carcinoma with pleomorphic, sarcomatoid or sarcomatous elements, carcinoid tumor, carcinomas of salivary-gland type, unclassified carcinoma. Non-small cell lung carcinoma (NSCLC) is the umbrella term that captures any type of malignant epithelial lung cancer other than small cell lung cancer, although there is emerging evidence that the subtype of NSCLC is important from a prognostic and therapeutic point of view. NSCLC arises from the epithelial cells from any part of the lung – anywhere from central bronchi to terminal alveoli. Most subtypes of NSCLC are associated with cigarette smoke, although adenocarcinomas may be found in patients who have never smoked. Patients with resectable disease may be cured by surgery or surgery followed by chemotherapy/radiotherapy. Local control can be achieved with radiation therapy in some patients with unresectable disease, but cure is seen only in a small number of patients. Stage has a critical role in the selection of therapy.
1.5 Staging

TNM is the staging system based on tumor (T), lymph nodes (L), and distant metastasis (M). NSCLC staging based on TNM 7th edition (Langfort 2010) is presented in Table 1-2.

To stage the disease, clinical (mainly images) or pathological (e.g. after surgical tumor and lymph nodes dissection) information may be used. Information used to determine staging may be obtained from the following: history and physical examination, contrast enhanced chest CT scan, Fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning, and brain MRI (or contrast enhanced brain CT scan), and mediastinoscopy.
### Table 1-2: Lung cancer staging based on TNM 7th edition

<table>
<thead>
<tr>
<th>T</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor &lt; 3 cm surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus. T1A ≤ 2 cm, T1B = 2-3 cm</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 3 cm but ≤ 7 cm, or tumor with any of the following features: Involves main bronchus &gt; 2 cm distal to carina, invades visceral pleura, associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung. T2A = 3-5 cm, T2B = 5-7 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 7 cm or any of the following: directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus &lt; 2 cm from carina without involvement of the carina, atelectasis or obstructive pneumonitis of the entire lung, separate tumor nodules in the same lobe</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe</td>
</tr>
<tr>
<td>N</td>
<td>Description</td>
</tr>
<tr>
<td>N1</td>
<td>Ipsilateral peribronchial/hilar lymph nodes involvement</td>
</tr>
<tr>
<td>N2</td>
<td>Ipsilateral mediastinal or subcarinal lymph nodes involvement.</td>
</tr>
<tr>
<td>N3</td>
<td>Involvement of contralateral mediastinal/hilar lymph nodes and/or ipsilateral/contralateral scalene/supraclavicular lymph nodes.</td>
</tr>
<tr>
<td>M</td>
<td>Description</td>
</tr>
<tr>
<td>M1</td>
<td>M1a: Separate tumor nodule(s) in a contralateral lobe or tumor with pleural nodules or malignant pleural or pericardial effusion. M1b: Distant metastasis</td>
</tr>
</tbody>
</table>

*UICC (Union for International Cancer Control, 2010)*
Staging:

IA: T1a-T1b N0 M0  
IB: T2a N0 M0  
IIA: T1a-2a N1 M0 or T2b N0 M0  
IIB: T2b N1 M0 or T3N0 M0  
IIIA: T3 N1 M0 or T1a-T3 N2 M0 or T4 N0-N1 M0  
IIIB: T4 N2 M0 or any T N3 M0  
IV: any T, any N, M1a-1b

1.6 TREATMENT OPTIONS FOR STAGE I NSCLC

1.6.1 SURGERY

For early stage NSCLC, surgical excision remains as the standard approach (Inada, Shirakusa et al. 2000). However, not all patients diagnosed with early stage NSCLC may have surgical option; in fact as many as 30% of patients with early-stage disease will not undergo surgery (Bogart, Scalzetti et al. 2003) and in elderly patients (older than 75 years) this number is almost doubled (60%) (Hayakawa, Mitsuhashi et al. 2001). Patients may be considered poor surgical candidates if they have poor lung function values, cardio-vascular disease, general frailty, and end organ dysfunction such as renal or hepatic insufficiency (Hung, Jeng et al. 2012).

Moreover, the risk of postoperative morbidity is not trivial, with a 30% to 40% incidence of postoperative complications and a 1% to 5% incidence of operative mortality (Torjesen 2011).

Silvestri et al (Silvestri, Handy et al. 1998) retrospectively reviewed mortality rates of 1,416 patients who underwent lobectomy in South Carolina. Mortality was less for those patients whose operation was performed by a board-certified thoracic surgeon as opposed to a general surgeon (3% vs. 5.3%). This was
confirmed in a large retrospective study performed by Goodney et al (Goodney, Lucas et al. 2005), who reviewed the outcomes on 25,545 patients who underwent either lobectomy or pneumonectomy for lung cancer. Operative mortality rates were lower for cardiothoracic (5.6%) and general thoracic (5.8%) surgeons than general surgeons (7.6%).

Although lobectomy or pneumonectomy has traditionally been considered the standard of care for resectable stage I NSCLC, the significance of lesser resection (i.e. segmentectomy, or wedge resection) in the treatment of early non–small cell cancer has attracted increased interest as a minimally invasive operation (Lee, Park et al. 2007; Balduyck, Hendriks et al. 2008).

Ginsberg et al. reported the results of a prospective randomized trial comparing limited resection to lobectomy in 247 patients with peripheral T1 lung cancers (Ginsberg and Rubinstein 1995). In this study, patients treated with limited resection had a threefold increase in local recurrence, a 75% increase in combined local and distant recurrence, and a 50% increase in death with cancer rate. There was no difference in operative mortality between the limited resection and lobectomy treatment groups, although there was a higher rate of postoperative respiratory failure requiring ventilator support in the lobectomy group.

1.6.2 Conventional radiotherapy

Historically, the treatment option for inoperable patients with early stage NSCLC was conventional conformal radiotherapy (3D-CRT) using typical radiation doses of approximately 55–70 Gy in 2 Gy fractions delivered over 4–7 weeks (Decker, Tanoue et al. 2006).
There is support for better local control when total dose is increased to more than 60 Gy in 30 fractions (Xu, Shi et al. 2002; Adkison, Khuntia et al. 2008). However, the 5 year OS remains poor; in the range of 5 to 30%, based on the patient, tumor and treatment factors, indicating the necessity of carefully selecting the patients for higher dose/modified fractionation radiotherapy (Rosenzweig, Mychalczak et al. 2000). In the study reported by Zhang et al. (Zhang, Yin et al. 1989) higher dose radiotherapy (69-70 Gy) was associated with better 5 year overall survival compared with the patients treated with radiotherapy dose between 55-61 Gy (36 vs. 27%).

To determine the effectiveness of radical radiotherapy in medically inoperable stage I/II non-small cell lung cancer (NSCLC) and the extend of treatment morbidities, Rowell et all, performed a systemic review on one randomized and 26 non-randomized studies (Rowell and Williams 2001). Individual studies were of varying size, ranging from 15 to 347 patients (median study size 60 patients). Overall survival in the studies was 50–93% at 1 year, 22–72% at 2 years, 17–55% at 3 years, and 0–42% at 5 years. Survival was better for T1 than for T2 tumors (range 29–37% vs. 24% at 5 years) and fell progressively as tumor size increased.

The randomized CHART trial (Saunders, Dische et al. 1996); showed benefit of hyperfractionated/accelerated radiotherapy with 2 and 4 year survival improvement from 24% and 12% for conventional radiotherapy to 37% and 18% for CHART groups. Most of the patients (130/169, 77%) had T2N0 tumors; 33 (20%) were T1N0 and only six (4%) were stage IIA.

The presence of comorbidity affects survival adversely and this has been reported by Haasbeek et al. from the Netherlands (Haasbeek, Palma et al. 2012). They retrospectively studied 47 patients with technically resectable stage I NSCLC. Three patients refused surgery and 44 patients were inoperable due to their comorbidities. Patients were treated with varying dose fractionation schedules from 32 Gy in 6 fractions to
56 Gy in 20 fractions. In Cox’s proportional hazards analysis, only tumor size was predictive for disease-specific survival, but only the presence of severe associated disease was predictive for overall survival ($p < 0.01$) and tumor size was not statistically significant ($p = 0.08$). Overall survival was 70%, 33%, and 15% at 1, 3, and 5 years, respectively.

The effects of weight loss and performance status have also been shown. In a study from Japan (Zhang, Yin et al. 1989); 49 patients with technically resectable stage I NSCLC were treated with 69.6 Gy radiotherapy; 1.2 Gy/fractions (twice daily fractionation). 29/49 patients had comorbidities therefore they were inoperable but 20/49 patients refused the surgery. In univariate analysis, age and gender did not influence the treatment outcome, whereas good performance status, absence of weight loss, and T1 stage were associated with better survival and relapse-free survival rates. Centrally located tumors tended to produce a poorer outcome than peripherally located tumors, but the difference was not significant ($p = 0.064$ for survival and $p = 0.081$ for relapse-free survival). Patients with T1 tumors had a better local control rate than those with T2 tumors: the 5-year local control rate was 71% for T1 tumors and 38% for T2 tumors ($p = 0.015$). In multivariate analysis, good performance status and weight loss had a positive significant influence on survival and relapse-free survival, while gender, age, T stage, and tumor location had no significant influence on outcome.

Median survival times in the studies with data on performance status was 23–24 months for those with ECOG performance status 0–1 or Karnofsky scores of 90–100 compared with 6–13 months for those with ECOG >2 or Karnofsky scores of 70–80 (Schiller, Cleary et al. 1997).

The most frequent toxicities related to conventional radiotherapy included tiredness, esophagitis in the range of 22%–64% (Zhang, Yin et al. 1989; Cheung, Mackillop et al. 2000) which could be severe in 4% of
the patients (Jeremic, Shibamoto et al. 1997), radiation pneumonitis, with the risk of approximately 20% which could be > grade 3 in 6% of patients (Zhang, Yin et al. 1989; Jeremic, Shibamoto et al. 1997; Cheung, Mackillop et al. 2000).

1.6.3 Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) was first introduced more than a decade ago to treat inoperable patients with stage 1 NSCLC (Blomgren, Lax et al. 1995). SBRT delivers very high radiation doses in a short period of time (e.g. often 48-60 Gy in 4-3 fractions). Requirements of such high dose radiotherapy include ensuring the accuracy and precision of the planning process needed for safe daily treatment.

Patients/tumors should be carefully selected when utilizing stereotactic radiotherapy. As surgical treatment remains the standard practice for patients with early stage NSCLC, inoperable patients are considered for SBRT. These patients usually have several comorbidities, in particular cardiopulmonary conditions that preclude them from surgical management. However they should be clinically stable enough to lie in the treatment position for an appropriate length of time. Patients need sufficient flexibility to maintain the arms in an elevated position (or an alternative position to get at least one arm away from the chest wall). This position allows utilizing different beam angles for the optimal target coverage while avoiding organs at risk (OAR).

Tumors selected for SBRT should be relatively small. In our center we have a maximum size limit of 5 cm (Taremi, Hope et al. 2012) which is consistent with many other centers’ policies (Timmerman, Paulus et al. 2010). Preferably the lesions should be away from the central structures (such as proximal bronchial tree and great vessels) and other OAR (such as stomach or liver) (Timmerman, McGarry et al. 2006; Baumann,
Nyman et al. 2009). Selected lesions in proximity of OAR may be treated with modified SBRT dose (e.g. 60 Gy in 8 fractions) (Haasbeek, Lagerwaard et al. 2011).

Lesions should be clearly identified and visualized on CT scan. This allows the use of cone-beam CT images for image-guided radiotherapy (Purdie, Bissonnette et al. 2007). At Princess Margaret Hospital (PMH) we not only treat early stage NSCLC, but also single or multiple pulmonary lesions (either from lung or other site’s primary) (Bissonnette, Franks et al. 2009; Dahele, Brade et al. 2009; Taremi, Hope et al. 2012).

Consistent, reproducible, and comfortable patient immobilization are very important for ensuring treatment accuracy to facilitate accurate treatment and to permit the small margins typical of SBRT treatment planning. There are several immobilization devices available (such as body frame and vacuum cushion). In our center we use either a vacuum cushion (Vac-Lok MEDTEC, Orange City, IA) or a chest board. The advances of using vacuum cushion is the comfort and reproducibility, however it does get deflated occasionally which makes it very inconvenient as the patient needs to be re-scanned and re-planned. It’s important to keep the patients as comfortable as possible to maximize their stability. Careful positioning in the immobilization device, supporting the hands and shoulders, and in selected patients, premedication with analgesia or an anxiolytic may need to be considered.

In addition to the patient, the tumor also needs to be immobilized as much as possible (Li, Purdie et al. 2011). As the tumor moves along with the respiratory motion, one way to reduce the tumor motion is to reduce the lung motion during the respiration. In our center, if the tumor motion is more than 1 cm (in superior/inferior direction); we use abdominal compression to limit this motion to less than 1 cm.
SBRT is a high-precision technique requiring precise delineation of both tumor(s) and normal structures. With the advances in radiotherapy planning such as imaging techniques that utilize four-dimensional computed tomography (4D CT) scans, CT images may be correlated with respiratory phases (Keall 2004). Using 4DCT imaging, the GTV (gross tumor volume) is delineated on the different datasets of 4DCT. In our center the least data sets used for contouring include maximum exhale and maximum inhale respiratory phases. However, in the majority of cases, we also use the information from other 4DCT data sets such as average, maximum intensity projection (mip) and helical. Although not required by our SBRT protocol, in selected patients intravenous CT contrast may be used to identify the GTV. When PET imaging is available, it is fused to the exhale 4DCT data set to help the contouring process. To minimize the target margin, we do not add any extra margin around the GTV for clinical target volume (CTV). Instead we add all the GTVs together (with no extra margin) to obtain internal target volume (ITV). For the setup uncertainty additional uniform margin of 5 mm is required (around the ITV) to generate the PTV (Dahele, Pearson et al. 2008).

OAR also need to be delineated. These include: trachea, proximal bronchial tree, esophagus, heart, spinal canal and the brachial plexus. In selected cases, other OAR such as stomach and liver may need to be contoured. After contouring all the targets and organ at risk, the delineated volumes are checked by the second radiation oncologist (as part of our quality assurance policy), as well as reviewed at multidisciplinary SBRT rounds.

One of the most important requirements in SBRT is to use image-guided radiotherapy to increase treatment precision (Haasbeek, Slotman et al. 2009). Integrated imaging devices such as cone-beam CT scan images, on the treatment units while the patient is on the radiotherapy couch, allows for CT scans to be performed prior to the treatment, to confirm that the patient and tumor are positioned correctly (Grills, Hugo
et al. 2008). Therefore this technique allows oncologists to reduce the ‘safety margin’ of normal lung treated alongside the tumor allowing for much higher doses to be delivered safely.

SBRT offers a high local control rate in the range of 90% (Baumann, Nyman et al. 2009; Timmerman, Paulus et al. 2010; Dworzecki, Idasiak et al. 2012). However, the rates of local recurrence increase as tumor size increases (T2 lesions), and when lower doses of SBRT are prescribed (Olsen, Robinson et al. 2011; Onishi, Shirato et al. 2011). Moreover, due to the radiologic changes after stereotactic radiotherapy, evaluation of treatment response may be difficult. These radiologic findings are quite common after SBRT, occurring in more than 50% of patients and sometimes may lead to misdiagnosis of tumor recurrence (Kimura, Matsuura et al. 2006; Takeda, Kunieda et al. 2008; Trovo, Linda et al. 2010).

A biologically effective dose is a method to compare the different dose fractionated radiotherapy schedules. There have been some controversies using BED calculation when treating the patients with the radiotherapy doses of 7 Gy or more per fraction (Fowler 2010). Although this method may overestimate the calculated effect of radiation, has been widely used in the literatures.

