1.1 BREAST RADIOTHERAPY

1.1.1 Historical Background

Cancer is an ancient affliction and a familiar enemy. Etymologically, cancer is Latin in origin, meaning crab [1] but its true linguistic roots remain obscure. It may be from its hard shell-like scirrhous appearance or may possibly due to the “claws” formed by the veins surrounding the tumour [2]. The history of breast cancer, like the history of medicine, is marked by progressive advances in medical understanding and treatment, which highlights the dialectic interplay between theory and therapy. The therapeutic rationale can be understood by the model paradigm of disease. For example, some early societies believed epilepsy was a form of spiritual possession and, thus, prescribed exorcism as a treatment. Therefore, effective treatment depends on a useful (but not necessarily accurate) theory of disease.

Though the scourge of cancer reaches back into prehistory, the Egyptians were the first, almost 5000 years ago, to describe breast cancer in their papyrus manuscripts and hieroglyphic inscriptions [3]. Cautery was the “preferred” method of removal but, not surprisingly, this treatment wasn’t highly popular because of the high risk of hemorrhage, infection and the considerable pain associated with the procedure.

The next advance arose in Greece. The Greeks, notably Hippocrates (460-377? BC) and Aristotle (384-322 BC), were the first to distinguish medicine as a science rather than as superstition. Natural processes, they thought, could be understood through reason. The mind is linked intimately with the body; a healthy body reflects a healthy mind and a healthy mind, a healthy body. Consequently, various psychological conditions could manifest as physical ailments and vice versa. They established and taught the doctrine of the four bodily humours based on this reductionist idea. The four humours (i.e. black bile/melancholic, phlegm/phlegmatic, yellow bile/cholic and blood/sanguine) were related to the four elements (i.e. earth, wind, fire and water). Disease was caused by an imbalance of these humours and treatment should, therefore, be directed at restoring this balance [4]. According to their theory of disease, melancholy was due to excessive black bile and the cause of cancer. Although simplistic and inaccurate, it was, nonetheless, a laudable first attempt at understanding unexplained phenomenon without resorting to deus ex machina. This remained the prevailing theory of disease for almost 2000 years.

The greatest Roman physician of his day was Claudius Galen (130-200 AD). Born in Pergamos (in Asia Minor), he gained fame and renown for his skilled treatment of gladiators. He eventually became the Emperor’s personal physician and wrote extensively, particularly his anatomic studies of animal dissections. The Romans believed in the doctrine of humours and followed most of the Grecian medical traditions. His writings were the unquestioned medical authority well into the Middle Ages. Galen was
a keen observer and believed cancer was curable only in its earliest stages and taught palliation in most cases [4].

After the Christianization of the Roman Empire, following its fall, the Catholic Church emerged as the great political power of the age. The Church completely dominated all scientific and religious thought during the Middle Ages. The adopted Aristotelian worldview remained the unchallenged church sanctioned dogma of the day until the great flowering of the Renaissance. The Renaissance was a time of great change, representing the democratization of truth away from a single dogmatic authority and the triumph of empirical reasoning over blind unexamined faith. Two important advances in the fields of surgery and pathology dramatically changed our understanding and treatment of breast cancer.

The first advance was in surgical technique. Ambroise Paré (1517-1590), the greatest surgeon of the Renaissance, favoured ligatures to control bleeding, reduce swelling and ease discomfort rather than cauterity and burning oil [5]. He also recommended surgery only if the cancer could be totally removed. The second major advance was pathophysiological. Andreas Vesalius (1514-1564), the renowned Flemish anatomist, produced his 7-volume folio masterpiece, De Humani Corporis Fabrica [6], which was the most accurate, up to date anatomy text of his day, correcting several long-standing errors of Galen [5].

