Predicting Respiratory Induced Tumor Motion Using External Surrogates

by

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Abstract

Breathing induced tumor motion is one of the major sources of geometric uncertainty in the delivery of external beam radiation therapy for thoracic and abdominal tumours. To mitigate this motion, the tumor position during treatment must be known in real time. Acquiring this knowledge directly is generally either not possible or costly in terms of time and dose to the patient. As an alternative, the tumor position can be obtained using a suitable surrogate.

In this study the ability of three external surrogates (skin markers, spirometer and respiratory belt) to predict tumor position in lung cancer patients was studied. The focus was on i) identifying the optimal surrogate, ii) quantifying the impact of such a surrogate on the Internal Margin (IM), and iii) characterizing the reliability of the surrogate during the course of treatment.

Our study showed that during normal breathing i) for tumor motions <7 mm none of the surrogates were effective, and ii) for tumour motions between 7 mm and 20 mm, the various combinations of skin markers and SPR could reduce the IM by approximately 7 mm. The surrogates did not necessarily perform the same during deep breathing. All skin markers and a row of markers placed on the upper abdomen were the two surrogates that were effective during deep breathing as well. They could result in a reduction of up to 13 mm in the IM. The respiratory belt was least effective in predicting tumor motion regardless of amplitude and breathing type

Comparison of surrogate-based margins on day-1 and day-20 of the treatment indicated that the surrogate-tumour relationship does not remain invariant in time. The prediction uncertainty grows and the surrogate becomes less effective. Therefore, the inter-fraction reproducibility of external surrogates in predicting lung tumor

motion is poor and the chance of geometric miss is high. Furthermore, analysis of non-surrogate-based case showed that tumor motion amplitude often increases throughout the course of treatment. Therefore, the non-surrogate approach should also be reassessed over a standard treatment course. Statistical analysis showed that for both cases assuming a 6 mm additional margin would provide adequate tumor coverage.

To my wife, Leila, my son, Arashk and my daughter, Baran

With special thanks to Dave Rogers and Joanna Cygler

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Glossary and Abbreviations

This glossary will contain abbreviations of commonly used terms in this thesis as well as definition of some cancer terminologies.

I. Abbreviations

3DCRT	Three Dimensional Conformal Radiation Therapy
ABC	Active Breathing Control
All markers	All eight skin markers (in this study)
AP	Anterior/Posterior
Belt	Respiratory Effort Belt (in this study)
Col	The central Column of skin markers (markers 2,5,7) (in this study)
CTV	Clinical Target Volume
cGy	Centigray
DB	Deep Breathing in lung cancer patients (in this study)
DI	Deep Inspiration
DIBH	Deep Inspiration Breath Hold
DRR	Digitally Reconstructed Radiograph
EBRT	External Beam Radiation therapy
EXP	Deep Expiration breath hold in normal volunteers (in this study)
FB	Free Breathing
FSB	Force Shallow Breathing
GTV	Gross Tumor Volume
Gy	Gray (unit of absorbed dose)
INSP	Deep Inspiration breath hold in normal volunteers (in this study)
MLC	Multileaf Collimator
NB	Normal Breathing (in this study)
NSCLC	Non Small Cell Lung cancer

One marker The central skin marker (marker 5) (in this study)

PTV Planning Target Volume

Row The central Row of skin markers (markers 4,5,6) (in this study)

RT Radiation Therapy

SCLC Small Cell Lung Cancer

SI Superior/Inferior

SPR Spirometer (in this study)

TCP Tumour Control Probability

TCP+ Uncomplicated Tumor Control Probability

II. Definitions

Adjuvant therapy Treatment given after the primary treatment to increase the chances of a cure

Biological therapy Treatment to stimulate or restore the ability of the immune system to fight cancer

Connectivity analysis Connectivity analysis is to analyze the connectivity between points, lines and areas in terms of distance, area, travel time, optimum path etc

Disparity A component of the process of computer stereo vision to calculate the distance to objects in an image by comparing the images taken by two cameras that are separated by a distance. The two images are shifted with respect to each other to find the parts that match. The shifted amount is called the disparity The computer can calculate distance to objects in the image from the disparity amount at which the two images best match.

Duty cycle The fraction of time a radiation beam is active during the delivery of a respiratory-gated treatment field

Epipolar Constraint A method that is used to reduce the solution space of the matching problem. The projection of a scene point in one image must be on the epipolar line which can be determined from the projection of the scene in the other image. The epipolar constraint can be uniquely characterised by a fundamental matrix which is a matrix encoding the information of the camera calibration and motion

Epipolar Line The epipolar plane contains the images of the scene point and intersects with the two image planes in two lines called the epipolar lines

Epipolar Plane Assuming that the relative camera motion between the two images is not a pure rotation, the scene point and the two camera centres then define a plane called the epipolar plane

Gate A device that restricts image acquisition or treatment delivery to a particular part of the respiratory cycle

Hormone therapy Treatment that adds, blocks, or removes hormones

Inter-fraction Occurring between treatment sessions

Intra-fraction Occurring within a treatment session

Local Invasive Capacity The capacity of a tumor to spread beyond the layer of tissue in which it started and to grow into the surrounding normal tissues.

Lung board A radiation therapy device that is useful when a patient must lie with his or her arms up over the head. It has handles that the patient grasps comfortably, thus facilitating the reproduction of the patient's daily treatment position.

Palliative therapy Treatment given to relieve the symptoms and reduce the suffering caused by cancer and other life-threatening diseases

Phase A particular stage in a periodic process (e.g., regular respiratory motion)

Radical therapy Curative radiation therapy

Range of motion Displacement between inhale and exhale

Respiratory gated The synchronization of imaging and radiation delivery with respiration, such that image acquisition/radiation delivery only occurs during a certain part of the respiratory cycle

Respiratory synchronized The synchronization of radiation delivery with respiration via movement of the linear accelerator or the patient such that the radiation beam is allowing the tumour during treatment

Spirometer A device that measures the volume of air entering and exiting the lungs

Staging Performing exams and tests to learn the extent of the cancer within the body, especially whether the disease has spread from the original site to other parts of the body. It is important to know the stage of the disease in order to plan the best treatment.

Triangulation The process of finding coordinates and distance to a point by calculating the length of one side of a triangle, given measurements of angles and sides of the triangle formed by that point and two other known reference points, using the law of sines.

CHAPTER 1

Introduction

1.0 Introduction

The American Cancer Society defines cancer as a group of diseases characterized by uncontrolled growth of cells and the ability of these abnormal cells to spread to distant sites.^[1] If the growth or spread is not controlled it can result in death. Cancer is the second leading cause of death after cardiovascular disease in Canada and the United States, accounting for at least 29% of all deaths and almost one-third of potential years of life lost.^[2,3] The latest report published by Statistics Canada estimates 159,900 new cases of cancer and 72,700 deaths from cancer in Canada in 2007.^[3] Worldwide, approximately 6.72 million people die of cancer every year.^[4] A review of some important cancer statistics is given in Table 1.1.

Currently, there are three major modalities for cancer treatment: surgery, chemotherapy and radiotherapy. Surgery is the treatment of cancer by the physical removal of the tumour. Chemotherapy is drug-based therapy, and radiation therapy is treatment by ionizing radiation. There are also several other (investigational) methods including hormonal therapy, biological therapy, hyperthermia and photodynamic therapy. Often, patients are treated by a combination of two or more therapy modalities.

1.1 Radiation Therapy

In radiation therapy, ionizing radiation is used to destroy cancerous cells. The radiation attacks the genetic material of the cells making it impossible for them to reproduce. This radiation is delivered by either brachytherapy or External Beam Radiation Therapy (EBRT). In brachytherapy, the source of ionizing radiation, i.e., radioactive source, is placed inside the patient's body in or near the tumour. In EBRT, the source of ionizing radiation is external and this method is sometimes referred to as Teletherapy. Sources for

Table 1.1 Review of some important cancer statistics in Canada ^[3]

Percentage of all deaths	29%
Yearly cost to the country	\$13 billion
Percentage of all men developing cancer	44%
Percentage of all women developing cancer	39%
Percentage of all men dying from cancer	28%
Percentage of all women dying from cancer	24%
Total number of new cases of cancer	159,900
Total number of cancer deaths	72,700
Percentage of lung cancer among all cancer deaths in men	29%
Percentage of lung cancer among all cancer deaths in women	26%
3 top cancers in men	Prostate-Lung-colorectal
Percentage among all cancers	56%
3 top cancers in women	Breast-lung colorectal
Percentage among all cancers	55%

EBRT include linear accelerators, X-ray tubes and radioactive sources such as Co-60. EBRT can be radical, adjuvant or palliative. These terms are defined in the glossary.

1.2 The position and extent of the tumour

In EBRT, irradiating the entire tumor is required for tumor control and cure. This is a complex task. For one thing, the tumor is usually not a well-defined volume with distinct boundaries. Secondly, there are geometric errors and/or uncertainties in the procedures because of patient motion, setup errors and tumor motion within the patient. For these reasons, the International Commission on Radiation Units and Measurements (ICRU) has provided definitions and guidelines for tumour delineation, specification and irradiation which will be discussed in the next section.

1.3 Review of ICRU Reports 50 and 62^[5,6]

In order to set guidelines for determining the volume of tissue that is to be irradiated in EBRT, the ICRU has released two reports, ICRU report 50 and a supplementary report ICRU report 62. These reports offer recommendations and strategies regarding various radiation therapy treatment margins and their magnitudes. The strategy relies on the definitions of GTV, CTV and PTV.

GTV-The Gross Tumour Volume (GTV) is the volume defined by the gross palpable or demonstrable tumour extent. The shape, size and location of the GTV may be determined by different diagnostic methods, e.g., CT, Magnetic Resonance Imaging (MRI), or Positron Emission Tomography (PET) as well as physical examination. Since the tumour cell density in the GTV is usually higher than elsewhere, it often requires a large radiation dose to destroy all tumour cells within this volume.

CTV- Clinical experience indicates that around the GTV there is generally subclinical involvement, i.e., individual malignant cells, small cell clusters, or microextensions, which cannot be detected by existing staging procedures. The volume surrounding the macroscopic tumor usually has a high tumor density close to the edge of the GTV with decreasing density towards the periphery of this volume (often a margin of about 1cm). The GTV, together with this surrounding volume of local subclinical involvement is defined as the Clinical Target Volume (CTV). This volume must be treated adequately in

order to achieve tumor control. In some cases a dose gradient over this volume may be desired and can be achieved by various 3DCRT and IMRT techniques. The determination of CTV requires the physician to consider the local invasive capacity of the tumor and its potential to spread during the period from diagnosis to treatment.

This definition of the CTV is based on general oncology principles and the experience and knowledge of the radiation oncologists, and is applicable to brachytherapy, external beam radiotherapy, and to some extent to surgery. Once the CTV is determined, the radiation oncologist will prescribe a dose contour around or dose distribution over the CTV volume to achieve a certain treatment goal, e.g., cure, palliation or local tumor control.

PTV- To ensure that all tissues included in the CTV receive the prescribed dose one must, in general, plan to irradiate a geometrically larger volume than the CTV. Geometric uncertainties such as intra-fraction patient motion, inter-fraction setup errors and tumor mobility within the patient are some of the factors contributing to this larger volume which leads to the concept of Planning Target Volume (PTV).

The PTV is a geometrical concept used to determine the appropriate beam sizes and arrangements, taking into consideration the net effect of all possible geometrical variations, in order to ensure that the CTV receives the prescribed dose. The expansion of the CTV generally depends on direction (e.g. Lateral, Sup/Inf), patient characteristics (age, weight and general health), organ or disease site (e.g. close to lung) and technology used (e.g. immobilization technique). When prescribing the dose to the CTV, the radiation oncologist must balance the treated volume (and probability of control) with the normal tissue toxicity of the surrounding normal tissue and Organs at Risk (OARs). The relationship among GTV, CTV, PTV and adjacent OAR is shown in Figure 1.1.

The definition of PTV was further modified in ICRU report 62, which was published as a supplement to ICRU report 50. ICRU report 62 provides guidance to optimize the planning target volume for external beam radiotherapy. In this report, internal organ

motion and daily patient setup error are considered as two major uncertainties that may compromise dose delivery to the CTV. Three scenarios (A, B, and C) for defining PTV are suggested in this report.

Figure 1.1 Graphic representations of the GTV, CTV, PTV and OAR, and their relationship.

Scenario A - In scenario A, to ensure that all parts of the CTV receive the prescribed dose during treatment, additional safety margins for geometric variations and errors must be assumed as follows. An Internal Margin (IM) is added for the possible target variations and the deformation in shape and size of the CTV relative to the bony anatomy. This defines the Internal Target Volume (ITV) (Figure 1.1). In addition, a Set-up Margin (SM) is further added to cover all potential variations/uncertainties in patient position relative to the radiation beam. Based on this scenario, the PTV can be represented as:

$$PTV = CTV + IM + SM \quad (1.1)$$

For stationary tumours, the IM is small because for these tumours the only contributing factor to the IM is any possible variation in shape and size of the tumor, and there is no internal tumor movement. Therefore, for these tumours, the margins added to CTV to

form the PTV are small. On the other hand, for tumours with intra-fraction motion, i.e., tumor movement during the treatment, the added margin is large due to a large IM (Figure 1.2).

Note that the PTV, CTV, IM, and SM presented in Equation 1.1 are all volume concepts. The simple linear addition of all geometric uncertainties could lead to an excessively large PTV that would encompass large amounts of surrounding normal tissue volumes or OAR's, potentially causing significant normal tissue complication.

Figure 1.2 Depiction of the Internal Margin (IM) for (a) a stationary tumor, and (b) a moving tumor. Note that for a moving tumor the IM can be substantially larger. Also note the oversimplification in the tumor shape and the added margins.

Scenario B - In scenario B, the treatment margin is calculated as the quadratic sum of two geometric uncertainties. With an assumption that the two sources of geometric errors are independent Gaussian distributions, the margin formalism is then described as $\sqrt{\sigma_{pe}^2 + \sigma_{om}^2}$, where σ_{pe} and σ_{om} are the geometric uncertainties due to patient setup error and internal organ motion respectively. The formation of the PTV using the quadratic sum of geometric uncertainties is to some extent more reasonable than that formed with Scenario A. However, such a quantitative approach is only relevant if all

uncertainties and their distributions are known, *i.e.*, in practice, only in a few sophisticated protocols.

Scenario C - In scenario C, a “global” safety margin is calculated using the quadratic approach for all sources of the geometric uncertainty, but the presence of Organs at Risk restricts the size of the treatment margins.

Regardless of the method undertaken to determine PTV, it is this volume that is irradiated during the treatment and it always includes the CTV plus some healthy tissue. Reducing the CTV-PTV margins would reduce the healthy tissue component of the PTV and would result in the exposure of a smaller volume of healthy tissue.

In order to keep the added margins that account for internal tumor motion as a separate entity from the setup margins, the two notations IM and SM will continue to be used throughout this thesis. However, that does not mean that scenario A is the preferred scenario. All of the findings could be equally applied to scenarios B and C as well. Furthermore, since the focus of this work is breathing induced tumor motion and its contribution to IM, two points must be made here. First, SM will not be included in the discussions but its existence and its independence from the changes in the IM is always presumed. Secondly, although the concept of IM concerns a broader class of tumor motions than just the breathing induced tumor motion, in this thesis, IM will be used to refer only to the margins that are added to mitigate breathing induced tumor motion.

1.4 TCP, NTCP, TCP+

In the previous section it was concluded that the PTV is the volume that receives radiation during the treatment. It was also noted that the PTV includes both the tumor that is composed of malignant tissue and the margins that mainly consists of normal tissue. Ionizing radiation does not differentiate between the cancerous and healthy cells and irradiates both indiscriminately. Therefore, radiation damage occurs to both groups of cells. Normal tissue irradiation causes complication and toxicity. In radiation therapy,

Tumour Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) are used to quantify the damage to tumour and normal tissues, respectively. The ideal value of TCP is 100% and that of NTCP is 0%. These two parameters are put together to form a single parameter called the probability of uncomplicated tumour control (TCP+) defined as:

$$\text{TCP+} = \text{TCP} (1 - \text{NTCP}) \quad (1.2)$$

TCP+, usually used to express the outcome of radiation therapy, should be maximized, ideally to 100%.

1.5 Improving the outcome of treatment

The objective of curative radiotherapy is to eradicate viable tumour while preserving host organ function, i.e., to minimize NTCP while maximizing or at least maintaining TCP, in short maximizing TCP+. The quality of a radiation therapy procedure can be assessed in terms of TCP+. The higher the TCP+, the more successful the treatment should be.

One way to improve TCP+ is to decrease the NTCP by considering the differences in radiobiological characteristics of the tumor and healthy tissue. It has been well established that the dose response relationships for cancerous and healthy cells are not the same.^[7] That is to say that given enough time and providing that the radiation dose is within certain limits, healthy cells are more capable than cancerous cells to repair themselves following an exposure to ionizing radiation. One approach that takes advantage of this difference between cancerous and healthy cells to mitigate NTCP is fractionation, which means delivering the dose in small fractions over many days. The effects of fractionation have been widely studied by many investigators.^[7,8]

Another way of improving TCP+ is to reduce the volume of healthy tissue that receives radiation by reducing the CTV-PTV margins. It has been well established that TCP is dose dependent^[9] while NTCP depends on both the dose and the volume of the irradiated

healthy tissue^[10-12] , i.e., larger exposed healthy tissue volume results in larger values of NTCP. Therefore, decreasing the margins and thus the volume of healthy tissue included in the treatment would improve the radiotherapeutic outcome, the TCP+. In fact, this approach can improve TCP+ through two different mechanisms as depicted in Figure 1.3. The first mechanism is maintaining the same prescribed dose, and thus the same TCP. This results in a decreased NTCP due to the decreased healthy tissue volume. The second mechanism involves escalating the prescribed dose to a point where the same NTCP is obtained. This will result in an improved TCP due to the escalated dose.

Consider the second method of improving TCP+ (i.e., reducing the CTV-PTV margins). The volume of the normal tissue included in the PTV, can be substantial. The larger the CTV-PTV margin, the bigger this volume will be. Therefore, reducing the PTV-CTV margins would decrease the healthy tissue component of the PTV, which translates to an improved probability of uncomplicated tumor control, TCP+, as described in the previous section. Reducing these margins would require a reduction in the IM and/or SM component of the margins. Setup margin (SM) reduction has been extensively investigated by many other investigators.^[13-20] This work concentrates on investigating the methods to reduce IM.

1.6 Breathing induced tumour motion

As mentioned before, the IM compensates for intra-fraction tumor motion. Intra-fraction tumor motion can have four causes: respiratory, skeletal muscular, cardiac, and gastrointestinal systems.

Of these four systems, respiratory is a major contributor to the intra-fraction tumor motion and is responsible for most motion in thoracic and lung tumours. Table 1.2 shows the magnitude of respiration induced tumour motion reported by various investigators. As can be seen in this table the magnitude of respiratory induced tumour motion and

Figure 1.3 The two mechanism by which TCP+ can be improved as a result of decreased volume of the irradiated healthy tissue.

Table1.2 Magnitude of respiratory motion reported by various investigators

Magnitude of Respiratory Motion			
Host Organ	Magnitude	Investigator	Comments
Lung	10-25 mm	Ohara et al. ^[21]	(normal)
	30-70	Ohara et al. ^[21]	(deep)
	12 mm	Seppenwoolde et al. ^[22]	
	0-13	Sixel et al. ^[23]	
	12 mm	Davies et al. ^[24]	
	0-50 mm	Chen et al. ^[25]	
	10 mm	Ross et al. ^[26]	
Kidney	18 mm	Balter et al. ^[27]	(AP)
	19 mm	Suramo et al. ^[28]	(SI)
	40 mm	Suramo et al. ^[28]	(SI, deep)
	5-16	Davies et al. ^[24]	
Liver	17 mm	Balter et al. ^[27]	
	25 mm	Suramo et al. ^[28]	(normal)
	55 mm	Suramo et al. ^[28]	(deep)
	14 mm	Harauz et al. ^[29]	
Prostate	3.3 mm	Malone et al. ^[30]	

therefore the added margin required to account for it can be substantial, especially in the case of lung. Example 1.1 demonstrates the contribution of this added margin to the volume of the irradiated healthy tissue as well as the significance of reducing it.

Example1.1: The significance of margins in healthy tissue irradiation

This example demonstrates the significance of adding margins to the tumor and the magnitude of healthy tissue volume that is exposed to ionizing radiation as a result of adding the margins. Note that this is an oversimplified scenario.

Problem: Suppose a spherical tumor is 5.0 cm in diameter. Calculate the volume of healthy tissue included in the irradiation for the following three different added margins:

(a) 1.0 cm, (b) 0.9 cm, and (c) 0.5 cm. Suppose that the same margin is added all around the tumor.

Figure 1.4 Tumor and the added margin

Solution: a) For the volume of the tumor:

$$D = 5.0 \text{ cm} \rightarrow R = 2.5 \text{ cm}$$

$$V = \frac{4}{3} \pi R^3 = \frac{4}{3} \times (31.4) \times (2.5)^3 = 65.4 \text{ cm}^3$$

Next we calculate the total volume, i.e., the volume of the tumor and that of healthy tissue that is included as a result of adding the margin. Since the margin is added all around the tumor, the diameter increases by twice the margin. Therefore, the total volume (tumor and healthy tissue) for case (a) is:

$$D = 5.0 + 2(1.0) = 7.0 \text{ cm} \rightarrow R = 3.5 \text{ cm} \rightarrow V = 179.6 \text{ cm}^3$$

The volume of healthy tissue only:

$$179.6 \text{ cm}^3 - 65.4 \text{ cm}^3 = 114.1 \text{ cm}^3$$

As seen here, the volume of the healthy tissue can be much larger than the tumor itself. In fact it is 1.75 times the size of the tumor. Following the same procedure for case (b) yields a value of 99.2 cm³ for the irradiated healthy tissue. The volume of the irradiated healthy tissue in this case is 14.9 cm³ smaller than case (a). This amount of normal tissue sparing is resulted from a reduction of only 1.0 mm in the margins. For case (c), volume

of the irradiated normal tissue and the spared normal tissue compared with case (a) are 47.6 cm^3 and 66.5 cm^3 respectively.

Therefore, for a tumor with a diameter of 5.0 cm, a 1.0 mm reduction in the margins leads to sparing 14.9 cm^3 of healthy tissue while a decrease of 5.0 mm in the margins could save as much as 66.5 cm^3 of healthy tissue.

Note that the volume of the healthy tissue that is spared as a result of decreasing the margins depends not only on the margin reduction but also on the size (radius) of the tumour. For a given margin, as the size of the tumour increases, the volume of healthy tissue included in the PTV increases because the inner radius of the healthy tissue (which is equal to the tumor radius) gets larger. Therefore, the effect of margin reduction becomes more pronounced for larger tumor sizes. For the simple case of a spherical tumor, the volume of the healthy tissue ($V_{\text{H.T.}}$) included in the added margin can be written as a function of the tumor size and the margin thickness as follows:

$$V_{\text{H.T.}} = \frac{4}{3} \pi (r^3 + 3Rr^2 + 3R^2r) \quad (1.3)$$

where r and R are the margin thickness and radius of the tumor respectively.

Therefore, for tumours that are affected by respiration, mitigating breathing induced tumor motion and the concomitant reduction in the IM can have a large impact on the volume of the irradiated healthy issue and potentially lead to an improved TCP+.

1.7 Methods to account for respiratory motion in radiotherapy

The methods, both clinical and experimental, that have been developed to reduce the impact of respiratory motion in radiotherapy can be broadly separated into five major categories: motion-encompassing methods, respiratory-gating techniques, breath-hold techniques, forced shallow-breathing techniques, and respiration-synchronized

techniques. These methods have been extensively discussed in the report of AAPM Task Group 76^[31] and will be briefly described in the following sections.

1.7.1 Motion-encompassing methods

Many radiotherapy facilities do not currently have methods that explicitly account for respiratory motion. Therefore, they account for respiratory motion by enlarging the field so that it encompasses the entire region within which the tumor is moving. In this approach, the respiratory-induced tumor motion that is present during the radiation delivery is estimated during CT imaging or with fluoroscopy during conventional simulation.

There are three CT techniques used to determine the range of tumor motion due to respiration. These are slow CT^[32-34], inhale and exhale breath-hold CT^[35-38], and four dimensional (4-D) CT or respiration-correlated CT^[39-51]. For these techniques, it is important to understand that the breathing patterns and, hence, tumor motion may change between simulation and treatment resulting in possible tumour misses. It should be noted that the radiation dose to the patient from these imaging procedures can be significantly larger than standard CT doses if no efforts are made to reduce CT dose.

1.7.2 Respiratory gating methods

The treatment procedure in gated therapy is essentially the same as the 3-D conformal radiation therapy approach except that in this case the beam is not ON at all times during the treatment. Respiratory gating increases the potential for CTV–PTV margin reduction by the administration of the radiation beam within a particular portion of the patient’s breathing cycle, commonly referred to as the “gate”. The position and width of the gate within a respiratory cycle are determined by monitoring the patient’s respiratory motion, using a respiration signal. The radiation beam is activated whenever the respiration signal is within a pre-set window of relative positions. Typically, a gate extends over a region of the breathing cycle where the motion of the tumor is estimated to be less,

compared with the rest of the respiratory cycle (such as exhale), or where the lung volume is maximal (such as inhale).

In gating, since the beam is not continuously ON, the treatment time is prolonged. The ratio of the time with beam on to the overall treatment time is referred to as the duty cycle and is a measure of the efficiency of the method. Increases in delivery time should be considered in the context of patient comfort, increased likelihood of patient movement and decreased patient throughput (and thus increased cost). Furthermore, there is a suggestion that during substantially longer treatments, tumor control may be reduced due to the increased intra-fraction repair of sublethally damaged tumor cells^[52,53], but at the same time normal tissue repair can also occur making this a very complex issue. In general one would like to choose the “gate” such that the duty cycle is not too small. However, since some tumor motion, referred to as “residual motion”, still occurs within the gate^[54], the choice of gate width will be a trade-off with the amount of this residual motion.

Monitoring respiratory motion in gating can be done using either an external respiration signal or internal fiducial markers.

- **External signal for gating**

The respiratory gating system most widely discussed in publications that uses external respiration signal is the Varian Real-time Position Management™ (RPM) system (Varian Medical Systems, Palo Alto, CA). This system is based on a device first reported by Gerig et al.^[55] BrainLab (Heimstetten, Germany) also has a respiratory gating device called “ExacTrac Gating/Novalis Gating®.” that uses external markers for gating the radiation beam. This device has an additional x-ray imaging capability that is used for verifying the reproducibility of the internal anatomy during treatment. Siemens Medical Systems (Concord, CA) also has an FDA-approved linear accelerator gating interface and an Anzai belt (by Anzai Medical Co., Japan, used for CT), also approved for use in therapy. Three dimensional video camera surveillance has also been studied for respiratory motion management.^[56] One consideration in using an external respiration

signal for gated RT is phase (time) shift between the surrogate signal and the tumor position as will be discussed in detail later in this thesis.

- **Internal signal for gating**

Internal fiducial markers have been used in a radiotherapy system developed jointly by Hokkaido University and Mitsubishi. [22,57-66] In this system, 2 mm diameter gold spherical fiducials are implanted in or near the tumor. The position of the fiducials is tracked in three dimensions using a pair of stereotactic kilovoltage x-ray imaging devices. The linear accelerator delivers radiation when all fiducials are within an acceptable distance of their desired (simulation) position. Although internal markers do not suffer from the phase shift problem, as did the external surrogates, a significant drawback is their invasiveness.

- **Gating and Intensity Modulated Radiation Therapy (IMRT)**

Respiratory gating can also be used in junction with IMRT or arc therapy. However, to date, there is no clinical system that uses gating in junction with Tomotherapy. It has been shown that dosimetry for gated IMRT delivery is essentially the same as that for delivery without motion. [67] However, the increase in treatment time is more pronounced for gated IMRT in which the product of the IMRT efficiency, typically 20% to 50%, and the gating duty cycle, 30% to 50%, [68,69] leads to a 4- to 15-fold increase in delivery time over conventional treatment. By treating at the highest dose rate, the increase in treatment time can be reduced. Respiratory gating for thoracic and abdominal tumours is still under study by several investigators. [41,68-74]

1.7.3 Breath-hold methods

The assumption upon which the breath hold techniques are based is that the tumor becomes stationary during the breath hold. The breath hold can be voluntary or forced. Breath hold techniques are predominantly used for lung cancer. If the breath hold is at inhalation, in addition to immobilization of the tumor, the RT outcome may improve as a result of reduced density of normal lung relative to the tumor which can further reduce

the amount of normal lung tissue in the high dose region thus reducing morbidity and improving the possibility of dose escalation.

Breast cancer is another type of cancer that can potentially benefit from breath hold, though through a different mechanism and to a lesser degree. The intra-fraction tumour motion during normal breathing is small for breast cancer tumours. But still, breath hold can improve the treatment by sparing the heart and lung. During inhale the diaphragm pulls the heart posteriorly and inferiorly away from the breast, and thus away from the high dose region which can result in a reduction of cardiac toxicity. The lung is also spared in the same way as it was for the lung cancer case.^[75-80]

The common breath hold techniques are Deep Inspiration Breath Hold (DIBH), Active Breathing Control (ABC), Self-held breath hold without respiratory monitoring, Self-held breath-hold with respiratory monitoring, and Breath-hold in combination with IMRT.

- **Deep Inspiration Breath Hold technique**

This technique was initially developed and clinically implemented primarily for conformal radiation treatments of Non Small Cell Lung Cancer (NSCLC) at the Memorial Sloan-Kettering Cancer Center (MSKCC).^[81-83] It is advantageous for treating thoracic tumors because a reproducible state of maximum breath-hold (Deep Inspiration Breath Hold [DIBH]) significantly reduces respiratory tumor motion and changes internal anatomy in a way that most of the time protects critical normal tissues. The DIBH technique involves verbal coaching of the patient to reproduce deep inhale breath-hold during simulation and treatment. The patient's breathing is monitored with a spirometer whose reading is displayed and recorded as a function of time. While watching the display, the therapist coaches the patient through a modified version of the slow vital capacity manoeuvre, consisting of a deep inhale, deep exhale, second deep inhale, and the breathhold.

The applicability of DIBH is limited by patient compliance: approximately 60% of the lung cancer patients at MSKCC cannot perform the manoeuvre reproducibly enough to

permit its use. Because DIBH is relatively demanding for patients, it is used only for compliant patients in whom the significant lung inflation allows treatment to a higher total dose than is possible with free breathing (FB). Dose escalation can be 10% or more with acceptable normal tissue dose-volume histograms and calculated lung complication probability.^[83]

Despite the reduced respiratory motion, in the MSKCC treatment method, the PTV margins were not reduced for three reasons: first, Deep Inspiration (DI) lung expansion allows sufficient target dose escalation with acceptable estimated lung toxicity, as described above; second, the margins protect against possible expansion of microscopic disease due to DI; and third, the treatment-planning dose-calculation algorithm (pencil-beam based) does not handle lateral disequilibrium in low-density tissue. Finally, an important concern with DIBH technique is the reproducibility of breath-hold.

- **Active Breathing Control**

Active Breathing Control (ABC) is a method to facilitate reproducible breath hold.^[78-84] The ABC method was developed at William Beaumont Hospital and is currently commercialized by Elekta, Inc. (Norcross, GA) as the Active Breathing Coordinator™. A device with similar capabilities, called the Vmax Spectra 20C, is available from VIASYS Healthcare Inc. The ABC apparatus can suspend breathing at any predetermined position and is often used at moderate or deep inhalation. The device consists of a digital spirometer to measure the respiratory trace, which is in turn connected to a balloon valve. In an ABC procedure, the patient breathes normally through the apparatus. When an operator “activates” the system, the lung volume and the breathing cycle stage at which the balloon valve will be closed are specified. The patient is then instructed to reach the specified lung volume, typically after taking two preparatory breaths. At this point, the valve is inflated with compressed air for a pre-defined duration of time, thereby “holding” the patient’s breath. The breath-hold duration is patient dependent, typically 15 to 30 seconds, and should be well tolerated to allow for repeated (after a brief rest period) breath-holds without causing undue patient

distress. As with DIBH, an important concern with ABC is reproducibility of breath-hold and the ability of the patient to comply.

- **Self-held breath-hold without respiratory monitoring**

As the name “self-held breath-hold techniques” implies, the patient voluntarily holds his/her breath at some point in the breathing cycle. During a breath-hold, the beam is turned on, and dose is delivered to the tumor. As part of the implementation of the self-held breath-hold technique, a control system has been developed ^[85,86] for the Varian C Series accelerators, which makes use of the “Customer Minor (CMNR)” interlock. The patient is given a hand-held switch that is connected to the CMNR interlock circuit. When the switch is depressed, the CMNR interlock is cleared at the console, allowing the therapist to activate the beam. When the switch is released, the CMNR interlock is active, turning the beam off and disabling any further delivery until the switch is depressed again. It should be noted that although the therapist is the only person who can turn the beam on, both the therapist and the patient can turn the beam off.