A biologically effective dose above 100 Gy has been recommended as a cutoff for adequate dose by Onishi et al (Onishi, Shirato et al. 2007). This was confirmed by other studies. For example, in a study from the Netherlands 58 central lesions in 56 patients were treated by SBRT using various dose fractionation schedules from 5 x 9 Gy to 5 X 12 Gy. With a median follow-up of 23 months, the actuarial 2-year local tumor control was 85% for tumors treated with a BED >100Gy compared to 60% for tumors treated with a BED of 100 Gy. Studies reporting SBRT outcomes have been summarized in Appendix 1.

Although SBRT offers the high rate of local control, when using this technique, the possibility of regional lymph nodes recurrence should be taken into account. A recent study from the Netherlands reported similar local control and distance recurrence rates in patients treated with SBRT vs. surgery however more
patients in SBRT group had locoregional recurrence ($p = 0.028$) (van den Berg, Klinkenberg et al. 2015). The author emphasized on the importance of mediastinal and hilar staging prior to SBRT.

Despite high local control rates, patients remain at risk of recurrence due to distant metastases, with the approximate risk of 20% within 2 years (Haasbeek, Slotman et al. 2009). In RTOG 0236, among 59 patients with a median follow-up of 34.4 months, only 1 patient had a primary tumor failure; while 11 patients experienced disseminated recurrence; the 3-year rate of distant failure was 22.1% (Timmerman, Paulus et al. 2010).

Toxicities may include tiredness (Taremi, Hope et al. 2012), pneumonitis (Linda, Trovo et al. 2011; Palma, Senan et al. 2011), chest wall pain or rib fracture (Pettersson, Nyman et al. 2009; Dunlap, Cai et al. 2010), skin necrosis (Hoppe, Laser et al. 2008), and brachial plexus injury (Forquer, Fakiris et al. 2009).

Patients with central tumors are at higher risk for airway toxicities. In the RTOG study (Timmerman, McGarry et al. 2006), Grade 3 to 5 toxicity occurred in a total of 14 out of 70 patients treated with SBRT to a total dose of 60 Gy in 3 fractions. Patients treated for tumors in the peripheral lung had 2-year freedom from severe toxicity of 83% compared with only 54% for patients with central tumors. The authors concluded that 60 Gy in 3 fractions should not be used for patients with tumors near the central airways due to excessive toxicity.

Toxicity can be minimized through careful attention to the radiation tolerance of normal structures, and newer approaches such as intensity modulated radiotherapy (IMRT), and volumetric modulated arc therapy (VMAT) to reduce the dose to organ at risk (OAR) (Van Houtte 2003; Dvorak, Georg et al. 2005; Seppala, Suilamo et al. 2012).
1.7 LITERATURE REVIEW ON CHEST WALL PAIN AND RIB FRACTURES

Due to the hypofractionation associated with SBRT, organs at risk (such as ribs and chest wall) will be subject not only to a high dose radiation, but also to a high dose per fraction of radiotherapy; which is associated with higher risks of late toxicities such as fibrosis and fracture.

Late effects in normal tissue after SBRT have been reported (Timmerman, Papiez et al. 2003; Nyman, Johansson et al. 2006) but few studies have been performed to establish clinical dose– and volume– response relationships in SBRT. Historical series consisting mainly of breast cancer patients report an incidence of chest wall pain and/or rib fracture of 1% to 6% after conventionally fractionated therapy (Pierce, Recht et al. 1992). Overgaard et al. reported a 6% incidence of spontaneous rib fracture after conventionally fractionated RT for breast cancer, with rates as high as 19% for more hypofractionated treatment (Overgaard 1988). There have been several studies reporting on chest wall toxicities and rib fractures in patients with breast cancer treated with radiotherapy/brachytherapy (Hepel, Tokita et al. 2009; Mutter, Liu et al. 2012). However, at the time when this thesis project was being designed, there was only one manuscript published on rib fractures after SBRT (Pettersson, Nyman et al. 2009). Since that time, there have been additional publications; some of the reports have been summarized in our published manuscript describing this thesis work (Chapter 4).

In this chapter, we have reviewed the literature related to SBRT associated rib fractures/ and chest wall pain in more detail. Some of the reported outcomes are in abstract format and some has been published as full papers. Although there are several published papers/abstracts on SBRT related chest wall toxicity/pain, the data about rib fractures are limited. Here we summarize published data in two main categories (rib fractures and chest wall toxicities). In each group we review abstracts and papers separately.
1.7.1 RADIOTHERAPY-ASSOCIATED RIB FRACTURE- PUBLISHED REPORTS

One of the very early studies on rib fracture was a retrospective study from Princess Margaret Hospital (Voroney, Hope et al. 2009); 9 out of 42 patients treated with SBRT to a total dose of 54-60 Gy in three fractions developed a total of 15 ipsilateral rib fractures. Median follow up was 17 months and all patients with fracture had tumors within 2 cm of the chest wall. Two fractures were asymptomatic and chest wall pain was observed in 11 patients (seven of whom had fractures). The median dose to rib fracture sites was 50.1 Gy (range, 17.1-76.4). This study was one of the first published data describing rib fracture as a late toxicity of SBRT; however detailed dosimetric information was not clearly identified.

One of the key papers on SBRT-related rib fracture is a study performed by Pettersson et al. In this study the dosimetric records of 33 inoperable patients with NSCLC treated with SBRT were analyzed. This group contoured only the ribs that received at least 21 Gy (81 ribs in 26 patients); of these 81 ribs, 13 had fractures and 68 did not (Pettersson, Nyman et al. 2009). The prescription dose was 45 Gy in 3 fractions and the minimum follow up was 15 months. They found that there was a strong association between risk of rib fracture and the small-volume/high-dose region of dose volume histogram parameters. They estimated the probability of rib fracture of 50% and 5% if 2 cm$^3$ of rib volume receive 49.8 and 27.3 Gy, respectively.

The relationship between dose and rib fracture was also confirmed in a study from Japan (Nambu, Onishi et al. 2011). In this study 41 patients of total of 177 patients treated with SBRT (48 to 70 Gy in 4 to 10 fractions) developed rib fracture. The maximum biologically effective dose (BED) for the chest wall around the tumor was calculated using a linear quadratic model ($\alpha/\beta = 3$Gy). The mean time to develop the rib fracture after SBRT was 21.2 months (4-58 months). No rib fracture was observed in cases in which the distance between the tumor and chest wall was more than 16mm. Maximum BED$_3$ of the chest wall in
patients with and without rib fracture, and threshold dose for rib fractured occurrence mean BED\textsubscript{3} of the chest wall was 240.7 \pm 38.8 Gy in 26 patients with rib fracture and 146.8 \pm 74.5 Gy in 22 patients without rib fracture (p value < 0.001). In this study ribs were not contoured individually however, the study still provides useful information, in particular confirming the relationship between dose and chest wall/rib toxicities as well as introducing the safe cut point distance (1.6 cm) between chest wall and tumor when treating lesions with stereotactic radiotherapy. Studies have been summarized in table 1-3.

### 1.7.2 Radiotherapy-Associated Rib Fracture: Abstracts

A PubMed search (2002-2012) has detected few abstracts on radiotherapy-induced rib toxicities: in a cohort study from Japan, rib fractures were observed in 26 patients (44 ribs) of total of 129 patients treated with SBRT (with the median follow up of 19 months) (Barriger, Forquer et al. 2012). Radiation-induced rib fractures were defined as rib fractures located in the radiation field, and dose-volume histogram analysis was conducted on the ribs that received over 20 Gy. The KM (Kaplan Meier) estimates of rib fracture at 3 years and 5 years were 35.3%, 53.7%, respectively. As a risk factor, chest wall - tumor distance (\geq 2cm vs. <2cm) was significantly correlated with radiation-induced rib fracture (p = 0.0001). The 5- year estimated risk of rib fracture is 53.5% vs. 3.0% (max dose: \geq 44.9 Gy vs. < 44.9 Gy), 61.8% vs. 2.0% (V40: \geq 0.43cc vs. <0.43cc), 54.0% vs. 2.1% (V30: \geq 1.35cc vs. <1.35cc), 51.5% vs. 8.4% (V20: \geq 3.64cc vs. <3.64cc), 30.2% vs. 14.6% (V10: \geq 6.01cc vs. <6.01cc), respectively.
1.7.3 RADIOTherapy-ASSOCIATED CHEST WALL PAIN-PUBLISHED REPORTS

There are several papers on radiotherapy chest wall toxicity. One of the first published papers was from Dunlap et al. who reviewed the data on 60 patients treated with various dose fractionations of SBRT and median follow up of 11 months (Dunlap, Cai et al. 2010). Grade 3 chest wall pain was observed in 17 patients and there were 5 rib fractures. The median interval to the onset of severe pain and/or fracture was 7.1 months. They estimated the risk of chest wall toxicity as 30% if 35 cm$^3$ of chest wall volume receives 30 Gy of radiation dose.

Chest wall volume receiving 30 Gy seems to be a prognostic factor for chest wall pain in patients treated with SBRT. In fact data was confirmed by another study performed by Mutter et al (Mutter, Liu et al. 2012). In this study dose-volume histogram values for the chest wall were reviewed in 126 patients treated with SBRT to a total dose of 40 to 60 Gy in 3 to 5 fractions. The chest wall was defined as 2 to 3cm two-dimensional expansion of the ipsilateral lung excluding the lung volume, the mediastinal soft tissue, and anterior vertebral body (CW3cm or CW2cm). With a median follow-up of 16 months, the 2-year estimated actuarial incidence of Grade > 2 CW pain was 39% (with the median time to onset of 9 months). Chest wall volume receiving 30 Gy (V30) was one of the strongest predictors ($p < 0.001$). CW2cm consistently enabled better prediction of CW toxicity. When a physical dose of 30 Gy was received by more than 70 cm$^3$ of CW2cm, there was a significant correlation with Grade > 2 CW pain ($p = 0.004$).

Both of these studies evaluated the dosimetric information in much detail and recommended the relationship between the dose-volume values of chest wall receiving the dose of SBRT and the risk of chest wall pain however none of them looked into clinical factors.
A few of other published papers evaluated other dosimetric values such as different volumes of chest wall receiving certain doses. In a study from Indiana University, the records of 311 patients (347 lesions) treated with SBRT from 2000 to 2008 were reviewed (patients were treated with various dose fractionation schedules) (Andolino, Forquer et al. 2011). All lesions were categorized as either non-chest wall or chest wall, defined as lesions in which at least the 50% isodose line or greater abutted any aspect of the adjacent chest wall. Chest wall and ribs were contoured in only 79 out of 203 chest wall lesions, and the data analysis regarding actual dose delivered to the chest wall and ribs was limited to these lesions (heterogeneity corrections was used for 59 of these 79 lesions). In this study, the rates of chest wall toxicity of any severity for chest wall and non-chest wall lesions were 21% and 3.5% respectively. They predicted a 10% risk of Grade I and greater chest wall toxicity when 15 cc and 5 cc of chest wall receives 30 Gy and 40 Gy, and a 30% risk of toxicity when 40 cc and 15 cc of chest wall receives 30 Gy and 40 Gy, respectively. From 18 rib fractures 11 (61%) were asymptomatic and only 19% (7 of 36) of all episodes of chest wall pain coincided with a documented rib fracture. They suggested that peripheral nerve damage, rather than direct rib injury, was the primary mechanism responsible for chest wall discomfort following SBRT. This study also did not look into clinical factors.

The relationship between radiotherapy dose and chest wall toxicity was also studied at University of Texas M. D. Anderson Cancer Center. They reported the data on 36 patients treated with SBRT for recurrent disease among patients previously given radiation therapy to the chest (Kelly, Balter et al. 2010). The majority of patients (72%) were treated with 50 Gy in 4 fractions and the rest were treated with a number of dose fractionation schedules. The median follow-up time after SBRT was 15 months. Overall, 11 patients (31%) experienced chest wall pain, of whom six required narcotics to control this symptom. The majority of these cases (> 65%) were treated for in-field tumor relapse, but there was no detailed report on dose/volume relationship and chest wall toxicity.
The rate of chest wall pain and rib fracture was significantly lower when lower dose of SBRT was used. Nagata et al. reported on a series of 45 patients with Stage I non–small-cell lung cancer who all received 48 Gy in 4 fractions via SBRT. With a median follow-up of 30 months, the authors did not cite any incidence of chest wall toxicity (Nagata, Takayama et al. 2005). Videtic et al. reported one case of Grade 2 chest wall pain among 28 pulmonary lesions treated with SBRT (Videtic, Stephans et al. 2010).

Higher doses of radiotherapy seem to increase the risk of chest wall pain and this has been shown in the study from Cleveland (Stephans, Djemil et al. 2011). In this study data from 86 patients treated with SBRT (50 Gy in 5 fractions or 60 Gy in 3 fractions) were reviewed. Median follow-up was 15.3 months. Mild late chest wall toxicity (grade 1 or 2) was seen in nine patients (10%) at a median of 8.4 months after treatment and was more common in the 60-Gy group (18% vs. 4% p = 0.028).

One of the studies that looked into both dosimetric and clinical factors was the study performed by Stephans et al.; his team analyzed data on 48 patients treated with SBRT to 60 Gy in 3 fractions (Stephans, Djemil et al. 2012). Median follow up was 18.8 months. There were 10 patients with late symptomatic chest wall toxicity (4 Grade 1 and 6 Grade 2) at a median of 8.8 months after SBRT. This group studied also clinical factors, however no patient characteristics (age, diabetes, hypertension, peripheral vascular disease, or body mass index) were predictive of toxicity, whereas there was a trend for continued smoking (p = 0.066). Volumes of chest wall receiving 30 through 60 Gy were statistically significant in multivariate analyses. Although in this study there was no significant association found between some clinical factors and SBRT-related chest wall toxicity, this group did not look at obesity or body mass index (BMI) as one of the potential prognostic factors. In the study performed by James Welsh, BMI was found to be a significant prognostic factor. In this study, a database of 268 tumors (in 265 patients) which were located within 2.5 cm from the chest wall and treated with SBRT to total dose of 50 Gy
in 4 fractions were reviewed (Welsh, Thomas et al. 2011). Chest wall was defined as subtraction of the outer edge of patient’s skin/chest wall from the total lung contour. Overall, 67 patients developed some form of chest wall pain, including 8 patients with rib fractures and the median time to onset of pain was 6 months. Fourteen patients (5%) developed acute pain, and 45 patients (17%) developed chronic pain (Grade 2 or 3 in 23/45). Chest wall pain was associated with the volume of the chest wall receiving 30 Gy. BMI was also strongly associated with the development of chest pain: patients with BMI>29 had almost twice the risk of chronic pain (p =0.03). Moreover, chest wall pain Grade 2 or above was present in 18% of diabetic patients compared with none of the non-diabetic patients (p = 0.057).