The spread of breast cancer to the regional axillary nodes and its importance as a poor prognostic indicator was recognized [7]. This observation shifted more clinical interest to the lymph nodes. After the discovery of the lymphatic vasculature, a new theory of disease implicating lymphatic abnormalities as the cause of cancer was proposed. Although risky and dangerous, treatment of choice was still surgical resection. Surgeons realized the cancer must be completely removed, including all its “filaments” and affected lymph nodes. John Hunter (1728-1793) taught mobile tumours could be resected but advised against surgery if the lymph nodes were involved [8].
The next major surgical advances were in antisepsis by Joseph Lister (1827-1912) and anesthesia by Crawford Long (1815-1878). For the first time, surgery became practical and relatively safe \[9\]. By the late 1800's, the theory of centrifugal spread was the accepted theory of disease. Breast cancer, like other cancers, was believed to be a progressive step-wise disease, spreading directly from the breast to the lymph nodes to other distant sites in a methodical, predictable and contiguous manner. Most women presented with locally advanced tumours the size of lemons. So it seemed natural to suggest that more extensive resection should result in more cures and better local control rates. The super radical approach culminated in 1894 when William Halsted (1852-1922), the pre-eminent American surgeon, first described the procedure for a radical mastectomy \[10\]. In a radical mastectomy, the whole breast gland, \textit{en bloc}, with draining lymph nodes and pectoralis muscles were removed. Unfortunately, the procedure was highly mutilating and associated with marked post-operative morbidity. Period records from Johns Hopkins Hospital, where Halsted was appointed, revealed an average 10-year survival rate of 12\% with a 30\% local recurrence rate. With better patient selection (i.e. staging) and better surgical technique, 10-year survival rates steadily climbed, improving to about 50\% by the 1950's.

By the 1930's, a small chorus of clinicians challenged the Halstedian dictum of \textit{more is better}. It became increasingly clear that patients with locally advanced disease were not
seem amenable to surgical resection. By definition, these patients were deemed inoperable [11] so they were instead referred to radiotherapy. Successful radium treatments were reported as early as 1907 by W. Heinatz [12]. Geoffrey Keynes (1887-1982), an English surgeon and the brother of economist John Maynard Keynes, proposed interstitial radium implants as primary treatment for early stage breast cancer in 1931 [13]. One of the earliest breast conserving proponents, François Baclessé (1896-1967), suggested early stage tumour excision be followed by irradiation [14]. The Netherlands Cancer Institute, between 1954-1966, treated early stage breast cancer patients with a partial mastectomy, axillary dissection and low dose orthovoltage radiation [15,16] but this program yielded an unacceptably high rate of local recurrence (i.e. 41%) so was discontinued. Cushman Haagensen, a prominent breast surgeon, recognized another subset of poor prognosis patients, those with axillary involvement, and suggested mastectomy be avoided due to its excessive morbidity and poor outcomes. For the most part, the medical establishment ignored or rejected their more conservative approach. Paradoxically, surgeons, still steadfast in their Halstedian model paradigm of centrifugal spread, attempted ever more radical and ever more mutilating procedures as they agonized over every local recurrence. According to Halsted, these recurrences were a sign of inadequate surgery. The heroic but often questionable efforts of the surgeon resulted in regowning mid-operation to prevent possible intraoperative tumour contamination, meticulous dissection and en bloc removal.

It was not until the last quarter century, with improved radiotherapeutic techniques and a better understanding of breast cancer's natural history, that surgeons' attitude towards breast conserving surgery changed. In 1971, Bernard Fisher presented the initial results of National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial [17] that demonstrated no survival advantage of radical mastectomy over mastectomy with radiation or mastectomy with delayed axillary dissection. The subsequent NSABP B-06 trial [18] demonstrated no survival advantage of total mastectomy over lumpectomy and primary (i.e. adjuvant) radiation therapy. However, radiation did significantly reduce the risk of local recurrence. The Milan I study [19], by Umberto Veronesi, demonstrated equivalence of radical mastectomy against quadrantectomy, axillary dissection and breast irradiation (50 Gy) with a boost (10 Gy) to the tumour bed. The EORTC 10801 study [20] compared radical mastectomy versus tumour excision (including microscopically incomplete margins of tumours up to 5 cm in size) followed by breast irradiation (50 Gy) and a boost (15-25 Gy) to the tumour bed and found them to be equal.