Studies have shown that the most reproducible position tends to be at deep inhale or deep exhale. This, along with the potential dosimetric advantages of increasing the lung volume ^[78,79,81,83,87], makes deep inhale the preferred point for breath-hold. Therefore, the discussion in earlier sections regarding the advantages of DIBH and ABC would be similar to the advantages with this method. The self-held breath-hold system is not commercially available. A description of materials and methods for assembling such a system are given in references 85 and 86. This mode of treatment relies heavily on the ability of the patient to perform a breath-hold independently and to control the CMNR interlock circuit.

- **Self-held breath-hold with respiratory monitoring**

This technique is the same as the previous technique with the advantage that the patient respiration is monitored and the beam-hold condition occurs automatically instead of being in the hands of the patient. Monitoring the breathing is done using a commercially available device (Varian RPM), to monitor patient respiration and to control dose

delivery. An additional advantage of this technique over Free Breathing (FB) respiratory-gated techniques (discussed later) is that the treatments can be delivered more efficiently because the radiation is delivered continuously during the breath-hold. Some other advantages of this technique over FB gating have been discussed by Berson et al.^[88]

- **Breath-hold in combination with IMRT**

As indicated above, breath-hold methods are applicable to IMRT. The technological requirements are similar to those for respiratory gating: an accurate signal is needed to enable and disable dose delivery. For dynamic MLC, this signal would also control the interruption and resumption of leaf motion, whereas for helical tomotherapy, the signal in addition would enable and disable couch motion.

1.7.4 Forced shallow breathing with abdominal compression

Forced shallow breathing (FSB) was originally developed for stereotactic irradiation of small lung and liver lesions by Lax and Blomgren at Karolinska Hospital in Stockholm^[89,90] and has been used elsewhere.^[91-98] The technique employs a stereotactic body frame with an attached plate that is pressed against the abdomen. The applied pressure to the abdomen reduces diaphragmatic excursions, while still permitting limited normal respiration. The accuracy and reproducibility of both the body frame and the pressure plate have been evaluated by several groups, with the most comprehensive assessment reported by Negoro et al.^[92] FSB has predominantly been applied to early stage lung and liver tumors without mediastinal involvement or nodal disease. Typically, FSB has been used for stereotactic treatments, although the technology is also applicable to conventional lung treatments.

1.7.5 Real-time tumor-tracking methods

Another means of accommodating respiratory motion is to reposition the radiation beam dynamically so as to follow the tumour's changing position, referred to as real-time tumor tracking. Real-time tumor tracking can in principle be achieved by using an MLC

or a linear accelerator attached to a robotic arm or, alternatively, by aligning the tumor to the beam via couch motion. There are presently two methods by which the treatment beam can be repositioned in real time in response to tumor motion. The first one is MLC repositioning.^[99-102] The second method for adaptation uses a robotic manipulator to move the entire linear accelerator with 6 degrees of freedom. The Synchrony™ Respiratory Tracking System integrated with the CyberKnife® robotic linear accelerator (Accuray Incorporated, Sunnyvale, CA) is a realization of this method for real-time tumor tracking. In this approach, the robot (CyberKnife image-guided radiosurgery system) is coupled through a real time control loop to an imaging system that monitors the tumor position and directs the repositioning of the linear accelerator.^[89,103-105] It has the advantage of adapting to the full 3-D motion of the tumor. Tumor tracking is an extremely desirable approach to mitigate breathing induced tumor motion because under ideal conditions, continuous real time tracking can eliminate the need for a tumor-motion margin in the dose distribution, while maintaining a 100% duty cycle for efficient dose delivery.

Detecting the tumor position is one of the most important and challenging tasks in real-time tracking. The most direct form of real-time tumor tracking currently involves imaging the target region during treatment at a sufficiently high frequency. Given the period and irregularity of breathing-induced motion, this requires several images per second, which is equivalent to near-continuous fluoroscopy. The more frequent this imaging procedure, the lower the delivery error; however the x-ray dose will also increase. In each image, it is necessary to automatically locate the tumor (or its surrogate) and calculate its 3-D coordinates, which are then automatically transmitted to the beam-delivery system. In general, locating the tumor (or its surrogate) *via* imaging automatically is not a trivial issue.

Currently, there are four possible means of locating the tumor during treatment: (1) real-time imaging of the tumor itself via, e.g., fluoroscopy; (2) real-time imaging of artificial fiducial markers implanted in the tumor; (3) inference of the tumor position from surrogate breathing motion signals; and (4) nonradiographic tracking of an active or

passive signalling device implanted in the tumor. All of these methods are currently under development or used clinically.

Direct tumor imaging - In certain situations, it can be possible to detect a lung tumor directly in radiographic/fluoroscopic images acquired during treatment. For example, Murphy^[106] has done so for a lung tumor using an amorphous silicon x-ray detector at an exposure level of approximately 0.050 cGy. It should however be noted that most lung tumors will not present a well-defined high-contrast object suitable for automatic segmentation and image registration, nor will tumors in the pancreas and liver. Therefore, it is usually necessary to use an artificial marker as a surrogate for tumor position.

Tumor location using implanted fiducial markers – High atomic number metal markers implanted in tumours such as lung, pancreas, or liver can be readily observed in x-ray images. However, three or more fiducial markers must be used to allow measurement of tumor translation and rotation, and to determine marker migration by monitoring the distance between markers. The size, dimension and design of the markers are patient/site dependent and are chosen to minimize marker migration and invasiveness while maximizing their detectability. As examples, 2-mm-diameter spherical gold balls have been used for pancreas by Murphy et. al.^[103] Chen^[104], Murphy^[107] and Shirato^[59] have used 0.8-mm by 4-mm cylindrical gold seeds implanted into or near lung tumours. Gold is a very suitable material for the markers in that it is biocompatible and its high radio-opacity makes it detectable in fluoroscopic images at exposures as low as 0.018 cGy per image.^[59] A detailed review and guidelines for implementation techniques for fiducial markers has discussed in the report of AAPM Task Group 75.^[108] To reduce radiographic imaging exposure, hybrid tumor-tracking techniques are also being developed that combine episodic radiographic imaging and continuous monitoring of external breathing signals. However, this technique is based on the premise that external motion surrogates can accurately predict the internal tumor position for the time interval between image acquisitions.^[89,104-107,109,110]

Tumor position prediction based on surrogate breathing signals - In situations where continuous fluoroscopic imaging of tumor position is not feasible, it is necessary to infer tumor position from external respiration signals. To succeed, this technique requires that there be a high level of correlation between the measured respiratory signal and the position of the tumor in three dimensions. If the correlation is simple and stationary, it can be sufficient to measure it before treatment using a fluoroscope to document tumor position simultaneously with the external respiratory signal. The observed correlation can then be used to predict tumor motion during treatment based on the surrogate position. However, the physiology of breathing motion suggests that a consistent correlation is not necessarily a safe assumption. ^[89,111-115] If the correlation is not stable, it should be monitored and updated continually during treatment by acquiring images of the tumor position synchronously with the respiratory signal. ^[105] This can be accomplished with adaptive filter algorithms, which are designed to predict nonstationary signals by periodically updating the empirical relationship between the input (e.g., breathing) and the output (e.g., tumor position) signals. ^[107]

Nonradiographic tumor tracking - Seiler et al. ^[116] have described a miniature, implantable radiofrequency (RF) coil that can be electromagnetically tracked in three dimensions from outside the patient. Balter et al. ^[117,118] have reported on the performance of a wireless RF seed-tracking system for tumor localization. The electromagnetic approach could provide an alternative to the use of radiological imaging to track the tumor position.

- **Tumour tracking and IMRT**

The most sophisticated and yet challenging tumour tracking methods involve those that attempt to synchronize IMRT delivery with respiratory motion. The primary advantage of these methods is that the patient is allowed to breathe freely and linear accelerator operation need not be interrupted (as in gated and breath-hold methods). Keall et al. ^[99] demonstrated the feasibility of such an approach and showed that the dosimetric results obtained with the motion-synchronized approach were very similar to those for the static IMRT delivery to stationary targets. A similar approach is feasible with tomotherapy by

superimposing the respiratory motion on some combination of the MLC leaves, primary collimators, and couch.

1.8 Comparison of methods to account for respiratory motion

1.8.1 Summary and assessment of the methods

In the previous sections, the methods that have been developed to reduce the impact of respiratory motion in radiotherapy were discussed. Evidently, the choice of method depends on a number of factors including specific patient situation, available technology in the facility, etc. However, one would still like to know which approach is the best, if any of the available methods is an option. Below, a summary of the characteristics of the methods is provided based on which a conclusion may be drawn regarding the preferred method. Each characteristic is labelled positive (+) or negative (-).

- **Motion-encompassing methods**

- (+) Does not require any (expensive) technology
- (+) Does not cause any discomfort to the patient
- (+) Does not require the patient to comply with any particular instructions
- (-) Does not address the issue of large IM
- (-) Results in high NTCP, especially for tumours with large motion

- **Breath-hold techniques**

- (+) Addresses the issue of tumor motion and thus reduces NTCP to some extent
(Does not resolve the issue completely)
- (+) Does not require any (expensive) technology
- (-) Causes some discomfort to the patient
- (-) Requires the patient to comply with the instructions
- (-) Invasive (some methods, e.g., ABC)
- (-) Subjective to some extent, lack of ensuring mechanisms
- (-) Patient dependent (some methods, e.g., DIBH)

- (-) Reproducibility of immobilization location is an issue (in ABC)
- (-) Can be less effective and even counter-effective if tumour-surrogate relationship is not established properly

- **Forced shallow-breathing methods**

- (+) Does address the issue of tumor motion and thus reduces NTCP
(Does not resolve the issue completely)
- (-) Invasive/ Uncomfortable
- (-) Still some breathing motion present

- **Respiratory gated techniques**

- (+) Does address the issue of tumor motion and thus reduces NTCP
(Very close to resolving the issue completely)
- (+) The approach employs more modern and sophisticated technology
- (+) Does not cause any discomfort to the patient
- (-) Require some patient compliance
- (-) Duty Cycle, i.e., prolonged treatment time
- (-) Some residual tumor motion present
- (-) Requires additional technology to be added to the system
- (-) Can be less effective and even counter-effective if tumor-surrogate relationship is not established properly

- **Respiration-synchronized (tumor tracking) techniques**

- (+) Does address the issue of tumor motion and thus reduces NTCP
(Can potentially resolve the issue completely)
- (+) No duty cycle, i.e., prolonged treatment time involved
- (+) No residual tumor motion present
- (+) Does not require patient's compliance
- (+) Does not cause any discomfort to the patient
- (-) Requires additional (expensive) technology to be added to the system

- (-) Can have negative impact if tumor-surrogate relationship is not established properly

1.8.2 Selecting the preferred method(s)

The above summary indicates that each method has some advantages and some disadvantages. The first three methods listed either do not address the issue of tumor motion or solve the problem only partially. The last two methods, i.e., gating and tracking, tackle the issue in a much more fundamental and systematic way but they required more advanced technology. Therefore, if financial issues are not a problem and are set aside, gating and tracking are the two methods of choice. Gating still suffers from prolonged treatment time and residual tumor motion, two problems that are resolved in tracking. Therefore, given all the options and having all the necessary technology available, tracking would be the method of choice while gating would be the next option. It must be noted that the conclusions just made does not imply that any of the methods discussed above should be totally ruled out as each method has its own advantages and may be more suitable and/or feasible for a given situation.

1.8.3 The requirements for the preferred method(s)

Fortunately, technology for gating and tracking is already available (RPM-CyberKnife) and these methods are being used in various clinics. However, since both approaches rely strongly on knowledge of tumor position, they can fail or have detrimental effects if not provided with such knowledge properly. Therefore, the accuracy and precision of our knowledge of tumour position is essential to these methods. An inaccurate knowledge of the tumor position can result in partly missing the tumor (lower TCP) and irradiation of a larger volume of normal tissue (higher NTCP). Each of these two factors can by itself result in a lower TCP+.

As discussed above, acquiring tumour position directly is very difficult and with today's technology impossible in most cases. A common and favourable alternative would be to

use respiratory surrogates to infer tumor motion indirectly. Internal markers implanted in the tumor offer the most accurate information regarding target position during treatment; however, they suffer from two drawbacks, additional dose to the patient and invasiveness. Therefore, the benefits of accuracy need to be weighed against the cost and invasiveness (and associated risk) of implanting markers in tumours as well as against possible marker migration. External surrogates, on the other hand, do not have these problems but they certainly have their own issues

A number of external surrogates for tumour position and/or respiratory gating have been investigated and reported in the literature. These surrogates include spirometer,^[119-130] respiratory effort belt,^[131-134] skin markers^[135], Co2 sensors, temperature sensors, etc.,^[136] Among these, the spirometer, belt and skin markers are the most widely used ones.

Although these surrogates are being used in gating, tracking and 4D-CT on a regular basis, there are still some issues regarding their performance that have not been completely resolved. Comparing their predictive ability and (possibly) identifying the best surrogate, studying the reliability of their prediction of tumor position and finally in the case of skin markers, identifying the optimal locations and number of markers are some of these issues that we wish to resolve in this work.

Several relatively recent studies have looked at these issues and have reported interesting results^[135,137-141], although some shortcomings can be observed in either the methods employed or in the results reported in these studies. For example, some of these studies did not investigate the predictive ability of the surrogates and reported only the correlation coefficient between tumor motion and the surrogate.^[137] Other studies suffer from too few subjects and hence become anecdotal.^[138,139] In another work, decoupling of the surrogates has been overlooked^[140,141] although multiple points on the body surface were considered, and hence the points were partly coupled and therefore could not provide completely independent information.^[140,141] In one very recent study on tumor motion using skin markers, the markers were placed on the chest right over the lung.^[135] The underlying presumption here being that these locations on chest would

correlate better with lung motion than locations on the abdomen. This is not necessarily true because during breathing the lungs mostly expand from the lower end (close to the diaphragm) which causes a highly correlated high amplitude motion of the abdomen.^[142]

In the present work, every effort has been made to avoid the above mentioned shortcomings and make the study a comprehensive investigation of tumor motion prediction by simultaneously evaluating several surrogates.

1.9 The goal of the work discussed in this thesis

The goal of this thesis is “To compare three common surrogates of tumour position/motion (spirometer, skin markers and respiratory belt) and identify the best surrogate.” The best surrogate is one that has good physical characteristics (tolerable/comfortable to the patient), has high predictive ability and is reliable over the course of treatment. To do this the three common surrogates (spirometer, respiratory effort belt and skin markers) have been assessed as follows:

- Which surrogate has the best predictive ability?**
- How much does the prediction ability reduce IM?**
- How reliable it is?**

The study consisted of three systematic steps as described in the next three sections.

1.9.1 Establish and test the performance of the modalities needed for the study

The first step in performing the experiments was to build, upgrade and test all the apparatus. The Machine-Vision for tracking skin markers, the belt, spirometer and Fluoro recording all needed to be adapted and integrated for this work.

The Machine-Vision System The Machine-Vision system used for the skin markers was still in its developmental stages and therefore, more work had to be done before it could

be used clinically. Before being used for human measurements, the metric performance of the device needed to be measured. These Machine-Vision system and related issues will be fully discussed in Chapter 2.

Spirometer The spirometer used in this experiment was assembled in our lab and its performance was tested prior to the onset of the study. Also proper data collection using an analog to digital converter was ensured. Some preliminary tests on human subjects were performed at this stage, also described in Chapter 2.

Respiratory effort Belt The respiratory effort belt used for the experiment was also assembled in-house. The belt was also tested for its performance and simultaneous data collection with the spirometer using the same analog to digital converter. In this case too, some tests on human subjects were performed. The respiratory belt will also be described in more detail in Chapter 2.

Fluoroscopy A method by which the analog fluoroscopy images of the patient could be digitized and stored on a personal computer was developed. The Fluoro system was also tested for its performance and proper data collection before the onset of the actual experiment on lung cancer patients. Testing of the fluoroscopy will be described in more detail in Chapter 2 as a part the materials and methods.

1.9.2 Experiment on normal subjects

Following the preparation and calibration of all the apparatus, Phase-I of the study was designed to see how well the respiratory effort belt (Belt) and skin markers could act as surrogates for breathing as measured by the spirometer which is considered the gold standard for breathing ^[121-130]. This phase was done on normal volunteers. The underlying presumption was that tumor motion and breathing were coupled and therefore a good surrogate for breathing would potentially make a good surrogate for tumor motion. This phase of the study will be covered in Chapter 3 and Appendix B.

1.9.3 Experiment on lung cancer patients

Phase-II of the study involved lung cancer patients. The aim of this phase of the study was to assess the ability of various modalities to act as surrogates for tumor motion. Lung tumours were chosen for the study because breathing induced tumor motion is most common and best observed in lung cancer. This phase of the study will be covered in chapters 4.

CHAPTER 2

Experimental Apparatus

2.0 Introduction

Four different modalities were employed in this study: The Machine-vision system that tracks skin markers to measure surface motion; respiratory effort belt to measure chest expansion; the spirometer (SPR) to measure breathing; and fluoroscopy to measure tumor motion.

Three of these modalities, skin markers, Belt and SPR were used with normal subjects to study surrogates for breathing; and all four modalities were used for patients to study surrogates for tumor motion

All of these modalities will be described fully in this chapter; and will be referred to in chapters 3 and 4. More details are included here for the Machine-vision system as it was developed and upgraded in our lab, and more work was required to bring it to a functioning level for the purpose of this study.

2.1 The Machine-Vision system

2.1.1 Description of the system

The Machine-Vision system used in this work is adapted from the Patient Positioning Monitoring (PPM) system developed and described previously by Gerig et al. ^[55,143,] and El-Hakim.^[144]

The system is comprised of two CCD cameras (KP-M1U, Hitachi Denshi, Ltd. Japan) attached to the ceiling of the simulation room, approximately 1.4 m apart and 2.5 m from the treatment couch. Attached to each camera is a pair of infrared lasers (820 nm wavelength and 30 milliwatts output), one on each side (Figure 2.1). In order to track surface motion, retro-reflective markers, 2.0 cm in diameter, are placed on the surface of the human or phantom subject. The lasers illuminate the markers and the markers reflect the infrared light back to the cameras. In order to enhance the contrast of the retro-reflective markers, the cameras are equipped with infrared filters that pass only 820 +/- 5 nm light. The camera images are captured *via* a frame-grabber (Matrox Meteor II) and are processed on the main CPU. The result is the time-stamped three-dimensional position of each marker at an average sampling frequency of 5 Hz. The system is capable of tracking up to 18 markers simultaneously.

2.1.2 Calibration of the cameras

Each time the cameras are adjusted or moved, the system loses calibration, that is, the computer does not know the distance between and the orientation of the two images that come from the cameras. Therefore, a calibration procedure is performed to re-establish the spatial relationship between the cameras. A custom made phantom as described in the next section is used for calibrating the cameras.

(a)

(b)

(c)

Figure 2.1 PPM camera system, a) One camera with the two infrared lasers on its sides, b) relative position of the two cameras on the ceiling of the simulation room, and c) the relative position of the cameras and the fluoroscopy couch. Arrows show the position of the cameras in (b) and (c).

- **The phantom**

The phantom used for calibrating the cameras is a 53x53 cm² square aluminium plate (1 cm thick) with 18 columns on it (Figure 2.2a). The columns have been placed at various locations on the surface of the slab, including the four corners and the center. The columns are all 2.0 cm in diameter but vary in height, ranging from 2 to 10 cm. The tip of each column is covered with a reflective marker. The coordinate system is such that the surface of the slab defines the XY plane with Z being perpendicular to it and the origin being at its center. The position of the center of each of the 18 markers (tips of the columns) relative to the origin of the phantom was measured on an optical flat by a traceable precision caliper to better than ± 0.01 mm.

- **The calibration procedure**

In the calibration procedure, the projection of each CCD matrix into three-space is accurately determined using the known positions of the 18 markers on the phantom. This establishes the cameras' positions and determines the corrections required for optical aberrations in the lens/CCD system. The target extraction and measurement process has been described in detail elsewhere.^[143,144] It consists of several hierarchical steps. The segmentation process reduces the image into a binary image using an automatic thresholding routine. Target candidates are isolated by performing connectivity analysis to separate images into blobs. Blob parameters such as area, perimeter and radius are used to identify an object as a target to be measured. Sub-pixel target locations are found by centroid or by edge fitting using the original greyscale image rather than the binary image. A correction due to circle projections into the image is applied to the centroid. Target locations from different images are then matched using selected constraints to aid in the matching process. Once targets have been successfully matched, the calculation of their 3D locations is made using the calibration parameters and triangulation. The iterative, hierarchical matching process is controlled by sets of constraints determined by scene and light intensity, geometric relationships, and *a priori* knowledge as follows:

(a)

(b)

(c)

Figure 2.2 (a)The calibration phantom and (b) its coordinate system. (c) The female thoracic phantom on the oscillating stage to simulate breathing

1) The epipolar line: To match a point in one image with its corresponding point in the other, the image coordinates of the point in the first image and the calibration parameters of the two images are used to determine the relationship between x and y coordinates of the corresponding point in the second image. This is a straight-line equation, and the image coordinates of all recognized points in the second image are tested to determine which fall on this line.

2) The disparity constraint: The expected range of disparity (the difference between the coordinates from the two images) is computed from two sources, the depth constraint using the known *a priori* expected range of depth as determined during setup and the already matched points from the earlier iterations.

3) The ordering constraint: If more than one point satisfies the above constraints, an ordering constraint is applied using a minimization of residuals.

2.1.3 System performance evaluation

Before employing the Machine-Vision system clinically, the metric ability of the system, i.e., accuracy, precision and the ideal system geometry needed to be determined.

From basic geometry, for relatively small angles between the cameras, the measurements of the Machine-Vision system are expected to be more precise when the point of interest is moving perpendicular to the image plane of both cameras and less precise when the point is moving towards or away from the cameras. Therefore, based on this argument, a coordinate system with the following origin and three orthogonal axes will be employed to study the characteristics of the Machine-Vision system (see Figure 2.3).

The Origin (O_{inh}) - The point where the lines passing through the central axis of the optical plane (optical projection) of the two cameras meet

The X axis (X_{inh}) - The line going through O_{inh} parallel to the camera baseline

The Z axis (Z_{inh}) - The line going through O_{inh} and the midpoint between the cameras

Figure 2.3 Geometric arrangement for measuring precision and accuracy on (a) X, (b) Y and (c) Z axes of the inherent coordinate system of the cameras

The Y axis (Y_{inh}) - The line going through O_{inh} perpendicular to both the Z and X axes

The orientation of these axes depends only on the camera geometry and they are considered the major axes of the inherent coordinate system of the cameras and thus denoted by the subscript “inh”. Note that the X, Y and Z axes employed by the Machine-Vision system to indicate the position of a point are those constructed by the calibration phantom at the time of calibration (Figure 2.2b). These latter coordinates are not inherent to the geometry of the system and would depend on the position and orientation of the calibration phantom at the time of calibration.

The performance of the system, i.e., its accuracy and precision is highly dependent on the system geometry, i.e., the way that the cameras are positioned with respect to each another. The dependence of the system performance on its geometry, specifically, on the ratio α as defined below has been shown in a previous work by Gerig et al ^[143]

$$\alpha = \frac{AB}{CO} \quad (2.1)$$

where AB is the cameras baseline (line connecting the center of the two cameras lenses); and CO is the line connecting point C, the midpoint of line AB and the origin O_{inh} .

The ratio α can also be expressed in terms of θ , the convergence angle between the two cameras defined as (see Figure 2.3):

$$\theta = 2 \text{Arc tan} \left[\frac{\frac{1}{2} AB}{CO} \right] = \text{Arc tan} \left[\frac{1}{2} \alpha \right] \quad (2.2)$$

Gerig et al. ^[143] have shown that the best results were obtained at a ratio of 0.7 which corresponds to a convergence angle between the two cameras of 38.6°. Every effort was made during both system characterization and subsequent procedures to set the cameras

as close to this configuration as possible, although significant performance testing was done for various angles to verify these results.

2.1.3.1 Accuracy and precision of the system

When using skin markers to measure surface motion, one is interested in measuring the distance that a point on the body surface moves. Therefore, the precision and accuracy of the system should be looked at in this context. The approach taken was to employ the Machine-Vision system to measure the distance between two markers that were at a fixed distance with respect to each other and compare the measured values with the true value. Such measurements were performed at different positions on each of the three orthogonal axes X_{inh} , Y_{inh} , Z_{inh} . (see Figure 2.3). An optical bench with a precision of $\pm 0.1\text{mm}$ was used for measuring position.

- **Procedure**

1-Two 2.0-cm-diameter circular skin markers were placed on a rectangular block of Styrofoam at a fixed distance of approximately 5 cm. The selection of this distance was based on the expected maximum range of chest and abdominal surface motion in human subjects.

2-The true distance between the two markers was measured with a precision of $\pm 0.1\text{mm}$ using digital vernier caliper and milling machine by a traceable precision caliper.

3- The optical bench was placed on the X_{inh} axis, and the Styrofoam block with the two markers on it was placed on the sliding platform of the optical bench.

4- The sliding platform was initially moved to one side of the optical bench close to edge of the common field of view of the two cameras. It was subsequently moved towards the other end of the bench in increments of approximately 5.0 cm until it reached the opposite edge of the field of view (a total distance of 70 cm). At each measurement

position of the block, the distance between the two markers was measured by the machine vision system.

5- The procedure was repeated placing the optical bench on the Y_{inh} and Z_{inh} axes.

- **Data analysis**

1- The ratio of the measured distances (between the two markers) to the true distance was calculated and expressed as percentages. The measured distances (and the percentages to the true values) were plotted vs. the position in space. Such a plot would give a measure of the accuracy of the system as a function of the position in space.

2- A polynomial curve was fitted to the plotted data. The spread (standard deviation) of the measurements about the fitted curve was calculated. This would give a measure of the precision of the system.

- **Results**

Figure 2.4a, b and c show the measured distances between the two markers vs. position in space for the three axes both in absolute value and as a percentage of the true value. The boxes on the figures show the approximate region where the human data will actually be taken. The results for the standard deviation of the measurements for the three axes are 0.09, 0.14 and 0.15 mm for X_{inh} , Y_{inh} and Z_{inh} axes respectively.

- **Discussion**

We expect by the nature of the equipment to have smooth continues slowly changing errors over the region of interest. Therefore, it is reasonable to fit a low order polynomial to the data. Then the value of the polynomial at any point is the % error (accuracy) and the distribution of the data about the fitted curve can be considered the precision.

As seen on Figure 2.4, the accuracy is better than $\pm 0.5\%$ for X and Y axes and better than $\pm 0.7\%$ for the Z axis in the region of interest. These inaccuracies will reflect as a

Figure 2.4 The measured (by the Machine-Vision system) distance between two fixed points on a block as a function of the block position on the three axes of the inherent camera coordinate system. The true value as well as the ratio of the measured to the true values as percentages are shown. The boxes show the region of clinical interest representing a cube of approximately $40 \times 20 \times 30 \text{ cm}^3$.

contraction or expansion in the measured distances. The degree of the contraction or expansion depends on the region in the space where the measurement is being made. Based on these values, if one assumes a displacement of 5.0 cm, the introduced error will be less than 0.5 mm.

The precision found for the three axes are better than 0.15 mm. This can be translated to ± 0.3 mm, if one looks at 95% confidence level (or ± 2 standard deviation).

None of the above values are significant in the context of the clinical radiation therapy when considering the uncertainties involved in the other procedures such as tumor delineation and/or the determination of the GTV-CTV margins by the physician.

- **Conclusion of accuracy and precision**

Based on the values found for the precision and accuracy, the Machine-Vision system is a suitable tool for measuring respiration induced surface motion with the required accuracy.

2.1.3.2 Temporal resolution

Temporal resolution (sampling frequency) depends on the performance of the video card and the CPU. The present system consists of a Pentium II 450 MHz and a Matrox Meteor II frame grabber card operating under Windows 98. The user interface and processing calls are written in Visual Basic, while the calibration and matching routines are C-based dynamic linked libraries. Under these conditions, the maximum sampling frequency is approximately 7 Hz while the average is 5 Hz. It is assumed that the introduction of a video card capable of simultaneous, 2-channel capture, a faster processor, and more efficient programming would significantly enhance the capture rate. Nonetheless, the current sampling rate is considered more than adequate for this application.

2.1.3.3 Clinical feasibility testing

So far, we have examined (characterized) the Machine-Vision system by its ability to measure the position of stationary objects. To further evaluate the performance of the system, its ability to track moving markers, its applicability to human subjects and its clinical feasibility need to be tested. A part of these tests were done by employing an oscillating stage that had been built in the department. The stage employs a rotating drum and cam arrangement to provide motion in 2D. A female thoracic anthropomorphic phantom placed on the stage could simulate breathing (Figure 2.2 (c)). For the preliminary tests on the human subjects, colleagues and fellow graduate students were asked to participate.

- **Tracking the position of moving markers**

In order to test the Machine-Vision system's ability to measure the position of moving markers, three retro-reflective markers were placed on the thoracic phantom placed on the oscillating stage and the motion of the markers were tracked with the Machine-Vision system (Figure 2.5 (a)). This was done for a variety of frequencies (0.2 Hz to 1.2 Hz) and various amplitudes of motion (2 cm to 10 cm) of the stage-phantom apparatus. The system could successfully track and record the position of the moving markers.

- **Evaluating the clinical feasibility of the system**

As will be described in Chapter 4, the final and main stages of the study will involve experiments on lung cancer patients where fluoroscopy will be employed to record tumor motion. In order to evaluate the clinical feasibility of the system and prepare for that stage, and also identify possible flaws in the procedure, the machine vision and the Fluoro unit were applied simultaneously on the oscillating stage and the thoracic phantom in the simulation room.

Three retro-reflective markers were placed on the phantom. Lead markers were placed at the center of each reflector so that the marker positions could also be visualized under fluoroscopy. A tangential breast treatment was simulated, while the oscillating table

(b)

Figure 2.5 (a) Tracking the position of moving markers using the female thoracic phantom and the oscillating stage, (b) Fluoro image of the same phantom and markers with the position of the markers identified by lead markers.

provided 40 mm peak to peak motion at a frequency of approximately 0.25 Hz (4 seconds per cycle). Fluoroscopy images of the medial tangent were captured *via* a frame grabber, and saved to an AVI file. Simultaneously, the markers' positions were tracked using the machine vision system. Figure 2.5(b) shows image frame captures from the fluoroscopy of the simulated breathing cycle. The lead markers have been enhanced for clarity of presentation. Note that in a true clinical situation, the targets would not be expected to move in phase with the tumor. The position of the lead markers on the Fluoro images (which is the same as the position of the skin markers recorded by the Machine-Vision system) and the position of the tumor determined using the Fluoro images (described in section 2.4) could be used to verify the phase shift between tumor motion and surface motion. Note that the phase shift is initially determined using cross correlation method described in Chapter 3.

- **Testing the system on human subjects**

Next, some preliminary experiments on human subjects were performed to test the applicability of the system to human subjects, identify potential sources of malfunctioning and ways to improve the procedure and finally to practice and prepare for the actual experiments. Several skin markers were placed on the chest and abdomen of the subject and the subject was asked to perform various types of breathing such as normal breathing, shallow breathing and deep breathing (Figure 2.6(a)). The system displayed successful performance in simultaneous recording of the position of several skin markers on a human subject. An example of the recorded position of three skin markers vs. time is depicted in Figure 2.6(b). The subjects showed no signs of difficulty with the tools, procedure or instructions.

2.1.4 Summary for the Machine-Vision system

The Machine-Vision system demonstrated the ability to measure the 3D coordinates of a stationary marker and several moving skin markers in real-time simultaneously with an accuracy and precision better than 0.7% and ± 0.15 mm respectively. For the expected

Figure 2.6 (a) Preliminary experiments with six skin markers on a human subject. (b) The vector displacement of markers A, B and C. The waveform with lowest and highest amplitude belongs to markers A and C respectively.

range of measurements and considering the 95% confidence level, the uncertainty in the measurements will be much less than 1 mm.

In the present configuration, the average sampling frequency of 5 Hz is adequate to resolve simulated breathing and actual human breathing. In-phantom and preliminary studies demonstrated the capability of the system to track surface motion in human subjects as well. The application of the Machine-Vision system with other modalities to measure breathing on normal volunteers will be discussed in Chapter 3. Chapter 4 contains the detailed procedure of the application of the Machine-Vision system, breathing measuring tool; and fluoroscopy to lung cancer patients.

2.2 Spirometer

A Spirometer (SPR) is a device that measures airflow into and out of the lungs. The airflow measurement gives an indirect measure of the lung volume. Spirometry is the most direct way for measuring breathing and has usually been considered the gold standard for measuring breathing in studies of breathing induced tumor motion. ^[121-130] There are several types of spirometer ^[145-148], but the function of all of them is to convert the airflow into an electrical signal.

The spirometer used in this study was a TSD117 Airflow Transducer (Medium Flow Pneumotachograph) with the associated accessories all provided by BIOPAC System Inc., Goleta, CA. (Figure 2.7). The pneumotach is a bi-directional differential pressure sensor with a built-in diaphragm that is sensitive to pressure change and can convert the airflow into a pressure signal. To measure breathing, the airflow from the mouth is guided to the pneumotach (spirometer) through a mouthpiece, a filter and a hose. When using the spirometer, a nose clip is placed on the subject's nose so that during the breathing, the air flows only through the mouth. The flow of air in the pneumotach causes a pressure change on its diaphragm. This pressure change is converted to a voltage change in the circuit and produces an electrical signal. A DA100C general-purpose transducer amplifier, also provided by BIOPAC System Inc., was used to

Figure 2.7. The various components of the spirometer used to measure airflow. (a) The diaphragm and the transducer; and (b) the related accessories: (A) mouthpiece, (B) air filter, (C) hose, and (D) nose clip.