Creach et al evaluated both dosimetric and clinical factors in patient with early-stage NSCLC treated with SBRT (Creach, El Naqa et al. 2012). A cohort of 140 patients treated with lung SBRT to total dose of 50 Gy in 5 fractions or 54 Gy in 3 fractions at the Mallinckrodt Institute of Radiology were reviewed. Median follow up was 22.5 months. The ipsilateral CW (defined as a 3 cm outward expansion from the ipsilateral lung) and ribs were contoured on each patient. Twenty-two patients (15.7%) developed chest wall toxicity (10 patients with isolated chest wall pain and 12 patients with rib fractures). The Kaplan Meier estimated risk of CW pain at 2 years was 20%. On univariate analysis of patient factors, elevated BMI (p=0.026) and connective tissue disease (p=0.036) correlated with CW pain. The percent of CW receiving 30, 35, or 40Gy was most predictive of CW pain on multivariate analysis using logistic regression, while V40 alone was predictive using Cox regression. A V30 threshold of 0.7% and V40 threshold of 0.19% was correlated with a 15% risk of CW pain.
1.7.4 Radiotherapy-associated chest wall pain-abstracts

There are a few strong abstracts that have been published and that are worth mentioning here. In particular in a study from Bongers et al. the group reviewed 500 patients’ data that underwent SBRT for stage 1 NSCLC using 60 Gy in 3 to 8 fractions (Bongers, Haasbeek et al. 2011). Median follow up was 33 months. They defined the chest wall as an expansion of the 2 cm of the lungs. Chest wall pain (any grade), severe chest wall pain (Grade 3) and rib fractures were observed in 11.4%, 2.0%, and 1.6%, respectively. Seven of 8 patients with rib fractures experienced pain. Dosimetric results revealed a trend linking severe chest wall pain and rib fractures with higher chest wall volumes irradiated to all dose levels. Multivariate analysis showed chest wall pain and/or rib fractures to be related to larger PTV volumes ($p = 0.025$) and smaller tumor-chest wall-distances ($p = 0.038$) compared to asymptomatic patients.

Another interesting published abstract is the study done by Confer et al. This group investigated the potential associations between the chest wall toxicity and post-treatment positron emission tomography (PET) SUV in patients treated with thoracic SBRT (Confer, Ali et al. 2011). The prescription dose was 39 to 60 Gy in 3-5 fractions. Median follow up was 13.6 months. FDG-PET scans were performed within 4 months after SBRT in 15 consecutive patients. Six of the 15 patients (40%) developed chest wall pain, and 3 patients (20%) suffered rib fractures. Post SBRT, median time to develop chest wall pain was 5.1 months, and to fracture was 9.2 months. The chest wall dose exceeded 55 Gy in six patients, of which two resulted in rib fracture and two resulted in pain without fracture. SUV within the chest wall exceeded 2.4 in three patients, all three of which later developed chest wall pain and they concluded that patients with higher, early PET avidity within the chest wall were more likely to have late chest wall toxicity.
1.7.5 Summary

There are data supporting a relationship between the radiotherapy dose and both chest wall pain and rib fracture (in particular in patients with lung lesions treated with SBRT). Although most studies have looked at the dosimetric information and chest wall toxicity, few studies have included both dosimetric and clinical factors in relationship to rib fractures. Rib fracture is less subjective than chest wall pain hence easier detect and score more accurately. Therefore we decided to perform a detailed study evaluating both clinical and dosimetric values in relationship with rib fractures in patients with lung lesions treated with stereotactic lung radiotherapy at Princess Margaret Hospital.
Table 1-3: Summary of reports on chest wall pain and rib fractures in patients treated with SBRT

<table>
<thead>
<tr>
<th>Study</th>
<th>pts</th>
<th>lesions</th>
<th>Dose</th>
<th>Med FU (Mo)</th>
<th>Rib Fractures</th>
<th>OAR Contoured</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pettersson</td>
<td>68</td>
<td>pts</td>
<td>45 Gy in 3 fr</td>
<td>29</td>
<td>7 pts with 13 rib fx</td>
<td>Only ribs receiving ≥ 21 GY 81 ribs</td>
<td>D₂ cm³: &lt;3 x 7.0 Gy, fx risk : 0% = 3 x 9.1 Gy, fx risk: 5% = 3 x 16.6 Gy, fx risk: 50%</td>
</tr>
<tr>
<td>(Pettersson, Nyman et al. 2009) Sweden</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tumor chest wall distance of 16 mm is a threshold value; Lowest BED₃ result is rib; fx was 154.2 Gy</td>
</tr>
<tr>
<td>Nambu (Nambu, Onishi et al. 2011) Japan</td>
<td>177</td>
<td>pts</td>
<td>48 Gy in 4 fr 60 Gy in 10 fr 70 Gy in 10fr</td>
<td>27</td>
<td>41 pts</td>
<td>Chest wall?</td>
<td>Adjacent ribs to the PTV Median dose to fx rib was 50 Gy; All pt with fx ribs had tumor within 2 cm of chest wall</td>
</tr>
<tr>
<td>Voroney (Voroney, Hope et al. 2009) Toronto</td>
<td>42</td>
<td>pts</td>
<td>54-60 Gy in 3 fr</td>
<td>17</td>
<td>9 pts 15 ipsilateral rib Fx</td>
<td>Adjacent ribs to the PTV</td>
<td>A volume of CW cm³ ≥70 receiving 30 Gy is significantly correlated with Grade ≥= 2 CW pain</td>
</tr>
<tr>
<td>Mutter (Mutter, Liu et al. 2012) USA, NY</td>
<td>126</td>
<td>pts</td>
<td>40 to 60 Gy in 5 fr</td>
<td>16</td>
<td>Chest wall toxicity grade: 1: 15% 2: 13% 3:15% 8 rib fx in 5 pt</td>
<td>Chest wall 2 to 3 cm expansion to the lung –lung volume: chest wall</td>
<td>5 cc and 15 cc of CW receiving 40 Gy predict a 10% and 30% risk of CW toxicity, respectively</td>
</tr>
<tr>
<td>Andolino (Andolino, Forquer et al. 2011) Indianapolis</td>
<td>347</td>
<td>lesions</td>
<td>18 to 72 Gy in 2 to 5 fr</td>
<td>19</td>
<td>36 cases of CWP and 18 rib fractures</td>
<td>3 cm expansion to the lung-lung volume: chest wall</td>
<td>Volumes of chest wall receiving 30 Gy (V30) through 70 Gy (V70) were all significant for chest wall toxicity</td>
</tr>
<tr>
<td>Stephans (Stephans, Djemil et al. 2012) USA, St. Louis</td>
<td>48</td>
<td>pts</td>
<td>60 Gy in 3 fr</td>
<td>18.8</td>
<td>10 cases with grade1-2 chest wall toxicities</td>
<td>3 cm expansion to the lung-lung volume: chest wall</td>
<td>5 cc and 15 cc of CW receiving 40 Gy predict a 10% and 30% risk of CW toxicity, respectively</td>
</tr>
<tr>
<td>Creach (Creach, El Naqa et al. 2012) USA, St. Louis</td>
<td># 140 pts</td>
<td>50 Gy in 5 fr</td>
<td>54 Gy in 3 fr</td>
<td>25</td>
<td>22 pts with CWP (CWP alone in 10 and with rib fracture in 12)</td>
<td>3 cm expansion to the lung-lung volume: chest wall</td>
<td>A V30 threshold of 0.7% and V40 threshold of 0.19% was correlated with a 15% risk of CW pain</td>
</tr>
</tbody>
</table>

pts: patients, fx: fractures; OAR: organ at risk; PMH: Princess Margaret Hospital; CWP: chest wall pain
CHAPTER 2

HYPOTHESES:

1- Clinical factors may affect the likelihood of radiotherapy induced bone injury (RIBI)
2- There is a relationship between the dose received by the rib and the risk of rib fracture; higher dose of radiotherapy is associated with higher risk for rib fracture

Based on the proposed hypotheses, the objectives include:

- Determine contributing clinical factors associated with rib fracture:
  Gender, Age, Diabetes, COPD, Tumor size, smallest 3D distance between the tumor and the rib
- Determine contributing Dosimetric factors associated with rib fracture:
  Dose volume histogram parameter, cut off point for absolute dose and volume
- Create a dose-event curve and create a nomogram

The next 2 chapters consist of full publications from our center. We will first review the outcomes and potential side effects related to lung stereotactic radiotherapy (Chapter 3) followed by rib injury as a late side effect of SBRT (Chapter 4). Although the excellent outcome of this technique justifies utilizing it in selected patients with pulmonary lesions (Chapter 3), we should be aware and cautious about the potential toxicities as some of these side effects such as rib injury/fracture may occur several months after completion of treatment (Chapter 4).

Both published papers were part of my research project during my fellowship-master degree program.
CHAPTER 3
STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR MEDICALLY INOPERABLE LUNG CANCER
PROSPECTIVE SINGLE CENTER STUDY OF 108 CONSECUTIVE PATIENTS

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ABSTRACT

Purpose: To present the results of stereotactic body radiation therapy (SBRT) for medically inoperable patients with stage I non-small cell lung cancer (NSCLC) and contrast outcomes in patients with or without pathologic diagnosis.

Methods/Materials: Between Dec 2004 and Oct 2008, 108 patients (114 tumors) were treated on prospective research ethics-board approved SBRT protocols at our cancer center. Pre-treatment whole-body FDG PET/CT was performed in 88/108 (81.5%) of patients. Pathologic diagnosis was unavailable in 33/114 (28.9%) lesions. SBRT schedules included 48Gy in 4 fractions (fr) or 54-60Gy/3 fr for peripheral lesions, and 50-60Gy/8-10 fr for central lesions. Toxicity and radiological response were assessed at 3-6 monthly follow up visits using conventional criteria.

Results: Mean tumor diameter was 2.4 cm (range: 0.9-5.7 cm). Median follow up was 19.1 months (range: 1-55.7 months). Estimated local control at 1 and 4 years was 92% (95% CI: 86%-97%) and 89% (95% CI: 81%-96%); cause specific survival (CSS) was 92% (95% CI: 87%-98%) and 77% (95% CI: 64%-89%) respectively. There was no statistically significant difference in local, regional, and distant control between patients with or without pathologically confirmed NSCLC. The most common acute toxicity was grade 1 or 2 fatigue (53/108 patients). No toxicities ≥ grade 4 were identified.

Conclusions: Lung SBRT for early-stage NSCLC resulted in excellent local control and CSS with minimal toxicity. Disease-specific outcomes were comparable for patients with or without a pathologic diagnosis. SBRT is an option for selected patients with proven or presumed early-stage NSCLC.
**Key Words:** Stereotactic Body Radiotherapy; Pulmonary nodules; radiotherapy toxicity; non-small cell, lung cancer; image-guided radiotherapy.

### 3.1 INTRODUCTION

The standard treatment for early stage non-small cell lung cancer (NSCLC) is surgical resection with 5 year overall survival (OS) rates of 82% and 68% for T1 and T2 tumors, respectively (Martini, Bains et al. 1995). Nearly 25% of patients with early stage NSCLC are deemed ‘medically inoperable’ due to other co-morbidities, while another 2-3.5% of patients decline surgery (Lathan, Neville et al. 2006). Radical radiotherapy has been offered to these patients, however depending on such factors as tumor size, dose-fractionation schedule and co-morbidity, overall survival has been disappointing - approximately 35 to 40% (Sibley, Jamieson et al. 1998).

SBRT aims to increase tumor control and survival by delivering substantially higher biologic effective doses (BED) than conventional radiotherapy. There is now a growing body of literature on the efficacy of SBRT in medically inoperable patients with early stage biopsy-proven NSCLC (Timmerman, Paulus et al. 2010).

However in patients with significant co-morbidities and limited lung function, biopsy may be considered unsafe and, therefore, contraindicated. These patients may be presumed to have lung cancer on the basis of radiologically suspicious lesions, including interval growth on serial imaging or increased metabolic activity on [18F]-fluorodeoxyglucose [FDG] PET imaging. Some authors have treated these patients with SBRT and reported early outcomes comparable to those with proven NSCLC (Verstegen, Lagerwaard et al. 2011). We aim to add to this body of literature by presenting our institutional experience with lung SBRT in a cohort of 108 consecutive patients. This manuscript reports response, pattern of failure and outcomes of
patients treated on a prospective REB-approved SBRT protocol, and, as a secondary objective, it reports results in the sub-group of patients with no tissue diagnosis.

3.2 MATERIALS AND METHODS

3.2.1 Patient Selection

Since September 2004, patients with T1-T2 N0M0 NSCLC and ECOG performance status 0-3 have been treated on prospective institutional research ethics board-approved lung SBRT protocols at Princess Margaret Hospital, a comprehensive cancer center in Toronto, Canada. Staging investigations included computed tomography (CT) of chest/abdomen, brain CT/MRI, whole-body FDG PET/CT, bone scan, blood work, and pulmonary function tests. Patients were deemed medically inoperable by an experienced thoracic surgeon and/or reviewed at a multi-disciplinary tumor board. Patients with synchronous early-stage NSCLC (up to 3 lesions) were eligible, as were patients with a previous history of lung or other primary cancers.

All patients either had biopsy proven NSCLC or pulmonary lesions that were deemed ‘suspicious’ based on evidence of interval progression on at least two serial CT imaging studies (minimum of 1 month apart) and/or increased FDG-uptake on PET scan. Suspicious pulmonary lesions were reviewed and assessed at multidisciplinary thoracic cancer rounds that included radiologists, thoracic surgeons, pathologists, and medical and radiation oncologists. Patients did not proceed to treatment unless there was agreement among lung cancer experts that the index of suspicion for cancer was sufficiently high.
3.2.2 Radiotherapy Planning and Delivery

Our lung SBRT treatment process has been previously described (Dahele, Pearson et al. 2008). Briefly, patients were immobilized in an evacuated cushion (VacLok, Civco Medical Solutions, Kalona, IA) and were simulated during free breathing using 4-dimensional respiratory-sorted CT (4DCT). When 4DCT was available, the gross tumour volume (GTV) was contoured on the end-exhale and end-inhale phases of tidal respiration; there was no expansion made to account for microscopic disease extent (CTV=GTV+0 cm). The internal target volume (ITV) was obtained by fusing the end-exhale and end-inhale CTV contours. The planning target volume (PTV) was created by adding a 0.5 cm isotropic setup margin around the ITV (Purdie, Moseley et al. 2006). Due to uncertainties in small field dosimetry, the minimum field size was set to 3.0 x 3.0 cm. Heterogeneity-corrected dose algorithms (Pinnacle, Philips, Madison, WI) were implemented in 2007 (Bissonnette, Franks et al. 2009).

Treatment plans consisted of 9-12 non-opposing, co-planar/non co-planar, beams with dosimetric criteria mandating that 95% of the PTV was covered conformally by the prescription dose and that 99% of PTV received 90% of the prescription dose. The most common dose fractionation schedules for peripheral tumors (away from central mediastinal structures) were 48Gy in 4 fractions (fr), 54Gy in 3 fr with heterogeneity correction or 60Gy in 3 fr with no heterogeneity correction delivered a minimum of 48 hours apart. Some T1 lesions also were treated with 54 Gy/3 fr, as long as the tumor was totally surrounded by lung parenchyma and there was no adjacent OAR. Less hypofractionated schedules, namely 60Gy in 8 fr and 50Gy in 10 fr (daily fractionation, 5 days per week) were selected for tumors close to dose-limiting central organs at risk (OAR). In March 2008, after analyzing the outcomes of patients treated with 50Gy/10 fr, this dose fractionated schedule was discontinued and was replaced by 60Gy in 8 fractions.
Treatment was verified using on-line cone-beam CT (CBCT) with volumetric image-guidance. CBCT images of the tumor were registered to contours and images from the 4DCT planning datasets and used to guide patient localisation (Jaffray, Siewerdsen et al. 2002; Purdie, Moseley et al. 2006; Sharpe, Moseley et al. 2006; Purdie, Bissonnette et al. 2007; Bissonnette, Purdie et al. 2008). During each treatment, CBCT images were acquired at a minimum before treatment and during treatment after delivery of all coplanar beams (intra-fraction scan); additional images were obtained in some patients after treatment. Pre-treatment CBCT (cone-beam CT) and patient repositioning were repeated until the patient was confirmed to be within ±3 mm and 3 degrees of the intended location.