1.1.2 Rationale

The implications of these breast studies were far-reaching and set the foundations of modern breast radiotherapy. First, it finally laid to rest the theory of centrifugal spread. Ever more radical surgery did not result in improved survival as they had hoped. Sec-
Second, primary whole breast radiotherapy following breast-conserving surgery significantly reduced the risk of local recurrences. Third, breast-conserving surgery plus primary breast radiotherapy was equally as good as mastectomy with respect to overall survival and local control. Fourth, the benefit of radiotherapy with respect to overall survival, although significant, must be small or easily confounded (otherwise, the survival advantage would already be confirmed). Fifth, the rationale for combining different treatment modalities such as surgery and radiotherapy was to reduce the overall treatment morbidity without compromising treatment outcomes. In other words, the therapeutic index of treatment was greater with multimodal therapy than surgery (or radiotherapy) alone.

There is growing evidence [21-24] primary breast radiotherapy does indeed improve overall survival but this benefit may be partially offset by a commensurate increase in radiotherapy-related deaths, notably cardiovascular events. The risk of fatal cardiac complications is related to the volume irradiated and the dose received by the heart [25-27]. Rutqvist et al [28] compared primary breast RT following modified mastectomy and mastectomy alone with respect to ischemic heart disease. Primary RT was significantly associated with ischemic heart disease (relative hazard=3.2). The study conclusions are based on older techniques, employing Co\textsuperscript{60}, which is associated with greater target dose inhomogeneity. Thus, these results cannot be directly extrapolated to newer treatment techniques. Nixon et al [29] found no significant increase in long-term cardiac-related mortality with modern treatment techniques. Nonetheless, comparing older with newer treatment techniques, provide very strong empirical evidence of a dose-volume effect relationship between heart and cardiac mortality.

The maximum heart distance (MHD) is an estimate of the amount of irradiated heart and is defined as the maximum distance of the heart contour to the medial field edge, measured parallel to the caudal field edge, as seen on a beam's eye view (BEV) of the medio-lateral tangential field. Our preliminary in-house patient review estimated the average left sided breast cancer patient population has a maximum heart distance of 1.6±0.6 cm (with a maximum value of 3.2 cm). Assuming the frequency is normally distributed, we expect around 83% of left-sided breast patients to have a MHD greater than 1.0 cm, 57%, greater than 1.5 cm and 27%, greater than 2.0 cm. A MHD of 2.0 cm is associated with approximately 2.5% risk of late excess cardiac mortality [30]. We hypothesize that primary radiotherapy would be most detrimental for the highest risk patient subset and that the inclusion of patients from other subsets may confound any survival improvements in the breast cancer population as a whole. Therefore, improved radiotherapy treatment in breast cancer would be of particular concern and interest for patients with large irradiated heart volumes (i.e. left-sided breast).
1.1.3 Intensity Modulated Radiotherapy

Intensity modulated RT (IMRT) deserves special mention due to its importance in improving breast RT. IMRT exploits the expanded degrees of freedom associated with non-uniform beams. By optimizing the beam’s non-uniform fluence profile, the dose distribution can be conformed around the target and, thereby, spare adjacent organs at risk. When properly utilized, IMRT reduces the theoretical error (see Sect. 1.2.3.2) but tends to be resource-intensive, hampering routine clinical implementation.

Various “class” IMRT solutions have been published [31,32] to improve overall treatment planning and delivery efficiency. Our approach uses anatomy based pre-defined segments, which serve as a compromise between minimizing the number of segments and maintaining reasonably shaped segments. The dose for unreasonable segments, such as small, off-axis, elongated segments, are often difficult to calculate accurately. Pre-defined segments ensure unreasonable segments are avoided altogether. Minimizing the number of segments reduces the number of free variables and can dramatically shorten the optimization time required for inverse planning.