Figure 2.8 The accuracy of the Spirometer as a function of air volume

amplify the signal. The amplified signal was then digitized and recorded. This was done using an analog to digital converter (ADC) model ADAC/5501MF manufactured by IOtech, Inc., Cleveland, Ohio which was mounted on the control computer and was capable of digitizing and recording the data at a rate of up to 125 Hz.

The SPR was tested for its proper performance and accuracy of its measurements using a calibration syringe with a volume of 2.92 L (Model CS-3000 AM Systems Inc., Everett, WA, USA) with a precision of ± 0.025 L. The calibration results indicated an accuracy of 2% for the spirometer (Figure 2.8).

Note that the spirometer measures the airflow and not the air volume directly. The procedure to obtain air volume from the airflow will be discussed in the next chapter. A drift in the calculated air volume was observed and corrected for as will be discussed in the next chapter.

2.3 Respiratory Belt

Another tool used for measuring breathing that is also common in Respiratory Therapy departments and has frequently been used in studies involving breathing is a Strain Gauge commonly referred to as Belt. This device consists of a variable resistor attached to an adjustable belt that wraps around the subject's chest or abdomen. It measures breathing by measuring the thoracic or abdominal expansion. When the subject breathes or otherwise expands his chest, the pressure on the variable resistor causes its resistance to change. The change in the resistance is then converted to a voltage change and produces a signal in the circuit. The signal is amplified, digitized and recorded, as was the case for the spirometer.

The Belt used in this experiment was a TSD201 respiratory effort transducer manufactured by BIOPAC System Inc., Goleta, CA. (Figure 2.9). An in-house built amplifier was used to amplify the signals produced by the belt. The amplified signal was

digitized and recorded using the same ADC as for the spirometer and at the same rate of 125 Hz.

Figure 2.9 The respiratory effort transducer (Belt)

2.4 Fluoroscopy unit and frame grabber

The fluoroscopy unit used to view the tumor motion during the experiments was a Siemens Mevasim Simulator manufactured by Siemens Medical Solutions, Germany. The unit had the following specifications (see Figure 2.1c):

Simulator model	Mevasim model No 57.974.92
Tube model and number	1171461 V 2101 OP 11 150/12/50
Image Intensifier model and number	1742352 G5297

and had been tested for HARP (Healing Arts Radiation Protection Act) compliance. The Fluoro images viewed on the monitor of the simulator were transferred to a computer and grabbed at a frequency of 20Hz using a Matrox Meteor-II frame grabber and the associated software (MIL-Lite), all provided by Matrox Electronics System Ltd., Canada. Also, an in-house developed software written in Visual Basic was used to time stamp and record the images, both as an AVI file and as a set of individual images in bmp format.

CHAPTER 3

Surrogates for Breathing

3.0 Introduction

In Chapter 2, the metric performance of the Machine-Vision system was characterized and the system was successfully used to measure surface motion in some preliminary experiments on human subjects. The capability of the system to track surface motion in human subjects can be used to examine the possibility of using surface motion as a surrogate for breathing and tumor.

A clinical trial was developed proposing an experiment with two phases, Phase-I to be performed on normal volunteers and Phase-II on lung cancer patients. The trial was reviewed by CREC (Clinical Research Evaluation Committee) of The Ottawa Hospital Regional Cancer Centre; and OHREB (Ottawa Hospital Research Ethic Board). Included in this review was the scientific merit, criteria for subject selection, experimental procedure and subject safety. It is noteworthy that there was no radiation dose to the normal volunteers and the extra dose to the patients as a result of the experimental procedures would not exceed 1% of their nominal dose from routine therapy. This is well within the accepted dose variation due to calculation, setup, planning and patient conformation deviation that is of the order of $\pm 5\%$ of prescribed dose.

Therefore, before applying the system to patients, a set of systematic experiments were designed to be conducted on normal volunteers to determine if the skin markers and Belt

could act as surrogates for breathing. In this phase of the study (Phase-I), three specific issues regarding the relationship of surface motion and chest expansion with breathing were considered. These issues are as follows:

- 1- Is surface motion a good surrogate for breathing?
- 2- Is the relationship between surface motion and breathing invariant in time?
- 3- Is the relationship between surface motion and breathing independent of breathing type?

The same questions can be asked regarding chest expansion (Belt). To answer these questions, surface motion, chest expansion and breathing need to be measured simultaneously in multiple sessions and for various types of breathing.

Surface motion can be measured using the Machine-Vision described in Chapter 2 to track the 3D position of skin markers placed on the chest and abdomen of the subjects. The spirometer, referred to as SPR in this study, is considered the “gold standard” for measuring breathing.^[121-130]

In addition to SPR which is a direct measure of breathing, a number of tools have been used as surrogates for breathing by various departments in hospitals such as respiratory therapy, diagnostic radiology and radiation therapy; or in studies that somehow involve breathing. These tools include the strain gauge (respiratory effort belt)^[131-134], temperature sensors such as a Thermistor or a thermocouple, and a CO₂ sensors^[136]. Among these tools, the respiratory effort belt is of particular interest as it is the tool commonly used in diagnostic radiology and 4DCT protocols for respiratory gating^[149,150] and is also used by Siemens Medical System for gated radiation therapy. The respiratory effort belt, often referred to as Belt in this document, was also included in this study to examine its correlation with SPR and ability to predict breathing.

3.1 Subjects, materials and methods

Three modalities will be used in Phase-I of this study to investigate the relationship between surface motion and chest expansion with breathing. These modalities are the Machine-Vision system and skin markers (which measures surface motion), Belt (which measures chest expansion) and SPR (which measures breathing). These modalities were fully described in Chapter 2. The detailed application of skin markers to human subjects will be described in the next section.

3.1.1 Skin markers

For the skin markers, a retro-reflective material produced by 3M Inc. was used which has been previously used safely on human skin with no resultant side affects. ^[143] The markers were cut in circles 2 cm in diameter. The criteria for choosing the number and location of the markers on the subjects are described next.

- **Criteria used to select the number and position of skin markers**

Several criteria were used to determine the number and the optimal location of the skin markers to be placed on the subject's skin. These criteria were as follows.

- 1- The anatomical location of the markers must be easily defined for reference by other investigators
- 2- The positions of the markers must be reproducible for successive experiments
- 3- The positions of the markers must have relevance to the intended study
- 4- The selected positions must be common to all subjects in order to be able to compare different subjects
- 5- The markers must be as numerous as possible and distributed over as large an area as possible on the subject's upper body in order to obtain the largest amount of information in an individual experiment
- 6- Markers must be visible to both cameras

(a)

(b)

Figure 3.1 (a) The configuration of skin markers on human subjects and their relative position to internal anatomy. (b) A normal volunteer during an actual experiment with the skin markers, SPR and Belt

Figure 3.2 The Lung board used during the treatment for lung cancer patients. It has handles that the patient grasps comfortably, thus facilitating the reproduction of the patient's daily treatment position.

Table 3.1 Characteristics of the normal volunteers who participated in Phase-I of the study

	Sex	Age	Height (cm)	Weight (kg)	Body Circumference (cm)		# Of markers	# Of experiments	Days between the experiments
					Xyphoid	Umbilicus			
1	M	31	183	88	96	93	9	5	2 - 2 - 2 - 13
2	M	27	175	68	89	73	9	5	4 - 8 - 3 - 1
3	M	29	183	84	93	92	9	5	2 - 3 - 1 - 5
4	M	34	193	100	105	102	9	5	2 - 4 - 8 - 5
5	F	31	165	52	68	69	9	5	2 - 2 - 2 - 1
6	M	34	175	72	91	86	9	6	3 - 1 - 1 - 2 - 1
Ave		31.0	179.0	77.3	90.3	85.8			3.2
STD		2.8	9.5	16.9	12.3	12.6			2.8

- 7- Markers must be far enough from one another so that they are not confused with one another by the software

Based on these criteria, it was decided to place nine markers on the subject's abdomen and chest as follows. The first and second markers are placed just below the suprasternal notch on the Xyphoid process and just above the umbilicus respectively. A third marker is placed midway between the first two. Then two markers are placed on either side of each of the first three markers to make it a total of nine markers. The latter markers are placed on the skin as far laterally as possible while still being simultaneously visible to both cameras (Figure 3.1a). The markers are numbered from 1 to 9 as shown in the figure. In performing the experiments, occasionally, one, two, or in two cases, three of the markers had to be removed. This was mainly due to the subject-specific anatomy or breathing pattern that caused either or both of criteria 6 and 7 not to be met.

3.1.2 Subjects

6 normal healthy volunteers without any known medical conditions were chosen from among colleagues and friends to participate in the study. Table 3-1 summarizes the characteristics of the subjects.

3.1.3 Performing the experiments

- **Number of experiments and breathing types**

Each subject was examined five times. On a few occasions where an experiment could not be completed due to equipment problems, the subject was asked to do a replacement experiment making it a total of six experiments for that subject. In one case the subject was not available for the last experiment, leaving only four sets of data for that particular subject. At the beginning of the first session, the procedure was fully described to the subject and a signed consent was obtained from him/her.

Each individual session comprised of the three following parts, each running for approximately 5 minutes:

- 1- Normal breathing (NB)
- 2- Deep inspiration breath hold (INSP)
Taking a deep breath in – holding breath – breathing out
- 3- Deep expiration breath hold (INSP)
Taking a deep breath in – breathing out – holding breath – breathing in

- **Time synchronization of the computers**

The internal clocks of different computers are not necessarily reporting the same time. Even if two computers are synchronized at some time, they will usually drift out of synch due to small differences in CPU clock speed. Therefore, in order for two or more computers to record simultaneous events at the same time, they need to be synchronized prior to measurement. As will be described in section 3.2.4, it is essential for the various computers used in this study to have the same internal clock time. For this reason the two computers, one running the Machine-Vision system and the other running the SPR and Belt were time synchronized at the beginning of each experimental session.

To do this, the two computers were connected via Ethernet cable and a time-synchronization routine was applied. In this routine, the internal clock of one computer is assigned as the reference and is called the MasterTime, and that of the other computer is assigned as the subordinate and is called the ClientTime. Then a time in the future is specified to both computers when the internal clock of the subordinate computer (ClientTime) would synchronize with the internal clock of the reference computer (MasterTime). The two computers will then record the same time. This procedure was repeated before each experiment because we found that the computers gradually lost their synchronization at a rate of 1 to 2 seconds per week.

- **Procedure**

The subject was asked to lie down on the Fluoroscopy couch in the supine position with their hands holding the lung board exactly the same way patients would during an actual treatment. The Lung board is a radiation therapy device that is useful when a patient must lie with his or her arms up over the head (Figure 3.2). It has handles that the patient grasps comfortably, thus facilitating the reproduction of the patient's daily treatment position. After the position of the subject was secured, the skin markers were placed on his/her chest and abdomen as described earlier. In order to reproduce the markers in the same positions on subsequent experiments, three dots were put on the subject's skin around each marker with a fine tip magic marker used by radiation therapists. In addition to that, pictures and measurements were also taken in case the dots were washed off or faded out. Next, the belt was put around the subject's chest between the top and middle row of markers. Finally, the nose clip and mouthpiece were put on the subject's nose and mouth (Figure 3.1b). The experiment began and was carefully monitored throughout to ensure the subject's comfort and equipment performance.

After the completion of the experiment for each breathing mode, the subject was given a rest. During the rest period, the data was checked for successful recording and general soundness. The experiment then proceeded to the next part where the subject was asked to perform another breathing mode.

3.2 Data analysis

In order to answer the three questions discussed at the beginning of this chapter, the data obtained from the normal subjects were analyzed with the focus on determining two factors:

- The correlation coefficient of surface motion and Belt with SPR
- The ability of the skin markers and Belt to predict SPR

The raw data was not readily usable for analysis. Therefore, the first step in analyzing the data was to process the data as described below.

3.2.1 Integrating spirometer data (obtaining tidal lung volume from airflow)

The SPR measures airflow while what is needed for our work is the instantaneous air volume in the lungs. One can in principle obtain the tidal lung volume by integrating the airflow. However, this requires that the lung air pressure does not change (significantly) during breathing. This assumption is not strictly valid as the air pressure does change by ± 4 mm Hg during breathing ^[151], but this change is very small compared with the atmospheric pressure of 760 mm and introduces an error of only about 0.5%. and is ignored for the remaining of this work. A Matlab code was written that would integrate the SPR (airflow) data and determine air volume from it. The belt data, however, which is a measure of chest expansion, did not have to be processed this way and could be used directly for data analysis. Figure 3.3 shows an example of the airflow measured by SPR, lung volume (obtained by integrating the airflow) and chest expansion measured by the Belt.

3.2.2 Accounting for the SPR baseline drift

After the spirometer data was integrated to acquire air volume, a significant time-dependent baseline drift was observed in the processed signal. The drift was corrected for using the method described by Low et. al. ^[42] and used by other investigators.^[137] In this method, the local minima in the spirometry signal are identified. The minima are fit to quadratic polynomial and the fit volume is subtracted from the signal to yield a drift-free air volume.

3.2.3 Data down sampling

The SPR and Belt data were acquired at a much higher frequency than the skin markers data, 125 Hz vs. 5 Hz. Therefore, when comparing the measurements, selected data were

Airflow, Lung volume and Chest expansion as determined by SPR and Belt

Figure 3.3 Demonstration of typical waveforms of airflow as measured by the SPR (top), lung volume derived from integrating the airflow (middle), and chest expansion as measure by the Belt (bottom) obtained from normal volunteers over a time span of approximately 1 min. (For visual purposes, amplitudes not to scale).

extracted from the integrated SPR data and the Belt data to match the time stamp of the skin marker data.

3.2.4 Correlation coefficient – Phase shift - Cross Correlation

The correlation coefficient (based on Pearson's correlation coefficient) between two variables X and Y is computed as follows:

$$r = \frac{\Sigma XY - \frac{\Sigma X \Sigma Y}{N}}{\sqrt{\left(\Sigma X^2 - \frac{(\Sigma X)^2}{N} \right) \left(\Sigma Y^2 - \frac{(\Sigma Y)^2}{N} \right)}} \quad (3.1)$$

The data acquired from the three different modalities (SPR, Belt, Skin markers) would not necessarily be in phase and a phase shift could exist between each pair. In such cases, a straight calculation of correlation coefficient does not represent the true coupling between the two sets of data, even if a perfect correlation exists. The true correlation can be determined only by taking into account the phase shift. This can be done using the cross correlation method, described below and demonstrated in Example 3.1 and Example 3.2. It is important to note that any prediction model would require a phase shift term as a fundamental element if the model is to succeed.

In the cross correlation method, one set of data is shifted in time with respect to the second and the correlation coefficient between the two sets is calculated as a function of the time shift. If one plots the correlation coefficient vs. the time shift, the height of the maximum peak on this plot shows the best correlation between the two sets while the position of the peak would indicate the phase shift between the two sets.

Figure 3.4 Demonstration of phase shift in an AC circuit. (a) An inductive circuit-voltage and current are out of phase, (b) a circuit with a capacitor, (c) resistive circuit-no phase shift, (d) an AC circuit with resistor and inductor, and (e) an AC circuit with resistor and a capacitor inductor. [Diagram adapted from Communications Museum of Macao, <http://macao.communications.museum>]

Example 3.1: Phase shift and cross correlation

A demonstrative case: AC circuits and Periodic functions

A very well known example of phase shift in physics is an AC circuit. Such a circuit may contain a resistor, an inductor and/or a capacitor. A circuit that contains inductors and/or capacitors is called a reactive circuit. In a reactive AC circuit, the voltage and the current do not reach their amplitude peaks at the same time. In other word, they are out of phase. In an inductive circuit, the voltage leads the current (reaches its maximum before the current does) (Figure 3.4a) while in a capacitor, the voltage lags the current (reaches its maximum after the current does) (Figure 3.4b).

A circuit that contains only resistors is called resistive circuit. In a resistive circuit, the voltage and the current reach their amplitude peaks at the same time. There is no phase shift between the voltage and the current in a resistive circuit and the current is “In-Phase” with the voltage (Figure 3.4c).

In an AC circuit that contains a resistor and an inductor, the inductor opposes a change in current and stores energy from the power supply in the form of a magnetic field. The inductor voltage V_L leads the inductor current I_L by 90° but the inductor voltage V_L leads the power supply voltage V_{PS} by a phase angle Φ (Figure 3.4d).

In an AC circuit that contains a resistor and a capacitor, as the capacitor opposes a change in voltage and stores energy from the power supply in the form of an electric field. The capacitor voltage V_C lags the capacitor current I_C by 90° and the capacitor voltage V_C lags the power supply voltage V_{PS} by a phase angle Φ (Figure 3.4e).

Note that in an ideal circuit, the sine-wave current through and voltage across any of the above circuit elements (resistor, inductor and capacitor) will have exactly the same frequency but different amplitudes and some phase shift. Also, the sine-wave voltage across the various components of such an ideal circuit will have exactly the same frequency but different amplitudes and some phase shift.

Figure 3.5 Two sine waves with a phase shift plotted vs. time (left) and plotted vs. each other (right). (a) Negative correlation of, $r = -1$, (b) no correlation, $r = 0$, (c) a positive correlation, $0 < r < 1$ and (d) perfect correlation, $r = 1$

Figure 3.6 (a) Two sine waves with a time delay and (b) the correlation coefficient as a phase shift is applied to one of the sine waves

Figure 3.5 shows two periodic functions, e.g. two sine waves for four different cases of phase difference. In each case the plot of the two waveforms against each other is also shown. Note that as one waveform is shifted in time against the other, the correlation coefficient (and the shape of the plot) changes from -1 (-45° line) to 0 (a circle) to some positive value (an ellipse) and finally to +1 ($+45^\circ$ line).

Figure 3.6 shows two periodic functions, e.g. two sine waves, with a time delay (phase shift); and the corresponding curve of correlation coefficient when one set is shifted in time against the other. In this case, the correlation coefficient curve reaches maximum and minimum periodically. This is because every time the shift equals the time delay plus a multiple of one complete period, the data is again in phase.

The importance of the phase shift is that it shows the time delay between the two coupled events. In the case of the AC circuit with a resistor and an inductor in Example 3.1, the time that it takes for the power supply voltage V_{PS} to reach its maximum after the inductor voltage V_L has reached its peak. A vital prerequisite to obtain this time delay correctly is to time the two events with the same clock or with two clocks that are synchronized. Otherwise, the phase shift obtained would show not just the delay between the events but the sum of the time difference between the events (delay) and the time difference between the clocks.

The precise determination of the phase shift has important implications in tumor tracking or gating in radiation therapy. In tumor tracking, the linear accelerator uses a signal from a surrogate to follow the tumor. If the phase shift between the surrogate and the tumor motion is not considered or an incorrect phase shift is applied, the beam follows the tumor with a delay. This means that not only doesn't the beam irradiate the intended malignant tissue but instead, it irradiates the healthy tissue. This can have serious consequences in terms of tumor control and normal tissue complication. The same argument is true for gating where the system uses a signal from a surrogate to turn the beam ON whenever the tumor is in the beam's eye view and OFF otherwise.

Figure 3.7 Lung volume obtained from SPR data (blue) and chest expansion as measured by Belt (red) (a) as originally obtained, and (b) after the optimal phase shift applied. Part (c) shows the change in correlation coefficient as a function of phase shift. Amplitudes in (a) and (b) are not to the scale.

Example 3.2: Phase shift and cross correlation

A typical data case: Phase shift between SPR and Belt

Figure 3.7 shows a typical case of SPR and Belt data obtained in this study. Figure 3.7a shows the data before any phase shift being applied. The correlation coefficient in this case is 0.82. Figure 3.7b shows the two data sets at the optimal shift that yields the highest correlation coefficient (0.93). Figure 3.7c shows the correlation coefficient vs. the applied shift as the two data sets were being shifted relative to each other in time to achieve the optimal correlation coefficient. The maximum correlation coefficient between the two data sets in this example is 0.93 and it occurs for a phase shift of 50 time increments. With each increment being 0.008 sec (corresponding to 125 Hz), this yields a phase shift of 40 msec between the SPR and Belt. In other words, in this case, the chest expansion lags the airflow into the lungs by 40 msec. That is, the maximum chest expansion happen 40 msec after the maximum air volume is in the lung. Note that this is not a general rule and it is not necessarily the case for all subjects. Not only isn't the time delay the same for all subjects but in fact as will be seen, for some subjects the phase shift is in the opposite direction, that is, the signal from the belt leads the signal from the SPR (chest expansion precedes the airflow).

3.2.5 Prediction - Linear regression

When examining the possibility of surface motion to act as a surrogate for breathing, in addition to determining the correlation, another approach is to see how well surface motion (skin markers) and chest expansion (Belt) can predict breathing (SPR). In order to do this, we can solve a simple linear model as follows.

$$\mathbf{SPR}_t = \mathbf{a}_0 + \Sigma(\mathbf{a}_i \mathbf{x}_i + \mathbf{b}_i \mathbf{y}_i + \mathbf{c}_i \mathbf{z}_i)_{t-\Delta t} \quad (3.2a)$$

$$\mathbf{SPR}_t = \mathbf{a}_0 + \mathbf{a}_1 \mathbf{Belt}_{t-\Delta t} \quad (3.2b)$$

where i is the skin marker number (1 to 9); and $\mathbf{x}_i$, $\mathbf{y}_i$ and $\mathbf{z}_i$ are the Cartesian coordinates of the corresponding skin marker. The orientation of $\mathbf{x}$, $\mathbf{y}$ and $\mathbf{z}$ axes are with respect to

Figure 3.8 The relationship of the three axes of the Cartesian coordinates system X, Y and Z with each other and with the subject and/or patient

the body lateral, superior inferior (SI) and anterior posterior (AP) respectively (see Figure 3.8).

The constants $\mathbf{a}_0$ and the coefficients $\mathbf{a}_i$, $\mathbf{b}_i$, $\mathbf{c}_i$ in the linear model shown in equation 3.2a and 3.2b are determined by the least squares method as follows. Suppose that the data set consists of the points (u_i, v_i) with $i=1,2,\dots,n$. We want to find the function f such that $f(u_i) \approx v_i$. To attain this goal, we suppose that the function f is of a particular form containing some parameters which need to be determined. For instance, suppose that it is linear, meaning that $f(u) = au + b$, where a and b are not yet known. We now seek the values of a and b that minimize the sum of the squares of the residuals (S):

$$S = \sum_{i=1}^n (v_i - f(u_i))^2 \quad (3.3)$$

A more general form of the linear regression is when v is to be defined a function of a n -dimensional vector U instead a single variable u so that function f becomes $f(U) = a_0 + a_1 u_1 + a_2 u_2 + \dots + a_n u_n$. The same approach is applied in this case except that the variables and the coefficients are in a matrix form. Eq 3.2a (skin markers) is a case of multiple (matrix) variables while Eq 3.1b (for Belt) is a case of a single variable.

One can now test the model by using skin marker or Belt data to predict breathing (SPR). The ability of skin markers or Belt to act as a surrogate for breathing can be measured in terms of the correlation coefficient and/or the difference between the measured and predicted values.

Here the phase shift is denoted by affixing the subscripts $\mathbf{t}$ and $\mathbf{t}-\Delta\mathbf{t}$ to the SPR and skin marker (or Belt) data respectively. The determination of the phase shift is as before. To find the phase shift and correct for it in the prediction case, the linear model is applied multiple times and each time the entire skin markers data (i.e., $\Sigma(\mathbf{a}_i \mathbf{x}_i + \mathbf{b}_i \mathbf{y}_i + \mathbf{c}_i \mathbf{z}_i)$ term in equation 3.1) or the Belt data is shifted against the SPR data by one increment of

time. The correlation coefficient is calculated at each time and the constant and the coefficients (in the linear model) that correspond to the highest correlation coefficient are the ones that are used for modeling purposes. The number of time increments that the data are shifted to yield the maximum correlation would indicate the phase shift and thus the time delay between breathing and surface motion. Note that in this case, it is possible to apply a different phase shift to each (coordinate of each) marker instead of shifting all skin marker data together. However, this may not be necessary if the phase shift for the points and coordinates used in modeling are close to one another.

3.3 Results

Due to the large amount of collected data in Phase-I, an inductive reasoning approach was taken to analyze and discuss the data for this phase. That is to say working "bottom up" or moving from specific observations to broader generalizations and finally finish by developing some general conclusions. Therefore, the focus was first on examining the relationship between motions of the surface (and Belt) and breathing for one subject (volunteer number 1) and one type of breathing (normal breathing). This was investigated both on one day (to see the level of correlation) and over 5 days (to see the reliability of the one-day results). Following that, other types of breathing (INSP and EXP) for this subject were looked at. Finally the same issues were considered for the study population. The complete results are reported in Appendix B. The primary findings are reported and discussed in this section.

Figure 3.9 shows typical data for a single skin marker collected by the Machine-Vision system for a normal subject. In this figure, the X, Y and Z coordinates of a single skin marker are shown during (a) normal breathing (NB), (b) deep inspiration breath hold (INSP) and (c) deep expiration breath hold (EXP). Figure 3.10 shows the SPR and Belt data for the same subject and for the same three types of breathing.

Figure 3.9 The motion of a skin marker in each of the principle axes as measured by the Machine-Vision system during (a) normal breathing, (b) deep inspiration breath hold, and (c) deep expiration breath hold. Note that for clarity the waveforms are baseline shifted.

Figure 3.10 The tidal lung volume as obtained from SPR data (blue), and chest expansion as measured by the Belt (red) during (a) normal breathing, (b) deep inspiration breath hold, and (c) deep expiration breath hold. Horizontal axis shows the sampling number. The amplitudes on the vertical axis have been re-scaled and cannot be used for comparison.

Table 3.2 The amplitude of the skin markers motion (in mm) in the three direction averaged over all subjects For the three types of breathing

(a) For normal breathing (NB)			
	X	Y	Z
mean	3.28	5.31	13.82
std	1.69	3.41	9.18
Min	0.99	1.74	2.09
Max	8.58	16.15	32.84

(b) For deep inspiration breath hold (INSP)			
	X	Y	Z
mean	7.76	14.14	23.12
std	3.83	5.62	10.18
Min	2.15	3.56	9.29
Max	16.39	28.64	44.46

(c) For deep expiration breath hold (EXP)			
	X	Y	Z
mean	7.28	13.60	22.23
std	4.34	5.61	10.82
Min	2.37	3.32	6.99
Max	17.79	30.65	46.00

Table 3.3 The correlation coefficient of each of the three components of skin marketer and Belt with SPR averaged over all subjects and all five experiments

	NB	INSP	EXP
X	0.71	0.66	0.65
Y	0.85	0.87	0.85
Z	0.93	0.91	0.93
Belt	0.95	0.91	0.95

Table 3.2 summarizes the observed motion of the skin markers in the three directions averaged over all patients. As can be seen, for all three types of breathing, the motion is highest in the Z (Anterior/Posterior) direction and lowest in the X (Lateral) direction.

Table 3.3 is a summary of correlation coefficients between the skin markers in X, Y and Z directions with SPR and the correlation coefficients between Belt and SPR for six volunteers over five experiments recorded for three types of breathing. It can be clearly seen that the Z component of the skin markers' motion and the Belt both correlate very well with the breathing for all three types of breathing. It is of particular note that the X component of the markers motion is particularly poorly correlated with breathing for all three breathing types. The correlation coefficients were compared by applying a t-test. The correlation coefficients between X, Y and Z with SPR were shown to be statistically different. The Z component has the highest correlation with SPR while X has the lowest correlation with SPR. However, no statistical difference was observed between the correlation coefficients of Z and Belt with SPR (see Table B.18 in Appendix B). Therefore, at the 95% confidence level, Z and Belt are superior to X and Y.

To see the inter-subject variability, the correlation coefficients averaged over all five NB experiments for each subject are shown in Table 3.4. Also Table 3.5 shows the 5-day average of the variation in the phase shift that was applied to obtain the best correlation coefficient during NB. Similarly, Table 3.6 and Table 3.7 address INSP for the whole population while Table 3.8 and Table 3.9 provide the same data for EXP.

As can be seen, in our population, the Belt and Z component of the markers show the best correlation with SPR for all three types of breathing over the full population for all five experiments. Further, the variation in the phase shift required to achieve the best correlation coefficient is much smaller for Z.

Finally, the correlation coefficients between the SPR and the Z components of each of the 9 markers are shown in figures B.5, B.6 and B.7 in Appendix B. These data include all 5 experiments, the three types of breathing and all subjects. The figures indicate that

Table 3.4 The 5-day average correlation coefficient of skin markers and Belt with SPR for the normal volunteers during NB

	V1	V2	V3	V4	V5	V6
X	0.79	0.80	0.71	0.74	0.65	0.60
Y	0.92	0.88	0.83	0.81	0.85	0.83
Z	0.96	0.97	0.92	0.85	0.94	0.94
Belt	0.95	0.96	0.96	0.94	0.95	0.96

Table 3.5 The 5-day average variation in the phase shift of skin markers and Belt with SPR for the normal volunteers during NB (in msec)

	V1	V2	V3	V4	V5	V6
X	281±333	404±355	448±349	252±229	637±451	653±400
Y	62±24	234±159	153±162	264±273	122±190	633±404
Z	66±12	158±15	76±9	221±94	35±7	244±285
Belt	39	53	63	37	19	35

Table 3.6 The 5-day average correlation coefficient of skin markers and Belt with SPR for the normal volunteers during INSP

	V1	V2	V3	V4	V5	V6
X	0.80	0.71	0.70	0.56	0.74	0.46
Y	0.96	0.98	0.86	0.85	0.80	0.78
Z	0.94	0.94	0.89	0.91	0.91	0.88
Belt	0.94	0.96	0.91	0.92	0.78	0.94

Table 3.7 The 5-day average variation in the phase shift of skin markers and Belt with SPR for the normal volunteers during INSP (in msec)

	V1	V2	V3	V4	V5	V6
X	332±243	872±438	140±210	411±420	584±563	760±468
Y	117±17	290±50	92±61	370±419	176±116	335±436
Z	135±17	243±89	79±6	164±17	53±27	105±56
Belt	79	68	95	222	52	71

Table 3.8 The 5-day average correlation coefficient of skin markers and Belt with SPR for the normal volunteers during EXP

	V1	V2	V3	V4	V5	V6
X	0.76	0.78	0.55	0.68	0.57	0.57
Y	0.96	0.96	0.81	0.81	0.78	0.79
Z	0.95	0.96	0.90	0.93	0.93	0.93
Belt	0.96	0.97	0.93	0.92	0.93	0.96

Table 3.9 The 5-day average variation in the phase shift of skin markers and Belt with SPR for the normal volunteers during EXP (in msec)

	V1	V2	V3	V4	V5	V6
X	345±502	644±327	694±384	433±441	484±383	654±316
Y	82±14	216±26	188±259	351±277	84±74	225±74
Z	90±22	155±75	97±36	232±8	32±12	174±63
Belt	50	93	71	210	40	110

although for a particular subject, some markers may correlate better or worse with SPR, a general conclusion that enable us to identify the best marker(s) cannot be drawn.

3.4 Conclusion

We concluded that, as many others have shown, the surface motion can be used as a surrogate for breathing. In particular, we have seen that the AP motion of the markers is the most reliable and shows the least day-to-day variation while, no one particular marker location was substantially better than any other for all subjects in our population. Further, our results indicated that the belt correlates well with SPR and can potentially act as an adequate surrogate for breathing. The correlation between Belt and SPR was similar to the correlation between Z component of skin marker (motion in AP direction) and SPR.

Our findings in this part of the study are in excellent agreement with the results of Cala et. al.^[152] where they concluded that spirometric volumes can be estimated very accurately and directly from chest wall surface markers. Also, our findings regarding the Belt agree with the observations made by Kubo and Hill^[136] indicating that strain gauge (belt) and pneumotachograph (SPR) track each other well.

In a more recent study on normal subjects and lung cancer patients, Koch et. al.^[140] have investigated the correlation between lung motion in 2D and surface motion for a variety of breathing types. They found a variety of correlations between the motion of the lung and surface motion. Their general finding was that lung motion in the SI direction correlated better with surface motion than lung motion in the AP direction did. It should be noted that in that study surface motion was measured using tubular markers that are placed around the body contour. This method of surface motion assessment as described in their paper is very similar to the belt techniques used in our study to measure chest expansion. While what we referred to as surface motion in our study was the 3D motion of skin markers attached to the body surface. The ability of 3D assessment of skin marker motion enabled us to distinguish between the motion of the markers in different directions and identify the best and the worst components of the motion. It is important

to note that the study done by Koch et. al measured lung motion directly as opposed to measuring breathing. This distinction between breathing and lung motion is very important and has often been overlooked by many workers. This will be discussed in the next chapter in terms of our findings of tumour motion in the chest.

In summary, surface motion (skin markers) and Belt are both viable surrogates for breathing and lead us to believe that they have the potential to act as surrogates for respiratory-induced tumour motion. This is examined in chapter 4.