### 3.2.3 Toxicity assessment, response assessment and follow-up (F/U)

Both the radiation oncologist or fellow and the clinical research associate (CRA) saw the patient at the time of their first fraction, midway through their treatment and at the end of treatment to assess the acute toxicities. Patients were followed at: 6 weeks, 3, 6, 9 and 12 months after treatment, every 6 months in the second year and yearly thereafter. On each visit, patients had a history/physical exam and toxicity and symptom assessment using CTCAE (Common Terminology Criteria for Adverse Events v3.0) (Trotti, Colevas et al. 2003) criteria.

At 3 months post treatment, a whole-body FDG-PET scan was performed to assess metabolic response to SBRT. In addition, patients had a chest CT scan (that included the upper abdomen) at 6 and 12 months post-treatment and every 6-12 months thereafter (more frequently if clinically indicated). A single observer (MT) evaluated the radiologic images for tumor response based on RECIST criteria (Therasse, Arbuck et al. 2000). All scans suspicious for progressive disease (PD) were reviewed and discussed at lung SBRT rounds, to determine whether the radiological changes were suggestive of tumor progression (i.e. local failure) or whether they were more likely post-SBRT changes.
Tumor progression in hilar, mediastinal or supraclavicular lymph nodes was considered regional failure. FDG PET scans and biopsies were considered when findings were suspicious, provided that the patients’ clinical condition permitted these. Input from radiologists, thoracic surgeons and the multi-disciplinary lung cancer conference was sought in most of these cases.

3.2.4 Statistics

Categorical variables were presented as proportions and continuous variables were described with means, medians and ranges. Probabilities of failure and cause specific survival were calculated using the cumulative incidence function. The differences between the groups of interest (i.e. patients with or without diagnostic pathology) were assessed using Gray’s test and overall survival was estimated using the Kaplan-Meier method (Pepe and Fleming 1989). Parameters were compared using the log-rank test. Cox proportional hazards regression was used to explore predictors of time to event outcomes. A stepwise model fitting process was used to select the best-fit multivariate model for overall survival. Logistic regression was used to identify predictors for treatment response. All analyses were performed using SAS v9.1 for Windows (SAS Institute Inc., Cary, NC) and all reported p-values were 2-sided.

3.3 RESULTS

One hundred eight consecutive patients with stage I NSCLC (biopsy proven or presumed suspicious lesions) were treated at our center from Dec 2004 to Oct 2008. Mean age was 72.6 years (range: 48.3-90 years) and median F/U was 19.1 months (range, 1-55.7 months). Patient and tumor characteristics are summarized in table 3-1 and treatment characteristics have been summarized in table 3-2.
Table 3-1: Patients (n=108) and Tumor (n=114) characteristics

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td><strong>Lesion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (≤ 3cm)</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>T2 (&gt;3 cm)</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td><strong>Anatomic Location of the tumor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right upper lobe</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Right middle lobe</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Right lower lobe</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Left upper lobe</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Left lower lobe</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td><strong>Cytological diagnosis of the tumor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adenocarcinoma</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Non-small cell lung cancer NOS*</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>No Biopsy/non-diagnostic sample</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td><strong>PET scan (patients)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-RT</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>3 months post-RT</td>
<td>67</td>
<td></td>
</tr>
</tbody>
</table>

* Not otherwise specified
Table 3-2: Treatment characteristics (114 lesions).

<table>
<thead>
<tr>
<th>Dose (Gy)/Number of fractions [BED${_{10}}$]</th>
<th>Number of lesions</th>
<th>Maximum tumor diameter (cm)</th>
<th>Mean [range]</th>
<th>§ (Mean Dose To GTV, Gy) [BED$_{10}$]</th>
<th>§ (Mean Dose To PTV, Gy) [BED$_{10}$]</th>
<th>Local Failures (LF)</th>
<th>Regional Failures (RF)</th>
<th>Distant Failures (DF)</th>
<th>LF + RF</th>
<th>LF + DF</th>
<th>RF + DF</th>
<th>LF + RF + DF</th>
</tr>
</thead>
<tbody>
<tr>
<td>60/3 [180]</td>
<td>31</td>
<td>2.5 [1-4.8]</td>
<td>70.63 [237]</td>
<td>68.03 [229]</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>54/3 [151.2]</td>
<td>20</td>
<td>3.4 [1-5.7]</td>
<td>67.41 [219]</td>
<td>63.22 [196]</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>48/4 [105.6]</td>
<td>43</td>
<td>1.8 [0.9-3.5]</td>
<td>60.24 [151]</td>
<td>56.23 [135]</td>
<td>2</td>
<td>0</td>
<td>7*</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>60/8 [105]</td>
<td>9</td>
<td>2.2 [1-3.3]</td>
<td>76.78 [150]</td>
<td>71.70 [136]</td>
<td>2</td>
<td>2**</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>50/10 [75]</td>
<td>11</td>
<td>3.6 [2-5.7]</td>
<td>57.69 [91]</td>
<td>56.07 [87]</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* One of the patients had two lesions (treated with 48 Gy/4 fr, and 54 Gy/3 fr). Only the lesion treated with 48Gy/4 fr was counted as DF.

** One of the patients had 1 lesion treated with 54 Gy/3 fr and 2 lesions treated with 60 Gy/ 8 fr. Only the lesion treated with 60GY/8 fr was counted as RF.

§ Mean value of the mean tumor dose treated with specific dose fractionation. As the dose prescribed to 60-90 % isodose covering PTV, target received higher dose than the prescription dose.

3.4 Patients and Pulmonary Lesions

There were 108 patients and 114 lesions (mean size 2.42 ± 1.14 cm). Four patients had two lesions treated and one patient had three lesions treated. In these cases the lesions were assumed to represent separate primary tumors. Of the four patients with two treated lesions, biopsies were performed on both lesions in one patient, one lesion in two patients and neither lesion in the fourth patient. In the patient with three treated lesions, only one was biopsied. Twenty-five patients had history of a previous lung cancer,
diagnosed on average, 4.9 years before the current SBRT (range: 0.14-14.7 years). Details of how this was treated are provided in table 3-3.

**Table 3-3**: Treatment characteristics of previous lung lesions in 25 patients with history of lung cancer

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Pneumonectomy</td>
</tr>
<tr>
<td>10</td>
<td>Lobectomy</td>
</tr>
<tr>
<td>5</td>
<td>Surgical excision *</td>
</tr>
<tr>
<td>3</td>
<td>Radiotherapy (with or without chemotherapy)</td>
</tr>
<tr>
<td>1</td>
<td>Combination of surgery, radiotherapy and chemotherapy</td>
</tr>
</tbody>
</table>

*The pathology report did not allow differentiation between a lobectomy and wedge resection*

Out of 108 patients, 80 patients (75.9%) had diagnostic pathology and 28 patients (24.1%) did not.

Whole-body FDG PET/CT scans were performed pre-SBRT in 91/114 lesions (79.8%). Seventy-one percent of lesions (81 lesions in 80 patients) had diagnostic pathology and 28.9% of lesions (33 lesions in 28 patients) did not. Of the 28 patients without a diagnostic biopsy, 13 patients had a previous history of lung cancer. The reasons for these patients not having tissue diagnosis are summarized in table 3-4. All lesions without diagnostic pathology were deemed highly suspicious for malignancy based on growth on serial CT images and/or increased FDG-uptake.

**Table 3-4**: Reasons for not having diagnostic tissue in 28 patients (33 lesions)

<table>
<thead>
<tr>
<th>Number of lesions</th>
<th>Reasons of not having biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Elevated risk of pneumothorax</td>
</tr>
<tr>
<td>18</td>
<td>Existence of diagnostic tissue from another primary lung lesion</td>
</tr>
<tr>
<td>5</td>
<td>Non-diagnostic sample</td>
</tr>
</tbody>
</table>
3.5 RESPONSE

3.5.1 Local Control

Early response assessment using RECIST criteria (Therasse, Arbuck et al. 2000) was based on the first scheduled CT scan, (which may have been the CT component of a PET/CT scan), typically at 3 month post SBRT, and the maximum response was based on the CT scan typically acquired 12 months post SBRT. At the early time point, complete response (CR) was seen in only 7% of evaluable lesions, and partial response (PR) in 68.4%, for an overall response rate (CR + PR) of 75.4%. At the time of maximum response there was a 30.5% complete response rate and 37.5% partial response rate, for an overall response rate of 68%. Stable disease (SD) was seen in 15% and progressive disease (PD) in 14%. Assessment of response was not possible in 3% of lesions because F/U scan was not available. After further evaluation of the 16 lesions initially categorized as progressive disease based on RECIST criteria, 10 lesions were felt to represent local failure for the following reasons: high PET uptake in 1 patient (SUV was 3.5, 1.7, and 7.0 pre-RT, 4 months post-RT and 10-months post-RT, respectively); slight increase in FDG-uptake in 1 patient (SUV was 1 and 1.5 at pre-RT and 3 months-post-RT, this failure was confirmed by surgery); biopsy in 3 patients (only one of these patients was candidate for salvage surgery); and presumed failure based on radiologic and clinical characteristics in 5 patients.

The other 6 lesions categorized as progressive disease on the basis of radiological RECIST criteria did not change further after a minimum of 1 year serial F/U scans and were therefore judged to represent mass-like post-SBRT fibrosis, as described in the literature (Takeda, Kunieda et al. 2008). The 10 local failures occurred in patients with (n=6) and without (n=4) an initial biopsy-proven diagnosis. Most of the local failures were in patients treated with 50Gy/10 fr (n =5), and 60Gy/8 fr (n = 2).
In all lesions, 1 year local control (LC) was 92% (95% CI: 86%-97%) and estimated 4 year LC was 89% (95% CI: 81%-96%). At 1 year, LC in lesions with biopsy proven NSCLC was 93% (95% CI: 87-98%) and in the non-biopsy proven group it was 87% (95% CI: 76-99%). This was not statistically different (Gray’s test P value: 0.41).

Overall, there was no significant difference in cause specific survival (CSS) or overall survival (OS) between patients treated with 54 or 60Gy/3 fr and those treated with 48 Gy/4 fr.

3.5.2 Patient Outcomes

Overall, 63/108 patients were alive at last follow-up and the estimated 1 year and 4 year OS rates were 84% (95% CI: 76-90%), and 30% (95% CI: 15-46%) respectively. The estimated 1-year and 4 year cause specific survival (CSS) was 92% (95% CI: 87-98%) and 77% (95% CI: 64-89%) respectively (Fig 3-1).

**Figure 3-1:** Overall Survival (OS) and Cause specific survival (CSS) in 108 patients with early stage NSCLC treated with SBRT
Forty-five patients died; 28 patients of causes unrelated to lung cancer including cardiopulmonary events (n=18), metastatic disease from a different primary tumor (n=6) and unrelated causes such as bowel obstruction (n=2), and stroke (n=2). There was no death related to SBRT toxicities.

A total of thirty-eight failures were detected in 31 patients: 10 were local failures (LF), 11 regional failures (RF) and 17 distant failures (DF) as illustrated in Fig 3-2.

**Figure 3-2:** Patterns of failure for the entire cohort (108 patients, 31 failures)

![Patterns of failure](image)

Kaplan Meier estimates of disease-free survival at 4 years for LF, RF and DF were 89% (95% CI: 75- 96%), 87% (95% CI: 82- 98%), and 83% (95% CI: 66- 88%) (Fig 2-3).
There was no statistically significant difference in failure-free survival between patients with or without diagnostic pathology (P value < 0.5).

Similarly there was no significant difference in OS and CSS between these two groups of patients (Fig 3-4 and 3-5).
Figure 3-4: KM estimation for overall survival in patients with diagnostic pathology (n=80) and non-biopsied lesions (n=28)

P value: 0.38

Patients at risk
No biopsy: N: 20  N: 10  N: 0  N: 0

Time (year)

Probability of survival
Even when excluding patients with a history of lung cancer and patients with multiple lesions, the differences in OS and CSS in the group of patients with and without diagnostic pathology remained insignificant.

In order to assess the factors affecting overall survival several clinical and dosimetric factors were studied using univariate analysis, including age, gender, tumor size, dose and the presence of diagnostic tissue. Only tumor size, gender and dose were significant. On multivariate analysis, the only factors that remained significant were dose and female gender.
3.5.3 Toxicity

The majority of patients tolerated the treatment very well. Of 108 patients, 29% denied any acute and 31% denied any late toxicity. The most common acute toxicity was fatigue, which occurred in 50% of patients (Table 3-5).

Table 3-5: Acute and late toxicities in 108 patients
(77 patients had acute toxicities and 74 patients had late toxicities)

<table>
<thead>
<tr>
<th>Acute Toxicity</th>
<th>Grade</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>43</td>
<td>10</td>
</tr>
<tr>
<td>Cough and/or Shortness of breath†</td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Chest wall pain</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Dyspepsia/dysphagia†</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Skin toxicity</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>102</td>
<td>31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Late Toxicity</th>
<th>Grade</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>Cough and/or Shortness of breath†</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Chest wall pain</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Rib fracture</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Skin toxicity</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>96</td>
<td>54</td>
</tr>
</tbody>
</table>

†each symptom was scored separately (e.g.; individual patient may have several symptoms).
* 9 grade 3 rib fractures in 3 patients
Four patients had grade 3 early toxicities (within 3 months of radiotherapy) including one patient with fatigue, two with dyspnea and one with chest wall pain.

Late toxicities (beyond 3 months after SBRT) were primarily respiratory and fatigue-related. Rib fractures were detected in 16 patients (14.8 %) and were mostly asymptomatic. Six patients had grade 3 late toxicities (3 rib fractures, two dyspnea and one pneumonia). There were no grade 4 or 5 toxicities.

3.6 DISCUSSION

Stereotactic body radiation therapy has evolved from an innovative research protocol to an accepted standard of care for medically inoperable patients with early stage lung cancer, with reported local control in the range of 80% - 98% (Onishi, Kuriyama et al. 2004; Nagata, Takayama et al. 2005; Nyman, Johansson et al. 2006; Dahele, Brade et al. 2009).

In our cohort, the estimated local control is 89% at 4 years, which is consistent with reported data. The importance of dose in local control of NSCLC is well documented (Kim, Ahn et al. ; Kong, Ten Haken et al. 2005).

We found that half of the local failures (5/10) occurred in patients treated with 50 Gy/10 fractions, which with a BED$_{10}$ of 75 is well below the suggested threshold dose of 100 (Onishi, Araki et al. 2004), and no local failures were observed in patients treated with 60Gy in 3 fractions. Of note, CT changes after SBRT may be hard to interpret (Takeda, Kunieda et al. 2008), and 6/16 lesions that met RECIST criteria for progressive disease (thus suspected of representing possible local failure) were subsequently found to be stable for at least a year of follow-up. These were therefore attributed to post-SBRT radiation fibrosis.
Biopsies may be non-diagnostic or have sampling errors, and PET scans may lead to false positive findings (Matsuo, Nakamoto et al. 2010). This is something that needs to be borne in mind as lung SBRT becomes more widely practiced, and if it is considered in borderline operable patients. Improved methods of response evaluation (Dahele, Freeman et al. 2011), and ongoing follow up are needed if surgical salvage is a consideration. Despite excellent local control, the estimated 4 year OS remains low - 30% at 4 years. Deaths were more likely due to causes unrelated to lung cancer. This likely reflects significant comorbidities in this elderly cohort. Univariate analysis demonstrated that tumor volume, gender and SBRT dose were variables associated with overall survival; on multivariate analysis, only female gender ($p = 0.02$) and dose ($p <0.001$) remained significant.

Although treatment was well tolerated in this elderly population, the rate of rib fractures was higher than often reported. Most of these fractures were associated with mild to moderate symptoms and the detection rate was attributed to the study methodology, which included rigorous evaluation of the ribs during review of CT scan images (Taremi, Hope et al. 2012).