Furthermore, there is increasing concern about the scatter dose to the contralateral breast and its association with second primary breast cancers. Several studies [33-35] do demonstrate a small but statistically significant increase in contralateral breast cancers. In light of this evidence, any unnecessary radiation exposure to the contralateral breast should be limited. Fewer beams with fewer segments will, in general, result in less scatter dose (from beam modifying devices). The practical implications to the treatment technique are that, all else being equal, the plan with the fewest segments will be preferred.

1.2 Radiotherapy

1.2.1 General

The general purpose of the thesis is: to improve radiotherapy treatment in breast cancer. The specific purpose is: to devise a class solution to reduce late cardiac complications for left-sided breast cancer patients that can be planned, delivered and implemented simply. The studies included in the thesis, in toto, constitute a diverse collection of papers directed towards the general goal of improving radiotherapy treatment in breast cancer. For the purposes of this thesis, a treatment is improved if its therapeutic index also improves.

1.2.2 Physical and Biological Phase Spaces

Radiotherapy can be decomposed into two conceptually related parts: physical and biological. The first part is concerned with the delivery of the physical dose in media. All radiotherapeutic interventions ultimately modify the physical phase space in the form
of absorbed dose. Usually, the dose is delivered by megavoltage photons from pre-arranged beams. Different treatment setups and techniques result in different dose distributions. If all the relevant interactions are well known and well described, then the absorbed dose is predictable. Much effort has been devoted to improving dosimetry [36-39]. Physical phase space modifiers, such as blocks and wedges, influence the absorbed dose.

The second domain, the biological phase space, is concerned with the accurate and precise understanding of the biological effect of the physical dose and the relationship between them. The biological phase space is closely related to radiobiological models where the physical phase space is (correctly) mapped to the biological phase space. It is important to note that the biological phase space corresponds, in fact, to the clinical decision-making process of a radiation oncologist. The biological phase space attempts to make explicit the implicit conversion every clinician makes from physical dose to biological outcome. Our knowledge of biological outcomes are, for the most part, derived empirically. Consequently, most of our experience and understanding are from older conventional treatment techniques, usually involving uniform homogeneous doses. Similar to physical phase space modifiers, biological phase space modifiers, such as radiosensitizers and concurrent chemoradiation, in conjunction with the absorbed dose, influence the biological outcome.

Photons are small quanta of electromagnetic energy. In radiotherapy, these high energy photons are usually generated by a linear accelerator and directed towards the patient. Energy is deposited into media by the photons in the form of charged radicals which are responsible for cellular damage. According to current radiobiological understanding [40], the critical target is the nuclear DNA and the magnitude of damage is, in part, related to the number of radicals, the charge of the radical and the kinetic energy of the radical. All things being equal, more dose will cause more DNA damage. At some point, the damage exceeds the repair capacity of the cell and the cell is rendered reproductively non-functional either through cell death or cell stasis.

An important but tacit assumption is similar dose distributions result in similar outcome and complication rates, all else being equal. It is based on this assumption that various treatment comparisons are made possible since the corollary states: better dose distributions result in better outcome and lower complication rates (and vice versa).

### 1.2.3 Improving Radiotherapy Treatment

According to our definition, improving radiotherapy treatment is identical to improving the therapeutic index. In general, radiotherapy treatment can be improved by: 1) reducing practical errors and/or 2) reducing theoretical errors. All improvements in radiotherapy can be categorized into these two types. Practical errors refer to the difference between what is delivered and what is intended (i.e. exactness) while theoretical errors
refer to the difference between what is intended and what is ideal (i.e. correctness). These distinctions are, by their nature, somewhat artificial since all errors are, ultimately, due to imperfect knowledge of the system. However, distinguishing different types and sources of errors can be helpful in directing efforts for improvement.