CHAPTER 4

Surrogates for Tumor Motion

4.0 Introduction

In Chapter 3, we examined the ability of skin markers and Belt to act as surrogates for breathing. In that chapter, it was shown that

- 1- Skin markers can be successfully used on human subjects
- 2- There is excellent correlation between surface motion (selected coordinates) and breathing (SPR) for various types of breathing (NB, INSP, EXP)
- 3- There is a high level of correlation between chest expansion (Belt) and breathing (SPR) for various types of breathing (NB, INSP, EXP)
- 4- The results for both skin markers and the Belt were reliable over several days

Based on the above findings, we concluded that both skin markers and Belt can act as surrogates for breathing and thus act as a clinical substitute for the current tools used to measure breathing.

This chapter now examines how well the three technologies can act as surrogates for tumor motion. Specifically we will address two questions:

1- How do the various surrogates compare in predicting tumor motion?

Is there a “best” or “worst” surrogate?

2- Are surrogates reliable in clinical practice?

How well does the tumour-surrogate relationship hold during a course of radiotherapy?

Are the surrogate-based margins established on day-1 valid on a later day, e.g., on day-20?

The answer to these questions lies in the determination and comparison of internal margins (IM) both for the non-surrogate based case and for various surrogates on different days. The concept of Internal Margin (IM) was introduced in Chapter 1 and was defined as that component of PTV that accounts for internal tumor motion. ^[6]

4.1 Subjects, materials and methods

In Phase-II of the study on lung cancer patients, breathing, surface motion, chest expansion and tumor motion are to be measured. Therefore, all four tools discussed in chapter 2 will be required. These tools are the Machine-Vision system and skin markers (to measure surface motion), Belt (to measure chest expansion), SPR (to measure breathing) and Fluoroscopy (Fluoro) unit along with a frame grabber (to view and record the tumor motion to be quantified). These modalities were fully described in Chapter 2. The use of skin markers on normal subjects was described in Chapter 3. The application and criteria for the skin markers are exactly the same for patients as they were for the normal subjects,

4.1.1 Subjects

10 patients with non-operable fluoroscopically visible primary lung tumors were selected based on their suitability for the experiment as described in the clinical trial (see Appendix A), and their agreement to participate. At the beginning of the selection

process, the procedure was fully explained to the patients and an REB approved signed consent form was obtained from those who were selected and agreed to participate. Table 4.1 summarizes the characteristics of the subjects.

4.1.2 Experimental procedure

Each patient was tested twice, once during the normal treatment simulation (in preparation for the treatment) prior to the first fraction of radiation therapy and again after four weeks of treatment. The same protocol was followed in both sessions as follows. At the beginning of each session, the three computers (one running the Machine-Vision, another reading the SPR and Belt data and the third acquiring the Fluoro images) were all electronically synchronized to a common time as described in chapter 3.

The patient was positioned on the simulator couch in the supine treatment position with their hands holding the lung board (see Figures 3.1 and 3.2). The skin markers were placed on the patient's chest and abdomen at the same locations on the skin as for the normal volunteers as described in Chapter 3. In order to be able to reposition the skins markers in the same positions for the second experiment, three dots were put around each skin marker using a magic marker. Also, pictures and measurements were taken as back up in case the marks were lost.

For the Fluoro unit, a radio-opaque grid was inserted between the x-ray tube and the patient to provide a linear scale for tumour motion and size for data analysis. Images were acquired at 70-75 kVp and 2.0- 3.0 mA. The unit was initially run for a short period of time for position adjustment purposes. During this preliminary Fluoro, the table was moved laterally and longitudinally to ensure that the tumor was approximately at the centre of the Field Of View (FOV).

For the Machine-Vision system, with a live view of the markers, the markers were observed during breathing to ensure that both cameras could view all the markers throughout the breathing cycle. Adjustment of the patient position was done if necessary.

Table 4.1 List of patients and some characteristics

Patient	Sex	Age	Tumor type	Tumour location	Total dose (Gy)	# Of fractions	Tumor size (cm ³)	Max size ¹ (cm)
1	F	58	NSCLC	RUL	66	33	107.47	6.7
2	M	65	NSCLC	Right Hilum	62.5	25	33.51	5.8
3	M	67	NSCLC	LUL	62.5	25	0.61	1.9
4	M	67	NSCLC	Lt Hilum	66	33	102.27	5.5
5	M	46	SCLC	LLL	60	30	0.93	3.0
6	M	66	NSCLC	Left Hilum	66	33	14.32	3.0
7	M	77	NSCLC	RLL	55	20	8.18	3.1
8	M	83	NSCLC	RLL	60	20	50.02	6.9
9	F	72	NSCLC	RUL	60	20	2.64	2.0
10	M	75	NSCLC	LLL	60	20	8.18	3.7
Mean		67.6			61.8		32.8	4.2
STD		10.4			3.5		41.1	1.9

NSCL- Non-Small Cell Lung Cancer

SCLC-Small Small Cell Lung Cancer

RUL- Right Upper Lobe

RLL- Right Lower Lobe

LUL- Left Upper Lobe

LLL- Left Lower Lobe

Rt Hilum- Rt Hilum

Rt Hilum- Rt Hilum

¹ Maximum size relates to the size of the tumour seen on diagnostic imaging prior to treatment (physicians' most accurate description of the size of the tumour)

Following that, a quick preliminary acquisition was run for the skin markers to ensure proper data collection by the system. For the first few patients, the scout acquisitions indicated data from marker number nine was intermittent indicating that this marker was not visible to both cameras simultaneously at all times during the breathing cycle. This marker was removed for these patients and subsequently, for the rest of the patients to ensure consistency in the study population. Thus for the patient population the number of skin markers was eight (markers 1 through 8) instead of the nine markers used for the normal volunteers.

Having established the position and orientation of the patient, the belt was put around the patient's chest between the top and middle row of markers and the patient was fitted with the nose clip and the SPR mouthpiece. A quick scout data acquisition procedure was also run for the SPR and Belt to test for their proper performance.

Once all preliminary tests were completed and the patient was positioned properly on the simulator table, staff left the room, all data acquisition systems were started and then the x-ray beam was turned on.

Each acquisition lasted for approximately 1 minute and data from all four modalities (Machine-Vision, SPR, Belt and Fluoro) were acquired simultaneously. During the experiment, the breathing instructions were given to the patient verbally via an intercom audio system from the console as follows. The patient was first asked to breathe normally for about 45 seconds (NB part). Following that he/she was asked to take two deep breaths, holding their breath for approximately 3 seconds at full inspiration each time (DB part). The patient was instructed to return to normal breathing just before the termination of the procedure. The gantry of the Fluoro unit was not moved or rotated during the experiment. Therefore, the recorded images were all anterior-posterior projections of the tumor and they were all of the same FOV.

4.2 Data preparation

4.2.1 Air/Lung volume determination, data down sampling and drift correction

As was the case in Phase-I, the skin markers and belt data measured the needed variable directly (surface motion and chest expansion) while the spirometer data (airflow) was integrated to yield the air/lung volume. Also, the time-dependent baseline drift observed in the processed SPR signal was corrected for as described for the normal volunteers. As before, the spirometer and belt data were acquired at a frequency of 125 Hz while the sampling rate for the Fluoro and the skin markers were 20 Hz and 5 Hz respectively. Therefore, selected data were extracted from the integrated SPR, Belt and Fluoro data to match the time stamp of the skin marker data.

4.2.2 Tumour position acquisition from recorded fluoroscopy images

The Fluoro images that had been selected (to match the frequency of the skin markers data) were analyzed off-line frame by frame by the radiation oncologist in our group to acquire tumour position vs. time in two directions, Sup/Inf and Lateral. Microsoft Photo Editor software was used to analyze the images sequentially. On each image, first the tumour was located and then a rectangular box was drawn around the entire tumor. To minimize the chance of confusing tumor with other normal structures, the fluoroscopic position of the tumor was compared to that seen on the patient's diagnostic CT scan obtained prior to treatment. The same size box was used to define the tumor on every image and the position of the top left corner of the box was recorded and used as the tumour position (Figure 4.1). For cases when there was obvious deformity of the tumor with respiration, an attempt was made to keep the centre of the tumor in the centre of the rectangle. For each case, the pixel position between two hash marks on the measurement grid (indicating a distance of 2 cm) was measured in pixels. This calibration factor was then used to determine the absolute magnitude of a) tumor size and b) tumor

Figure 4.1 A typical fluoroscopy image in the AP direction that was acquired from patients. The box that was placed around the tumor during image analysis is shown in black. The red box indicates the region within which the tumor moves when the patient breaths. The arrows on the image indicate the 2 cm scale at the isocenter.

position. Note that the 2 cm distance between the hash marks is valid at an SAD (Source to Axis Distance) of 100 cm. Therefore, although an SAD of 100 cm was used during the experiment, a 2.5% inconsistency is still present for the calibration if one assumes a tumour position of ± 2.5 cm from the 100 cm plane.

4.3 Data Analysis

4.3.1 Linear regression and Cross correlation

Upon the completion of data collection and preparation, four sets of data were available for each one of the two experiments on each patient: Belt data; SPR data; skin markers data; and tumor data. Note that the skin markers data included the data for 8 markers in the three X (lateral), Y (Sup/Inf) and Z (AP) directions, making a total of 24 pieces of skin marker data. Also, the tumor data had two components, the motion in the lateral direction (X) and the motion in the Sup/Inf direction (Y).

To predict tumour position from the surrogates, the data from the normal breathing part of the first experiment (NB-1) was divided into two parts, (NB-1a and NB-1b). A linear model as shown in Equations 4.1a to 4.1c, was applied to part “a” of the normal breathing in experiment 1 (NB-1a) to establish a relationship between the tumor and each surrogate (SPR, Belt and skin makers). The model was applied to X and Y motion separately.

Tumour_t = a₀ + a₁ SPR_{t-Δt}	For SPR	(4.1a)
Tumour_t = a₀ + a₁ Belt_{t-Δt}	For Belt	(4.1b)
Tumour_t = a₀ + Σ(a_i x_i + b_i y_i + c_i z_i)_{t-Δt}	For Skin Markers	(4.1c)

The constant (**a₀**) and the coefficients (**a₁** in the case of SPR and Belt; and **a_i b_i c_i** in the case of skin markers) in each equation were determined using the least squares method. The model was subsequently used to predict the X and Y tumour position in parts NB-1b and DB-1 of Experiment 1, and NB-2 and DB-2 of Experiment 2 (Figure 4.2).

Figure 4.2 A typical breathing waveform obtained from the SPR data for the two experiments on a patient showing part 1 of the normal breathing in experiment 1 (NB-1a) that was used to establish the tumor-surrogate relationship for this patient and this surrogate; as well as parts NB-1b and DB-1 from the same experiment and part NB-2 and DB-2 from the second experiment where the relationship was subsequently used to predict the tumor position for this patient.

The cross correlation analysis described in Chapter 3 was applied here. In this case the phase shift was applied to the surrogate data (SPR data, Belt data or the entire set of skin markers data) to maximize correlation with the tumor motion data (in either X or Y direction) one step at a time. At each time step, the linear model was applied, the constant and parameter(s) were calculated and the tumor position was predicted for concurrent data (i.e., for Experiment NB-1a itself). The matching between the tumor and surrogate that resulted in the highest correlation coefficient between the measured and predicted tumor position for this part yielded the phase shift. The same phase shift was applied when using the surrogate data to predict tumor position in the rest of Experiment-1 and in Experiment-2.

4.3.2 Internal Margin (IM) determination

The approach taken to answer the questions posed at the beginning of this chapter was to determine the margins required to irradiate the tumor to a certain level for each surrogate and for the non-surrogate based case and compare these margins. This will be discussed below in the section dealing with the scoring function.

Figure 4.3 depicts a typical example of tumor position prediction by a surrogate. The predicted and measured tumor positions, along with the difference between the two, are shown. The difference curve shown in this figure is very important in that the amplitude of this curve determines the required IM during the treatment when the surrogate-based model is applied. This will be described in the next section.

Figure 4.4 is a depiction of the IM for a non-surrogate and a surrogate based treatment of a moving tumor. In part (a) of this figure, a field that is large enough to cover the entire region occupied by the moving tumor is shown (non-surrogate based case). Part (b) of the figure shows a (hypothetical) case where a perfect surrogate is used and hence there is no error or uncertainty in the prediction. In this case, no internal margins is needed as the

Figure 4.3 An example of the predicted and measured tumor position and the difference. Note that the error defines the required Internal Margin (IM) when using the surrogate to track the tumour. (Figure from P05 (patient number 5) data for normal breathing (NB-1b); Surrogate, SPR; tumour motion in the Y (Sup/Inf) direction)

Figure 4.4 Internal Margin (IM) for a non-surrogate based, a perfect surrogate and an imperfect surrogate. Note that for the surrogates based case, the uncertainty (error) in prediction defines the required IM.

position of the tumor is known precisely. Therefore, a radiation field just as large as the tumor can track the tumor and irradiate it completely at all time. Finally, Figure 4.4(c) depicts a more realistic scenario where the surrogate has some uncertainty in its prediction. In this case, the radiation field size must be increased by an amount equal to the uncertainty in the predicted tumor position. In other words, the uncertainty defines the internal margin.

Note the difference in the nature of the two margins for the non-surrogate based and surrogate based cases (Figure 4.4(a) and Figure 4.4(c)). In the non-surrogate based case, the margin equals or directly relates to the amplitude of the tumor motion. In the surrogate based case, the margin equals or directly relates to the uncertainty in prediction (Figure 4.5). Therefore, the surrogate-based IM depends on the uncertainty in the surrogate prediction of the tumor position. Figure 4.6 shows an example of a good prediction (small IM) and an example of a poor prediction (large IM).

- **Surrogates**

The three surrogates considered in this work are the SPR, Belt and skin markers. For the skin markers we examined the use of “All markers”, as well as three other combinations. These combinations were central column (Col), central row (Row) and the central marker, i.e., marker number five 5 (One Marker) as shown in Figure 4.7. The reason for considering these other combinations was to see how crucial the number of markers is in the ability of the skin markers to predict tumor motion. In other words, are that many makers needed and if not which combination is best?

It was observed that for all marker locations on the patient chest, the marker motion measured in the X direction (Lateral) was usually quite small and the X coordinate of the data was dominated by noise (also seen and discussed in Chapter 3). This was confirmed by low correlation between this coordinate and breathing in the case of normal volunteers, as well as a poor correlation between this coordinate and tumor motion. Therefore, ignoring the X coordinate of the markers could be beneficial. This was examined by looking at “All markers”, once with all three coordinates and the again with

Figure 4.5 The IM's in non-surrogate-based (A), and surrogate-based cases (B). Note the difference in the nature of the two margins. In non-surrogate based case, the margin relates to the amplitude of the tumor motion. In surrogate based case, the margin relates to the uncertainty in prediction

Figure 4.6 Demonstration of the predictive ability of the surrogates. (a) Example of good prediction, (b) example of poor prediction

Surrogates

Figure 4.7 The various surrogates. Note that in the case of skin markers, four different combinations were investigated: All Markers, Row, Col, and One marker.

Tumor model

Figure 4.8 The ellipsoid tumor model and its relation to the box that was put around the tumor when analysing the fluoro images

the exclusion of the X coordinates. The prediction excluding the X component was slightly better than that including X although the difference was not statistically significant. Therefore, the model excluding the X coordinates was used and this is what will be meant by ‘All Markers’ in all future discussions.

For the case of a single marker (One marker), instead of using the three coordinates X, Y and Z, the projection of the motion on the XZ plane was used. This was done to create a case similar to that used by some commercial systems such as RPM (Varian Medical Systems). This way the validity of their procedure could be tested as well.

- **Scoring Function**

In clinical situations, one is normally not looking for a margin that would guarantee the exposure of the entire tumor volume to 100% of the prescribed dose. Such a margin often results in the exposure of a large volume of healthy tissue and therefore clinicians usually compromise the tumor coverage in order to reduce the normal tissue irradiation. The final decision is made by the physician based on the type and location of the tumor, the surrounding tissue and the presence of any organ at risk near the tumor site. Clinically, most planning systems allow you to prescribe to a Dose Volume Histogram (DVH) such that a certain percentage of the target volume (95% or 100%) would receive a minimum dose, e.g. 95% of the prescribed dose. For the purpose of this study, the radiation oncologists in the group were consulted and it was agreed to use the 100% volume, 95% dose as the scoring function in comparing various IM's. At the cellular level, this means that every cell in the tumor would receive at least 95% of the prescribed dose. Note that this is different from 95% of the tumor volume receiving at least some minimum prescribed dose. In the latter case, there may be cells in other 5% of the tumor that receive zero dose.

- **Tumor Model: An Ellipsoid**

The determination of the IM requires the size and shape of the tumor to be known. However due to the complexity of such an approach, the tumor was modeled as a known geometrical shape with its dimensions acquired from the box that was put around the

tumor during Fluoro image analysis. Given that the A/P dimension of the tumor was not available from the data, it was felt by the radiation oncologists in the group that for this work it was reasonable to model the tumour as an ellipsoid. Therefore, the tumor was assumed to be an ellipsoid with two of its three major axes equal to the two sides of the box that was created during Fluoro image analysis. The third axis of the ellipsoid (the dimension of the tumor with no information available) was assumed to be equal to the lateral axis (Figure 4.8). This assumption was agreed upon by the two radiation oncologists of our group as a good approximation of the actual tumor shape and size. The shape and size of the tumor was considered invariant with time during the treatment.

Another assumption that was made in determining the IM's was to assume that the radiation field had a zero penumbra, that is to assume a Heaviside or step function for the dose distribution in the field (Figure 4.9). With this assumption, time inside the beam edge is the same as dose, i.e., "100% tumor volume being irradiated to 95% of the prescribed dose" is the same as "100% of the tumor volume being in the field 95% of the time". This simplification makes the data analysis possible without requiring any further assumptions regarding the actual dose distribution, as time would serve that purpose.

- **Dose-volume histogram**

Given the shape and size of the tumor and the dose distribution, a method is required to obtain the desired scoring function for tumor coverage, in this case 100% volume, 95% dose (or time). In order to do this, an Excel file was developed to generate dose-volume (time-volume) histograms. The measured tumor size and tumor position as well as the position predicted by each surrogate for NB and DB were entered into the file. For a given margin, the volume of the tumor that would fall within the field at any given time was calculated by integration. Binning the data and plotting the volume vs. time gave a dose volume histogram for this margin (Figure 4.10)

The file was designed and automated such that the margin could be changed and the calculation and plotting be automatically changed accordingly. From the resulting DVH's one could determine the margin for the desired tumor coverage, in this case 100%

Figure 4.9 Depiction of idealistic and realistic dose distribution

Figure 4.10 An example of a generated Dose-Volume Histogram (DVH)

volume, 95% time (dose). Further macros were written to observe various margins for one surrogate, or the behaviour of various surrogates for a given margin simultaneously (Figure 4.11).

Therefore, one could directly extract the IM's necessary for the desired tumor coverage for the non-surrogate case and for each surrogate. This could be done for either experiment 1 or experiment 2; or for the two breathing types, NB and DB.

4.4 Results

4.4.1 Tumor motion amplitude

The amplitude of tumor motion in the two directions was determined using the results of tumor motion quantification done by Fluoro image analysis and was calculated by taking the difference between the lowest and the highest positions of the tumor (Max-Min). This was done separately for the Lateral (X) and Sup/Inf (Y) directions. The measured tumor motion amplitudes for all 10 patients are shown in Tables 4.2(a) through 4.2(d). These results include normal breathing (NB) and deep breathing (DB) in both Lateral and Sup/Inf direction during the first and the second experiments.

4.4.2 Internal Margins

The method for determining the IM from the DVH was described earlier in this chapter. The complete set of IM's extracted from the DVH's both for the non-surrogate based case and for the various surrogates are given in Tables 4.3 through 4.6. The margins shown here are the margins needed for 100% tumor volume covered 95% of the time. Tables C.1 through C.4 in Appendix C show the margins needed to cover 100% of the tumor volume 100% of the time. As pointed out before, the former is what is actually being used in the data analysis that follows while the latter is listed for reference purposes.

Figure 4.11 Dose-Volume histogram. (a) Comparison of various surrogates for a typical margin (3 mm) and (b) comparison of target coverage for different margins for one surrogate (All skin markers), the 100% volume, 95% dose is indicated by a star;

Table 4.2 Amplitude of tumour motion in Lateral (X) and Sup/Inf (Y) directions (in mm) for a) normal breathing, experiment 1 (NB-1a and NB-1b); b) normal breathing, experiment 2 (NB-2); c) deep breathing, experiment 1 (DB-1) and d) deep breathing, experiment 2 (DB-2)

(a) NB-1			(b) NB-2		
Patient	X	Y	Patient	X	Y
P01	7.50	4.50	P01	8.40	5.40
P02	5.90	4.00	P02	6.60	12.80
P03	3.67	4.27	P03	7.17	13.07
P04	3.80	13.80	P04	10.60	17.30
P05	2.98	12.78	P05	8.18	18.58
P06	3.50	6.75	P06	6.20	9.05
P07	3.60	8.50	P07	4.10	7.10
P08	6.89	17.89	P08	9.79	18.69
P09	5.46	6.76	P09	5.26	3.56
P10	4.50	20.20	P10	5.50	20.50
Mean	4.78	9.94	Mean	7.18	12.60
STD	1.57	5.88	STD	2.06	6.09
Min	2.98	4.00	Min	4.10	3.56
Max	7.50	20.20	Max	10.60	20.50

(c) DB-1			(d) DB-2		
Patient	X	Y	Patient	X	Y
P01	15.40	8.80	P01	9.80	10.90
P02	9.00	9.30	P02	6.20	13.40
P03	4.57	4.57	P03	9.17	9.27
P04	13.80	51.40	P04	10.20	32.00
P05	9.48	19.28	P05	6.48	22.58
P06	5.10	8.05	P06	5.70	8.25
P07	5.70	12.40	P07	4.00	7.60
P08	21.59	44.49	P08	10.09	42.19
P09	10.86	12.66	P09	10.86	5.06
P10	5.40	24.30	P10	9.60	24.80
Mean	10.09	19.52	Mean	8.21	17.60
STD	5.51	16.11	STD	2.38	12.32
Min	4.57	4.57	Min	4.00	5.06
Max	21.59	51.40	Max	10.86	42.19

Table 4.3 Internal Margins (IM) in mm needed to cover 100% tumour volume 95% of the time for NB-1b where tumour-surrogate relationship is established in the earlier part of the same session (NB-1a)

Patient	Non-surrogate	All Markers	One Marker	ROW	COL	SPR	BELT
P01-X	4.8	3.5	3.3	3.6	3.7	3.3	3.2
P02-X	3.6	3.5	3.3	3.5	3.6	3.4	3.4
P03-X	2.7	1.4	1.2	1.5	1.3	1.2	1.8
P04-X	2.1	1.8	1.3	1.6	2.0	1.4	1.3
P05-X	1.9	1.8	1.6	1.9	1.8	1.6	1.7
P06-X	2.0	1.7	2.0	1.9	1.9	2.0	2.2
P07-X	2.7	2.4	2.5	1.9	2.3	2.4	2.4
P08-x	4.3	4.5	3.9	3.9	4.4	4.3	4.2
P09-X	4.4	3.5	3.5	3.2	3.1	3.3	3.3
P10-X	3.3	2.5	2.2	2.6	2.2	2.2	2.0
P01-Y	2.7	2.6	2.7	2.6	2.3	2.6	2.1
P02-Y	1.5	1.4	1.5	1.8	1.7	1.9	1.5
P03-Y	3.7	2.0	1.6	1.8	1.9	1.5	2.7
P04-Y	11.7	3.2	3.5	3.5	4.0	7.1	6.4
P05-Y	10.5	4.6	5.3	4.4	4.3	4.6	4.9
P06-Y	4.8	4.8	4.7	4.8	4.5	4.9	4.6
P07-Y	5.1	3.6	3.2	3.4	3.6	3.4	4.0
P08-Y	12.5	3.8	3.1	4.2	5.2	5.4	10.8
P09-Y	5.5	2.9	4.0	3.5	3.2	3.7	4.0
P10-Y	17.9	4.5	5.2	4.5	4.8	4.0	7.4
Mean	5.4	3.0	3.0	3.0	3.1	3.2	3.7
STD	4.3	1.1	1.2	1.1	1.2	1.5	2.3
Min	1.5	1.4	1.2	1.5	1.3	1.2	1.3
Max	17.9	4.8	5.3	4.8	5.2	7.1	10.8

Table 4.4 Internal Margins (IM) in mm needed to cover 100% tumour volume 95% of the time for DB-1 where tumour-surrogate relationship is established in the earlier part of the same session (NB-1a)

Patient	Non-surrogate	All Markers	One Marker	ROW	COL	SPR	BELT
P01-X	10.9	7.2	8.9	8.4	8.7	6.1	10.1
P02-X	4.0	3.5	4.0	3.7	3.9	3.9	3.7
P03-X	3.0	1.8	1.4	2.2	1.6	1.5	2.6
P04-X	8.0	4.2	5.0	5.9	5.2	6.3	5.6
P05-X	6.7	6.6	5.7	5.9	5.4	5.8	5.8
P06-X	2.3	2.1	1.9	1.9	2.0	2.1	2.2
P07-X	3.9	3.0	3.6	3.3	3.5	3.3	3.3
P08-x	18.4	15.3	13.7	17.8	17.4	15.9	16.2
P09-X	9.3	6.6	5.4	6.3	6.1	4.9	4.9
P10-X	3.4	4.0	2.4	4.1	3.7	2.8	2.9
P01-Y	4.8	4.6	3.9	5.4	4.6	4.2	4.3
P02-Y	5.9	5.6	5.4	5.8	6.8	5.3	5.7
P03-Y	3.9	2.7	2.7	3.5	2.9	2.8	3.5
P04-Y	46.4	10.7	13.0	14.7	12.4	40.5	15.2
P05-Y	14.7	10.4	9.2	8.8	9.8	9.2	9.6
P06-Y	5.3	4.4	4.1	4.5	4.8	4.5	4.7
P07-Y	9.2	5.5	4.4	6.8	5.3	4.8	5.5
P08-Y	40.0	22.6	24.8	23.6	38.9	30.4	37.7
P09-Y	11.0	3.1	6.0	4.1	3.3	6.9	4.4
P10-Y	22.1	14.7	10.5	12.3	12.6	9.2	11.8
Mean	11.7	6.9	6.8	7.4	7.9	8.5	8.0
STD	12.0	5.3	5.5	5.6	8.3	9.9	8.1
Min	2.3	1.8	1.4	1.9	1.6	1.5	2.2
Max	46.4	22.6	24.8	23.6	38.9	40.5	37.7

Table 4.5 Internal Margins (IM) in mm needed to cover 100% tumour volume 95% of the time for NB-2 where tumour-surrogate relationship is established in the previous session (NB-1a)

Patient	Non-surrogate	All Markers	One Marker	ROW	COL	SPR	BELT
P01-X	5.3	3.5	2.9	3.5	3.8	2.9	3.6
P02-X	3.0	2.8	2.4	2.7	2.9	2.3	2.5
P03-X	5.7	6.2	3.4	4.2	3.3	3.9	5.8
P04-X	4.7	4.9	4.1	4.2	3.9	4.1	4.0
P05-X	3.4	3.2	3.2	3.1	3.1	3.2	3.0
P06-X	2.7	2.9	2.6	2.7	2.6	2.8	2.6
P07-X	2.3	2.3	2.3	2.6	2.4	2.4	2.4
P08-x	5.4	4.4	4.4	4.7	4.6	4.9	5.1
P09-X	3.9	2.3	2.2	2.6	2.9	2.6	3.1
P10-X	4.0	3.1	2.1	3.5	3.0	3.0	2.0
P01-Y	2.3	2.3	2.0	1.8	1.6	1.9	1.9
P02-Y	6.4	4.2	5.1	5.8	6.3	3.6	6.1
P03-Y	9.1	7.8	6.1	5.9	7.9	6.7	8.9
P04-Y	11.9	6.5	7.6	7.4	6.7	7.0	6.0
P05-Y	14.4	10.2	10.1	11.2	10.6	12.1	13.0
P06-Y	5.6	5.2	4.4	4.1	4.8	4.9	4.4
P07-Y	4.7	4.2	4.2	4.4	4.1	4.2	4.4
P08-Y	15.4	2.9	4.9	3.7	12.0	5.4	12.2
P09-Y	2.1	1.9	2.1	2.0	2.0	2.1	2.1
P10-Y	18.5	4.7	3.8	5.0	5.3	10.4	9.6
Mean	6.5	4.3	4.0	4.2	4.7	4.5	5.1
STD	4.8	2.1	2.1	2.2	2.8	2.7	3.3
Min	2.1	1.9	2.0	1.8	1.6	1.9	1.9
Max	18.5	10.2	10.1	11.2	12.0	12.1	13.0

Table 4.6 Internal Margins (IM) in mm needed to cover 100% tumour volume 95% of the time for DB-2 where tumour-surrogate relationship is established in the previous session (NB-1a)

Patient	Non-surrogate	All Markers	One Marker	ROW	COL	SPR	BELT
P01-X	5.1	4.3	3.6	3.9	4.5	3.8	3.6
P02-X	3.7	3.2	3.0	3.0	3.3	2.9	3.0
P03-X	7.6	6.4	5.0	5.4	6.1	5.6	6.3
P04-X	6.3	5.2	4.6	6.0	5.8	5.0	4.4
P05-X	3.3	3.3	3.2	3.3	3.2	3.6	3.0
P06-X	2.9	2.1	2.1	2.5	2.1	1.8	2.2
P07-X	2.4	2.6	2.6	2.5	2.4	2.5	2.4
P08-x	6.3	5.9	5.3	5.7	5.7	4.9	4.5
P09-X	9.8	3.3	3.7	5.8	4.6	4.3	5.4
P10-X	5.2	5.3	2.7	5.1	4.3	3.4	3.6
P01-Y	5.2	4.6	4.8	4.8	4.7	4.7	4.9
P02-Y	6.9	4.8	4.7	5.3	5.2	4.5	5.6
P03-Y	7.8	6.7	6.2	5.9	6.7	6.6	6.9
P04-Y	24.3	7.4	7.3	6.2	8.6	7.7	7.5
P05-Y	19.4	10.9	7.4	12.4	11.3	13.9	14.4
P06-Y	5.4	4.3	4.7	4.1	4.8	4.8	4.1
P07-Y	5.7	4.3	4.1	4.5	4.9	4.6	4.7
P08-Y	37.7	23.9	34.9	18.7	36.5	26.2	27.5
P09-Y	3.9	2.0	2.8	2.6	2.2	2.8	2.8
P10-Y	21.9	17.8	9.6	11.1	9.0	13.6	13.1
Mean	9.5	6.4	6.1	5.9	6.8	6.3	6.5
STD	9.1	5.4	7.0	3.9	7.4	5.7	5.9
Min	2.4	2.0	2.1	2.5	2.1	1.8	2.2
Max	37.7	23.9	34.9	18.7	36.5	26.2	27.5

4.5 Discussions

4.5.1 Tumor motion amplitude

Tumor motion amplitudes for various organs reported in the literature by other investigators were shown in Table 1.2, and as can be seen the magnitude of respiratory motion for tumours in the abdomen and thorax can be substantial. The amplitudes of tumour motion in lung measured in this study were shown in Tables 4.2(a) to 4.2(d). The mean and standard deviation of these amplitudes in the X and Y direction, both separately and combined, are shown in Table 4.7. An overview of the values in both Table 4.2 and Table 4.7 reveals that for most patients the amplitude of tumor motion in the Sup/Inf direction (Y) is larger than that in the Lateral (X) direction. This observation has been tested for the following hypothesis by applying a one tailed student t-test for all four cases (NB-1, DB-1, NB-2 and DB-2).

H_0 : Tumor Amplitude in the Y direction = Tumor Amplitude in the X direction

H_1 : Tumor Amplitude in the Y direction > Tumor Amplitude in the X direction

The results are summarized in Table 4.8(a). These results indicate that at the 95% C.L., H_0 is rejected for all four cases. Therefore, it can be concluded that for this study group, the amplitude of tumor motion in the Sup/Inf direction is significantly larger than the amplitude in the Lateral direction (i.e., $Y > X$).

Figure 4.12 shows a plot of the tumor amplitudes in the two directions during NB-1 for all patients. The larger tumor amplitudes in the Y direction compared with X can be clearly observed in this figure. This is consistent with reports by other investigators such as Hanley et. al. ^[81] where a larger tumor motion was observed in the Sup/Inf direction compared with the Lateral direction.