The attributes of this study include prospective collection, standardized follow up with rigorous toxicity and outcome evaluation, and a longer follow up period than has often been reported. In addition, most patients underwent staging with PET/CT, and attempts were made where possible to obtain diagnostic tissue from pulmonary nodules. Nonetheless, despite these efforts, histological confirmation was not available in 33/114 lesions (in 30 out of these 33 instances, lesions were evaluated with a pre-SBRT PET scan). Patient selection including rigorous pre-radiotherapy staging investigations are the cornerstone to identifying patients most likely to benefit from the treatment (Christie, Pennathur et al. 2008). Obtaining diagnostic tissue before treatment is important but biopsy is not without risk and patients with severe emphysema or COPD may not tolerate even a minor pneumothorax (Yeow, See et al. 2001). Furthermore,
biopsy may not provide accurate diagnostic information, due to inadequate sampling (false negative) (Winning, McIvor et al. 1986).

Additional diagnostic tools such as FDG PET/CT scanning may help in determining whether a nodule is at high-risk for malignancy. Whole body FDG PET/CT scan is also a valuable staging tool for NSCLC (Fletcher 2002; Abe, Baba et al. 2009; Li, Wu et al. 2009), with sensitivity of 95% and specificity of 80% respectively (Gould, Maclean et al. 2001) (Rodriguez Fernandez, Gomez Rio et al. 2007). The outcome of radically treating suspicious pulmonary nodules without definitive diagnosis has been reported in a number of series (Fritz, Kraus et al. 2008; Dahele, Brade et al. 2009). Inoue et al reported 3 and 5 year OS for 115 patients with suspected NSCLC but no diagnostic tissue, treated with SBRT (median follow up was 14 months) (Inoue, Shimizu et al. 2009). Patients with tumor size < 2 cm had 3 and 5 year OS of 89.8%, whereas patients with tumors larger than 2 cm had lower OS (60.7 % and 53.1% respectively).

We found no difference in OS or CSS between patients with and without cytological proof of malignancy, suggesting that our approach to selecting patients for SBRT, with multi-modality evaluation, can result in a safe and effective treatment. Given that the subsequent clinical course in the presumed NSCLC patient group is comparable to the proven NSCLC group, and that the treatment was associated with acceptable toxicity, SBRT likely offers these patients the best chance of local control and survival. However, the number of patients in the biopsy vs. no-biopsy group was uneven, limiting the ability to compare outcomes; this study was not specifically designed to prospectively evaluate the difference between these two patient groups. Additional patient data (e.g. pooled multi-institutional data) will therefore be helpful to confirm the results of this sub-group evaluation.

Other potential limitations of our study include a relatively low number of events, in particular local failures, aforementioned challenges of documenting local failure in patients who may not be appropriate for invasive
procedures, competing risks of death, difficulties accurately ascertaining the cause of death, and determining whether a new lung lesion is a distant metastases or a metachronous primary tumor. These limitations are not limited to our series, and they will continue to pose challenges to investigators in the field of lung SBRT.

2.7 CONCLUSION

In conclusion, the present study demonstrates promising local control, CSS, and toxicity profile for medically inoperable patients with biopsy-confirmed or clinically suspicious early-stage NSCLC treated with SBRT. Selected patients without a tissue diagnosis, who have progressive pulmonary nodules on serial imaging or high-risk nodules by other criteria, may be considered for SBRT with the anticipation of similar outcomes to patients with biopsy proven disease.
CHAPTER 4
PREDICTORS OF RADIOTHERAPY INDUCED BONE INJURY (RIBI) AFTER STEREOTACTIC LUNG RADIOTHERAPY

Radiation Oncology. 2012 Sep 17; 7:159; doi: 10.1186/1748-717X-7-159
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Conflict of interest notification: This study was supported in part by Elekta Oncology Systems.
ABSTRACT

Background: The purpose of this study was to identify clinical and dosimetric factors associated with radiotherapy induced bone injury (RIBI) following stereotactic lung radiotherapy.

Methods: Inoperable patients with early stage non-small cell lung cancer, treated with SBRT, who received 54 or 60 Gy in 3 fractions, and had a minimum of 6 months follow up were reviewed. Archived treatment plans were retrieved, ribs delineated individually and treatment plans re-computed using heterogeneity correction. Clinical and dosimetric factors were evaluated for their association with rib fracture using logistic regression analysis; a dose-event curve and nomogram were created.

Results: 46 consecutive patients treated between Oct 2004 and Dec 2008 with median follow-up 25 months (m) (range 6 – 51m) were eligible. 41 fractured ribs were detected in 17 patients; median time to fracture was 21m (range 7 – 40m). The mean maximum point dose in non-fractured ribs (n=1054) was 10.5 Gy ± 10.2 Gy, this was higher in fractured ribs (n=41) 48.5 Gy ± 24.3 Gy (p < 0.0001). On univariate analysis, age, dose to 0.5 cc of the ribs (D_{0.5}), and the volume of the rib receiving at least 25 Gy (V_{25}) were significantly associated with RIBI. As D_{0.5} and V_{25} were cross-correlated (Spearman correlation coefficient: 0.57, p < 0.001), we selected D_{0.5} as a representative dose parameter. On multivariate analysis, age (odds ratio: 1.121, 95% CI: 1.04 – 1.21, p = 0.003), female gender (odds ratio: 4.43, 95% CI: 1.68 – 11.68, p = 0.003), and rib D_{0.5} (odds ratio: 1.0009, 95% CI: 1.0007 – 1.001, p < 0.0001) were significantly associated with rib fracture.
Using $D_{0.5}$, a dose-event curve was constructed estimating risk of fracture from dose at the median follow-up of 25 months after treatment. In our cohort, a 50% risk of rib fracture was associated with a $D_{0.5}$ of 60 Gy.

**Conclusions:** Dosimetric and clinical factors contribute to risk of RIBI and both should be included when modeling risk of toxicity. A nomogram is presented using $D_{0.5}$, age, and female gender to estimate risk of RIBI following SBRT. This requires validation.
4.1 BACKGROUND

SBRT has superior local tumor control when compared to conventionally fractionated radiotherapy (Timmerman, Paulus et al. 2010). However due to the large doses per fraction, the risk of late normal tissue toxicities such as radiation induced bone injury (RIBI) may be increased (Onimaru, Shirato et al. 2003). Rib fracture following SBRT has been reported by a number of groups (Pettersson, Nyman et al. 2009; Voroney, Hope et al. 2009; Dunlap, Cai et al. 2010), including our own (Voroney, Hope et al. 2009). We previously found that out of 42 patients treated with 54 or 60 Gy in 3 fractions, 9 patients developed a total of 15 fractured ribs after a median follow-up of 17 months. The median radiation dose to the fractured rib was 50.1 Gy. The current report explores in detail the relationship of rib dose to subsequent rib fractures risk in a larger group with longer follow up. The primary objective of this study was to identify dosimetric and clinical risk factors for RIBI. The secondary objective was to generate a nomogram estimating risk of rib fracture from these factors.

4.2 METHODS

From Oct 2004 to Dec 2008, 127 medically inoperable patients with T1-2N0M0 non-small cell lung carcinoma (NSCLC) were treated on a prospective institutional research ethics board-approved lung SBRT protocol at Princess Margaret Hospital. Patients were treated with several dose fractionation schedules: 5 Gy x 10 fractions (n = 12), or 7.5 Gy x 8 fr (n = 10) for centrally located tumors, and for peripheral tumors 12 Gy x 4 fr (n = 52), 18Gy or 20 Gy (the latter was used prior to heterogeneity correction) x 3 fr (n = 53) (Taremi, Hope et al. 2011). Ribs or chest wall were not considered as organ at risk and therefore were not contoured. Post-treatment, the follow up schedule included clinic visits and thoracic imaging - chest x-ray 6 weeks after SBRT and chest CT scan at 3, 6, 9 and 12 months, every 6 months in the second year and yearly thereafter. The Common Terminology Criteria for Adverse Events (CTCAE) v3.0 was used to score
acute and late toxicity (Trotti, Colevas et al. 2003). A subset of consecutive patients treated with 18 or 20 Gy x 3 fractions and with more than 6 months follow up was selected for this study as we had previously observed rib fractures in this group and we had not observed fractured ribs with other schedules such as 48 Gy in 4 fractions or 50 Gy in 10 fractions.

### 4.2.1 Detecting Fractured Ribs

Because the radiology reports inconsistently reported fractured ribs and some rib fractures are known to be asymptomatic (Voroney, Hope et al. 2009), identification of RIBI was systematically performed in three steps: 1) abstracting information from serial imaging reports, 2) review of all serial follow up imaging by two independent observers (a radiation oncology fellow and a radiology fellow). Any cases with discrepancy were discussed to obtain agreement, 3) 20% of all RIBI events were reviewed randomly by a staff radiologist resulting in 100% agreement on the fracture site and 88% agreement on the fracture date (defined as the date that the first sign of periosteal distortion was observed). In the cases with date discrepancy, the radiologist detected the fractured ribs on the scan performed 6 months earlier. Grading of rib fractures was performed using the radiological as well as clinical prospectively collected toxicity data, as per CTCAE v3.0 (Trotti, Colevas et al. 2003), rib fractures were graded radiologically and clinically from prospective toxicity data (Table 4-1).
Table 4-1: Common Toxicity Criteria for Adverse Events v3.0 (CTCAE) for fracture and pain

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture</td>
<td>Asymptomatic, Radiologic findings only</td>
<td>Symptomatic but non-displaced</td>
<td>Symptomatic and displaced or open wound with bone exposure</td>
<td>Disabling</td>
<td>-</td>
</tr>
<tr>
<td>Pain</td>
<td>Mild pain not interfering with function</td>
<td>Moderate pain, Pain or analgesics interfering with function but not interfering with ADL</td>
<td>Sever pain, pain or analgesics severely interfering with ADL</td>
<td>Disabling</td>
<td>-</td>
</tr>
</tbody>
</table>

4.2.2 Dosimetric Evaluation

To obtain dosimetric rib data, each rib was individually contoured on the primary CT data set used for SBRT treatment planning. Ribs were delineated from the costovertebral to the costosternal/costocartilage area bilaterally, using threshold contouring tools (1080 to 2400 HU) and with manual review and correction in the radiation treatment planning system (Pinnacle, v8.0, Philips Medical Systems, Fitchburg, WI, USA). A representative diagnostic CT scan showing the fractured rib(s) for each patient with RIBI was registered to the treatment planning CT scan using the fractured rib as the region of interest for image fusion. The fracture site was contoured by a single observer (MT) and 3D CT registration information (x, y and z) for each fractured rib and callus were documented for quality assurance (QA) purposes. A staff radiation oncologist reviewed and approved a subset of the contoured fractures with high levels of agreement. It is important to note that although the analysis was performed using the maximum point dose to the ribs, in 37 fractures (12 patients) this was not the same as the maximum dose to the fracture site. The most likely explanation was considered to be contouring subjectivity and difficulty in determining the exact fracture site boundaries.
The dose calculation grid (resolution of 0.25cm x 0.25cm x 0.25cm) was adjusted in all patients to cover all ribs and each SBRT plan was re-computed with heterogeneity correction (Davidson, Ibbott et al. 2007) while maintaining the planned monitor units.

Resulting planning data was exported using the RTOG format and the dosimetric information extracted using CERR (Computational Environment for Radiotherapy Research) (Deasy, Blanco et al. 2003).

### 4.2.3 Data collection and analysis

Clinical patient data was extracted from the prospectively collected institutional SBRT database. This included: age, sex, comorbidities (chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM)), number/location/date of fractured ribs, history of traumatic rib fractures, tumor size, date of SBRT treatment, date of last follow up or death and a history of cancer metastasis to the bone.

Dosimetric data extracted from the re-computed plans and dose volume histogram (DVH) included: rib $D_V$ (minimum absolute dose received by volume $V$), ribs $V_D$ (absolute volume receiving at least dose $D$), maximum/mean/median point dose to the ribs, GTV (gross tumor volume), the minimum 3D distance between the GTV and any rib, the minimum 3D distance between the GTV and any fractured ribs, and cumulative dose-volume histogram (DVH) for each individual rib.

The correlation between dose and volume was examined using the Spearman correlation. Univariate logistic regression was used to test the association of various predictors with the risk of fracture. Since each patient could have multiple fractures, spearman repeated measures have been taken into consideration.
A modified stepwise model fitting process was used to select the best fit multivariate model. Maximum likelihood estimation was used to select thresholds for dose and volume. All analyses were performed using SAS v9.1 for Windows TM and all reported p-values were 2-sided, a p-value of < 0.05 was considered significant. Using the multivariate model, a nomogram was generated and its receiver operating characteristic (ROC) calculated to assess its discrimination power.

A final logistic model was generated estimating RIBI risk at a median follow up of 25 month based on the ‘all rib’ analysis.

Probability of fracture:

\[ P = \frac{1}{1+e^{-(a+bX)}} \]

\( P \) is the probability of a fracture (1), \( e \) is the base of the natural logarithm (about 2.7); \( a \) and \( b \) are the parameters of the model. The value of \( a \) yields \( P \) when \( X \) is zero, and \( b \) adjusts how quickly the probability changes with changing \( X \).

### 4.3 RESULTS

#### 4.3.1 Patient Characteristics

From Oct 2004 to Dec 2008, 48 consecutive patients treated with 18 or 20 Gy x 3 fractions and followed for > 6 months, two were excluded from this analysis - one had rib fracture at baseline, pre-SBRT, the other had rib fracture associated with a bone metastasis. Thus, 46 patients with 49 tumors (3 patients had 2 tumors) were analyzed. Median age was 73 years (range: 48 to 89 years) and median follow up was 25 months (range: 6 to 51m). There were 22 male and 24 female patients with similar median age (73 year) but median follow-up was slightly higher in female group (26.2 vs. 22.7 months) as shown in Table 4-2.
### Table 4-2: Clinical factors in 46 patients treated with lung SBRT

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>46</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td><strong>Median Age (year) (range)</strong></td>
<td>72.8 (48.3-89.6)</td>
<td>72.6 (58-89.6)</td>
<td>72.8 (48.3-85.5)</td>
</tr>
<tr>
<td><strong>Median follow up time (Months) (range)</strong></td>
<td>24.9 (6-51.2)</td>
<td>26.2 (6-51.2)</td>
<td>22.7 (7.6-48.5)</td>
</tr>
<tr>
<td><strong>Number of patients with rib fracture</strong></td>
<td>17</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td><strong>Number of fractured sites</strong></td>
<td>43</td>
<td>30</td>
<td>13</td>
</tr>
<tr>
<td><strong>8 pts with DM</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with no fracture</td>
<td>6</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Patients with fracture</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>29 pts COPD</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with no fracture</td>
<td>18</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Patients with fracture</td>
<td>11</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td><strong>Mean (± SD) Tumor size (cm)</strong></td>
<td>2.6 ± 1.2</td>
<td>2.7 ± 1.2</td>
<td>2.6 ± 1.2</td>
</tr>
<tr>
<td><strong>Closest 3-D distance from tumor to the ribs (cm) (range)</strong></td>
<td>0.96 (0 – 3.28)</td>
<td>1.01 (0 – 3.28)</td>
<td>0.88 (0 – 2.76)</td>
</tr>
</tbody>
</table>

*DM: Diabetes Mellitus, ** COPD: Chronic Obstructive Pulmonary Disease

17 of 46 patients (37%) were identified as having developed rib fractures with a total of 41 fractured ribs and 43 fracture sites. Of 17 patients with fractured ribs, 11 (with 30 fractures) were female and 6 (with 13 fractures) were male (Table 4-3).