Table 4.7 The mean and standard deviation (sample variation) of tumour motion amplitude for the two types of breathing, on day-1 and day-20 in Lateral(X) and Sup/Inf direction (Y) in mm

Breathing type-Experiment	X	Y
NB-1	4.8 ± 1.6	9.9 ± 5.9
DB-1	10.1 ± 5.5	19.5 ± 16.1
NB-2	7.2 ± 2.1	12.6 ± 6.1
DB-2	8.2 ± 2.4	17.6 ± 12.3

Table 4.8 The results of the t-test comparing various aspects of tumour motion amplitude Confidence level: 95% ; Reject H0 if P<0.05

(a)

Null Hypothesis	Alternative Hypothesis	t-value	P-value	Results	Conclusion
H0: Y1=X1 NB	H1: Y1>X1 NB	2.63	0.014	Reject H0	For NB-1 Y>X
H0: Y1=X1 DB	H1: Y1>X1 DB	2.24	0.026	Reject H0	For DB-1 Y>X
H0: Y2=X2 NB	H1: Y2>X2 NB	3.16	0.006	Reject H0	For NB-2 Y>X
H0: Y2=X2 DB	H1: Y2>X2 DB	2.55	0.016	Reject H0	For DB-2 Y>X

(b)

Null Hypothesis	Alternative Hypothesis	t-value	P-value	Results	Conclusion
H0: DB-1=NB-1	H1: DB-1>NB-1	3.58	0.001	Reject H0	For day-1 DB>NB
H0: DB-2=NB-2	H1: DB-2>NB-2	2.18	0.020	Reject H0	For day-20 DB>NB

(c)

Null Hypothesis	Alternative Hypothesis	t-value	P-value	Results	Conclusion
H0: NB-2=NB-1	H1: NB-2>NB-1	3.53	0.001	Reject H0	For NB NB-2>NB-1
H0: DB-2=DB-1	H1: DB-2>DB-1	1.42	0.086	Cannot Reject H0	For DB Uncertain

Figure 4.12 The amplitude of tumor motion in lateral (X) and Sup/Inf (Y) direction during normal breathing (NB). Data from Table 4.2 (a)

Two more questions were posed and the relevant hypotheses were tested. First question was whether the tumor motion amplitude during deep breathing is (significantly) larger than that during NB. Note that by definition deep breathing involves higher amplitude in air volume signals (SPR). However, whether larger air volume in the lung always results in larger amplitude of tumor motion is not necessarily implied. The results of t-test for comparing NB and DB are shown in Table 4.8(b). The results indicate that the amplitude of tumor motion during deep breathing is significantly larger than that for normal breathing. This is again consistent with other results reported in the literature such as those reported by Ohara et. al.^[21] for lung and by Suramo et. al.^[28] for kidney and liver.

The second question is whether the tumor motion amplitude changes from day-1 to day-20. The results of comparison of tumor motion amplitude on day-1 and day-20 shown in Table 4.8(c). indicate that for NB, the amplitudes change (usually increasing) from day-1 to day-20 while for DB they are not significantly different. This issue has important clinical implications for cases where no surrogate is used to gate or track the tumor. In such cases, a change in tumor motion amplitude in time would mean that the margins have to be re-established. Otherwise, the tumor may be somewhat missed or the normal tissues may receive unnecessary radiation. This issue will be revisited in section 4.5.3 where the reliability of the margins for both the surrogate and the non-surrogate based cases are discussed.

4.5.2 Comparison of the intra-session performance of various surrogates

In this section the ability of various surrogates to predict tumor motion will be compared. The predictions discussed here are based on a tumor-surrogate relationship established on the same day at the beginning of the session (intra-session performance). First, a discussion of hypothetical outcomes for a surrogate's performance will be presented and then the performance of various surrogates during normal breathing and deep breathing will be discussed separately.

4.5.2.1 Hypothetical cases for a plot of surrogate based vs. non-surrogate based margins

The primary clinical reason for employing surrogates for tumour motion is to reduce the margins needed to irradiate the tumor. The more a surrogate can result in the reduction of the required IM for a specified tumour coverage, the better that surrogate is. An ideal surrogate is one that can reduce the IM to zero. Therefore, if one plots the IM for the surrogate-based case vs. the IM for the non-surrogate-based case for a number of subjects, the plot should ideally lie on the X axis, i.e., all the surrogate based margins shrink to zero regardless of their non-surrogate-based values. This, however, won't be the case in a real clinical situation, as we are not dealing with perfect surrogates. So what can we expect? In the next section, we look at the various possible scenarios for such a plot.

There are four simple possibilities when the IM for the surrogate-based case is plotted vs. the IM for the non-surrogate based case. These are shown in the graph of Figure 4.13. The relationship of the two margins (non-surrogate based and surrogate based) for these four cases is depicted in a very simplified form in Figure 4.14.

1-Perfect surrogate A perfect surrogate would predict the tumor position with no uncertainty involved. This would be the ideal case since an exact prediction would cause the IM to shrink to zero and there will be no need for margins when gating or tracking (Figure 4.14a). Therefore, the plot of surrogate-based IM vs. the non-surrogate-based IM for this scenario will be a horizontal line lying on the horizontal axis. (Line a in Figure 4.13)

2- Effective surrogate with a threshold Next, consider a surrogate that can predict the tumor position with a constant uncertainty or with a threshold value K . Therefore, in gating or tracking one has to assume some margins to account for this uncertainty. The value of this margin would be K (Figure 4.14b). Therefore, in this model, if the non

Figure 4.13 Hypothetical outcomes of plotting surrogate-based IM's vs. non-surrogate-based IM's

Figure 4.14 The field view of the (four) possible cases of the surrogate based IM in comparison with the original non surrogate based IM

-surrogate based margin is larger than K , it would be reduced to K when applying the surrogate-based model. This results in the plot of surrogate based IM's vs. non-surrogate based IM's to be a horizontal line with slope equal to zero and Y-intercept equal to K (line b in Figure 4.13). However, if the non-surrogate based margin is already smaller than K then the model cannot improve the situation and internal margins would remain the same. In fact, it could actually be detrimental if one still insists on applying the model to such cases because then it would change the IM from a value that is smaller than K to K (the dotted tail of line b in Figure 4.13). Note that K represents the uncertainty in the entire model, and would also include the physician's resolution of tumor definition. The inter- and intra- physician variability in digitizing the tumour position is a major source of error. This issue has been pointed out by other investigators.^[145,157-162] For example, Gao^[153] has shown that there is a significant random and systematic error in delineating the tumour even for well defined organs such as the prostate.

3- Ineffective surrogate-Zero impact Consider a situation where the surrogate produces a constant (DC) signal that is independent of tumour motion. In this case, the difference between the predicted and measured tumor motion would be the same as the measured tumor motion. In other words, the uncertainty in the prediction (or the surrogate based margins) is the same as the non-surrogate based margins. Therefore, the use of the surrogate would not make any improvement in the values of IM and the IM's would remain the same whether or not a surrogate is used to predict the tumor position (Figure 4.14c). This is represented by line c in Figure 4.13 that has a slope equal to 1.

4- Detrimental surrogate - Negative impact Finally, if the surrogate mispredicts the tumour position, i.e., the uncertainty in prediction is greater than the non-surrogate- based margins, then the surrogate would cause the situation to deteriorate and there is no sense in applying the surrogate-based model. This is depicted as line d in Figure 4.13. This can

happen in a situation where the phase relationship between the surrogate and tumor motion changes increasing the error in predicted position. So the difference between the predicted and measured tumor motion would be larger than the measured tumor motion.

4.5.2.2 Intra-session comparison of surrogates for normal breathing (NB)

Figure 4.15 is a plot of the surrogate based (case of normal breathing - one skin marker) vs. non-surrogate based IM where the surrogate-tumor relationship was determined in the same session. What is observed here is that for tumor motions (non-surrogate based IM) between zero and approximately 5.0 mm, the trend looks like line c in Figure 4.13 (ineffective surrogate) while for cases where the non-surrogate based IM's are greater than 5.0 mm, the use of the surrogate systematically reduces the IM to about 5.0 mm. This is similar to line b in Figure 4.13 (surrogate with a threshold) where the threshold is approximately 5.0 mm.

Similarly, Figure 4.16 shows surrogate based vs. non-surrogate based margins for all surrogates, again for normal breathing and where the surrogate-tumor relationship was established in the same session. Two regions can be identified on this graph.

Region-1 is where the non-surrogate based IM's are less than 5.0mm. In this region, the fitted lines for the surrogates look like line c in Figure 4.13. The slopes of these lines are close to 1.0. This is confirmed by the t-test results for the slopes shown in Table 4.9. This implies that if the non-surrogate based IM is less than 5.0mm, none of the surrogates make any significant improvement in the internal margin.

Region-2 on the graph of Figure 4.16 is where the non-surrogate based IM's are greater than 5.0mm. (between 5.0mm and 18.0mm). In this region, it can be seen that a linear fit to the various combinations of skin markers and the spirometer are similar to line b in Figure 4.13 (surrogate with a threshold). The respiratory Belt, however, stands alone and its corresponding fitted line falls somewhere between lines b (surrogate with a threshold) and c (ineffective surrogate) in Figure 4.13.

Figure 4.15 The surrogate-based IM vs. non-surrogate-based IM for a single skin marker (“One marker”) during NB where the tumor-surrogate relationship is established intra-fraction

Figure 4.16 The surrogate-based IM vs. non-surrogate-based IM for all surrogates during NB where the tumor-surrogate relationship is established intra-fraction.

Table 4.9 The slopes of the lines in region-1 of Figure 4.16. The slopes are tested for their equality to 1. H_0 : Slope=1; C.L.=95%, Reject H_0 if $P < 0.05$

	Slope	t	P
All markers	0.80	1.43	0.177
One marker	0.71	1.92	0.078
ROW	0.71	2.11	0.055
COL	0.72	2.02	0.065
SPR	0.72	1.70	0.114

Table 4.10 (a) The slopes and thresholds of the lines in region-2 of Figure 4.16, (b) Test on the equality of slopes to one another, and (c) test on the equality of the slopes to 0.

	Slope	Threshold
All markers	0.12	3.8
One marker	0.07	4.2
ROW	0.08	4.0
COL	0.14	4.3
SPR	0.04	4.9
BELT	0.34	6.7

(a)

Test on the equality of slopes for various combinations of skin markers. H_0 : $m_1=m_2=m_3=m_4$ (Reject if $P < 0.05$)

DF1=3 DF2=12
F=0.159 P=0.92

Cannot reject → "Slopes are equal" is not inconsistent with data

(b)

Test on the equality of slopes for various combinations of skin markers and SPR. H_0 : $m_1=m_2=m_3=m_4=m_5$ (Reject if $P < 0.05$)

DF1=4 DF2=15
F=0.137 P=0.97

Cannot reject → "Slopes are equal" is not inconsistent with data

(c)

	slope	t	P
All markers	0.12	1.60	0.208
One marker	0.07	0.57	0.610
ROW	0.08	1.71	0.186
COL	0.14	2.22	0.114
SPR	0.04	0.21	0.846

To examine the surrogates more closely and compare their effectiveness in Region-2, two aspects of the data (fitted lines) are considered. The first is how close the fitted line is to horizontal (slope). The closer the slope is to zero the more the surrogate would resemble an effective surrogate with a threshold. The second consideration is the threshold. The threshold can be determined from the Y-intercept, but this approach is only valid for surrogates with a zero slope in region-2. A more general approach for small but non-zero slopes is to take the average of the data points in this region as the threshold.

Therefore, a comparison of the surrogates in region-2 can be made by comparing the slope and the threshold. Such data are shown in Table 4.10(a). As can be seen in this table, the slope for the Belt is too large to consider it as a good surrogate with threshold and hence it is not reasonable to report its threshold. Therefore, based on both the graph (Figure 4.16) and the values for the slope, we can conclude that the **respiratory Belt is the least effective surrogate in predicting tumor motion.**

As for the rest of the surrogates (SPR and various combination of skin markers), their slopes range from 0.04 to 0.14, much closer to zero than the Belt. More detailed analysis of these surrogates by comparing slopes^[153] indicates that:

- 1- The slopes of various combinations of skin markers are not significantly different from one another (see Table 4.10b for the results of F test).
- 2- The slopes of various combinations of skin markers and SPR are not significantly different from one another (see Table 4.10b for the results of F test).
- 3- The slopes of various combinations of skin markers and SPR are not significantly different from zero. (see Table 4.10c for the values and the results of t test).

These findings suggest that both the various combinations of skin markers and the SPR have slopes that are not significantly different from one another and are not significantly different from zero. Therefore, for normal breathing and when the tumor-surrogate relationship is established in the same session, the various combinations of skin markers and SPR can be considered effective surrogates with a threshold.

The next step is to consider the thresholds for various combinations of skin markers and SPR. Other things being equal, the surrogate with a smaller threshold is considered a better surrogate. As described earlier, the average surrogate-based IM from all data points in region-2 will be used as the threshold. Such values are shown for various combinations of skin markers and SPR in Table 4.10a. It can be seen that the threshold for the various combinations of skin markers are clustered around a threshold of 4.0 while for the SPR its value is 4.9. Based on the values for the threshold, the surrogates can be arranged in the following order (from best to worst):

All markers – Row – One marker – Col – SPR

However, since there is only a small difference amongst the threshold for these surrogate, a t-test can be performed to see whether the thresholds are significantly different from one another. These thresholds and the non-surrogate IM for all surrogates are listed in Table 4.11. The t-test is set to compare the threshold for each surrogate with “All markers”. In other words the average IM for each surrogate and the average IM for “All marker” are tested for equality. The results shown at the two bottom rows of Table 4.11 indicate that there is not a statistically significant difference in the thresholds for the above surrogates.

Therefore, based on the findings for the slope and threshold, the performance of various combinations of skin markers and the SRP cannot be differentiated, while the performance of the Belt is poor compared with the rest of the surrogates. It is important to note that if more data were available, these surrogates may show a difference in their performance. The conclusions drawn here are based on our study with only 10 subjects and as such have a low statistical power. Note however, that although small, the population size used in this study is much larger than in most similar studies. See for example studies done by Yan et. al.^[135], Hoisak et al.^[138] and Koch et. al. and Liu et al.^[140,141] where the population size ranges from 3 to 7 patients.

Table 4.11 Details of calculating the threshold for each surrogate in region-2 of Figure 4.16. Each threshold is tested for its difference from that of All markers

Data point	Non Surrogate based IM (mm)	All markers (mm)	One marker (mm)	ROW (mm)	COL (mm)	SPR (mm)	BELT (mm)
1	5.5	2.9	4.0	3.5	3.2	3.7	4.0
2	10.5	4.6	5.3	4.4	4.3	4.6	4.9
3	11.7	3.2	3.5	3.5	4.0	7.1	6.4
4	12.5	3.8	3.1	4.2	5.2	5.4	10.8
5	17.9	4.5	5.2	4.5	4.8	4.0	7.4
Average	11.6	3.8	4.2	4.0	4.3	4.9	6.7
t-value			1.37	1.54	1.76	1.50	2.50
P-value			0.12	0.10	0.08	0.10	0.03
Is the threshold for this surrogate significantly different from the threshold for All markers			No	No	No	NO	Yes

Table 4.12 The reduction in the IM introduced by various combination of skin markers and SPR in region-2 of Figure 4.16.

Data point	All markers	One marker	Row	Col	SPR
1	2.6	1.5	2.0	2.3	1.8
2	5.9	5.2	6.1	6.2	5.9
3	8.5	8.2	8.2	7.7	4.6
4	8.7	9.4	8.3	7.3	7.1
5	13.4	12.7	13.4	13.1	13.9
Mean	7.8	7.4	7.6	7.3	6.7
Std	3.98	4.25	4.13	3.87	4.50

Table 4.13 Summary of the important results of evaluating various surrogates

	SPR	All combinations of skin markers combined	All combinations of skin markers and SPR combined
Slope	0.04	0.10	0.09
Threshold (mm)	5.0	4.1	4.2
Average reduction in IM (mm)	6.7 ± 4.5	7.5 ± 3.7	7.4 ± 3.8
Average non-surrogate IM in region-2 = 11.60 mm			

A point about the SPR that is worth mentioning is that although it has a relatively large threshold (5.0 mm), it has a low value of slope (0.04). This low slope suggests that spirometer may be a suitable surrogate for tumor motion with non-surrogate IM's beyond values in Region-2 in Figure 4.16 (IM's > 18mm), but this is yet to be confirmed by data. This issue will be revisited in the section discussing deep breathing.

Also, of interest in comparing the various surrogates is looking at the reduction in the IM that a surrogate can provide. Table 4.12 shows the reductions in IM introduced by skin markers and SPR. Table 4.13 summarises the most important characteristics for a) SPR, b) various combinations of skin markers, and c) SPR and various combinations of skin markers combined. Based on the values shown in Table 4.13, the following statement could be made:

For non-surrogate-based IM's greater than 5.0 mm (with an average of 11.6 mm), SPR can reduce the treatment margins by an average of 6.7 mm to 5.0 mm; and various combinations of skin markers can on average reduce the IM's by 7.5 mm to 4.1 mm.

Before concluding this section, it is worthwhile to report the effectiveness of surrogates in terms of tumor amplitude. Recall that in Figure 4.16, the graph was divided into two regions. Region-1, where the non-surrogate based IM's were less than 5.0 mm and region-2, where the non-surrogate based IM's were greater than 5.0 mm. The findings were also expressed in terms of this classification. However, one is usually interested in the range of amplitude of tumor motion where a surrogate is effective

Table 4.14 and Figure 4.17 show the tumor amplitude and the IM's side by side. The values shown in Table 4.14 indicate that on average, the tumor amplitude is 2.0 mm larger than the non-surrogate based IM (IM for 100% tumor volume 95% of the time).

Note that, if our scoring function had been 100% tumor volume being covered 100% of the time, the non-surrogate based IM and tumor amplitude would have been the same.

Figure 4.17 Amplitude of tumor motion and the non-surrogate based IM during normal breathing. Average difference between amplitude and IM ~ 2 mm. Data from Table 4.14.

Table 4.14 Amplitude of tumor motion and the non-surrogate-based IM during NB-1 in the two directions in mm.

	Amplitude	IM	Difference
P01-X	7.5	4.8	2.7
P02-X	5.9	3.6	2.3
P03-X	3.7	2.7	1.0
P04-X	3.8	2.1	1.7
P05-X	3.0	1.9	1.1
P06-X	3.5	2.0	1.5
P07-X	3.6	2.7	0.9
P08-X	6.9	4.3	2.6
P09-X	5.5	4.4	1.1
P10-X	4.5	3.3	1.2
P01-Y	4.5	2.7	1.8
P02-Y	4.0	1.5	2.5
P03-Y	4.3	3.7	0.6
P04-Y	13.8	11.7	2.1
P05-Y	12.8	10.5	2.3
P06-Y	6.8	4.8	2.0
P07-Y	8.5	5.1	3.4
P08-Y	17.9	12.5	5.4
P09-Y	6.8	5.5	1.3
P10-Y	20.2	17.9	2.3
Mean	7.4	5.4	2.0
STD	5.0	4.3	1.1
Min	3.0	1.5	0.6
Max	20.2	17.9	5.4

However, since we have been looking at 100% tumor volume 95% of the time, the non-surrogate IM is smaller than the tumor amplitude.

Based on the average difference between the tumor motion amplitude and the IM for 100% tumor volume 95% of the time, the statement made earlier in terms of IM can be expressed in terms of tumor motion amplitude as follows:

For normal breathing and when the tumor-surrogate relationship is established intra-session then for tumor motion amplitudes larger than 7.0 mm, the average non-surrogate based IM (100% tumor volume 95% of the time) is 11.6 mm and SPR can reduce the IM by 6.7 mm to about 5.0 mm, and the various combinations of skin markers can on average reduce the IM by 7.5 mm to 4.1 mm.

Summary and conclusion for Intra-session surrogate assessment during NB

In this section, it was concluded that for NB, when the tumor-surrogate relationship is established and applied on the same day (intra-session), Belt is not an effective surrogate while SPR and skin markers are equally effective. Let's see how these findings fall within the context of current clinical practice and the related literature.

Comparing our results for normal volunteers and patients, it can be seen that the performance of SPR and skin markers is similar. For volunteers, skin markers (with the exception of the X coordinate), showed good correlation with SPR. For patients, both skin markers and SPR showed to be good predictors for tumor motion. Note that for the patients, the X coordinate of the markers was excluded from the data analysis.

It is noteworthy that in the volunteers phase, the Belt showed a good correlation with SPR. But when the two were examined as surrogates for tumor motion, SPR proved to be an effective surrogate while Belt was ineffective. Possible explanation for this inconsistency can be: 1) Lung cancer patients breath differently compared with healthy people. Note the age difference in the two groups too, (67.6 ± 10.4 for patients vs.

31.1±3.2 for volunteers); and 2) insufficient data in the case of patients may have caused an overestimation of the difference between Belt and SPR.

Kubo and Hill ^[136] have compared Belt and SPR and have shown that the two track each other well in lung cancer patients. However, their study did not measure how well Belt and SPR compare in predicting tumor motion.

Also of significant importance regarding the results for Belt and SPR is the application of these two modalities in 4D-CT and gated PET/CT imaging. Our results indicate that the use of SPR for gating purposes as done by Low et. al.^[42] and D'Souza et. al.^[122] is more reliable than Belt as has been employed by Wink et. al.^[149] and Martinez-Moller et. al.^[150]

We also found that various combinations of skin markers can effectively and equally predict tumor motion. Included in this combination was the 2D projection of the motion of a single skin marker on the epigastrium. Therefore our findings validate the use of a similar configuration in the RPM system (Varian Medical Systems) in conjunction with 4D-CT^[48,49] or gated radiotherapy.^[41,70] These findings also suggest that the approach of using the belt for gated radiotherapy (such as the one used by Siemens Medical Systems) should be done with great caution.

4.5.2.3 Intra-session comparison of surrogates for deep breathing (DB)

The data for tumor amplitude during deep breathing were shown in Table 4.2(c) and (d). The values of observed amplitude of tumor motion for deep breathing are larger than NB and range up to more than 50 mm. Also the results of the statistical tests comparing the amplitudes in the lateral and Sup/Inf directions were shown in Table 4.8(a). As in NB, we see that for DB, the amplitude of tumor motion in the Sup/Inf direction is generally larger than that in the lateral direction for the population of this study.

The required IM's for deep breathing for 100% volume, 95% of the time were shown in Tables 4.4 for experiments 1 and in Table 4.6 for experiment 2. The corresponding values for 100% volume, 100% time can be found in Tables C-1 and C-4 in Appendix C.

Figure 4.18 shows surrogate based IM's vs. non-surrogate based IM's for the deep breathing during experiment 1 where the tumor-surrogate relationship is established on the same session. Based on the sorted non-surrogate based IM's shown in Table 4.15, three distinct regions for the data on Figure 4.18 can be identified. The slopes and the thresholds of the fit to the data in these regions for the various surrogates are listed in Table 4.16 and are shown in Figure 4.19 a. The three regions identified on Figure 4.18 can be described and characterized as follows:

Region-1 The region where the non-surrogate based IM's are less than 7.0mm. In this region, all the fitted lines have slopes close to 1.0 (line (a) in Figure 4.19a), suggesting that the surrogates are all ineffective in this region. This is confirmed by the two green lines in Figure 4.19b which show the average IM for the non-surrogate based and the surrogate based cases for this region are effectively the same.

Region-2 This region on the graph of Figure 4.18 is where the non-surrogate based IM's are between 7.0 mm and 12.0 mm. The surrogates do not all have the same slope in this region (line (b) in Figure 4.19a). "One marker" shows an exceptionally poor performance. This surrogate and the Belt can be identified as ineffective surrogates for region-2. For Col (column of markers) and SPR, the slopes are not significantly different from zero (see Table 4.17). Therefore, these two surrogates can be considered as surrogates with a threshold. Finally, the best slopes (closest to zero) in region-2 belong to "All markers" and Row, 0.09 and 0.00 respectively.

Therefore, for deep breathing when the non-surrogate IM is between 7.0 mm and 12.0 mm (region-2 of Figure 4.18), the slope for four of the surrogates are not significantly different from 0 (All, Row, Col and SPR). The threshold values for these surrogates are

Figure 4.18 The surrogate based IM vs. non-surrogate based IM for all the surrogates during deep breathing where the tumor-surrogate relationship is established intra-fraction

Table 4.15 Sorted IM's for DB-1 in mm

Patient/ Direction	Non- surrogate	All Markers	One marker	ROW	COL	SPR	Belt
P06-X	2.30	2.10	1.90	1.90	2.00	2.10	2.20
P03-X	2.97	1.67	1.37	2.17	1.57	1.47	2.57
P10-X	3.40	4.00	2.40	4.10	3.70	2.80	2.90
P03-Y	3.87	2.27	2.67	3.47	2.87	2.77	3.47
P07-X	3.90	3.00	3.60	3.30	3.50	3.30	3.30
P02-X	4.00	3.50	4.00	3.70	3.90	3.90	3.70
P01-Y	4.84	5.44	3.94	5.44	4.64	4.24	4.34
P06-Y	5.35	4.35	4.05	4.45	4.75	4.45	4.65
P02-Y	5.90	5.60	5.40	5.80	6.80	5.30	5.70
P05-X	6.68	6.68	5.68	5.88	5.38	5.78	5.78
P04-X	8.00	4.20	5.00	5.90	5.20	6.30	5.60
P07-Y	9.20	5.50	4.40	6.80	5.30	4.80	5.50
P09-X	9.26	6.46	5.36	6.26	6.06	4.86	4.86
P01-X	10.86	10.16	8.86	8.36	8.66	6.06	10.06
P09-Y	10.96	3.26	5.96	4.06	3.26	6.86	4.36
P05-Y	14.68	10.98	9.18	8.78	9.78	9.18	9.58
P08-X	18.39	14.69	13.69	17.79	17.39	15.89	16.19
P10-Y	22.10	14.70	10.50	12.30	12.60	9.20	11.80
P08-Y	39.99	20.29	24.79	23.59	38.89	30.39	37.69
P04-Y	46.40	10.70	13.00	14.70	12.40	40.50	15.20

Table 4.16 The slopes of the fitted lines and the thresholds for various surrogates during DB for the three regions on Figure 4.18.

	Region-1		Region-2		Region-3	
	Slope	Threshold	Slope	Threshold	Slope	Threshold
All markers	1.04	3.8	0.09	5.3	0.09	14.7
One marker	0.98	3.5	0.96	5.9	0.25	14.2
ROW	0.95	4.0	0.00	6.3	0.21	15.4
COL	1.03	3.9	0.20	5.7	0.37	18.2
SPR	0.97	3.6	0.27	5.8	0.95	21.0
BELT	0.90	3.9	0.65	6.1	0.45	18.1
IM ¹	4.3		9.7		28.3	

¹ Average IM for non-surrogate-based case (mm)

Table 4.17 Test on the slope of the fitted lines to the data in region-2 and region-3 of the plot of DB data (Figure 4.18)

Ho: Slope=0		Reject if P<0.05		H1 Slope≠0		
Region	Surrogate	Slope	t-value	P-value	Results	Conclusion
Region-2	Col	0.19	0.22	0.85	Cannot reject Ho	Slope not significantly different from 0
	SPR	0.27	0.69	0.50	Cannot reject Ho	Slope not significantly different from 0
Region-3	All markers	0.09	0.47	0.67	Cannot reject Ho	Slope not significantly different from 0
	One marker	0.25	1.21	0.31	Cannot reject Ho	Slope not significantly different from 0
	Row	0.21	1.10	0.35	Cannot reject Ho	Slope not significantly different from 0
	Col	0.37	0.85	0.46	Cannot reject Ho	Slope not significantly different from 0
	Belt	0.45	1.15	0.33	Cannot reject Ho	Slope not significantly different from 0

(a)

(b)

Figure 4.19 (a) The slopes, and (b) the average surrogate-based IM (~threshold) of the fitted lines in the three region of Figure 4.18

listed in table 4.16). Their average threshold is 5.8mm. Which means they can reduce the margins from the non-surrogate values to 5.8 mm.

Region-3 The third region on the graph of Figure 4.18 is where the non-surrogate based IM's are greater than 12.0 mm. (between 12.0 mm and 47.0 mm). In this region, SPR shows exceptionally poor performance with a slope of 0.95. This is very close to 1.0 and implies that SPR is an ineffective surrogate in this region. Although the slopes for the Belt and Col are not very close to 0, when a t-test is performed on these slopes, they prove not to be significantly different from 0. The threshold values for Col and Belt are 18.2 mm and 18.1 mm respectively.

The best slopes in this region belong to "One marker", Row and All markers, with values 0.25, 0.21 and 0.09 respectively and with our limited data are shown not to be significantly different from 0. (see Table 4.17). The threshold for these three surrogates are 14.2 mm, 15.4 and 14.4 respectively. This means that they can decrease the IM's from the non-surrogate values to about 15.0 mm. Note that "One marker" showed poor performance in region-2 of DB while it is now showing good performance in region-3 of DB. This can be due to lack of sufficient data or an inconsistency in the coupling between this surrogate and tumor.

As was done for the NB, it is important to also report the findings regarding deep breathing in terms of amplitude as well as surrogate based IM's. Table 4.18 and Figure 4.20 show the relationship between the non-surrogate based internal margins and the amplitude of tumor motion during deep breathing. As the figure shows, there is a direct correspondence between the two. On average, the amplitude of tumor motion is approximately 3 mm larger than IM (the internal margin for 100% volume, 95% of the time). Therefore, the three regions defined for deep breathing can be expressed in terms of amplitude instead of IM by simply adding 3 mm to all the IM's

Table 4.18 Amplitude of tumor motion and the non-surrogate based IM during DB-1 in the two directions in mm

Patient/Direction	Amplitude	IM	Difference
P01-X	15.4	10.9	4.5
P02-X	9.0	4.0	5.0
P03-X	4.6	3.0	1.6
P04-X	13.8	8.0	5.8
P05-X	9.5	6.7	2.8
P06-X	5.1	2.3	2.8
P07-X	5.7	3.9	1.8
P08-X	21.6	18.4	3.2
P09-X	10.9	9.3	1.6
P10-X	5.4	3.4	2.0
P01-Y	8.8	4.8	4.0
P02-Y	9.3	5.9	3.4
P03-Y	4.6	3.9	0.7
P04-Y	51.4	46.4	5.0
P05-Y	19.3	14.7	4.6
P06-Y	8.1	5.3	2.7
P07-Y	12.4	9.2	3.2
P08-Y	44.5	40.0	4.5
P09-Y	12.7	11.0	1.7
P10-Y	24.3	22.1	2.2
Mean	14.8	11.7	3.2
STD	12.7	12.0	1.4
Min	4.6	2.3	0.7
Max	51.4	46.4	5.8

Table 4.19 Summary of the performance of the various surrogates for the two types of breathing. A check mark indicates effectiveness while an X means being ineffective

Surrogate	Range of amplitude for tumour motion(mm)					Performance in the three effective regions ¹
	NB		DB			
	Region-1	Region-2	Region-1	Region-2	Region-3	
	0.0 - 7.0	7.0 - 20.0	0.0 - 10.0	10.0 -15.0	15.0 - 50.0	
All markers	X	√	X	√	√	√√√
One marker	X	√	X	X	√	√X√
ROW	X	√	X	√	√	√√√
COL	X	√	X	√	X	√√X
SPR	X	√	X	√	X	√√X
BELT	X	X	X	X	X	XXX

¹Region-2 for NB and Region-2 and Region-3 for DB

Figure 4.20 Amplitude of tumor motion and the non-surrogate based IM during deep breathing. Average difference between amplitude and IM ~ 3 mm

Summary and conclusion for Intra-session surrogate assessment during DB

The finding regarding the intra-session performance of the surrogates during deep breathing in this section indicated that:

- 1- None of the surrogate was effective for tumor motion amplitude of less than 10 mm
- 2- Belt was not effective for any value of tumor motion
- 3- One marker was ineffective for amplitudes between 10 and 15 mm
- 4- SPR and Col were ineffective for amplitudes of 15 to 50 mm

As opposed to the NB where all the surrogates (except Belt) were effective beyond a certain minimum amplitude (7 mm), now in the case of DB three of the surrogates (One marker, SPR and Col) proved to be ineffective in one of the two regions beyond a certain minimum amplitude (10 mm).

The ineffectiveness of SPR for amplitudes between 15 and 50 mm indicates that the relationship between tumor and SPR breaks down for DB with amplitudes beyond 15 mm. This means that tumor motion is not well coupled with breathing for deep breathing at high amplitudes. This finding has very important implications for techniques such as DIBH^[74,80-83,85,127,128] and ABC^[78,79] that employ breath hold to mitigate breathing induced tumor motion. Also any method that employs SPR as a surrogate for breathing^[42,122], should do so with caution. The reliability of SPR during breath hold will be revisited in the next section.

Another finding in the deep breathing analysis that can have important implications in gating for both imaging and therapy was the ineffectiveness of “One marker” as a surrogate for tumor motion at amplitudes between 10 and 15 mm during deep breathing. As has been earlier discussed, a single marker at the epigastrium is employed in the Varian RPM system as a surrogate for tumor. Although for NB, we showed that this surrogate is effective and validated its use as a surrogate for tumor motion, here we see that it can fail if the breathing pattern/amplitude changes. Let’s emphasize that our

conclusions are coming from a relatively small sample. But these exceptional “failures” indicate that a surrogate may not be as robust as originally thought and its use could be deleterious in the clinic.

The findings regarding Belt for DB once more puts doubt on the Belt as a surrogate for tumor motion. Therefore, caution should be used when the Belt is employed for gated radiotherapy (e.g., by Siemens Medical Systems) or when investigators report its use for 4D-CT or gated PET/CT imaging. ^[149,150]

Finally, the fact that Col and “One markers” were ineffective surrogate for some amplitudes during deep breathing implies that the conclusion reached for NB indicating that the various combinations of skin markers are equally effective surrogate does not necessarily hold for deep breathing

4.5.2.4 More on SPR

The following observations can be made about the SPR based on the preceding findings.

- 1) When discussing NB in section 4.5.2.2, a point was made about the possibility of SPR being a (more) suitable surrogate for breathing with amplitudes higher than 20.0 mm. The findings of section 4.5.2.3 regarding deep breathing showed that, at least for deep breathing, this is not true and in fact the performance of SPR deteriorates at high amplitudes during deep breathing and SPR is the least effective surrogate in the region of 20.0 plus amplitude.
- 2) SPR has always been considered the gold standard for breathing and by extension for the respiratory induced tumor motion. The first part of the statement is true in that the SPR measures air flow in and out of the lung. However, assuming that the respiratory induced tumor motion is also measured directly by the SPR may be incorrect. This is because while it is true that “whenever one breathes the tumor moves” but the statement “whenever one is not breathing the tumor does not move” is not necessarily true. Figure

4.21 depicts our model of the mechanics of breathing and the coupling between muscles, various surrogates and tumor. As this figure shows contraction of the muscles in the chest, abdomen and diaphragm can cause tumor motion a) indirectly by affecting the lung and causing airflow or b) directly even if the airflow is completely blocked. This can be physically demonstrated by anyone holding his breath while simultaneously trying to move the chest muscles.

Figure 4.22 shows an example of tumor motion during breath hold for one of our subjects that confirms this point. The figure shows that as expected during the breath hold, the SPR reported a DC signal and therefore, predicted no tumor motion. However, skin markers did detect and predict a motion for the tumor during the breath hold period. Therefore, while the motion was missed by the SPR, skin markers were able to pick it up.

One could certainly argue that the type of tumor motion just described during breath hold is not a breathing induced motion but a muscular motion instead. Although strictly speaking this is a valid argument, distinction between the two causes for tumor motion has been overlooked in studies where SPR has been used to monitor tumor motion.^[119-123] In such studies, it was always assumed that during the breath hold if the SPR indicates that there is no breathing then there is no tumor movement; while what was just called the muscular motion could have been present. Therefore, at best SPR can only suggest that there is or there is not a breathing induced tumor motion, but it cannot ensure that there is no otherwise induced tumour motion in the absence of breathing.

Skin markers do not suffer from this shortcoming and as shown are able to detect both the breathing induced and the muscular induced tumor motion. This is because not only does breathing cause both surface motion and tumor motion but also muscular contraction (during breath hold) causes both surface motion and tumor motion. Therefore, skin markers would detect the tumor motion whether the tumor moves as a result of breathing/airflow or as a result of muscular contraction. In other words, the motions of tumor and body surface (skin markers) are coupled regardless of the cause. In the case of SPR, breathing causes both airflow and tumor motion, however, muscular contraction can

Figure 4.21 The mechanism of breathing and the relationship (coupling) between various pairs of actions. Note that it is possible for the tumor to move even if the airflow to the lung is restricted or blocked.

Figure 4.22 A case of tumor motion during breath hold. (a) The spirometer has not been able to predict the tumor motion during breath hold while (b) the skin markers have been able to predict the motion. Tumor motion is shown in blue and surrogate prediction in red.

cause tumor motion without necessarily causing airflow. Therefore, the motion of tumor and airflow (SPR) are not necessarily coupled at all times and their coupling depends on the cause of tumor motion.

4.5.2.5 A summary of the findings for comparison of various surrogates

Table 4.19, page 134 summarizes the results for the five distinct regions, regions 1 and 2 for normal breathing (NB); and regions 1, 2 and 3 for deep breathing (DB). A check mark (✓) for a surrogate means that it is an effective surrogate with threshold; and an X means that the surrogate is ineffective. The table shows that none of the surrogates were effective in region-1 of NB or region-1 of DB. However, they demonstrated mixed results in the remaining three regions (region 2 in NB and regions 2 and 3 in DB). The Belt never showed any effectiveness. “One marker”, Col and SPR were effective in region2 of NB but each failed in one of the two regions for DB. **The two surrogates that were consistently effective predictors were Row and “All markers”.**

4.5.3 Reliability

In the previous sections different surrogates were compared in terms of their ability to predict tumor motion and to reduce the margins required to irradiate the tumor to the specified level. Note that the predictions were based on the tumor-surrogate relationship established on the same day. As a result of the comparison, certain conclusions could be made about the surrogates. Most surrogates showed a predictive ability that depended on the amplitude of the tumor motion and the breathing type. However, on the two extremes, the Belt proved to be an ineffective surrogate under all circumstances while two combinations of skin markers (“All markers” and Row) proved to be effective (with threshold) for a variety of tumor amplitudes and breathing types.

Having characterized the surrogates in terms of their predictive ability, now consider the second question, investigating the reliability of surrogates over a course of treatment. Because when using a surrogate, aside from the predictive ability of the surrogate that

determines the surrogate-based IM's, one would want to know whether such margins remain the same throughout the course of radiotherapy. To be more specific, one would like the answer to the following question.

Are the surrogate-based margins established on day-1 valid on a later day, e.g., on day-20?

What does this exactly mean in terms of the predictive ability of the surrogate? The surrogate-based margins were defined earlier as being equal or directly related to the uncertainty in predicting the tumor position by the surrogate. Therefore, the two statements “the surrogate based margins remain the same from day-1 to day-20” and “the uncertainty of the surrogate in predicting tumor motion remain the same from day-1 to day-20” have the same meaning. Both statements indicate that the tumor-surrogate relationship would remain invariant in time and has not deteriorated.

Generally speaking, the change in IM's from day-1 to day-20 (or any later day) can be in one of the following three different forms (Figure 4.23).

- 1- The required margins on day-20 are the same as on day-1.
- 2- The required margins on day-20 are larger than those established on day-1. In this case, using day-1 margins on day-20 would result in some tumor misses.
- 3- The required margins on day-20 are smaller than those established on day-1. This means that day-1 margins are too large for day-20 and therefore, applying the same margins as day-1 on day-20 would result in some unnecessary normal tissue irradiation on day-20.

Note that even if the non-surrogate-based approach is taken, this is still a valid question: Are the initial margins set by the radiation oncologist at the beginning of the treatment valid over the full course of treatment? Although the cause of the change in the required margins in the two cases (surrogate-based and non-surrogate-based case) are different the effects are the same.

Figure 4.23 The three possibilities regarding the change in the required margins from day-1 and day-20 and the effects on tumour and normal tissue

In the non-surrogate-based case, a change in the required margins from day-1 to day-20 occurs due to changes in the amplitude of the tumor motion (decrease or increase). If this change is not accounted for it can result in tumor misses or extra normal tissue inclusions. To avoid these consequences, more simulation must be performed and new margins set as often as necessary. ^[161]

In the case of the surrogate-based model, a change in the required margins from day-1 to day-20 occurs as a result of change in the tumor-surrogate relationship. In this case, the relationship established on day-1 would not be valid on day-20 resulting in the uncertainties in the predictions on day-1 to be different from the uncertainties in the predictions on day-20 and different margins would be required on day-1 than day-20. Applying day-1 margins on day-20 would result in either tumor miss or extra normal tissue inclusion, as was the case for the non-surrogate-based case. In order to avoid the consequences in this case, the tumor-surrogate relationship must be re-established as often as necessary.

In the next two sections both the surrogate-based and the non-surrogate-based cases are investigated for the reliability of the established margins.

4.5.3.1 Surrogate-based case

In order to investigate the reliability of surrogates in predicting tumor motion, surrogate-based IM's on day-1 and day-20 are determined and compared. To do that, the following steps are taken.

- 1- The tumor-surrogate relationship established on day-1 (Experiment NB-1a) is used to predict the tumor motion on both day-1 (Experiment NB-1b) and day-20 (Experiment NB-2).

- 2- The ellipsoid model and the scoring function (100% volume, 95% of the time) described earlier is applied to calculate the surrogate-based IM's on both day-1 and day-20
- 3- day-20 IM's are compared with day-1 IM's to see if they differ significantly.

As a reminder, note that the surrogate-based IM's would exactly equal the uncertainty (error) in the prediction if "100% volume, 100% of the time" is used as the scoring function. However, since in this study, "100% volume, 95% of the time" was used as the scoring function, IM's are now slightly smaller than prediction uncertainty.

In the evaluation of the predictive ability of the surrogates, "All skin markers" and Row proved to be the two effective surrogates for a variety of situations. Therefore, one of these two surrogates should be chosen to study the reliability issue. Let's focus on "All skin markers".

Figure 4.24 shows the required margins in surrogate-based model (~error in prediction) for day-1 and day-20 side by side. This figure indicates that in most patients the required margins for day-20 are larger than those for day-1. Figure 4.25 depicts the difference between day-1 and day-20 margins, i.e., the change in the IM's. The statistics for this figure indicates that the change in IM's from day-1 to day-20 ranges from -1.20 mm to 5.80 mm (average 1.27 mm). This confirms quantitatively the observation made from Figure 4.24. Therefore, if no precautions are taken and the tumor-surrogate relationship established on day-1 is applied throughout the treatment, on day-20, it results in tumor miss.

Given that the margins (i.e., uncertainties in the prediction) proved not to remain the same from day-1 to day-20, the question becomes how to avoid the consequences (tumor miss or extra normal tissue irradiation). As mentioned earlier an obvious solution is to re-establish the tumor-surrogate relationships. This approach would of course resolve either consequence (tumor miss or extra normal tissue irradiation). However, in a clinical

Figure 4.24 Surrogate-based IM's on day-1 and day-20 for "All skin marker". Note that in most cases, the required margins increase

Change in IM (mm)	
Mean : 1.27	STD : 2.20
Min : -1.20	Max : 5.80

Figure 4.25 Change in required IM from day-1 to day-20 for surrogate-based case ("All Skin markers"). Not that for ΔIM 's above the horizontal axis, the change in IM results in tumour miss while for ΔIM 's below the horizontal, the change in IM results in unnecessary normal tissue irradiation.

Figure 4.26 (a) ΔIM from day-1 to day-20 for surrogate-based case, and (b) the distribution of ΔIM . (c) The distribution after adding a safety margin of 6 mm, and (d) the ΔIM 's after the addition of the 6 mm

setting, it is either impractical or costly in terms of time and dose to the patient to establish a new tumor-surrogate relationship several times.

An alternative that can somewhat improve the outcomes and at least avoid tumor misses is to add a constant value to the day-1 margins to obtain a more favourable margin for day-20. What this will do is to provide a higher confidence level in tumor coverage at the cost of irradiating more normal tissue (for the entire population). The next task is to determine the value of such a constant.

A systematic approach to determine the value of the constant is to acquire data from a large population of patients and use the mean and dispersion in the margin changes for that population. The population in this study was not large enough to lead to a universal value for the constant in question; however, the approach can still be described based on the available data from the relatively small population of the study.

Figure 4.26a shows the change in IM sorted by size. The largest increase in the required margins is located on the left side of the figure and indicates that day-1 margins are too small for day-20 by 5.80 mm and the tumor is missed by that much (the margin is insufficient and thus assigned a negative value, -5.80 mm). On the opposite end (right side of the graph), is a case where day-1 margins are too large for day-20 by 1.20 mm. In this case, the tumor is covered to the desired level completely. However, healthy tissues are being irradiated unnecessarily by 1.20 mm (the margin exceeds the required values and thus assigned a positive value, +1.20 mm).

Figure 4.26b shows the distribution of the margin changes, ΔIM for the population in this study. It shows that using day-1 margins on day-20 results in some tumor miss in 70% of the cases; and in unnecessary irradiation of some normal tissue in the other 30%. Let's suppose that one would like to modify the margins such that the desired tumor coverage is attained in 99% of the cases so that there is only 1% chance of tumor miss. Such a modification would result in a distribution of ΔIM that is shown in Figure 4.26c. The relevant statistics for this transformation are shown on Figure 4.26. The results indicate

that adding 6.4 mm to all the margins would provide the coverage just specified (100% volume, 95% of the time in 99% of the cases). Figure 4.26d shows the ΔIM 's which are all now on the plus side.

Although, the changes in margins just discussed was between two specific days (day-1 and day-20), it is not clear when during the course of the treatment that change has taken place. Therefore, in principle, instead of applying the extra 6.4 mm to the margins on day-20, one should add the additional margins beginning day-1. This would result in (almost) no tumor misses but is usually accompanied by the (unnecessary) inclusion of some extra healthy tissue.

The above findings and discussions indicated that a) the surrogate-based margins are not invariant in time, and b) including an additional 6.4 mm to the margins will provide the desired tumor coverage in 99% of the cases.

4.5.3.2 Non-surrogate-based case

One would now quite justifiably wonder how the margins in the non-surrogate-based case hold. Note that the common clinical practice in most centres is to set the margins on the simulation day (just before the first treatment session) and apply the same margins throughout. Are those margins invariant in time? To be more specific, one would like the answer to the question that was asked for the surrogate-based case, i.e.,

Are the non-surrogate-based margins established on day-1 valid on a later day, e.g., on day-20?

Figure 4.27 shows the required margins for day-1 and day-20 in the non-surrogate-based case side by side. This figure indicates that, in this case too, day-20 margins are usually different for day-1 margins and as before are mostly larger. Figure 4.28 depicts the difference between day-1 and day-20 margins, i.e., the change in the IM's for the non-surrogate-based case. The statistics for this figure indicates that the change in IM's from

Figure 4.27 Non-surrogate-based IM's on day-1 and day-20. Note that as was the case for the surrogate-based case, in most cases, the required margins increase

Change in IM (mm)	
Mean : 1.16	STD : 2.11
Min : -3.40	Max : 5.40

Figure 4.28 Change in required IM from day-1 to day-20 for non-surrogate-based case. Note that for Δ IM's above the horizontal axis, the change in IM results in tumour miss while for Δ IM's below the horizontal, the change in IM results in unnecessary normal tissue irradiation.

day-1 to day-20 ranges from -3.40 mm to $+5.40$ mm (average 1.16 mm). How do these findings compare with those of the surrogate-based case?

Figure 4.29 shows ΔIM for both the surrogate-based and the non surrogate-based cases side by side with the corresponding statistics. The results of the t-test done on the data indicate that there is no statistically significant difference between the two sets of ΔIM 's.

Let's now see how the margins for this case can be modified to provide the desired tumor coverage in 99% of the cases. Using the same approach that was taken for the surrogate-based case, the value of the constant to be added to all the margins for the non-surrogate-based case turns out to be 6.1 mm (Figure 4.30). This is very close to the value of 6.4 mm found for the surrogate-based case. However, it is not an unexpected result in that the two sets of ΔIM 's had proved not to be significantly different.

4.5.3.3 What about the SPR?

Although the SPR proved not to be an effective surrogate for some tumor amplitude and breathing types, since it is widely used as a surrogate for tumor, it is worthwhile to investigate its reliability as well. Figure 4.31 shows IM's on day-1 and day-20 and the difference between the two (ΔIM) for SPR. The statistics indicate that the change in margins in this case range from -1.31 mm to $+7.50$ mm with an average of $+1.31$ mm. This average indicates that when the SPR is used as the surrogate, the required margins for day-20 are generally larger than those for day-1. This is similar to the findings for "All skin markers" and the non surrogate-based case.

For comparison, the three ΔIM 's (non-surrogate-based, "All markers" and SPR) are plotted on one graph and shown in Figure 4.32. The three plots follow the same trend and look very similar. The ΔIM 's are also tested in pairs to see whether they are significantly different with one another. The results of the t-test are shown in Table 4.20 and indicate that there is no significant difference among them.

Figure 4.29 Comparison of the $\Delta IM'$ from day-1 to day-20 for surrogate-based and non-surrogate-based cases. T-test results ($t = 0.34$, $P = 0.74$) indicate that ΔIM 's for the two cases are not significantly different.

Figure 4.30 Δ IM's for the non-surrogate based case (a) before and (b) after adding the (6 mm) safety margin. Note that the data shown in (a) is the same data as in Figure 4.28 but sorted to correspond to the data on Figure 4.26. In this case, too, in order not to miss the tumour, ~6 mm has to be added to day-1 margins. The approach for figuring out the additional margin is the same as that used for the surrogate based case (see Figure 4.26).

Change in IM (mm)	
Mean : 1.31	STD : 2.48
Min : -1.60	Max : 7.50

Figure 4.31 Comparison of the required IM's on day-1 and day-20 for the SPR-based case. The IM's on both days and their differences are shown. Note that in most cases the required margins increase from day-1 to day-20.

Figure 4.32 Comparison of ΔIM 's for the three cases: Non-surrogate-based case, "All skin marker" and SPR.

Table 4.20 The results of the t-test for comparison of ΔIM 's for the three cases: Non-surrogate-based case, "All skin marker" and SPR. Each pair has been compared for the null hypothesis H_0 : ΔIM 's for the two cases are not significantly different

Comparing ΔIM for		t-value	p-value	Results	Different?
Non-surrogate	All markers	0.33	0.74	Cannot reject H_0	No
Non-surrogate	SPR	0.35	0.73	Cannot reject H_0	No
All markers	SPR	0.10	0.92	Cannot reject H_0	No

4.5.4 The volume effect

Everything discussed so far has been in terms of margins. In using the surrogates for NB breathing, it was shown that surrogates can reduce the margins 6.0 mm to 12.0 mm depending on the surrogate and the amplitude of the tumor motion. Also, in adding the safety margin to compensate for possible changes in the required margins, it was concluded that adding about 6.0 mm to the margins would provide the desired tumor coverage throughout.

The order of magnitude for these margins are very small (<1 cm) and may sound insignificant and therefore, their effect in radiation therapy may not be readily obvious. However, when one considers the following two points, the significance of their effect can become quite clear.

- 1- Tumours and healthy tissues being irradiated are in 3D so everything is raised to the third power when calculating volumes.
- 2- The margins encompass a relatively large volume of (tumorous) tissue and however thin they may be, they still add a substantially large volume of tissue.

Let's look at the effect of these small changes in the margins on the normal tissue volume for a hypothetical case with the following assumptions:

- Applying surrogate-based model results in 8 mm reduction in the margins (4 mm on each side or 4 mm all around)
- To account for the change in margins 6 mm is added to the margins (3 mm on each side or 3 mm all around) throughout the treatment
- The (simplified) radiation field is square both Laterally and Sup/Inf

Figure 4.33a shows the tumor and margins for the non-surrogate-based case. The margins here include IM to account for breathing induced tumor motion and the safety margin

Figure 4.33 An idealized depiction of the tumor, margins for breathing induced tumor motion and margins to compensated for possible changes in the IM's during the course of the treatment for a circular (spherical) field.

Figure 4.34 The same idea as in figure 4.33 but shown for a square (cubic) field.

added to correct for possible changes in the margins. Figure 4.33b shows the surrogate-base case with the margins for the breathing induced tumor motion reduced. The safety margins are the almost the same in both cases as the calculations showed in previous sections. Figure 4.34 is the same as Figure 4.33 except for the field that is now changed to a cubic one for simplicity.

Figure 4.35a compares the irradiated normal tissue for the non-surrogate and surrogate-based cases and the volume of normal tissue that is spared as result of reducing the margins by only 4 mm as function of the field size. The figure shows that for 6 cm x 6 cm field size 4 mm reduction in margins would result in about 76 cm³ of normal tissue being saved and the normal tissue sparing will be more than 380 cm³ for a 13 cm x 13 cm field size. This magnitude of normal tissue sparing can result in a substantial improvement in the NTCP because NTCP is a function of both dose and the volume of the irradiated healthy tissue as shown below.

According to Lyman-Kutcher-Burman (LKB) model, ^[155,156] NTCP is calculated as follows

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} \exp\left(-\frac{t^2}{2}\right) dt \quad (4.2)$$

where t is defined as :

$$t = \frac{D - TD_{50}(v)}{m - TD_{50}(v)} \quad (4.3)$$

v is the partial volume of the organ being irradiated, D is the dose and $TD_{50}(v)$ (the tolerance dose for partial volume v) is defined as

$$TD_{50}(v) = \frac{TD_{50}(1)}{v^n} \quad (4.4)$$

Figure 4.35 (a) The effect of using surrogates to reduce IM on normal tissue sparing as a function of the field size. (b) The way figure (a) would change when the safety margin is added in either non-surrogate-based or surrogate-based cases. (c) Comparison of normal tissue saving with and without adding the safety margins. The horizontal axis shows the size of the side of square radiation field.

$TD_{50}(1)$ is the tolerance dose for the whole organ, i.e., the dose that causes a certain end point in 50% of the population in 5 years. m and n are parameters with organ specific values. Their values for lung are $m=0.18$ and $n=0.87$.

So as the volume of irradiated healthy tissue (v) increases, $TD_{50}(v)$ increases and as a result, t increases (note that in Eq 4.3, D is much larger than m). A larger t would yield a larger NTCP from Eq 4.2.

As discussed earlier, there is a possibility that the required margins to irradiate the tumor to a certain level change during the course of the treatment. This will mostly result in tumor misses which translates to reduced TCP. It was suggested that one way to correct for this possible margin change would be to add an extra “safety” margin to the present margins. Figure 4.24b depicts the effect of adding such margins for both non-surrogate and surrogate-based cases. Since a better tumor coverage is achieved as a result of adding this margin, in both cases a better TCP is obtained. Also, in both cases, NTCP would increase (because adding this extra margin is accompanied by irradiating more healthy tissue). However, a gap still exists between the two cases indicating that surrogate-based case yields a much better NTCP compared with the non-surrogate-based case. As a matter of fact, this gap widens when the safety margin is added, i.e., the normal tissue sparing becomes even more pronounced. This should not be surprising because as a result of reduced margins the irradiated volume in the surrogate-based case is smaller than that in the non-surrogate-based case. Therefore, the 3 mm safety margin is added around a smaller volume in the case of surrogate-based case the extra normal tissue that is irradiated is less. Therefore, the difference in the irradiated normal tissue between the two cases becomes more. Figure 4.35c shows the normal tissue sparing (as a result of applying surrogate-based model) both before and after adding the extra 3mm safety margins

4.6 Summary of tumor surrogates

In this chapter we addressed two questions. First, how the various external surrogates for tumor motion compare, and second how reliable these surrogates are. A prediction model with IM as its final outcome was employed. Similar models have been suggested by Vedam et al,^[70] Yan et al.^[135] and have been used by others.^[137-138]

Regarding tumor amplitude in the two directions (lateral and Sup/Inf), we found that for the study population in this work, the amplitude of tumor motion in the Sup/Inf direction is in general larger than that in lateral direction by a statistically significant margin.

Comparison of the surrogates during normal breathing and for a case where the tumor-surrogate relationship was established in the same session indicated that:

- 1- For tumor amplitudes less than 7 mm, none of the surrogates were effective
- 2- For tumor amplitudes between 7 mm and 20 mm, the performance of various combinations of skin markers and the SRP cannot be differentiated, these surrogate can on average reduce the IM by 7.4 mm
- 3- The performance of the Belt is poor compared with the rest of the surrogates

Furthermore, comparison of the surrogates during deep breathing for the case where the tumor-surrogate relationship was established in the same session indicated that:

- 1- For tumor amplitudes less than 10 mm, none of the surrogates is effective
- 2- For tumor amplitudes between 10 mm and 15 mm, “All markers” and “Row” were the two most effective surrogates. Col and SPR were less effective. Belt and One marker proved to be ineffective
- 3- For tumor amplitudes between 15 mm and 50 mm, “All markers”, “One marker”, and Row were effective and could reduce the IM’s by an average of

approximately 13 mm. Belt and Col were less effective while SPR showed an exceptionally poor performance and was ineffective

Therefore, the two surrogates that were consistently effective predictors for tumor motion were “All markers” and Row. An interesting finding about SRP was that the performance of SPR deteriorates at high amplitudes during deep breathing. Also SPR showed that it cannot detect tumor motion during breath hold.

Regarding the reliability of the surrogates, a comparison of the required margins for the case when “All skin markers” is used as the surrogate on day-1 and day-20 of the treatment showed that:

- 1- Δ IM's from day-1 to day-20 ranges from -1.20 mm to 5.80 mm with an average of 1.27 mm which implies some tumor miss, will occur on day-20 if day-1 margins are applied.
- 2- Adding 6.4 mm to all the margins would provide the desired tumor coverage in 99% of the cases

The above findings and discussions indicated that the surrogate-based margins are not invariant in time.

Also, investigating the reliability of the non-surrogate-based case indicated that:

- 1- Δ IM's from day-1 to day-20 ranges from -3.40 mm to $+5.40$ mm with an average of 1.16 mm which implies some tumor miss will occur on day-20 if day-1 margins are applied.
- 2- Adding 6.1 mm to all the margins would provide the desired tumor coverage in 99% of the cases

For the reliability of the SPR, it was found that the change in margins from day-1 to day-20 range from -1.31 mm to $+7.50$ mm with an average of $+1.31$ mm. Like the other two cases, this average implies some tumor miss on day-20 if day-1 margins are applied.

Finally it should be noted that although the magnitude of the IM's and the reductions in the IM's that can result from employing various surrogates are small, their effect on normal tissue is not. This is because 1) margins are raised to the third power when it comes to volume, and 2) the margins wrap around a relatively large volume of tumor and therefore the volume of the margin can be substantial even if the margin is thin

4.7 Summary of some recent related studies

The issue of external surrogates and their ability to predict tumor motion has been investigated in several other studies using somewhat similar approaches. ^[135, 137-141]

In our study, multiple skin markers were placed on the lower chest and abdomen and various combinations of the markers were compared with SPR and Belt. "All markers" and Row (a lateral row of three marker on the abdomen) showed superiority over other combinations of markers ("One marker" and Col) and over the other two surrogates (SPR and Belt) for different types of breathings and over a wide range of tumor motion. The superiority of including more markers as found in this study has also been shown by Yan et al ^[135] However, the difference between the two studies is that 1) in this work the results were reported in terms of IM while their work reported correlation errors, and 2) in this work the skin markers were placed on the lower chest and abdomen while in their study the markers were placed on the upper chest. Their selection of position for the markers may not be the best because as discussed earlier, during breathing, lung mostly expands from the bottom and its motion is mostly translated to an abdominal motion as opposed to chest motion. Therefore, assuming that markers that are placed right above the lung (and the tumor) may provide a better correlation is not necessarily true.

Regarding SPR, in a comparison of surface motion and SPR in terms of their correlation with tumor motion, Hoisak et. al. ^[137] have shown that SPR is a better predictor and a more reliable surrogate for tumor compared with surface motion. Our study found no

significant difference between SPR and surface motion during normal breathing and found SPR a less effective surrogate than skin markers for deep breathing.

Regarding reliability, our findings in this study showed that both for skin markers and SPR the tumor-surrogate relationship changes from day-1 to day-20 of the treatment, i.e., the relationship is not invariant in time. This is in agreement with the findings of another work by Hoisak et al ^[138], where they concluded that the tumour-surrogate relationship changes and reestablishment is necessary.

We reported our results as internal margins while most other studies report correlation coefficients. In the second of two related works by Koch, Liu et. al, ^[140-141] the final results are reported in terms of IM's. In that work MRI scans have been used to acquire tumor motion and tubular markers for surface motion. The tubular markers used by this group wraps around the body contour. This would more resemble the respiratory belt that is used to measure abdominal or chest expansion rather than markers to measure surface motion.

CHAPTER 5

Conclusions and Scope for future work

This thesis examines two problems of clinical interest in radiation oncology. The first is an examination of surrogates for breathing and the second is an examination of surrogates for tumor motion.

5.1 Surrogates for breathing

The purpose of this phase of the study was to examine if skin markers and Belt could act as suitable surrogates for breathing. The question arises primarily because most studies have assumed that breathing and tumor motion are synonymous. [74-78-79-84-82-83-85-127-128] This would imply that a relationship between surrogate and breathing can be extended to the relationship between surrogate and tumor.

This part of the study examined the correlation between surface motion (skin markers) and breathing and the correlation between chest expansion (Belt) and breathing. The spirometer (SPR) was considered the gold standard for breathing as suggested in the literature [121-130]. We studied these correlations in 6 normal volunteers, each for 5 individual sessions, each sessions being several days apart. In each session we examined the surrogate-breathing relationship for 3 types of breathing: normal breathing (NB), deep inspiration breath hold (INSP) and deep expiration breath holds (EXP).

To measure surface motion we used a machine vision system that can track multiple skin markers in 3D. This system enabled us to measure the motion of the markers in three dimensions and study the individual vector components separately. Our findings indicated that there is no advantage in three dimensional tracking of the markers. We found that the AP motion of the markers correlated best with SPR. This motion shows the least day-to-day variation and is the most reliable. On the other hand, the X component of the marker's motion is particularly poorly correlated with breathing for all three breathing types. Further, our results indicated that the Belt correlates with SPR to the same degree as the Z component of skin markers. We also observed that in our population, no one particular marker location was substantially better than any other for all subjects. At the 95% confidence level, the Z component of the marker motion and Belt were superior surrogates of breathing than the X and Y components of the marker motion. Further, the variation in the phase shift session to session that was required to achieve the best correlation coefficient was much smaller for the Z component.

Our findings for surrogates of breathing in normal volunteers were in excellent agreement with the results of work done by Cala et. al. ^[156] where they concluded that spirometric volumes can be estimated very accurately and directly from chest wall surface markers. In a study of correlation between lung motion and surface motion for a variety of breathing types, Koch et. al. ^[140] concluded that the lung motion in the Sup/Inf direction correlated better with surface motion than did AP motion of the lung. However, they looked at lung motion directly while in our study we strictly looked at airflow. As was described in chapter 4, the two do not necessarily mean the same thing. Our results indicating that the Belt correlated well with SPR agrees with observation made by Kubo and Hill ^[136], that Belt and SPR track each other well.

Our findings in this phase can be summarized as follows:

- 1- For all three types of breathing, the amplitude of surface motion is greatest in the Z (Anterior/Posterior) direction and least in the X (Lateral) direction

- 2- No advantage was found in using all 3 coordinates of the motion vector for skin markers. Best correlation was found for Z component of the markers' motion
- 3- No individual marker position was superior in all candidates, but for an individual candidate some markers positions were superior to others over all experiments. These positions were not consistent between subjects
- 4- No significant difference was observed between the Belt and skin markers as a surrogate for breathing (for the three breathing types)

In summary, we concluded that, as many others have shown, the surface motion (skin markers) and Belt can both be used as viable surrogates for breathing and lead us to believe that they have the potential to act as surrogates for respiratory-induced tumour motion.

5.2 Surrogates for tumour motion

In the study of normal volunteers, we concluded that both skin markers and Belt can act as surrogates for breathing. Next we examined how well the three technologies can act as surrogates for tumor motion, that is, how do their predictive abilities compare and how reliable they are. SPR, Belt and four different combinations of skin markers (Col, Row, One marker and All Markers) were studied in 10 lung cancer patients. A prediction model using the ICRU defined Internal Margin as the scoring function similar to those suggested by and used by other investigators^[70,135,137-138] was employed. 100% volume receiving at least 95% of the time was used as the scoring function in comparing various IM's. An ellipsoid model for the tumor shape and a step function for the dose were assumed.

We found that the amplitude of tumor motion in the SI directions was generally larger than that in the Lateral direction, and generally larger for DB than NB. These findings are consistent with other results reported in the literature.^[21,28] Also, a change in the

amplitude (usually increase) was observed from day-1 to day-20 for NB. For DB the amplitudes on day-1 and day-20 were not significantly different.

In comparing of the intra-session performance of various surrogates we found that for NB the performance of various combinations of skin markers and the SPR are not significantly different, while the performance of the Belt is poor compared with the rest of the surrogates. For tumor motion amplitudes larger than 7.0 mm, SPR and Skin markers can reduce the IM to 5.0 mm. For tumor motion amplitudes smaller than 7.0 mm, none of the surrogates were effective. Respiratory Belt was ineffective regardless of tumor amplitude.

It is noteworthy that in the volunteer phase, the Belt showed a good correlation with SPR. But when the two were examined as surrogates for tumor motion, SPR proved to be an effective surrogate while Belt was ineffective. Also of significant importance regarding the results for Belt and SPR is the application of these two modalities in 4D-CT and gated PET/CT imaging. Our results indicate that the use of SPR for gating purposes as done by Low et. al.^[42] and D'Souza et. al.^[22] should be more reliable than Belt as has been employed by Wink et. al.^[149] and Martinez-Moller et. al.^[150]

Our findings also validated the use of a single skin marker in the RPM system (Varian Medical Systems) in conjunction with 4D-CT^[48,49] or gated radiotherapy.^[41,70] Our findings also suggest that the approach of using the belt for gated radiotherapy (such as the one used by Siemens Medical Systems) should be done with great caution.

For DB, our results indicated that 1)none of the surrogates was effective for tumor motion amplitude of less than 10mm, 2)Belt was not effective for any value of tumor motion, 3)One marker was ineffective for amplitudes between 10 and15 mm, and 4)SPR and Col were ineffective for amplitudes of 15 to 50 mm

The ineffectiveness of SPR at amplitudes beyond 20.0 mm during DB suggests that the relationship (coupling) between tumor and SPR breaks down at high amplitudes. This

means that tumor motion is not well coupled with breathing for deep breathing at such amplitudes. It also suggests that assuming that the respiratory induced tumor motion is measured directly by the SPR may be incorrect. Furthermore, tumor motion can be caused by both breathing and by muscular motion, as was evidenced by the tumor motion which was observed in this study during breath hold. This gives another reason why the motion of tumor and airflow (SPR) are not necessarily coupled at all times as their coupling depends on the cause of tumor motion. Distinction between the two causes for tumor motion has been overlooked in studies where SPR has been used to monitor tumor motion.^[119-123] In such studies, it was always assumed that during breath hold if the SPR indicates no air flow then there is no tumor movement, but as we have shown muscular based tumour motion could have been present. Skin markers can detect both the breathing induced and the muscular induced tumor motion. Note that skin markers can detect tumor motions missed by the SPR. This finding has very important implications for techniques such as Deep Inspiration Breath Hold (DIBH)^[74,80-83,85,127,128] and Active Breathing Control (ABC)^[78,79] techniques that employ breath hold to mitigate breathing induced tumor motion. Also any method that employs SPR as a surrogate for breathing^[42,122], should be performed with caution

Regarding a single skin marker, although for NB, we showed that “One marker” is effective and validated its use as a surrogate for tumor motion, this work has demonstrated that using a single skin marker can fail if the breathing pattern/amplitude changes. Although our conclusions are from a relatively small sample, these exceptional “failures” indicate that this surrogate may not be as consistent as originally thought. This could have negative implications for the Varian RPM system used for DIBH.