Anatomic locations of fractured ribs are shown in Figure 4-1. Median time to development of a fractured rib was 21 months (range: 7 - 40m) as shown in Figure 4-2.
**Figure 4-1**: Anatomic locations of 41 fractured ribs in 17 patients with RIBI

*Rib cage photo modified from Gray's anatomy of the human body*

**Figure 4-2**: Kaplan Meier curve for fractured rib as an event (n= 46 patients)

In patients with multiple rib fractures, the fracture sites were in proximity to each other (Table 4-3). Two patients had bilateral fractured ribs however the dose to the fractured ribs was so low in one of these
patients (pt # 9 in table 4-3) that radiotherapy cannot be considered the primary risk factor. In such cases other clinical factors may play the more important role.

Thirteen of 17 patients with rib fracture had at least two fractured sites. Detailed dosimetric information for each fractured rib and the callus in 17 patients with rib fracture has been summarized in table 4-3.
Table 4-3: Max point dose to the callus in 17 patients with rib fractures (43 calluses in 41 fractured ribs) has been shown. Max point dose to the fractured rib was not located on the callus in 14/17 patients.

<table>
<thead>
<tr>
<th>Patients N = 17</th>
<th>Number of rib fractures N = 41</th>
<th>Callus N = 43</th>
<th>Callus max point dose (Gy)</th>
<th>Highest max Point dose to fractured rib (Gy)</th>
<th>Highest max point dose to callus (Gy)</th>
<th>Lowest max point dose to fractured rib (Gy)</th>
<th>*Mean dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td>Lt rib 5 68.52</td>
<td>Lt rib 5 68.52</td>
<td>Lt rib 6 61.85</td>
<td>65.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lt rib 6 62.40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td></td>
<td></td>
<td>Lt rib 5 76.39</td>
<td>Rt rib 5 73.6</td>
<td>Rt rib 5 6.80</td>
<td>41.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lt rib 6 73.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lt rib 10  7.58</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lt rib 11  1.16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
<td>Lt rib 3 64.63</td>
<td>Rt rib 4 61.54</td>
<td>Rt rib 4 23.15</td>
<td>43.89</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Lt rib 4 61.45</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
<td>Lt rib 3 88.05</td>
<td>Rt rib 6 87.91</td>
<td>Rt rib 4 13.17</td>
<td>50.61</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Lt rib 4 24.07</td>
<td></td>
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<td>Lt rib 4 13.17</td>
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<td>Lt rib 5 68.39</td>
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<td></td>
<td></td>
<td>Rt rib 6 87.91</td>
<td></td>
<td></td>
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<td>5</td>
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<td></td>
<td>Lt rib 4 50.10</td>
<td>48.54</td>
<td>48.54</td>
<td>49.32</td>
</tr>
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<td>6</td>
<td>2</td>
<td>Rt rib 5 59.56</td>
<td></td>
<td>Rt rib 4 59.56</td>
<td>29.76</td>
<td>29.76</td>
<td>42.29</td>
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<td></td>
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<td></td>
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<td>Rt rib 5 25.03</td>
<td></td>
<td></td>
<td></td>
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<td>7</td>
<td>2</td>
<td>Rt rib 3 69.36</td>
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<td>Rt rib 3 58.79</td>
<td>49.05</td>
<td>49.05</td>
<td>59.20</td>
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<td>Rt rib 4 58.79</td>
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<td>Rt rib 4 49.5</td>
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<td></td>
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<tr>
<td>8</td>
<td>1</td>
<td>Rt rib 5 35.12</td>
<td></td>
<td>Lt rib 7 35.84</td>
<td>35.12</td>
<td>35.12</td>
<td>35.48</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td></td>
<td></td>
<td>Lt rib 7 21.82</td>
<td>0.7</td>
<td>0.45</td>
<td>11.26</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>Lt rib 7</td>
<td>0.48</td>
<td>71.39</td>
<td>Rt rib 3</td>
<td>70.84</td>
<td>23.37</td>
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<td></td>
<td></td>
<td>Rt rib 2</td>
<td>23.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rt rib 3</td>
<td>70.84</td>
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<tr>
<td>11</td>
<td>4</td>
<td>Lt rib 5</td>
<td>68.39</td>
<td>75.34</td>
<td>Lt rib 6</td>
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<td></td>
<td></td>
<td>Lt rib 7</td>
<td>48.85</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Lt rib 8</td>
<td>3.25</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>12</td>
<td>3</td>
<td>Rt rib 4</td>
<td>69.86</td>
<td>69.86</td>
<td>Rt rib 4</td>
<td>69.86</td>
<td>10.64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rt rib 5</td>
<td>10.64</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Rt rib 6</td>
<td>68.37</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Lt rib 6</td>
<td>62.03</td>
<td></td>
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<td></td>
<td></td>
<td>Lt rib6</td>
<td>12.16</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Lt rib 7</td>
<td>66.40</td>
<td></td>
<td></td>
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<td>13</td>
<td>2</td>
<td>Lt rib 8</td>
<td>44.04</td>
<td>50.38</td>
<td>Lt rib 9</td>
<td>50.38</td>
<td>44.04</td>
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<tr>
<td></td>
<td></td>
<td>Lt rib 9</td>
<td>50.38</td>
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<td>14</td>
<td>2</td>
<td>Lt rib 10</td>
<td>44.04</td>
<td>50.38</td>
<td>Lt rib 10</td>
<td>50.38</td>
<td>44.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lt rib 9</td>
<td>50.38</td>
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<td>15</td>
<td>3</td>
<td>Rt rib 5</td>
<td>23.46</td>
<td>72.44</td>
<td>Lt rib 7</td>
<td>69.07</td>
<td>23.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lt rib 7</td>
<td>69.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lt rib 8</td>
<td>66.96</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>Rt rib 11</td>
<td>0.10</td>
<td>0.56</td>
<td>0.1</td>
<td>0.10</td>
<td>0.33</td>
</tr>
<tr>
<td>17</td>
<td>1</td>
<td>Rt rib 5</td>
<td>44.07</td>
<td>64.18</td>
<td>44.07</td>
<td>44.07</td>
<td>54.12</td>
</tr>
</tbody>
</table>

* Mean dose is the average of the lowest and highest maximum point doses to the fractured rib(s)

Of patients identified with fractures, the original radiologic reports did not report fracture in 3 out of 17 patients (18%). In those patients in whom rib fractures were reported, the number and first reported date of fracture were incomplete. Overall, a total of 15 out of 41 rib fractures (37%) were not noted in the original
report and the first date of reported fracture was on average 5 months (range: 0 to 18m) later than was detected in this study.

Clinical (chest wall pain) and radiologic (rib fracture) toxicities are shown in figure 4-3. Chest wall pain was detected in 7/29 patients (24%) without rib fracture and in 14/17 patients (82%) with rib fractures.

Figure 4-3: Grading of chest wall pain (n = 21 patients with reports of chest wall pain >0) and rib fractures (n = 17 patients, 43 fractures) based on CTCAE criteria

Patients with chest wall pain received higher dose of radiation to the ribs compared to patients without chest wall pain (62.76 Gy, range: 28.4-88.05 Gy vs. 47.21 Gy, range: 15.9-73.19 Gy; p value: 0.008) (Table 4-4).
Table 4-4: Mean Maximum point dose to the ribs in patients with or without chest wall pain

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of pts</th>
<th>Mean Maximum Point Dose (Gy) (range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with chest wall pain</td>
<td>21</td>
<td>62.76 (28.4-88.05)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Patients without chest wall pain</td>
<td>25</td>
<td>47.21 (15.9-73.19)</td>
<td></td>
</tr>
</tbody>
</table>

*Wilcoxon-Mann-Whitney test was used to obtained the p-value

4.4 Dosimetric Factors:

After re-contouring, 1095 ribs were available for analysis; in some patients some of the whole ribs could not be contoured because they were not fully included in the planning CT scan images (less than 5% in ribs 1 and 2 but more than 50% in ribs 11 and 12).

All individual fracture sites were contoured separately however in the majority of cases (37 fracture sites in 12 patients) the maximum dose to the fracture site was not the maximum dose to the fractured rib therefore as mentioned above the analysis was performed using the maximum point dose to the ribs.

Analyzing per patient, using the maximum dose received by any rib in each patient, a significant difference (p = 0.02) was noted between 29 patients with no rib fracture (50.2 Gy ± 17.7 Gy, range: 21.6 to 73.2 Gy) vs. 17 patients with rib fracture (63.7 Gy ± 15.3 Gy, range: 26.6 to 88 Gy). There was no significant difference (p = 0.09) between the mean maximum dose to the first fractured rib (52 Gy +/-24.9 Gy, range: 3.9 - 76.4 Gy) compared to subsequent fractured ribs (50 Gy+-/- 19 Gy, range: 19.6 - 71.2 Gy).
Assuming each rib was independent, out of 1095 ribs, 41 had fractures and 1054 did not. In non-fractured ribs, the mean maximum point dose was $10.5 \text{ Gy} \pm 10.2 \text{ Gy}$ (range: 0.2 to 87 Gy) compared to $48.5 \text{ Gy} \pm 24.3 \text{ Gy}$ (range 0.6 to 88 Gy) in fractured ribs; this was statistically significantly different ($p < 0.001$).

While many dosimetric parameters were correlated with rib fracture, $D_{0.5}$ and $V_{25}$ appeared to have the highest individual correlations (Figure 4-4).

**Figure 4-4:** Maximum likelihood curve for fractured ribs

Dx: Absolute dose to a certain volume (0.5-10 cc) of the ribs

Vx: Absolute volume receiving certain dose (15-50 Gy) of the ribs

To evaluate the impact of including ribs receiving very low dose of radiotherapy on correlations, ribs receiving less than 1, 5, 10, 15, 20 and 25 Gy were excluded sequentially from the profile-likelihood modeling process. Both $D_{0.5}$ and $V_{25}$ were well correlated in all sub-groups. As $D_{0.5}$ and $V_{25}$ were cross-correlated (Spearman correlation coefficient: 0.57, $p < 0.001$), we selected $D_{0.5}$ as a representative dose parameter that could be included in subsequent modeling efforts. Using $D_{0.5}$, a dose-event curve was constructed estimating risk of fracture from dose at the median follow up of 25 months after treatment (Figure 4-5).
Figure 4-5.a: D0.5 for patients with fractured ribs ( ▲ ) and without fractured ribs ( ◦ ); calculated probability of fracture at the median follow up of 25 months based on D0.5.

Figure 4-5.b: Distribution of 17 patients with fractured rib per D0.5 dose groups (10 Gy bin size), and calculated probability of fracture
4.5 Combining Clinical and Dosimetric Factors:

On univariate analysis, correlations with RIBI were found with age (p=0.045), but not with gender, COPD or diabetes. In terms of dosimetric factors, all $D_x$ and $V_x$ were significant on univariate analysis, as discussed above; $D_{0.5}$ was used for multivariate analysis.

On multivariate analysis, age (p = 0.003), female gender (p = 0.003) and rib $D_{0.5}$ (p <0.0001) were variables that were significantly associated with RIBI (Table 4-5).
Table 4-5: Univariate and multivariate analysis on predictors for rib fractures (repeated measures have been taken into consideration).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.083</td>
<td>1.002 - 1.172</td>
<td>0.045</td>
</tr>
<tr>
<td>Gender-F</td>
<td>2.256</td>
<td>0.656 - 7.756</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes Mellitus-yes</td>
<td>0.51</td>
<td>0.091 - 2.876</td>
<td>0.45</td>
</tr>
<tr>
<td>COPD-yes</td>
<td>0.97</td>
<td>0.275 – 3.386</td>
<td>0.96</td>
</tr>
<tr>
<td>Tumor size</td>
<td>1.037</td>
<td>0.982 -1.095</td>
<td>0.19</td>
</tr>
<tr>
<td>Smallest 3D distance between the tumor and closest rib</td>
<td>0.408</td>
<td>0.152 – 10.970</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Multivariate Analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>6 % CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>1.121</td>
<td>1.04 – 1.21</td>
<td>0.003</td>
</tr>
<tr>
<td>Gender-F</td>
<td>4.43</td>
<td>1.68 – 11.68</td>
<td>0.003</td>
</tr>
<tr>
<td>D0.5</td>
<td>1.0009</td>
<td>1.0007 - 1.0011</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

A nomogram was generated based on this multivariate model. The nomogram estimates risk of RIBI at 25 months median follow up in our cohort of patients (Figure 4-6) based on pre-treatment factors including age, gender and D0.5.

Figure 4-6: RIBI nomogram based on gender, age and D0.5 in 46 patients treated with SBRT at Princess Margaret hospital, estimating risk of rib fracture at median follow up of 25 month
A receiver operating characteristic (ROC) curve for the nomogram demonstrated an area under the curve (AUC) of 0.93.

4.6 DISCUSSION

Radiation induced bone injury (RIBI) has been reported as the radiotherapy toxicity in a number of studies (Onimaru, Shirato et al. 2003; Center, Bliuc et al. 2007; Pettersson, Nyman et al. 2009; Voroney, Hope et al. 2009; Lundstedt, Gustafsson et al. 2010; Monticciolo, Sincleair et al. 2010; Soliman, Cheung et al. 2011; Stephans, Djemil et al. 2011; Taremi, Hope et al. 2011). The incidence of RIBI in patients treated with lung SBRT has been variably reported as ranging from 0% to more than 50% (Hepel, Tokita et al. 2009; Voroney, Hope et al. 2009; Dunlap, Cai et al. 2010). The variability may be due to differences in treatment technique and dose-fractionation, reported outcomes, selection criteria, follow up procedures, whether or not available radiography was reviewed specifically for rib fractures, and the process of analysis. For example, Pettersson et al. (Pettersson, Nyman et al. 2009) analyzed the planning information of 33 patients treated with 45 Gy in 3 fractions. With a median follow up of 29 months, 13 fractured ribs were identified in 7 patients. They estimated that delivering 49.8 Gy to 2 cm$^3$ ($D_2$) of ribs was associated with a 50% risk of fracture. In this study ribs receiving less than 21 Gy were excluded. In our study the value of $D_{0.5}$ had the maximum likelihood (MLL) value; however we included all the ribs in our analysis. To evaluate the impact of including the ribs receiving low dose RT, we repeated the MLL curves excluding the ribs receiving <25 Gy in a stepwise process however, the value of $D_{0.5}$ remained the significant MLL cut point. In our cohort, a 50% risk of rib fracture was associated with a $D_{0.5}$ of 60 Gy.
This was consistent with data from Stephans et al. (Stephans, Djemil et al. 2011) who found that in 45 patients treated with 60 Gy in 3 fractions there was no chest wall toxicity observed with a minimum absolute chest wall point dose of less than 67.5 Gy.

Similar findings have been reported by Nambu et al. (Nambu, Onishi et al. 2011). In this study with a median follow up of 33 months, RIBI was observed in 41 (23.2%) patients. BED calculation with $\alpha/\beta$ ratio of 3 was used for dose comparison. There was no rib fracture observed in patients in whom the maximum point dose to the chest wall was less than 218 BED (approximately equal to 40 Gy in 3 fractions) but rib fracture was considered “inevitable” when the BED was more than 250 Gy. Although there is controversy surrounding the use of the LQ model in SBRT (Park, Papiez et al. 2008; Wang, Huang et al. 2010) this data supports a dose-response relationship for rib fracture. Explanations for Pettersson et al (Pettersson, Nyman et al. 2009) having a 50% risk of RIBI with lower SBRT doses could include confounding clinical variables, and the small sample size. The relationship between delivered dose to the ribs and the risk of fracture has also been studied by Chollet et al. (Chollet, Nagda et al. 2009) who found no rib fractures in 15 patients treated with 50 Gy in 5 fractions within the median FU of 13 months. Although a lower maximum point dose to the chest wall might be related to the lack of event in these patients, the potential risk for chest wall toxicity should be weighed carefully against the potential benefit of higher SBRT dose in terms of tumor control probability (Taremi, Dahele et al. 2009).