The findings regarding Belt for DB puts more doubt on the Belt as a surrogate for tumor motion. Our study suggests that caution should be used when the Belt is employed for gated radiotherapy (e.g., by Siemens Medical Systems) or when investigators report its use for 4D-CT or gated PET/CT imaging.^[149,150]

Finally, Col and “One markers” were ineffective surrogates for some amplitudes during deep breathing, which is inconsistent with the results for NB where it was shown that the various combinations of skin markers are equally effective surrogates.

Having characterized the surrogates in terms of their predictive ability, we then investigated the reliability of surrogates over a course of treatment, i.e., whether the surrogate-based margins established on day-1 were valid on a later day, e.g., on day-20. This is also a valid question for non-surrogate-based margins.

Based on the day-1 analysis this part of the study focused on “All skin markers” and SPR and measured the change in IM’s from day-1 to day-20. We found that for both “All skin markers” and SPR the surrogate-based margins are not invariant in time, but usually increased over time. Further, we found that for the non-surrogate-based case, the IM’s change from day-1 to day-20 by a similar amount. There was no statistically significant difference in the IM change from day-1 to day-20 between the three cases (two surrogates and the non surrogate). In all three cases, it was estimated that expanding the day-1 IM by an additional 6 mm would provide adequate tumor coverage on day-20.

Although the margins being discussed are quite small, their effect in radiation therapy is significant because the volume of normal tissue that can be spared as result of small margin reductions can be substantial. This can in turn result in a substantial improvement in the NTCP. As discussed earlier, there is a possibility that the required margins to irradiate the tumor to a certain level change during the course of the treatment. This will mostly result in tumor miss which translates to reduced TCP. Adding a 6 mm margin was suggested to correct for this possible margin change. This extra margin would result in a better tumor coverage and thus a better TCP, but at the cost of an increased NTCP. It was shown, that because both the surrogate-based and non-surrogate-based IM’s require an additional margin between day-1 to day-20, a substantial gain (reduced NTCP) can still be present using a surrogate-based model yielding a much better TCP+. In fact, it was shown that the difference between the surrogate-based and the non-surrogate-based cases becomes more pronounced when the safety margin is added.

Finally, our study found no significant difference between SPR and skin markers during NB but found SPR to be a less effective surrogate than skin markers for DB. Two surrogates were consistently effective predictors for tumor motion for both NB and DB, “All markers” and Row. An interesting finding about SPR was that the performance of SPR deteriorates at high amplitudes during deep breathing. Also SPR showed that it cannot detect tumor motion during breath hold.

Regarding reliability, our findings in this study showed that for both surrogate-based and non-surrogate-based cases, the IM’s do not remain invariant in time. An additional margin is required to account for this change.

The conclusions drawn here are based on our study with only a relatively small population and as such have a low statistical power. Nonetheless, the population size used in this study is much larger than in most similar studies.

Conclusions

Our results indicated that there is no value in employing a surrogate to mitigate tumor motion for amplitudes less than 7 mm. For normal breathing various combinations of skin markers and SPR proved to be equally effective while for deep breathing some combinations of skin markers (a column of three markers and a single marker) and SPR did not show consistent effectiveness. Belt proved to be an ineffective surrogate regardless of the amplitude of tumor motion and the breathing type. Based on these results and considering the fact that skin markers are easy to apply and do not cause any discomfort to the patient, multiple skin markers can be used clinically as a suitable surrogate for tumor motion. This is strictly true if the tumor-surrogate relationship is established on the same day as it is applied. The reliability was poor for both the surrogate-based model the non-surrogate-based case requiring re-establishment of the margins or assuming an additional margin to prevent tumor misses.

5.3 Scope for future work

It occurs to me that both in medicine and in general, sometimes a technological advance moves faster than the science behind it. That is to say, new tools are made all the time for no apparent need for them or without their scientific basis having been fully established. Of course, one could argue that it is better to do something while we are waiting for the science to figure things out completely. That is not an invalid argument, although at times a faulty technology may be employed for too long before it is discovered to be ineffective or even harmful. But in any case, a scientific approach to technological advances is a necessity.

Tumor motion and trying to mitigate it is such an issue. Although advanced technological tools have been developed in the recent years for gating and tracking (RPM and CyberKnife), more studies like this one need to be done to justify their use. With this in mind we undertook this study on surrogates for tumor motion and tried to answer some of the questions involved. However, more often than not, when one tries to answer one question, more questions are posed than answered. It takes efforts from many people to answer all the questions.

It would be beneficial to expand the present study in two ways. First, incorporating CT images which have better resolution and can give 3D tumor position, and secondly, adding more data points both in terms of the number of subjects and the number of time points. This can tell us whether the change in IM is gradual, random, related to treatment, etc. An extension to this work could be incorporating NTCP and TCP to calculate and report the final results in terms of TCP+.

The results of this work suggest that surface markers might have a role in mitigating against motion artifacts in PET (1/2 hr acquisition) since tumor motion is an important issue in PET imaging, and would be an interesting future study. Another interesting study would be to couple the skin marker technique with image guided systems (e.g. cone CT)

to minimize setup error and study the effect of establishing the surrogate-tumour relationship each day.

A significant challenge for the machine vision system employed in this study is the geometric view requirements. It would be interesting to do a head to head comparison with RPM, which has minimal geometric constraints, in the same patients at the same time to see whether two cameras (i.e., 3D surface tracking) is truly advantageous over 2D tracking.

Determining how to use these motion surrogates with various types of IMRT (e.g. dynamic MLC, step and shoot, Tomotherapy etc.) without making the delivery extremely inefficient would also seem to be a natural extension of this work.

Finally, as emphasized several times, our study suffered somewhat from a relatively small population size. More reliable results can be obtained with an increased population size and incorporating other modifications suggested earlier.

Appendix A

Clinical Proposal and Supplements

A clinical trial was written proposing an experiment with two phases, Phase-I to be performed on normal volunteers and Phase-II on lung cancer patients. The trial was reviewed by CREC (Clinical Research Evaluation Committee) of The Ottawa Hospital Regional Cancer Centre; and OHREB (Ottawa Hospital Research Ethic Board). Included in this review was the scientific merit, criteria for subject selection, experimental procedure and subject safety. It is noteworthy that there was no radiation dose to the normal volunteers and the extra dose to the patients as a result of the experimental procedures would not exceed 1% of their nominal dose from routine therapy. This is well within the accepted dose variation due to calculation, setup, planning and patient conformation deviation that is of the order of $\pm 5\%$ of prescribed dose.

This appendix will include the approved clinical trial and both of the consent forms given to volunteers and to lung cancer patients.

**A proposal for a human trial to determine the Reliability and
Reproducibility of a Machine Vision System as a control device
in Gated Radiation Therapy**

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Eligibility Criteria

1. Patient with biopsy proven non-small cell lung cancer who will be treated radically Yes _____ No _____
2. Patient has a tumour that is easily visible on a chest x-ray
Yes _____ No _____
3. Patient will be able to tolerate the use of a spirometer
Yes _____ No _____

ABSTRACT

The geometric uncertainty introduced by respiration induced intra-fraction tumor motion is a well-documented clinical problem in radiation therapy and is usually mitigated by increasing the volume of irradiated tissue surrounding the clinical target volume (CTV). Reducing this uncertainty, or proactively accounting for it, would allow a decrease in field size with a concomitant reduction in normal tissue complication probability (NTCP) while maintaining the same tumour control probability (TCP). To achieve this clinically, it is necessary to track tumor motion or a surrogate. We hypothesize that surface motion of the chest and upper abdomen can play this role.

A Machine Vision System for measuring the position of retro-reflective markers has been developed at the ORCC. The system has been able to measure the position of stationary markers with a precision and accuracy of better than 0.08 mm 0.7 mm respectively.

In this work we propose to determine if this technology can be used to track tumour motion with an aim to developing a tool to gate the radiation therapy beam as the target oscillates through the cross section of the beam. This proposal is for a study to investigate the applicability and reliability of machine vision and the measurement of chest surface motion as a surrogate for tumour motion through two distinct non-interventional stages:

1. Determine the phase and vectoral relation of various areas of the chest surface in normal volunteers as a function of respiration as measured independently with a spirometer and a respiratory effort transducer.
2. Augment routine CT and fluoroscopy studies to determine the three dimensional relationship between respiration induced target/organ motion and the surface motion of the chest in patients with pulmonary and hepatobiliary malignancies

Reliability and Reproducibility of The Machine Vision System For Potential Application in Gated Radiation Therapy

1. Introduction

1.1. Background

Radiation therapy is one of the primary modalities used in the treatment of many cancers, including lung cancer. The objective of curative radiotherapy is to eradicate viable tumor while preserving host organ function. Therefore radiotherapy would ideally irradiate only malignant tissues to a tumouricidal dose. However, physical, biological and conformational constraints preclude the achievement of this ideal. It has been well established that the probability of controlling local disease (Tumor Control Probability - TCP), is dose dependent. Maximizing the TCP requires that both the visible gross tumor volume (GTV) and the surrounding volume containing microscopic extensions (clinical target volume -CTV), be irradiated to the maximum safe dose. Modeling based on a phase I study of dose escalation in the treatment of non-small cell lung cancer with radiation alone suggests that conventional doses in the range of 60-70 Gy have only about a 15-20% chance of achieving local control, and the same study projects that in order to achieve a 30 month local progression free survival of 50% doses of 84.5 Gy are warranted in this disease. (Martel (1999)).

It is also well established that the probability of excessive normal tissue damage or Normal Tissue Complication Probability (NTCP) increases with both the dose and the volume of tissue irradiated (Withers (1988), Niemierko (1993), Jackson (1993)) and is considered a principal limiting factor in achieving local tumor control. Therefore, every attempt must be made to mitigate NTCP while maximizing or at least maintaining TCP. Fractionation, that is delivering the dose in small fractions over many days, is one of the methods to mitigate NTCP. The effects of fractionation have been widely investigated (Emami (1991), Hall(2000)). Another mechanism to mitigate NTCP is to minimize geometric uncertainties in tumor position which emanate from tumor motion due to breathing, especially in lung and liver cancer (Koelbl (1999)).

Minimization of these uncertainties necessitates a knowledge of the geometric relationship between the tumor position and the radiation beam at all times during treatment. It is proposed that one method of establishing this geometric relationship is to use the patient surface as a surrogate for tumour motion. Subsequently it should be possible to dynamically intervene through beam gating or positional correction based on this *apriori* geometric information.

1.2. Gross Tumor Volume (GTV), Clinical Target Volume (CTV), and Planning Target Volume (PTV)

In order to achieve tumor control, the GTV and the surrounding microscopic disease must each be irradiated to their own tumouricidal dose. ICRU 50 and 62 define this total volume as the Clinical Target Volume (ICRU 50 (1993), ICRU 62(1999)). Uncertainties in the CTV delineation, intra fraction patient motion, inter fraction setup errors and tumor mobility within the patient require that a volume of tissue surrounding the CTV be included as part of the Planning Target Volume (PTV). Reducing these uncertainties reduces the PTV and hence the volume of tissue which must be irradiated resulting in a reduction in the NTCP while maintaining the same TCP. Many strategies have been developed to reduce these uncertainties, most of which focus on geometric uncertainty. These include the use of CT for target delineation (Emami (1978)), patient immobilization devices (Crook (1995), Malone(2000)), setup aids such as laser systems (Engelmeirer (1987))and fiducial marker systems (Verhey(1982), Verhey (1995)). None of these strategies diminish the uncertainty introduced by intra-fraction tumor motion induced by patient breathing. The ultimate goal of this work is to develop a method by which this uncertainty can be measured, monitored and reduced.

1.3. Radiotherapy in the Treatment of Lung Cancer

The use of three-dimensional conformal radiation therapy (3D-CRT) for lung cancer has allowed for improved shaping of the high dose volume to the target and significantly reduced volumes of normal lung, esophagus, heart and spinal cord in the high dose volume. Nonetheless, known tumor motions of up to 2.5 cm requires that significant

boundaries be placed around the CTV, significantly increasing the high dose volume even in these conformal techniques (Balter (1996), Lujan (1999)). It is believed within the radiation therapy community that better precision in dose delivery will facilitate reduced treatment volumes allowing for higher doses and/or lower NTCP. It is also assumed that higher doses will translate into better TCP and enhanced overall survival. Early evidence in lung cancer supports this hypothesis but only phase I and II data exist to address dose escalation alone which as yet has not established proven outcomes (Hayman (2001) , Rosenzweig (2000)). Randomized data exist for both concurrent chemo-radiation and strategies that accelerate the delivery of the radiation dose (e.g.CHART) showing benefit in terms of improved local control leading to improved survival (Furuse (1999), Curran (2000), Saunders (1999)). By extension, it is hoped that volume reduction will allow a further increase in either radiation or chemotherapy and hence improved local control and survival.

As a result of normal tissue exposure, lung toxicity still remains the dose and possibly the TCP limiting factor (Yorke (2002), Armstrong (1993)). To achieve further gains with radiation therapy, it is essential that methods be developed to mitigate against respiratory induced target motion in order to achieve safe dose escalation.

2. Existing Strategies to Mitigate Against Breathing Induced Tumor Motion

The problem of target motion associated with the treatment of thoracic lesions has been recognized previously (Balter et al, Englesman et al) To date, two approaches have been used to reduce the effect of this motion: 1) controlled patient breathing and 2) respiratory gating.

2.1. Controlled Breathing

Several investigators have proposed the use of breath hold techniques such that the radiation dose is delivered to a still thorax, that is the entire dose is delivered during a single phase of the respiratory cycle. It is then assumed that the target has a fixed

geometric relationship to the patient surface. In one such method, known as the deep inspiration breath hold (DIBH) technique, the patient is instructed to hold his breath at full inspiration using a slow vital capacity maneuver (Hanley (1999), Mah (2000), Sixel (2001)). This maneuver begins with the patient in quiet tidal breathing, followed by a slow deep inspiration, slow deep expiration, then another slow deep inspiration to maximal inspiratory level and breath hold. A spirometer is used to monitor the patient's respiration level. With this technique, a small cohort of patients have been able to hold their breath for an average duration of 12-16 seconds, requiring approximately 15 breath holds per treatment session (fraction). Although this technique was useful in demonstrating feasibility, it is not clinically viable primarily due to the time consuming and cumbersome requirement for the daily use of a spirometer during dose delivery (it should be noted that only about 1/3 of all patients can tolerate DIBH. (personal communication – Dr. Ken Rosenzweig). Furthermore, there is no geometric feedback to the operator and the reproducibility of the tumor position is questionable. In a variation of this technique, Wong *et al* (1999) have pioneered the Assisted Breathing Control (ABC) device, which monitors tidal lung volume during treatment and uses a modified critical care respirator to force a breath hold at a predetermined point in the patient's respiratory cycle (Wong (1999), Dawson (2001)). Since the breath hold is forced at the same phase of respiration, the geometric reproducibility may be improved. However, the ABC uses airflow information, which may be weakly correlated with tumor position. Moreover, the invasive nature of the ABC device makes it unsuitable for routine use in radiotherapy. In general, existing breath hold techniques are unsuitable for radiotherapy, particularly if the patient has impaired pulmonary function.

2.2. Respiratory Gated Radiotherapy

Another approach to the same problem is to gate the radiation therapy beam during a specific portion of the respiratory cycle without controlling for a forced breath hold (Ohara (1989), Kubo (1996), Sontag (1998), Mageras (2001), Chen (2001)). This approach allows the patient to breathe freely or in a learned fashion, while the radiation beam is turned on and off (gated) using a control signal based on the phase of the patient's respiration. To date, radiotherapy beams have been gated on several different

trigger signals including airflow (Kubo (1996)), thermistors, (Kubo (2000)) strain gauges (measurement of abdominal distension) (Kubo(2000)) , CO₂ sensors (Sontag (1999)) and video monitoring of a light emitting diode (LED) target placed on the patient's abdomen (Kubo (2000), Vedam (2001)). However, each of these existing gating techniques suffers from one or more limitations including the fact that they are invasive and/or inherently one-dimensional. Fluoroscopic studies of tumor motion due to breathing have been performed and tumor motion has been shown to be a complex three-dimensional function of respiration. Furthermore, internal target motion does not always have a direct phase or amplitude correlation with breathing patterns (Gerig (2002)) Because of this complex relationship, a three-dimensional assessment of respiration induced patient motion correlated with internal target motion is necessary before treatment margins can be reduced and the radiotherapy dose escalated.

3. Methods

3.1. Apparatus: Patient Position Monitoring (PPM)

A machine vision based computer system, known as the Patient Position Monitoring System (PPM) has been developed and clinically tested at the Ottawa Regional Cancer Centre as an adjuvant to patient setup (Gerig (1994)). The system consists of two CCD-TV cameras, each with a monochromatic diffuse IR (810 nm) light to illuminate retro-reflective targets placed on the patient surface. A significant portion of the light incident upon the targets is reflected back to the CCD cameras providing a large signal to noise ratio and inherent contrast. In the radiotherapy environment the cameras are mounted in the treatment room, focused at the treatment unit isocenter (that point in space where the linac gantry and collimator axes of rotation intersect). The images from the cameras are captured using a digital frame grabber and analyzed on a personal computer. The system is based on the fact that any point in three-dimensional space has a unique projection onto the two separate planes represented by each matrix in the CCD camera. The unique point in three space is determined through a calibration process that establishes an *apriori*

knowledge of the exact location of each cameras' CCD matrix with respect to a reference coordinate system.

The calibration is accomplished using a precision three-dimensional phantom oriented at a known position with respect to the linac isocenter. The phantom consists of an aluminum base and a series of calibrated rods of different length placed at various locations on the base. The top of each post has a retro-reflective target to act as a known source. The centroid of each of these targets is accurately known (± 0.025 mm). Measurement of these targets by the PPM system provides a calibration matrix.

3.2. PPM Performance Parameters

Accuracy, precision and reproducibility are indicators of system performance and reliability. A series of tests were performed using a standards lab-traceable optical bench as a gold standard with a known accuracy of better than 0.5 mm over its entire range of motion. These studies show the system as configured in our lab has a precision of better than 0.08 mm and an accuracy of better than 0.7 mm. Temporally, the system is capable of sampling approximately 10 target positions per second.

3.3. Study Design

3.3.1 Determination of the phase and vectoral relationship between various areas of the chest surface in normal volunteers as a function of respiration as measured independently with a spirometer and a respiratory effort transducer.

The aim of this phase of the study is to determine the vectoral and phase relationship of points on the body surface as a function of respiration. This study is broken down into two sub phases:

1. Demonstrate that the system can reliably detect the breathing induced surface motion of a human subject.

2. To measure the phase and vectoral relationship between different points on a subjects' surface as a function of breathing cycle and breathing pattern (normal shallow breathing, deep inspiration breath hold, deep expiration breath hold). These measurements, benchmarked against a spirometer and a respiratory effort transducer (which measures chest expansion), will be used to establish inter and intra subject reproducibility and the reliability of surface points as surrogates of breathing cycle for each of the three breathing patterns.

Ten healthy normal volunteers will be chosen. The subject will lie supine on a radiation therapy tabletop, in direct view of both PPM CCD cameras. On each subject's chest and upper abdomen nine radio-opaque retro-reflective markers will be placed at predetermined locations. These small, (approximately 15 mm) optical circular targets have been used safely with no resultant skin side effects (Gerig (1994)). The targets may be left on the volunteer until their retro-reflective surface degrades (usually in 4 to 5 days) or can be removed after each experiment and replaced the following day. Each target center has a 2.0 mm diameter hole that can be used for repositioning the targets against semi-permanent skin marks drawn on the subject. Prior to the beginning of each experiment, the PPM system will be calibrated and a standard quality assurance procedure will be performed to benchmark system performance. In addition, an ambient light image is acquired by each CCD camera to record the exact target positions on the volunteer's chest.

A spirometer will be used to monitor breathing during the experiment. A separate channel on the PPM computer will record the spirometer data and time stamp it against the PPM target position measurements. In addition the volunteer will be fitted with the respiratory effort transducer which measures the change in circumference of the chest. The output of this transducer will be read on a separate channel of the PPM computer's analog-to-digital converter (ADC) and time-stamped against the spirometer and PPM recordings. Each subject will then be instructed to breathe in each of the three breathing patterns (normal shallow breathing, deep inspiration breath hold, deep expiration breath hold). They will be asked to maintain each of these breathing patterns for 5 minutes (to

simulate a nominal radiation treatment time with gating). The experiment will be repeated up to 5 times on each volunteer over a period of several weeks. During each experiment the PPM system will acquire target data at a rate of at least 5 Hz.

The experimental data will be analyzed off line. The spirometer and respiratory effort data will be correlated to the PPM data through their respective time stamps. From these data we would hope to establish:

- 1) The relationship between the spirometer and respiratory effort data.
- 2) The ability of PPM to measure surface motion as a function of breathing cycle.
- 3) The phase relation between markers placed at different positions on the body surface as a function of breathing cycle and type of breathing
- 4) The inter and intra subject variability of surface motion as a function of the type of breathing
- 5) The ability of the PPM markers to act as a surrogate for monitoring patient breathing cycle and amplitude.

3.3.2 Augment routine CT and fluoroscopy studies to determine the three dimensional relationship between respiration induced target/organ motion and the surface motion of the chest in patients with pulmonary and hepatobiliary malignancies.

Eligible patients are those with either non-small cell lung cancer or small cell lung cancer who will be receiving radical radiation as part of their treatment. Their tumors should be visible on a normal chest x-ray and they should be able to tolerate a spirometer for monitoring their breathing.

Patients with pulmonary malignancies normally get at least 1 and often 2 planning CT scans. From these scans a radiation therapy treatment plan is designed and a radiation prescription is given. Subsequently, but prior to treatment delivery, the patient is placed in the treatment position (usually supine with arms extended over their head) on the

couch of a therapy simulator. Under fluoroscopy, the treatment fields are simulated geometrically. The radiation oncologist observes the treatment field borders with respect to internal anatomy and the visible tumour volume as a function of breathing cycle. The radiation oncologist adjusts the field borders to ensure that each radiation field encompasses the dynamic CTV during all phases of the respiratory cycle.

We plan to augment both the CT and fluoroscopy studies as follows:

- ❑ Prior to the planning CT, radio opaque markers will be placed on the patients' chest and upper abdomen (normal respiration) in the same position as the PPM markers will be placed during subsequent fluoroscopy measurements. In addition, the patient will be fit with the respiratory effort transducer.
- ❑ In one session, perform the routine planning CT plus three additional scans: one with the patient holding their breath at maximal inspiration, one at maximal expiration and one slow (4sec) CT where the respiratory effects are averaged into the reconstructed scan.
- ❑ During these scans the patient's breathing will be monitored with the respiratory effort transducer placed around the patient's chest.
- ❑ During the treatment planning process, which occurs subsequent to the CT, establish the vector relationship between each of the radio opaque markers and the target volume. The relationship will be established with respect to the target centre of mass, and each of its principal extents (superior, inferior, left, right, posterior and anterior)
- ❑ Prior to the routine fluoroscopy, the standard PPM retro-reflective markers augmented by radio-opaque markers, will be placed on the patient's chest and upper abdomen at exactly ($\pm 0.5\text{mm}$) the same positions as per the radio-opaque markers used during the CT scan.
- ❑ During the routine fluoroscopy the patients' breathing will be monitored with a spirometer, the respiratory effort transducer will measure their chest expansion, and the position of each PPM marker will be monitored by the PPM camera

system. The signals from each of these will be captured by computer and time stamped for later synchronization and analysis.

- ❑ The physician will perform the standard fluoroscopy process and adjust the field borders as per routine treatment. The video fluoroscopy image will be captured by a video card, time stamped and recorded with a PC.
- ❑ The patient will then proceed through the standard treatment process.
- ❑ For those patients scheduled for boost field, treatment the fluoroscopic study will be repeated as described above.

This data will be analyzed offline. The spirometer, respiratory effort, video fluoroscopy and PPM data will be temporally matched through their respective time stamps. From these data we would hope to:

1. Establish the temporal vector relationship between each of the radio opaque markers (and hence the PPM makers) and the target volume using three methods: The fluoroscopically defined tumour motion (only in the plane of the Beam's Eye View), the slow CT scan which will integrate quiet respiratory motion and the 2 CT scans acquired at the extremes of maximum inspiration and expiration to determine the reliability of surface markers as a surrogate for tumour motion.
2. For each subject, determine the correlation between the 3D CT determined target extents and the projected (2D) fluoroscopic target extents, as benchmarked against spirometry to determine the reliability of fluoroscopy as a true measure of planar projected target motion.
3. Correlate the phase and amplitude of the tumour motion and PPM target motion with the spirometric data to establish if spirometry is a reliable tool to track tumor motion.
4. Correlate the motion of the tumour and PPM target motion with the respiratory effort transducer data to establish if chest expansion is a reliable tool to track tumour motion.
5. For each patient simulate radiotherapy gating on the fluoroscopic images using spirometry, chest expansion and PPM surface target position as the gating signal.

6. Apply the fluoroscopic based gating to the 3D CT targets using the correlation relationships established above.
7. For those patients who have had repeat fluoroscopic investigations prior to the start of their boost field treatments, determine the reproducibility of the PPM, target volume, spirometry and chest expansion relationships established prior to radiation therapy
8. Using the methods described by Lyman (1989, 1992) calculate an estimate of changes to NTCP and TCP (Zaider (2000, 2001) based on the simulations of target and normal tissue dose distributions

We propose to make these measurements on 20 patients.

3.3.2.1 Radiation safety considerations

Radiation therapy for lung cancer involves a process whereby doses of up to 66 Gy (66000 mGy) are delivered to the volume of tissue which is felt to harbor disease. In addition the dose to the normal tissues coplanar to the target volume as well as the full volume of normal tissue within 5 cm superior and inferior of the target receive doses of the order of 5 to 50% of the target doses (3300 to 33000 mGy). Further, as a result of head leakage from the linac, the remainder of the patient receives a whole body dose of the order of 60 mGy.

As a standard part of the treatment preparation process a patient will receive a standard planning CT of the chest, with a concomitant dose of approximately 30 mGy to the volume being scanned. Thus for each CT the patient's tissues in the vicinity of the tumour will receive a dose of less than 0.05% of the dose delivered by therapy, while tissues superior and inferior of the target will receive doses of ranging from 0.03 to 0.3% of the doses they receive as a result of therapy. In this study we are proposing that a patient will receive 3 CT scans in addition to the normal clinical practice. These additional scans will be restricted to the volume of tissue nominally defined by the 3300 mGy isodose line and hence these tissues will receive an additional 0.9% of the dose received by therapy.

In addition to planning CT scans, patients normally have a fluoroscopy after the initial treatment planning is complete, but prior to treatment. The fluoroscopic field size is delineated by field trimmers, isolating the diagnostic radiation to the therapeutic dose region. The nominal dose from fluoroscopy is a function of time, KVp, and mA. Based on current practice, a patient would receive less than 10 mGy for a 30 second fluoroscopy session. In this proposed study a patient would receive one fluoroscopy in addition to standard practice, resulting in an additional dose to the target tissues of less than 0.02% of the nominal treatment dose.

In summary the additional radiation exposure that a patient's tissues will receive as a result of this study will not exceed 1% of their nominal dose from routine therapy. To put this in context the nominal accepted dose variation due to calculation, setup, planning and patient conformation deviation is of the order of +/- 5% of prescribed dose and thus the additional dose received by the patient is less than 25% of the accepted dose variations. The decision to administer radiation therapy has already weighed the potential risk of leakage, scatter and uncertainty in dose delivery against the medical benefit to the patient, from which we conclude that the addition of the dose concomitant with the proposed study to the patient cohort considered here dose not represent any measurable increased risk.

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Volunteer Information and Consent Form

Rev. Aug. 23, 2004

A proposal for a human trial to determine the Reliability and Reproducibility of a Machine Vision System as a control device in Gated Radiation Therapy (Local #OTT 04-04, OHREB #2004431-01H)

WHAT IS THE BACKGROUND?

This is a clinical trial (a type of research study). Clinical trials only include patients or volunteers who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

WHY IS THIS STUDY BEING DONE?

The kind of treatment used for lung cancer depends on how far the cancer has spread beyond the chest. If the cancer stays in the chest area but cannot be removed by surgery, then the usual treatment is radiation therapy and often chemotherapy. Sometimes if patients are not well enough to withstand surgery for an early lung cancer they are treated with radiation with the intention of curing their cancer.

Right now, when we plan radiation treatments for lung cancer we are limited by the amount of normal healthy tissues that receive high doses of radiation. In some other types of cancer there is evidence that reducing the side effects of radiation by using smaller radiation fields offers the opportunity to safely deliver higher doses of radiation. This tends to lead to better control of the cancer and better cure rates.

This study is looking at several ways in which we might improve our ability to localize lung cancers, understand how they move with breathing and determine if we can take advantage of this to reduce the size of the radiation field used for treatment.

Volunteer Role:

We are asking ten volunteers who do not have cancer to participate in studies. These studies include correlating the movement of your chest wall with breathing. In order to correlate measurements with your breathing we will monitor your breathing with a spirometer (an instrument that will allow us to measure air flow as you breathe). As well we will look at a respiratory effort transducer (a belt-like piece of equipment) that will tell us how much your chest moves when you breathe. These will be correlated with the movement of 9 small markers that will be placed on your chest wall whose movement can be tracked accurately with an optical based tracking system. These markers have been used previously will no effects on the skin. These measurements may be repeated on up to 5 separate occasions.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

30 people will take part in this study. The study should take about 12 months to complete.

ARE THERE RISKS TO TAKING PART IN THE STUDY?

There are no risks to you as part of your participation in the study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you choose to participate in this study, there may or may not be direct benefit to you. Information learned from this study may benefit patients in the future.

Affiliated with University of Ottawa Faculty of Medicine
Affilié à la Faculté de Médecine de l'Université d'Ottawa
A Cancer Care Ontario Centre - Eastern Region
Le centre action cancer Ontario de l'est

WHAT ABOUT CONFIDENTIALITY?

Every effort will be made to keep your personal information confidential.

Qualified representatives of the following organizations may inspect the study records and receive information from your participation for quality assurance and data analysis:

- The Ottawa Hospital Research Ethics Board, which oversees the ethical conduct of this study at The Ottawa Hospital Regional Cancer Centre.

The organizations listed above will keep information about you confidential, to the extent permitted by applicable laws, in the following manner:

- Your name will not be used in any reports about the study
- You will be identified only by a study code and initials
- Your name will not be disclosed in any report or publication resulting from the study or in any documents leaving The Ottawa Hospital Regional Cancer Centre, unless required by law.

WHAT ARE THE COSTS?

You will not be paid for taking part in this study.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

You are under no obligation to participate in the study. Participation in this trial is voluntary and you may choose not to participate or to withdraw from the study at any time without giving a reason.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

If you have questions about taking part in this study you can talk to the doctor who is in charge of the study at this institution. That person is Dr. R MacRae at (613) 737-7700, Ext 6169.

This protocol has been approved by The Ottawa Hospital Research Ethics Board. This Board considers the ethical aspects of all hospital research projects using human subjects. If you have any questions concerning this study or your rights as a research subject, you may contact any of the following people:

- The Vice-President, The Ottawa Hospital Regional Cancer Centre, (613) 737-7700, Ext. 8880.
- The Chairperson of The Ottawa Hospital Research Ethics Board, (613) 798-5555, Ext. 14902.

My signature below means I have read this volunteer information and consent form, (or it has been read to me), I have had the opportunity to review any questions with the study team members and I agree to participate in this study. A copy of this patient information and consent form will be given to me.

Patient's Name (Please Print)

Patient's Signature

Date

Name of Investigator/Person Conducting the
Informed Consent Discussion (Please Print)

Signature of Investigator/Person Conducting the
Informed Consent Discussion

Date

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WHAT IS THE BACKGROUND?

This is a clinical trial (a type of research study). Clinical trials only include patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

You are being asked to take part in this study because you have lung cancer and you have been offered treatment that includes radiation.

WHY IS THIS STUDY BEING DONE?

The kind of treatment for lung cancer depends on how far the cancer has spread beyond the chest. If the cancer stays in the chest area but cannot be removed by surgery, then the usual treatment is radiation therapy and often chemotherapy. Sometimes if patients are not well enough to withstand surgery for an early lung cancer they are treated with radiation with the intention of curing their cancer.

Right now, when we plan radiation treatments for lung cancer we are limited by the amount of normal healthy tissues that receive high doses of radiation. In some other types of cancer there is evidence that reducing the side effects of radiation by using smaller radiation fields offers the opportunity to safely deliver higher doses of radiation. This tends to lead to better control of the cancer and better cure rates.

This study is looking at several ways in which we might improve our ability to localize lung cancers, understand how they move with breathing and determine if we can take advantage of this to reduce the size of the radiation field used for treatment. These studies include measuring the relationship of 9 markers placed on your chest with the tumor position on the normal x-ray and CT scan studies that are done. These markers have been used previously with no effects on the skin. In addition, we will be doing three more CT scans to determine how much the lung cancer moves when you breathe. In order to correlate measurements with your breathing we will monitor your breathing with a spirometer (an instrument that will allow us to measure air flow as you breathe). As well we will look at chest wall motion with a belt-like transducer called a respiratory effort transducer that will tell us how much it moves when you breathe.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

30 people will take part in this study. The study should take about 12 months to complete.

Affiliated with University of Ottawa Faculty of Medicine
Affilié à la Faculté de Médecine de l'Université d'Ottawa
A Cancer Care Ontario Centre - Eastern Region
Le centre action cancer Ontario de l'est

WHAT IS INVOLVED IN THE STUDY?

Please see the flow diagram of the study:

Treatment:

The need for chemotherapy and radiation will be decided with you and your cancer doctors, as it is not always indicated for every patient. The specific details of your treatment will be decided between yourself and your doctor. Participation in this study will not affect those decisions. The additional CT scans and monitoring of your breathing during radiation planning will not affect decisions about your planned treatment.

You can participate in other clinical trials evaluating the type of therapy given for your lung cancer and your oncologists will discuss this with you if you are also eligible for another trial.

HOW LONG WILL YOU BE IN THE STUDY?

Once your radiation planning has been completed the study is finished. No ongoing follow-up will be needed for the study and your oncologist will follow up based on standard clinical practice.

You can choose not to participate in this study or stop participating at any time and your doctor will continue to treat you with the best means available. If you choose to stop participating in the study, we encourage you to talk to your doctor first.

WHAT ARE THE RISKS OF THIS STUDY?

Additional Radiation Risks from the Three Extra CT Scans

As a result of your participation in this study, you will have 3 additional CT scans. It is not anticipated that the increased exposure to radiation from these CT scans will cause any additional side effects or increase your risk from radiation exposure. Please talk to your cancer doctor about this if you have any concerns.

Reproductive Risks:

If you are pregnant, you will not be allowed to participate in this study. As the effects of this treatment may cause harm to a fetus (unborn child), men and women who are capable of having children must use reliable methods of birth control (i.e. birth control pills, condoms, approved contraceptive implant, intrauterine device) throughout the study to prevent pregnancy. As the drugs may pass into the breast milk, to protect nursing children from contact with the drug(s), mothers should not breast feed during the study. If you become pregnant while on the study, you must notify your study doctor immediately, who will discuss the medical options with you and your partner.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you choose to participate in this study, there may or may not be direct benefit to you. Information learned from this study may benefit other patients in the future.

You can get treatment for lung cancer without being on this study.

WHAT ABOUT CONFIDENTIALITY?

Every effort will be made to keep your personal information confidential.

Qualified representatives of the following organizations may inspect your relevant medical records (relating to the study) and study records and receive information from your relevant medical/study records for quality assurance and data analysis:

- The Ottawa Hospital Research Ethics Board, which oversees the ethical conduct of this study at The Ottawa Hospital Regional Cancer Centre.

This information may include test results, reports of operations, x-rays or other body scan reports and questionnaires relating to the study.

The organizations listed above will keep information about you confidential, to the extent permitted by applicable laws, in the following manner:

- Your name will not be used in any reports about the study
- You will be identified only by a study code and initials
- Your name will not be disclosed in any report or publication resulting from the study or in any documents leaving The Ottawa Hospital Regional Cancer Centre, unless required by law.

WHAT ARE THE COSTS?

There is no cost for the additional CT scans or monitoring of your breathing. You will not be paid for taking part in this study.

WHAT ABOUT COMPENSATION?

In the event of a research-related injury, you will be provided with appropriate medical treatment. Although no funds have been set aside to compensate you in the event of injury or illness related to the study treatment or procedures, you are not waiving your legal rights by agreeing to participate in this study. The study doctor, the study sponsor, The Ottawa Hospital Regional Cancer Centre and the hospital still have their legal and professional responsibilities.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

You are under no obligation to participate in the study. Participation in this trial is voluntary and you may choose not to participate or to withdraw from the study at any time without giving a reason. This will not affect the standard of treatment you receive now or in the future.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

If you have questions about taking part in this study you can talk to your doctor. Or, you can meet with the doctor who is in charge of the study at this institution. That person is Dr. R MacRae at (613) 737-7700, Ext 6169.

This protocol has been approved by The Ottawa Hospital Research Ethics Board. This Board considers the ethical aspects of all hospital research projects using human subjects. If you have any questions concerning this study or your rights as a research subject, you may contact any of the following people:

- The Vice-President, The Ottawa Hospital Regional Cancer Centre, (613) 737-7700, Ext. 6880.
- The Chairperson of The Ottawa Hospital Research Ethics Board, (613) 798-5555, Ext. 14902.

My signature below means I have read this patient information and consent form, (or it has been read to me), I have had the opportunity to review any questions with my study doctor, I agree to participate in this study and authorize access to my relevant medical records as explained above. A copy of this patient information and consent form will be given to me.

Patient's Name (Please Print)

Patient's Signature

Date

Name of Investigator/Person Conducting the
Informed Consent Discussion (Please Print)

Signature of Investigator/Person Conducting the
Informed Consent Discussion

Date

Appendix B

Surrogates for Breathing

As fully discussed in Chapter 3, before applying the skin markers, Belt and SPR to lung cancer patients, a set of systematic experiments was designed to be conducted on normal volunteers to determine if the skin markers and Belt could act as surrogates for breathing. The goal of this phase of the study, referred to as Phase-I, was to address three specific issues regarding the relationship of surface motion and chest expansion with breathing. These issues were as follows:

- 1- Is surface motion a good surrogate for breathing?
- 2- Is the relationship between surface motion and breathing invariant in time?
- 3- Is the relationship between surface motion and breathing independent of breathing type?

The experimental procedure was fully described in Chapter 3 and some important results were shown in that chapter. However, since there was a large number of tables to report the results, most of the detailed results were moved to this appendix. Also, as noted in chapter 3, due to the large amount of collected data in Phase-I, an inductive reasoning approach was taken to analyze and discuss the data for this phase. That is to say working "bottom up" or moving from specific observations to broader generalizations and finally finish by developing some general conclusions. Therefore, the focus was first on the relation between surface motion (and Belt) and breathing for one subject (volunteer number 1) and one type of breathing (normal breathing). This was investigated both on one day to see the level of correlation, and over 5 days, to see the reliability of the

results. Following that, other types of breathing (INSP and EXP) for this subject were looked at. Finally the same issues were considered over the population of the study.

The complete results are reported in this Appendix while some important results are presented and discussed in chapter 3. Each set of results are provided to address a specific question. Therefore they precede by the question that they try to answer.

The following points must be made about the reported results.

- 1- Correlation Coefficient will always mean the best correlation coefficient obtained as a result of shifting one set of data with respect to the other.
- 2- Reported phase shifts refer to the phase shifts that result in the highest correlation coefficients
- 3- When considering more than one Correlation Coefficient (over several points or several days) the mean is reported however, for the phase shift, the quantity itself does not have any significance (at least for the purpose of this work). Instead, what is important is the consistency in the phase shift. That is to say the variation (or the standard deviation) of the phase shift become important. Therefore, for the phase shift only the variation (STD) that is an indication of the change is reported. That means that the mean and STD's reported for the phase shifts are in fact the mean and STD's of the variation (standard deviation) in the phase shift not mean and STD of the phase shift itself.
- 4- The results are reported to address specific questions. Therefore, each set of results is preceded by a question that the results are intended to address.

Q1: How well do the surrogates correlate with breathing (SPR) for one subject on a given day?

To answer this question, one subject, one type breathing, and an experiment on a single day will be considered. To show the level of correlation between breathing (SPR) and

the surrogate, the correlation coefficient and phase shift calculated as described before will be shown.

Figure B.1(b) shows the best correlation coefficients between skin markers (and Belt) and SPR for volunteer number 1 (V1) for normal breathing. In this figure, the 3 coordinates (X, Y, Z) for each point are grouped together. The idea has been to identify the skin marker(s) whose motion correlate the best with the SPR; in other words, find the best point(s) on the skin to place the markers.

Figure B.1(a) depicts the same data, this time grouped on a different basis, i.e., all the like coordinates grouped together. This would explicitly mean that all X coordinates of the nine markers are shown first followed by all the Y coordinates and so on. For each coordinate, the mean of the correlation coefficients of the 9 points were found to be 0.71, 0.86 and 0.92 for X, Y and Z coordinates respectively. The best correlation coefficient between Belt and SPR was 0.88.

The phase shifts which yielded the correlation coefficients in Figure B.1(b) are shown in Figure B.2(a) with the corresponding mean and standard deviations shown in Figure B.2(b)

Q2: Reliability-How well the relationship between breathing (SPR) and surrogates (skin markers and Belt) for one subject hold over several (non-consecutive) days?

To answer this question change in the correlation coefficient and phase shift was observed over five (non-consecutive) days and the relevant statistics (mean for correlation coefficient, and the standard deviation for the phase shift) were calculated.

Figure B.3 shows the mean of the correlation coefficients of each coordinates of each skin marker over 5 days. To compare the three coordinates, the values on Figure B.3 were averaged for each coordinate and 0.79, 0.92 and 0.96 were obtained for X, Y

(a)

(b)

Figure B.1 The best correlation coefficients between surrogate (the various coordinates of the 9 skin markers and the Belt) and breathing (SPR) for volunteer 1 (V1) on day-1 during normal breathing. For the skin markers, in (a) the three coordinates of each marker are grouped together while in (b) the same coordinates of all marker are grouped together in (b)

Figure B.2 The phase shift between surrogates (the various coordinates of the 9 skin markers and the Belt) and breathing (SPR) for volunteer 1 (V1) on day-1 during normal breathing. (a) For individual coordinates of each marker, (b) average for each coordinate over all markers. The phase shift between the Belt and SPR is shown on both graphs

Figure B.3 The average correlation coefficients between surrogate (the various coordinates of the 9 skin markers and the Belt) and breathing (SPR) for volunteer 1 (V1) over five days during normal breathing.

and Z respectively. These average value for the correlation coefficient between SPR and Belt over 5 days was 0.95.

For phase shift, as described earlier, what is important is the change in the phase shift from day to day. Therefore, the standard deviation (STD) in the phase shift that is a measure of variation or change over 5 days becomes the relevant statistic here. Figure B.4(a) shows the STD in phase shift for individual coordinates of each point, X1 to Z9. The Mean and standard of these variations in the phase shift for X, Y and Z are 281 ± 333 ms, 62 ± 24 ms, 66 ± 12 ms respectively. The variation in the phase shift between Belt and SPR over five days is 39 ms (Figure B.4(b)).

Q3: How does the relationship between breathing (SPR) and surrogates (skin markers and Belt) and its reliability compare for different breathing types (INSP, EXP)

i) On one day

Table B.1 shows the correlation coefficients between breathing (SPR) and the surrogates (skin markers and Belt) for the three types of breathing for subject 1 on day-1. For the skin markers, the correlation coefficients are shown as the averages over nine markers for each of the three X, Y and Z coordinates.

Table B.2 shows the phase shift (in msec) for the three types of breathing for subject 1 on day-1 (note that these values are the actual phase shifts and not the variation in the phase shift).

ii) Reliability of the results over 5 days

Correlation coefficients

The mean correlations correlation coefficients between the surrogates and SPR over 5 days for the three types of breathing are shown in Table B.3. Note that for skin markers, first for each coordinate (X, Y and Z) the average value of the correlation coefficient over all nine markers on each day is calculated and then these average values are used to calculate the 5-day average.

Figure B.4 The variation (standard deviation) in the phase shift between surrogates (the various coordinates of the 9 skin markers and the Belt) and breathing (SPR) for volunteer 1 (V1) over five days for normal breathing. (a) For individual coordinates of each marker, (b) average for each coordinate over all markers. The variation of the phase shift between the Belt and SPR is shown on both graphs

Phase shift

The change (STD) in the phase shift between SPR and the surrogates over the 5 days are shown for the skin markers and Belt in Table B.4. Note that for the skin marker the following approach is taken for each coordinate (we use X as an example):

- 1- The 5-day variation (standard deviation) in the phase shift between X1 (X coordinate of point 1) and SPR is calculated
- 2- The same is done for X2 to X9
- 3- The mean and std of the variation of all X's is determined

Note that for the Belt, what is reported is the 5-day variation (standard deviation) in the phase shift between the Belt and SPR.

Q4: How well the findings for one subject apply to the study population?

A) For one day

Tables B.5 shows the correlation coefficients between the surrogates and SPR for individual subjects during NB on day-1. Note that for the skin markers, the correlation coefficients are shown as the averages over nine markers for each of the three X, Y and Z coordinates.

Tables B.6 shows the phase shifts between the surrogates and SPR for individual subjects during NB on day-1. Note that the values reported in this table represent the phase shifts not the variation in the phase shift. These values are reported mainly for comparison of the three types of breathing and as it was pointed out earlier, the magnitude of phase shift is in principle insignificant.

Tables B.7 and Tables B.8 show the correlation coefficients and phase shifts between the surrogates and SPR for individual subjects during INSP; and Bs A.9 and Tables B.10 show the same data for EXP.

Finally to see the performance of the surrogates over 5 days for the study population, Tables B.11 to B.16 show the 5-day averages of the data for individual subjects. Note

that the correlation coefficients and the variation in the phase shift reported in these tables are calculated as described previously described in this appendix. Table B.17 includes the correlation coefficient between the surrogates and SPR over the entire study population and over five days for the three types of breathing. Table B.18 shows the results of statistical tests on comparing the values shown in Table B.17. These results are discussed in chapter 3.

Q5: Is there a proffered position for the markers on the skin?

To investigate this issue, the correlation coefficients between the Z components of the individual markers and the SPR are shown in figures B.5, B.6 and B.7. These data includes all 5 experiments, the three types of breathing and all subjects. The figures indicate that no individual marker position is superior in all candidates, but for an individual candidate some markers positions are superior to others over all experiments. It is noteworthy that since skin markers are easy to use and do not cause any discomfort to the patient/subject, there is no reason to try to reduce the number of markers. The negative effect of including the bad markers in predicting breathing would be minimal as a linear model gives less weight to those markers that do not correlate well with breathing.

NOTE: The results included in this Appendix are referred to and discussed in chapter 3.

Table B.1 The correlation coefficient of skin markers and Belt with SPR on day-1 for volunteer 1 (V1) for three types of breathing. For the skin markers for each coordinate the average value over all nine markers is shown

	NB	INSP	EXP
X	0.71	0.91	0.82
Y	0.86	0.96	0.98
Z	0.92	0.91	0.96
Belt	0.88	0.94	0.94

Table B.2 The phase shift (in msec) of skin markers and Belt with SPR on day-1 for volunteer 1 (V1) for the three types of breathing. For the skin markers, for each coordinate the average value over all nine markers is shown. Note that these values are the actual phase shifts and not the variation in the phase shift

	NB	INSP	EXP
X	-176± 566	305±89	-32±536
Y	-168 ± 228	167±32	24±46
Z	45± 134	129±147	73±145
Belt	-120	-416	-216

Table B.3 The 5-day average correlation coefficient of skin markers and Belt with SPR for volunteer 1 (V1) for the three types of breathing.

	NB	INSP	EXP
X	0.79	0.80	0.76
Y	0.92	0.96	0.96
Z	0.96	0.94	0.95
Belt	0.95	0.94	0.96

Table B.4 The 5-day variation in the phase shift (in msec) of skin markers and Belt with SPR for volunteer 1 (V1) for the three types of breathing.

	NB	INSP	EXP
X	281±333	332±243	345±502
Y	62±24	117±17	82±14
Z	66±12	135±17	90±22
Belt	39	79	50

Table B.5 The correlation coefficient of skin markers and Belt with SPR on day-1 for individual subjects for NB. For the skin markers, for each coordinate the average value over all nine markers is shown

	V1	V2	V3	V4	V5	V6
X	0.71	0.81	0.86	0.74	0.70	0.64
Y	0.86	0.87	0.87	0.75	0.90	0.84
Z	0.92	0.98	0.97	0.84	0.94	0.97
Belt	0.88	0.97	0.98	0.79	0.95	0.97

Table B.6 The phase shift (in msec) of skin markers and Belt with SPR on day-1 for individual volunteers during NB. For the skin markers, for each coordinate the average value over all nine markers is shown. Note that these values are the actual phase shifts and not the variation in the phase shift

	V1	V2	V3	V4	V5	V6
X	-22±71	16±75	23±8	6±89	-82±112	-20±110
Y	-21±28	12±80	-23±50	23±88	-3±8	-18±63
Z	6±17	39±9	10±11	-9±85	-3±11	6±9
Belt	-15	-22	-21	-22	-21	-15

Table B.7 The correlation coefficient of skin markers and Belt with SPR on day-1 for individual subjects for INSP. For the skin markers for each coordinate the average value over all nine markers is shown

	V1	V2	V3	V4	V5	V6
X	0.91	0.86	0.68	0.64	0.48	0.40
Y	0.96	0.98	0.82	0.70	0.65	0.82
Z	0.91	0.92	0.80	0.88	0.93	0.88
Belt	0.95	0.93	0.93	0.86	0.97	0.96

Table B.8 The phase shift (in msec) of skin markers and Belt with SPR on day-1 for individual volunteers during INSP. For the skin markers, for each coordinate the average value over all nine markers is shown. Note that these values are the actual phase shifts and not the variation in the phase shift

	V1	V2	V3	V4	V5	V6
X	38±11	25±69	31±4	-8±103	-46±91	-12±98
Y	21±4	35±9	15±5	-41±118	41±17	-34±82
Z	16±18	59±41	15±8	29±69	5±15	10±29
Belt	-52	-44	-29	25	-30	-25

Table B.9 The correlation coefficient of skin markers and Belt with SPR on day-1 for individual subjects for EXP. For the skin markers for each coordinate the average value over all nine markers is shown

	V1	V2	V3	V4	V5	V6
X	0.82	0.74	0.28	0.67	0.50	0.44
Y	0.98	0.98	0.91	0.79	0.68	0.75
Z	0.96	0.96	0.88	0.95	0.89	0.86
Belt	0.94	0.98	0.88	0.91	0.91	0.96

Table B.10 The phase shift (in msec) of skin markers and Belt with SPR on day-1 for individual volunteers during EXP. For the skin markers, for each coordinate the average value over all nine markers is shown. Note that these values are the actual phase shifts and not the variation in the phase shift

	V1	V2	V3	V4	V5	V6
X	-4±67	53±106	-130±106	13±83	-34±71	33±36
Y	3±6	30±9	12±4	16±89	-19±35	-47±66
Z	9±18	60±44	12±9	37±33	-2±11	11±22
Belt	-27	-29	-24	-10	-39	-25

Table B.11 The 5-day average correlation coefficient of skin markers and Belt with SPR for various volunteers during NB

	V1	V2	V3	V4	V5	V6
X	0.79	0.80	0.71	0.74	0.65	0.60
Y	0.92	0.88	0.83	0.81	0.85	0.83
Z	0.96	0.97	0.92	0.85	0.94	0.94
Belt	0.95	0.96	0.96	0.94	0.95	0.96

Table B.12 The 5-day average variation in the phase shift (in msec) of skin markers and Belt with SPR for various volunteers during NB

	V1	V2	V3	V4	V5	V6
X	281±333	404±355	448±349	252±229	637±451	653±400
Y	62±24	234±159	153±162	264±273	122±190	633±404
Z	66±12	158±15	76±9	221±94	35±7	244±285
Belt	39	53	63	37	19	35

Table B.13 The 5-day average correlation coefficient of skin markers and Belt with SPR for various volunteers during INSP

	V1	V2	V3	V4	V5	V6
X	0.80	0.71	0.70	0.56	0.74	0.46
Y	0.96	0.98	0.86	0.85	0.80	0.78
Z	0.94	0.94	0.89	0.91	0.91	0.88
Belt	0.94	0.96	0.91	0.92	0.78	0.94

Table B.14 The 5-day average variation in the phase shift (in msec) of skin markers and Belt with SPR for various volunteers during INSP

	V1	V2	V3	V4	V5	V6
X	332±243	872±438	140±210	411±420	584±563	760±468
Y	117±17	290±50	92±61	370±419	176±116	335±436
Z	135±17	243±89	79±6	164±17	53±27	105±56
Belt	79	68	95	222	52	71

Table B.15 The 5-day average correlation coefficient of skin markers and Belt with SPR for various volunteers during EXP

	V1	V2	V3	V4	V5	V6
X	0.76	0.78	0.55	0.68	0.57	0.57
Y	0.96	0.96	0.81	0.81	0.78	0.79
Z	0.95	0.96	0.90	0.93	0.93	0.93
Belt	0.96	0.97	0.93	0.92	0.93	0.96

Table B.16 The 5-day average variation in the phase shift (in msec) of skin markers and Belt with SPR for various volunteers during INSP

	V1	V2	V3	V4	V5	V6
X	345±502	644±327	694±384	433±441	484±383	654±316
Y	82±14	216±26	188±259	351±277	84±74	225±74
Z	90±22	155±75	97±36	232±8	32±12	174±63
Belt	50	93	71	210	40	110

Table B.17 The correlation coefficient of each of the three components of skin marketer and Belt with SPR averaged over all subjects and all five experiments

	NB	INSP	EXP
X	0.71	0.66	0.65
Y	0.85	0.87	0.85
Z	0.93	0.91	0.93
Belt	0.95	0.91	0.95

Table B.18 The statistical testing for comparing the population-averaged correlation coefficient between SPR and various surrogates for the three types of breathing

H0: r1=r2						Reject H0 if P < 0.05	
H1: r1>r2							
r1 and r2 are the correlation coefficients of the two surrogates specified							
r1	r2	NB		INSP		EXP	
Y	X	t=5.00	P=0.002	t=5.16	P=0.002	t=11.30	P<0.001
		Reject		Reject		Reject	
		r1>r2		r1>r2		r1>r2	
Z	X	t=6.18	P<0.001	t=5.53	P=0.001	t=8.05	P<0.001
		Reject		Reject		Reject	
		r1>r2		r1>r2		r1>r2	
Z	Y	t=6.30	P<0.001	t=1.51	P=0.09	t=2.85	P=0.02
		Reject		Cannot Reject		Reject	
		r1>r2				r1>r2	
Belt	Z	t=1.51	P=0.09	t=0.13	P=0.45	t=1.78	P=0.07
		Cannot Reject		Cannot Reject		Cannot Reject

Figure B.5 Correlation coefficient of the Z component of each skin marker with SPR for all 5 experiment during NB

Figure B.6 Correlation coefficient of the Z component of each skin marker with SPR for all 5 experiment during INSP

Figure B.7 Correlation coefficient of the Z component of each skin marker with SPR for all 5 experiment during EXP

Appendix C

Internal Margin Data

In clinical situations, one is normally not looking for a margin that would guarantee the exposure of the entire tumor volume to 100% of the prescribed dose. Such a margin often results in the exposure of a large volume of healthy tissue and therefore clinicians usually compromise the tumor coverage in order to reduce the normal tissue irradiation. The final decision is made by the physician based on the type and location of the tumor, the surrounding tissue and the presence of any organ at risk near the tumor site. Clinically, most planning systems allow you to prescribe to a DVH such that a certain percentage of the target volume (95% or 100%) would receive a minimum dose, e.g. 95% of the prescribed dose. For the purpose of this study, the radiation oncologists in the group were consulted and it was agreed to use the 100% volume, 95% dose as the scoring function in comparing various IM's. At the cellular level, this means that every cell in the tumor would receive at least 95% of the prescribed dose. Note that this is different from 95% of the tumor volume receiving 100% of the prescribed dose. In the latter case, there may be cells in other 5% of the tumor that receive zero dose.

The method for obtaining the internal margins from the developed Dose-Volume histograms (DVH) was described in chapter 4. The complete set of IM's extracted from the DVH's both for the non-surrogate based case and for the various surrogate were shown in Tables 4.3 through 4.6. The margins shown in those tables for 100% tumor volume covered 95% of the time. Tables C-1 through C 4 in this Appendix will include margins for 100% tumor volume 100% of the time.

Table C.1 Internal Margins (IM) needed to cover 100% tumour volume 100% of the time for NB-1b where tumour-surrogate relationship is established in the earlier part of the same experiment (NB-1a). All margins are in mm.

	Non-surrogate	All Markers	One Marker	ROW	COL	SPR	BELT
P01-X	7.5	5.3	5.7	6.2	5.5	5.5	4.9
P02-X	5.9	5.6	5.7	5.4	5.4	5.7	5.6
P03-X	3.7	2.0	1.8	2.1	2.1	2.0	2.2
P04-X	3.8	3.5	3.6	3.5	3.7	3.3	3.1
P05-X	3.0	3.1	2.6	2.9	2.9	2.6	2.7
P06-X	3.5	3.4	2.8	3.0	2.8	3.2	3.1
P07-X	3.6	3.4	3.2	3.4	3.4	3.3	3.5
P08-x	6.9	6.8	6.1	6.1	7.1	6.2	6.8
P09-X	5.5	4.8	4.8	5.0	4.3	5.0	4.8
P10-X	4.5	3.9	3.6	3.9	3.9	3.7	3.4
P01-Y	4.5	5.3	4.3	4.3	4.1	4.6	4.6
P02-Y	4.0	3.6	3.4	3.3	3.8	3.0	3.4
P03-Y	4.3	2.6	2.0	2.3	2.5	2.2	3.5
P04-Y	13.8	5.5	5.9	6.2	5.6	9.0	8.0
P05-Y	12.8	5.6	5.9	5.3	5.6	5.2	6.9
P06-Y	6.8	6.5	6.4	6.0	6.0	6.8	6.8
P07-Y	8.5	5.1	5.4	4.5	4.5	5.6	6.7
P08-Y	17.9	7.0	5.6	6.8	9.6	7.5	13.6
P09-Y	6.8	4.1	5.3	4.7	4.3	5.3	5.9
P10-Y	20.2	7.1	7.3	6.7	7.0	6.2	8.6
Mean	7.4	4.7	4.6	4.6	4.7	4.8	5.4
STD	5.0	1.5	1.6	1.5	1.8	1.9	2.7
Min	3.0	2.0	1.8	2.1	2.1	2.0	2.2
Max	20.20	7.10	7.30	6.79	9.59	9.00	13.59

Table C.2 Internal Margins (IM) needed to cover 100% tumour volume 100% of the time for DB-1 where tumour-surrogate relationship is established in the earlier part of the same experiment (NB-1a). All margins are in mm.

	Non-surrogate	All Markers	1 Marker	ROW	COL	SPR	BELT
P01-X	15.4	13.4	12.7	15.4	15.1	9.7	13.5
P02-X	9.0	8.7	9.0	8.3	8.8	9.0	9.4
P03-X	4.6	2.4	2.2	3.1	2.4	2.1	3.4
P04-X	13.8	10.1	10.3	11.6	11.2	12.7	11.0
P05-X	9.5	9.4	7.8	8.3	7.7	7.9	8.2
P06-X	5.1	4.2	4.4	4.1	4.3	4.5	4.5
P07-X	5.7	5.5	5.7	5.2	5.7	5.5	5.5
P08-X	21.6	17.3	16.2	20.2	19.3	18.6	19.5
P09-X	10.9	8.1	6.8	7.7	7.6	6.3	6.4
P10-X	5.4	5.8	4.8	7.0	6.1	4.4	4.9
P01-Y	8.8	8.1	8.0	9.4	7.7	7.8	8.1
P02-Y	9.3	9.6	8.5	7.9	9.7	8.8	9.1
P03-Y	4.6	5.6	3.6	4.3	4.7	4.6	5.0
P04-Y	51.4	27.2	26.1	31.3	26.4	46.9	26.1
P05-Y	19.3	12.0	11.5	13.1	12.7	10.5	12.4
P06-Y	8.1	7.0	7.6	7.3	7.6	7.1	7.3
P07-Y	12.4	8.6	7.3	11.0	8.4	7.2	7.9
P08-Y	44.5	28.7	29.0	29.9	45.6	38.0	43.8
P09-Y	12.7	5.2	10.4	7.5	5.5	8.5	6.3
P10-Y	24.3	17.1	12.7	16.6	14.8	12.7	16.6
Mean	14.8	10.7	10.2	11.4	11.6	11.6	11.4
STD	12.7	7.1	6.8	7.9	9.8	11.2	9.5
Min	4.6	2.4	2.2	3.1	2.4	2.1	3.4
Max	51.4	28.7	29.0	31.3	45.6	46.9	43.8

Table C.3 Internal Margins (IM) needed to cover 100% tumour volume 100% of the time for NB-2 where tumour-surrogate relationship is established in the previous session (NB-1a). All margins are in mm.

	Non-surrogate	All Markers	1 Marker	ROW	COL	SPR	BELT
P01-X	8.4	6.1	6.5	7.8	6.8	5.9	6.9
P02-X	6.6	4.8	5.7	4.6	5.7	5.8	5.8
P03-X	7.2	7.4	5.4	5.7	5.3	5.5	8.1
P04-X	10.6	10.1	7.9	7.8	8.2	8.3	7.8
P05-X	8.2	4.5	4.5	4.2	4.3	4.4	4.7
P06-X	6.2	6.3	5.6	5.0	5.9	5.5	6.7
P07-X	4.1	4.6	4.4	4.7	4.6	4.6	4.3
P08-x	9.8	8.8	8.4	9.0	8.6	9.7	9.7
P09-X	5.3	4.0	4.4	4.5	4.9	4.7	4.8
P10-X	5.5	5.6	3.7	5.9	4.7	4.2	3.4
P01-Y	5.4	5.0	5.1	4.8	4.3	4.8	4.3
P02-Y	12.8	10.0	10.9	12.3	12.6	9.7	12.0
P03-Y	13.1	10.4	7.7	7.7	10.0	8.7	11.3
P04-Y	17.3	12.8	12.3	12.0	10.9	12.3	12.1
P05-Y	18.6	15.8	15.9	16.2	16.2	16.4	18.2
P06-Y	9.1	8.7	8.1	7.6	9.5	8.2	8.2
P07-Y	7.1	7.3	6.5	6.8	7.0	6.6	6.9
P08-Y	18.7	6.9	7.6	7.2	16.2	8.2	18.1
P09-Y	3.6	3.2	3.9	3.9	3.6	4.0	3.4
P10-Y	20.5	6.2	5.1	7.0	6.8	13.1	12.8
Mean	9.9	7.4	7.0	7.2	7.8	7.5	8.5
STD	5.2	3.2	3.1	3.2	3.8	3.4	4.4
Min	3.6	3.2	3.7	3.9	3.6	4.0	3.4
Max	20.5	15.8	15.9	16.2	16.2	16.4	18.2

Table C.4 Internal Margins (IM) needed to cover 100% tumour volume 100% of the time for DB-2 where tumour-surrogate relationship is established in the previous session (NB-1a). All margins are in mm.

	Non-surrogate	All Markers	1 Marker	ROW	COL	SPR	BELT
P01-X	9.8	8.8	7.6	8.2	8.9	8.0	7.2
P02-X	6.2	5.8	6.9	6.1	6.5	6.9	6.9
P03-X	9.2	7.4	6.6	7.5	8.9	7.4	9.2
P04-X	10.2	8.7	7.9	9.6	9.7	8.3	7.2
P05-X	6.5	6.5	7.2	6.5	7.5	7.1	7.2
P06-X	5.7	4.9	4.4	4.8	4.4	3.8	4.2
P07-X	4.0	4.0	3.9	3.9	3.9	3.9	3.6
P08-x	10.1	9.3	9.2	9.1	9.0	9.1	7.9
P09-X	10.9	4.5	4.5	9.6	5.5	5.3	6.8
P10-X	9.6	10.0	6.6	9.6	8.2	7.6	7.4
P01-Y	10.9	10.8	11.1	10.9	10.3	10.8	10.8
P02-Y	13.4	10.5	11.9	10.7	11.0	10.4	12.5
P03-Y	9.3	8.0	8.0	8.0	8.0	8.8	9.7
P04-Y	32.0	17.0	17.2	16.2	18.3	17.0	18.8
P05-Y	22.6	12.4	12.9	16.4	15.5	20.2	16.0
P06-Y	8.3	7.3	7.6	6.3	7.3	7.6	7.8
P07-Y	7.6	5.8	6.4	6.2	6.6	6.2	6.5
P08-Y	42.2	26.7	45.1	27.3	41.6	29.6	35.9
P09-Y	5.1	3.3	4.6	4.8	3.7	4.7	4.7
P10-Y	24.8	22.0	13.2	17.3	14.0	22.2	19.3
Mean	12.9	9.7	10.1	9.9	10.4	10.2	10.5
STD	9.9	6.0	8.9	5.6	8.2	6.8	7.4
Min	4.0	3.3	3.9	3.9	3.7	3.8	3.6
Max	42.2	26.7	45.1	27.3	41.6	29.6	35.9

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