In our study, $D_{0.5}$ and other dosimetric parameters were all correlated with the risk of developing RIBI but inclusion of clinical variables, notably age and gender, improved the predictive model. We have created a nomogram based on these 3 dosimetric and clinical parameters. As an illustration (Figure 4-6), a 75 year old woman who received a planned dose of 50 Gy to 0.5 cc of a rib has an estimated 40% risk of RIBI
within the first two years of follow up. A man of the same age and with the same D0.5 would in contrast have about a 15% risk of RIBI.

Strengths of our study include the long median follow up time (25 months) and careful radiologic review. As RIBI is a late toxicity, to accurately assess event rate, it is important to follow these patients closely, not only with clinical exam but because many rib fractures are asymptomatic, also with serial CT scans. Initially, radiology reports did not always identify the presence of a new rib fracture. Fifteen fractured ribs were not reported and overall there was an average of 5 months latency in reporting fractured ribs. This highlights the importance of spreading knowledge in the radiology community about the pattern of late toxicity that can be seen with SBRT. Furthermore, to minimize potential sources of error, our group of patients was selected to be as homogenous as possible - all had more than 6 months follow up and all were treated with 54 or 60 Gy in 3 fractions. Additional strengths are: prospective data collection as part of REB-approved institutional protocol (Taremi, Hope et al. 2011), exclusion of patients with other causes of rib fractures such as bone metastases or trauma, standard contouring of ribs and planning, evaluating multiple different DVH values, and including clinical and dosimetric factors.

Symptomatic chest wall toxicity has been observed in patients with lung cancer treated with stereotactic radiotherapy (Baumann, Nyman et al. 2006; Lagerwaard, Haasbeek et al. 2008). Dunlap et al (Dunlap, Cai et al. 2010), reported chest wall pain in 20 and rib fracture in 5 out of 60 lung SBRT patients treated with various dose fractionation schedules. Their analysis only included those patients with tumors located within 2.5 cm of the chest wall or those whose maximum point dose to the chest wall exceeded 20 Gy. With median follow up of 11 months, they reported 30% risk of chest wall pain or rib fracture if 35cm$^3$ of the chest wall received more than 30 Gy. The fact that the ribs were not evaluated separately and the patients received several dose fractionation schedules makes it difficult to compare their results to the current study.
In our cohort, 14 patients with rib fracture had chest wall pain (in comparison to 7 patients without rib fracture). The majority of these cases had grade 1 or 2 chest wall pain however; there were 3 cases of grade 3 chest wall pain in the group of patients with rib fracture (Figure 4-3). Moreover ribs received statistically significant higher dose in patients with chest wall pain in comparison to ones without chest wall pain (Table 4-3). This justifies an attempt to reduce the dose to the ribs if and when possible. The dose constraints identified are most useful in situations where the tumor is sufficiently far away from ribs that planning and optimization efforts to reduce dose can be useful without decreasing tumor dose or increasing lung dose. Attention to radiation planning technique in order to limit hot spots/D0.5 in the chest wall and adjacent ribs, without compromising PTV coverage may be beneficial. Currently, it is our institutional policy to contour any ribs adjacent to the PTV and attempt to spare them without compromising PTV coverage. Advanced RT techniques such as VMAT and IMRT might also help with this. Our group has chosen to use the 48 Gy in 4 fraction schedule for tumors less than 3 cm that are immediately adjacent to the chest wall as we have not yet observed a high rate of fracture in this group while tumor control remains excellent.

Our study had a number of limitations. First, the study set was limited to patients with three fractions; it is unclear if the model derived will have similar correlations with RIBI in patients treated with different dose fractionations. Second, due to the small sample size and limited events, it was not possible to divide the data into training and testing sets to allow internal model validation. Therefore, our nomogram model requires subsequent validation on another dataset. Nevertheless, it may help to improve the general understanding of RIBI risk and to emphasize the need for clear discussion with potentially high-risk patient groups who are treated with SBRT. Third, the clinical factors explored in the current study were limited by data availability. There are other clinical factors that could potentially play a role in RIBI, such as cough, corticosteroid use, and presence of osteoporosis that should be explored in future investigations. In addition, the dosimetric study was based on rigid rather than deformable registration and on delivered
rather than received dose. Several factors may play a role in determining the actual dose received by the ribs such as variation in daily positioning and breathing motion. Assessment of cone-beam CT set up images in combination with deformable image registration and dose accumulation may help to identify the impact of these factors and suggest further risk reduction strategies.

4.7 Conclusions

Radiation oncologists, diagnostic radiologists and other specialists who see patients post SBRT, as well as patients themselves should be aware of and informed about the late toxicities related to lung SBRT, including rib fracture. Risk factors for RIBI include increasing age, female gender, and high RT dose to 0.5cc of nearby ribs. A nomogram incorporating these factors may be useful in estimating individual patient risk, though internal and external validation of this model is needed.
5.1 Evidence supporting SBRT

Stereotactic radiotherapy is an acceptable management for inoperable patients with early stage NSCLC (Timmerman, Park et al. 2007; Timmerman, Paulus et al. 2010; Timmerman 2010; Zimmermann, Wulf et al. 2010; Taremi, Hope et al. 2012). As mentioned in chapter 1, different techniques, planning process and radiation dose have been utilized in different centers. Based on the tumor (e.g. GTV size) and treatment factors (the radiotherapy dose/fractionation schedule), the reported local control varies from 75% to 95% (Onishi, Kuriyama et al. 2004; Baumann, Nyman et al. 2009; Olsen, Robinson et al. 2011; Onishi, Shirato et al. 2011).

Timmerman et al (Timmerman, Paulus et al. 2010) reported the results of stereotactic radiotherapy in 55 patients with biopsy proven NSCLC treated with 54 Gy in 3 fractions. All tumors were less than 5 cm in size and located peripherally (e.g. 2cm away from proximal airways). With the median FU of 34.4 months, 89% of tumors responded to radiotherapy either as complete or partial response (Therasse, Arbuck et al. 2000). The 3 year local control was 97.7% and 3 year OS 56%. Despite excellent local control, 22% of patients developed distant metastasis. The author reported of 8 cases with grade 3 musculoskeletal toxicities. But the detailed information was not provided. One of the explanations of the high local control in this group of patients is the large dose of radiotherapy per fraction, and centers treating patients with different dose fraction schedules reported somewhat different results.
Reported outcome from Princess Margaret Hospital (Taremi, Hope et al. 2012) is comparable to outcome reported by RTOG. For 108 consecutive inoperable patients with early stage NSCLC (114 lesions) who were treated with SBRT with various dose fractionations schedule (50 Gy in 10 fractions to 60 Gy in 3 fractions), the cause specific survival (CSS)/OS were 92/84% and 77/30% in 1 and 3 years respectively. The local control was 89% in 4 years, although only 1 of 51 lesions treated with 54-60 Gy in 3 fractions failed locally. Most failures were in the group of patients treated with 50 Gy in 10 fractions (5/11 lesions failed locally), in which the tumors were located more centrally near the midline structures (such as airways and esophagus). In some of these patients tumor coverage had to be compromised in order to safeguard the organs at risk. The mean dose to PTV (BED\textsubscript{10}) was 56.07 Gy. Despite the excellent overall local control OS was poor in this frail elderly population as the causes of death were attributed to the patients' comorbidities. In fact when treating operable patients with stereotactic radiotherapy, the outcome becomes comparable to the surgical approach. For example, Lagerwaard from the Netherlands (Lagerwaard, Verstegen et al. 2012) reported the outcome of 177 potentially operable patients that elected to have SBRT instead of surgical excision. The dose of SBRT was 60 Gy in 3 to 5 fractions. With a median follow up of 31.5 months, the median overall survival was 61.5 months, and 1-year and 3-year survival rates of 94.7% and 84.7%, respectively. Toxicity was mild, with grade ≥3 radiation pneumonitis and rib fractures in 2% and 3%, respectively. Five patients developed rib fractures, 2 of which were treated with 60 Gy in 3 fractions, 1/5 patients were treated with 60 Gy in 5 fractions and 2/5 patients were treated with 60 Gy in 8 fractions. Detailed dosimetric analysis for ribs/chest wall was not reported. The author concluded that the outcome of SBRT (3 year OS of 85%) was comparable with VATS procedure (87%) or open thoracotomy (82%) (Schuchert, Pettiford et al. 2009; Schuchert, Abbas et al. 2012).
Wedge resection was compared to SBRT in a study performed by Grills (Li, Galvin et al. 2012). One hundred twenty-four patients with early stage NSCLC (ineligible for anatomic lobectomy) underwent wedge resection (n = 69) or image-guided lung SBRT (n = 55). Patients treated with SBRT mostly were inoperable (95%) and only a small proportion refused surgery (5%). The dose of SBRT was either 48 (T1) or 60 (T2) Gy in four to five fractions. The results between the two arms were comparable. At 30 months, no significant differences were identified in regional recurrence, loco-regional recurrence, distant metastasis, or freedom from any failure (P > .16). SBRT reduced the risk of local recurrence (LR), 4% versus 20% for wedge (P = .07). Although the pathologic diagnosis is essential for the treatment of primary lung cancer, in some cases the diagnostic tissue is not available. This could be related to false negative results (Winning, McIvor et al. 1986), or risk of biopsy related toxicities such as pneumothorax (Yeow, Su et al. 2004). Interestingly the reported outcome and toxicities are similar in the group of patients with or without diagnostic pathologic sample. Inoue et al from Japan (Inoue, Shimizu et al. 2009) reported the outcome of 115 patients treated in 12 institutions in Japan within a period of 10 years. The 3 and 5 year OS were 90% in tumors < 2 cm. However the outcome was somewhat inferior in patients with larger tumor (> 2 cm) with 3 Y OS of 60% and 5 Y OS of 50%. Similarly in reported outcome from Princess Margaret cancer center (Taremi, Hope et al. 2012), there was no significant difference in failure free survival in patient with or without diagnostic pathologic findings.

5.2 Rib fracture as a late side effect of SBRT

Although using high dose radiotherapy in lung cancer is not a new concept (Onishi, Kuriyama et al. 2004), this technique started to be utilized worldwide since published data from North America (Timmerman, McGarry et al. 2006). Since then there have been several published papers from all around the world not only evaluating tumor outcomes, but also reporting potential toxicities. However as stereotactic-related
toxicities occur late (typically after 6 months), our knowledge about toxicities is yet to be completed. To assess the late side effects related to this technique, patients should be followed up for a long time. As mentioned in chapter 1, several toxicities related to SBRT have been reported such as dermatitis, chest wall pain, rib fracture, tiredness/fatigue, airway toxicities/collapsed lung, brachioplexopathy and dysphagia.

Several studies looked into the stereotactic related chest wall/rib injury; however, these studies are widely variable and heterogeneous in methodology and analysis. Stereotactic radiotherapy-related rib fractures and chest wall toxicities have been discussed in much detail in Chapter 1.

In a remarkable study published by Dunlap (Dunlap, Cai et al. 2010), different dose fractionation schedules were used to treat patients with early stage non-small cell lung cancer. It's important to know that we still don't have a clear understanding about the dose conversion method when using a very high dose of radiotherapy in very small number of fractions. As mentioned in chapter 1, although the most commonly used technique for BED (biologic equivalent dose) conversion is LQ model (Schultheiss, Zagars et al. 1987), the accuracy of this model is questionable. Therefore, some authors have recommended to use different techniques such as universal surviving curve (Park, Papiez et al. 2008) or generalized LQ model (Andratschke, Zimmermann et al. 2011).

Therefore, with the lack of universal acceptable dose calculation system, we elected to choose only one dose fractionation schedule which is 54 to 60 Gy in 3 fractions. This dose/fractionation schedule is widely used in different centers including RTOG study, hence making the comparison of our data easier. Moreover, the dose of 54 Gy in 3 fractions (using heterogeneity correction) is considered the same as 60 Gy in 3 fractions (without heterogeneity correction, as was used in RTOG study) (Franks, Purdie et al. 2010).
It is important to note that from all of our patients that were treated on prospective study with a regular close follow up; we have not yet found any case with rib fracture in patients treated with other dose fractionation. This supported our selection of patients. However, the lack of detecting rib fracture in other dose/fractionation group is not completely clear. Although one reasonable theory is due to lower dose of delivered radiotherapy, a longer follow up is needed to confirm this theory.

Although the detailed information about chest wall pain was available, our study was not designed to analyse this symptom separately. Our reasons for this included: 1) the perspective of chest wall pain varies in different individuals and is quite subjective. Same pain that is considered mild in a patient may be graded as moderate to severe with effect on the daily activities by a different patient. Similar concept applies in using narcotic medications as some patients may not use narcotic even in severe pain while others may want to take narcotic even in mild form of pain; 2) chest wall pain, itself, is multifactorial and it is quite difficult to minimize the confounding factors when studying potential risk factors. There are several causal factors reported for chest wall pain such as COPD, Cough, and CHF; 3) not all the cases of chest wall pain are related to rib fracture. In our study from 21 patients with chest wall pain, 14 had rib fractures and 7 did not. However we noted that moderate to severe chest wall pain (e.g. grade 2-3) were found in patients with multiple rib fractures (n=9). With all these in mind, and to minimize the confounding factors, we decided to study only the rib fracture as the individual stereotactic related toxicity in patients treated with 54 to 60 Gy in 3 fractions of SBRT.
5.3 Strengths of the study

One of the important features in our study is our detailed methodology such as contouring each rib individually, from costo-vertebra to the costo-sternal angle (and to costo-cartilage in more inferior ribs, such as ribs 8 to 12). There is no doubt that contouring more than one thousands ribs is time consuming, however to obtain more accurate results all ribs need to be included in the analysis. This is quite unique to our study. In the Pettersson study, only ribs receiving more than 20 Gy were contoured (Pettersson, Nyman et al. 2009). This excluded more than 711 ribs (33 patients x 24 ribs = 792 -81 contoured ribs). In some studies such as Dunlap et al (Dunlap, Cai et al. 2010), ribs were not even contoured individually and all were considered as part of one structure called chest wall. In fact they reported neither the risk of rib fractures individually nor any specific dose volumetric values for rib fractures.

As discussed in Chapter 4, in our study we used a three-step approach detecting fractured ribs. Based on our data there was a gap not only in the number of reported fractured ribs but also in the timing of reported fractures (with the delay of approximately 5 months). This may explain why we had more reported rib fractures in our patients compared to other studies (as the other groups were dependent on the radiologic reports/or patients’ complaints to detect the fractured ribs). In fact, 15 fractures could have been missed if we had relied solely on the radiologic reports to detect the fractured ribs. This may be considered as an important learning experience and the importance of spreading the knowledge of late radiation toxicities to our patients, radiation oncologists and radiologists.

Not only did we contour all the ribs but also we re-planned all cases (with the same monitor unit) and we made sure that the whole scanned rib cage was included in the dose calculation. We also corrected for
heterogeneity in all plans (using the same used monitor unit as in the treated plans). With this we had a more complete, accurate and unique group of patients to minimize the confounding factors as much as possible.

In terms of data collection, we used MATLAB and CERR system and transferred them through RTOG format (Appendix2). We collected all the dose-volume values of each rib (as an example; right rib 1 DVH has been shown in Appendix3) for quality assurance. The data were randomly reviewed. In our study $D_{0.5}$ and $V_{25}$ had the most relevant importance (Appendix 4 and 5).

To evaluate the impact of including the ribs receiving low dose RT, we repeated the maximum likelihood curves excluding the ribs receiving <25 Gy in a stepwise process. However, the value of $D_{0.5}$ remained at the significant MLL cut point. As $D_{0.5}$ and $V_{25}$ are significantly cross correlated (spearman correlation coefficient 0.57, $p<0.0001$), only $D_{0.5}$ was used for analysis. This is in consistency with reported data (Pettersson, Nyman et al. 2009), however the value is different in our study and this might be related to the fact that we did include all the ribs, $D_x$, and $V_x$ values. In our cohort, a 50% risk of rib fracture was associated with a $D_{0.5}$ of 60 Gy (Appendix6) but based on Swedish study (Pettersson, Nyman et al. 2009), the estimation of delivering 27.3 Gy was associated in 50% risk of fractured ribs.

Finally, we have created a nomogram based on dosimetric and clinical information. Although, the nomogram still needs validation, it may help us estimate the risk of rib fracture in an individual patient. For example estimated risk of rib fracture in a 75 year old lady with $D_{0.5}$ of 60 Gy is about 70% (Appendix7), which is much higher than in a man of the same age and with the same planning criteria (risk of rib fracture of 15-20%). This emphasizes the importance of clinical factors when estimating the risk of rib fracture.
5.4 Limitations of the study

The studied clinical factors included: history of diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), age and gender. These clinical factors were selected based on the availability of data. However, there are several other factors that have not been assessed in our study, such as history of severe cough, steroid medication and bone density. It’s important to note that there are significant numbers of clinical confounding factors that make the study even more difficult. For example, COPD has been found to be a risk factor in rib fracture (Suissa and Ernst 2004; Gonnelli, Caffarelli et al. 2010; Seggev 2012) most likely related to the long term steroid use (Adinoff and Hollister 1983; Steinbuch, Youket et al. 2004; De Vries, Bracke et al. 2007). Patients with COPD may cough more often and severe cough has been shown to be a risk factor for rib fracture too (Hanak, Hartman et al. 2005; Bosio, Young et al. 2008).

Steroids may have a role in rib fractures. For example, the European study on Cushing’s syndrome has shown that there was a high risk of osteoporosis and rib fractures in these patients. In this study (Valassi, Santos et al. 2011) males had more vertebral and rib fractures compared to females (52 vs. 18% for vertebrae; P<0.001 and 34 vs. 23% for ribs; P<0.05). It seems that the actual cause of rib fracture is related to the osteoporosis (OP) caused by steroids (Sajjan, Barrett-Connor et al. 2012). This may explain the significance of the female gender on the risk of rib fracture in our study. Many of our patients had COPD and some of these patients did receive steroid (most commonly prednisone) prior to, during or after treatment. We did not study the history of taking steroids or the bone density on our patients as this was outside the limit of this study. However, we should keep these cofactors in mind when estimating the risk of rib fracture.
We have found that age and gender are significantly related to rib fracture. On univariate analysis, correlations with RIBI were found with age (p=0.045), but not with gender. On multivariate analysis, age (p = 0.003), female gender (p = 0.003) were significantly associated with RIBI (Chapter 4). This is consistent with the published data (Cho, Stout et al. 2006). In a study from the Mayo clinic (Wuermser, Achenbach et al. 2011), an age- and sex-stratified random sample of 699 patients was reviewed. Risk factors for falling predicted rib fractures as well as bone mineral density (BMD) were strongly age-related. After age-adjustment, BMD was associated with rib fractures in women but not men. Importantly, rib fractures attributed to severe trauma were associated with BMD in older individuals of both sexes.

Other potential clinical factors related to the risk of rib fracture that have not been analyzed in our study include: obesity (Welsh, Thomas et al. 2011) and prior low-trauma fracture (Center, Bliuc et al. 2007).

Finally we used our data to obtain a nomogram predicating the risk of stereotactic radiotherapy bone injury in our patients’ population; in-operable patients with early stage NSCLC treated with 54 to 60 Gy in 3 fractions within 2 year follow up (Appendix 7). Based on this nomogram, being a female adds 25 points which demonstrate the importance of gender on rib fracture. To the best of our knowledge this is the first time that a nomogram has been presented to predict the risk of rib fracture in these patients. Unfortunately, our nomogram has not been validated yet. As in our center, we did not have any other group of patients treated with stereotactic radiotherapy that have rib fracture, we could not validate our data internally. However, we are going to validate our data externally and this is one of our future plans.
5.5 Future directions

As mentioned above, there are multiple clinical factors that may be considered when estimating the risk of radiotherapy induced rib fractures. These factors might be the subjects for future studies. One of these factors is the effect of long-term steroid therapy on bone density and the risk of rib fracture. Obtaining detailed prospective information about the steroid therapy such as the administered dose and duration of treatment is important to evaluate this factor. One way to look at the magnitude of this effect would be to obtain a baseline bone density scan, and compare it with one done at 6 months post-treatment (the timeframe at which late radiotherapy side effects usually begin to manifest). This may help us identify patients at higher risk for rib fracture and justify further study evaluating the effect of osteoporosis medications in this group of patients.

Moreover, our study has evaluated the delivered dose and not the actual received dose. Therefore, another potential future study would be to review cone-beam CT images in order to determine the actual received dose, and compare the values with the delivered dose.

Technically, there are ways to improve the delivered dose and to spare organs at risk. These may include utilizing IMRT or VMAT (Volumetric Modulated Arc Therapy) in treating patients with early stage lung cancer. VMAT has been used and compared with common delivery technique in peripheral small lung lesions treated with SBRT. This technique allows fast delivery of treatment while providing superior conformity index. Some studies have shown highly conformal plans for tumors of head and neck, brain, and prostate treated with RapidArc technique (Kjaer-Kristoffersen, Ohlhues et al. 2009; Lagerwaard, Meijer et al. 2009; Verbakel, Cuijpers et al. 2009). In the study published from the Netherlands (Ong, Verbakel et al. 2010), RapidArc therapy was used in 18 patients with early stage
NSCLC and tumor size < 70 cm$^3$. IMRT was also utilized for tumor adjacent to the chest wall. In addition to improving the conformity index, RapidArc plans reduced the dose to the chest wall. However this technique may raise some dosimetric complexity in terms of dose calculation and it may result in dose inhomogeneity within the PTV.

It is important to remember that the result of our study has not been validated internally or externally. It is our aim to review the prospective data on the same patients' population with longer follow up as well as in the patients treated with different dose fractionation schedules. At the time of this study, we had only observed rib fracture in patients treated with 54-60 Gy in 3 fractions. Since then, there have been cases identified with chest wall pain and rib fracture in the group of patients treated with 48 Gy in 4 fractions. Using a similar designed study, we are planning to validate our data internally. In addition, there is an ongoing study in VU University Medical Center in the Netherlands evaluating the risk of rib fractures in a similar group of patients. Our data may be validated externally with this center and this is the subject of our future study.

Finally, the ongoing RTOG study (randomizing patients to SBRT arm vs. lobectomy arm) may help us in selecting the appropriate management plan for borderline operable patients with early stage NSCLC.

5.6 Conclusions

Dosimetric and clinical factors contribute to risk of RIBI and both should be included when modeling risk of toxicity.
References


### Appendix 1

**Summary of Reported SBRT Outcomes in Patients with NSCLC**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Dose</th>
<th>Tumors</th>
<th>Outcome</th>
<th>RIBI and/or Chest Wall Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lagerwaard (Lagerwaard, Versteegen et al. 2012) The Netherlands</td>
<td># 177 operable</td>
<td>60 Gy in 3/5/8 fr</td>
<td>60% T1 40% T2</td>
<td>3Y LC: 93% 3 YOS: 85%</td>
<td>5 pts with RIBI: 2 pts treated with 3 fr 1 pt treated with 5 fr 2 pt treated with 8 fr</td>
</tr>
<tr>
<td>Taremi (Taremi, Hope et al. 2012) Toronto</td>
<td># 108 inoperable</td>
<td>50 Gy in 10 fr 60 Gy in 8 fr 48 Gy in 4 fr 54-60 Gy in 3 fr</td>
<td>75% T1 25% T2</td>
<td>4Y LC : 89% 3Y CCS : 77% 3YOS : 30%</td>
<td>16 pts with RIBI all were treated with 54-60 Gy/3 fr</td>
</tr>
<tr>
<td>Timmerman (Timmerman, Papiez, et al. 2010) North American</td>
<td># 55 inoperable</td>
<td>54 Gy in 3 fr</td>
<td>80% T1 20% T2</td>
<td>3y LC: 07.6% 3Y OS: 56%</td>
<td>Grade 3 toxicities: 8 MSK, 2 skin</td>
</tr>
<tr>
<td>Inoue (Inoue, Shimizu, et al. 2009) Japan</td>
<td># 115 43 Operable 72 inoperable</td>
<td>30 to 70 Gy in 2 to 10 fr</td>
<td>93 % T1 22% T2</td>
<td>3Y OS in T≤ 2 cm 90% and in T&gt; 2 cm 61%</td>
<td>1 rib fracture</td>
</tr>
<tr>
<td>Stephans (Stephans, Djemil et al. 2009) Cleveland</td>
<td># 86 inoperable</td>
<td>50 Gy in 5fr 60 Gy in 3 fr</td>
<td>76% T1 24% T2</td>
<td>1 Y LC: 97-98% 1Y OS: 77-83%</td>
<td>mild (grade 1-2) chest wall toxicity: 7/38 pts (18%) in pt treated with 60Gy/ 3 fr 2/56 pts (4%) in pts treated with 50 Gy/5 fr</td>
</tr>
<tr>
<td>Fritz (Fritz, Kraus et al. 2008) Germany</td>
<td># 40: 37 inoperable 3 refused Sx</td>
<td>30 Gy in one fr</td>
<td>Tumors ≤ 10 cm 55% T1 45% T2</td>
<td>3Y LC: 80% 3Y OS: 53%</td>
<td>RTOG grade 4 rib fracture in 5% (2/40 pts)</td>
</tr>
<tr>
<td>Nyman (Nyman, Johansson et al. 2006) Sweden</td>
<td># 45 inoperable</td>
<td>45 Gy in 3 fr</td>
<td>40% T1 60% T2</td>
<td>3Y CCS: 67% 3Y OS: 55%</td>
<td>4 pt with chest pain 2 pt with rib fracture</td>
</tr>
<tr>
<td>Zimmermann (Zimmermann, Geinitz et al. 2005) Germany</td>
<td># 30 inoperable</td>
<td>24 to 37.5 Gy in 3-5 fr Prescribed to 60% isodose line</td>
<td>17% T1 83% T2</td>
<td>2Y CSS: 95% 2 y OS: 75%</td>
<td>1 pt (3%) rib fracture</td>
</tr>
<tr>
<td>Study</td>
<td>Institution</td>
<td>#</td>
<td>Status</td>
<td>Treatment</td>
<td>Tumor Stage</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td>---</td>
<td>--------</td>
<td>-----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Andratschke (Andratschke, Zimmermann et al. 2011)</td>
<td>Norway</td>
<td>#92</td>
<td>Inoperable</td>
<td>24 to 45 Gy in 3 to 5 fr</td>
<td>34% T1 66% T2</td>
</tr>
<tr>
<td>Videtic (Videtic, Stephans et al. 2010)</td>
<td>Mayo Clinic</td>
<td>#26</td>
<td>Inoperable</td>
<td>50 Gy in 5 sequential fr</td>
<td>79% T1 21% T2</td>
</tr>
<tr>
<td>Kelly (Kelly, Balter et al. 2010)</td>
<td>USA</td>
<td>#36</td>
<td>Previously treated with radiotherapy</td>
<td>40-50 Gy in 4 fr 4 pts with other dose/fr</td>
<td>Stage 1-2 (44%) Stage 3-4 (56%)</td>
</tr>
<tr>
<td>Fakiris (Fakiris, McGarry et al. 2009)</td>
<td>Indianapolis</td>
<td>#70</td>
<td>Inoperable biopsy proven NSCLC</td>
<td>60 to 66 Gy in 3 fr</td>
<td>49% T1 51% T2</td>
</tr>
<tr>
<td>Bradley (Bradley, El Naqa et al. 2010)</td>
<td>St. Louis, USA</td>
<td>#91</td>
<td>Inoperable</td>
<td>54 Gy in 3 fr 45 Gy in 5 fr</td>
<td>64% T1 36% T2/T3/M1</td>
</tr>
<tr>
<td>Chang (Chang, Balter et al. 2008)</td>
<td>TX, USA</td>
<td>#27</td>
<td>Isolated recurrent disease</td>
<td>40 Gy in 4 fr (7 pts) escalated to 50 Gy in 4 fr (20 pts)</td>
<td>48% stage 1 52% stage 2</td>
</tr>
<tr>
<td>Kawase (Kawase, Takeda et al. 2009)</td>
<td>Japan</td>
<td>#379</td>
<td>Inoperable?</td>
<td>50 Gy in 5 fr 48 Gy in 4 fr</td>
<td>N/A</td>
</tr>
</tbody>
</table>

OS: overall survival; YOS: year overall survival; CSS: cause specific survival; LC: local control; RIBI (radiotherapy induced rib fracture); fr: fraction; Pts: patients; MSK: musculoskeletal; Sx: surgery
Appendix 2

Extracting data through RTOG to a PC data base, and from PC using MATLAB (CERR) system. QA on MATLAB data was done randomly.

<table>
<thead>
<tr>
<th>structure</th>
<th>vol</th>
<th>mmPost</th>
</tr>
</thead>
<tbody>
<tr>
<td>mb1</td>
<td>24.57E+03</td>
<td>49.14E+03</td>
</tr>
<tr>
<td>mb2</td>
<td>22.30E+03</td>
<td>111.05E+03</td>
</tr>
<tr>
<td>mb3</td>
<td>25.91E+03</td>
<td>189.51E+03</td>
</tr>
<tr>
<td>mb4</td>
<td>31.96E+03</td>
<td>207.98E+03</td>
</tr>
<tr>
<td>mb5</td>
<td>39.71E+03</td>
<td>202.98E+03</td>
</tr>
<tr>
<td>mb6</td>
<td>42.28E+03</td>
<td>214.09E+03</td>
</tr>
<tr>
<td>mb7</td>
<td>42.76E+03</td>
<td>216.59E+03</td>
</tr>
<tr>
<td>mb8</td>
<td>34.24E+03</td>
<td>204.38E+03</td>
</tr>
<tr>
<td>mb9</td>
<td>32.65E+03</td>
<td>192.03E+03</td>
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<td>mb10</td>
<td>21.77E+03</td>
<td>123.82E+03</td>
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<tr>
<td>mb11</td>
<td>13.39E+03</td>
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<td>mb12</td>
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<td>mb13</td>
<td>24.25E+03</td>
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<td>12.05E+03</td>
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<td>86.02E+03</td>
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<tr>
<td>mb24</td>
<td>6.50E+04</td>
<td>2.43E+04</td>
</tr>
</tbody>
</table>
Appendix 3

DVH of all right rib #1 in 46 patients with early stage NSCLC treated with SBRT.
Appendix 4

Max likelihood curve of absolute dose to the certain volume (0.5 – 10 cc) of the ribs; indicating the significance of $D_{0.5}$
Appendix 5

Max likelihood curve of absolute volume of the ribs receiving certain dose (15 to 50 Gy) cc; indicating the significance of $V_{25}$
Appendix 6

Probability of rib fracture based on $D_{0.5 \, c}$
Appendix7

Risk of rib fracture in a 75 year old lady with $D_{0.5}$ of 60 Gy within a median FU of 2 years

![Graph showing risk factors for rib fracture]