**Radiotherapeutic Chain**

![Diagram of the radiotherapeutic chain with various procedural links.](image)

**1.2.3.1 Practical errors**

Practical errors are related to the inherent stochastic uncertainty between the delivered and the intended dose and may depend on many factors such as geometrical uncertainty, sampling error (introduced by imaging), and organ movement. They make no assumptions as to the correctness of the target volume. Within the physical phase space, we wish to achieve some desired dose distribution, usually encompassing some given target volume, inside the patient. Typically, numerous procedural steps, including treatment planning and delivery, are followed to achieve an adequate dose distribution. In this sense, the physical phase space is like a radiotherapeutic chain, composed of many interlocking links, representing the individual procedural steps (Figure 1-2). Each link takes the output of the previous link, performs some operation and makes the result available for the next link. The strength of the link is inversely related to the uncertainty introduced by its operation. Therefore, the overall strength of the chain can be improved in 2 ways: 1) strengthening the weakest link or 2) eliminating the weakest link.
The latter is actually a specific instance of the former since removing a link is functionally equivalent to making that link infinitely strong.

Margins are added to the CTV to ensure it receives the intended dose distribution. The more procedural links in the chain, the greater the overall treatment uncertainty and, therefore, the wider the required margin. By reducing practical errors, smaller margins are required which spares more adjacent normal tissue (i.e. improves therapeutic index).

1.2.3.2 Theoretical errors

Theoretical errors are more difficult to quantify since it depends on treatment’s deviation from its theoretical ideal. The ideal treatment plan is defined as the plan with the greatest therapeutic ratio (for a given degree of freedom and knowledge). At its limit, with infinite degrees of freedom and perfect knowledge, the theoretical ideal converges to the “perfect” treatment where high dose is delivered to the tumor clonogens and no dose everywhere else since this situation, in principle, maximizes the therapeutic index. In general, minimizing theoretical errors (in the physical phase space) will tend to conform the 3D dose cloud around the tumor clonogens (which is the “correct” CTV) while minimizing practical errors will tend to reduce the required target margin.

Theoretical errors are harder to quantify than practical errors since one must know what the ideal treatment plan is beforehand. In practice, this is very difficult to know a priori since the therapeutic indices for various treatments are constrained by incomplete knowledge and also indirectly depend on the degrees of freedom associated with the treatment.

Consider a spherical CTV, irradiated by 2 rectangular parallel-opposed fields. Conceptually, we can increase the degrees of freedom by allowing the beam’s gantry angle to freely vary. The theoretical error is reduced if the beams are set perpendicular to each other such that the treated volume is better conformed to the spherical CTV (compared to the parallel beam setup). More conformal dose distributions result in better sparing of normal tissue and, therefore, improve the therapeutic index. In this sense, the perpendicular beams are more “correct” than the parallel beams. If we increase the degrees of freedom further by allowing 3D conformal (rather than rectangular) beams, then even more conformal dose distributions are possible. By applying similar arguments, we could increase the degrees of freedom even more by implementing non-uniform beams (as used in IMRT) with similar results. Degrees of freedom need not be limited to just beam fluence modulation since allowing non-coplanar beams will increase it as well.

It is, however, not necessarily true that merely increasing the degrees of freedom will always reduce the overall error. It is possible that reducing theoretical errors may be offset by an increase in practical errors. Although one may, in theory, be able to con-
form the dose distribution tightly around the CTV and spare nearby organs at risk (ORs), in practice, this may not be possible. For example, if the CTV and OR are 5 mm apart but the required target margin is 10 mm, then it will be exceedingly hard to satisfy both constraints.

Less obvious but more challenging is the problem of target volume. Generally, the clinician is assumed to delineate the “correct” CTV but clearly this is not always the case. Incorrect target delineation is a theoretical error in the sense that it deviates from the true (i.e. “correct”) target. However, without more information, as provided by functional imaging and pathological studies, qualifying, let alone quantifying, this type of error is very difficult.

1.3 THESIS OVERVIEW

It is difficult to determine the best treatment technique for a given treatment volume since the best treatment technique cannot always be known or knowable, a priori. However, which available treatment technique is the best for a given treatment volume is decidable.

Prior to the introduction of non-uniform beams, the standard beam orientation in breast radiotherapy consisted of two opposing tangential beams, which is (nearly) optimal for uniform beams. If we increase the degrees of freedom by allowing non-uniform beam profiles such as IMRT, an optimal non-uniform treatment plan at least as good as the optimal uniform treatment plan must necessarily exist. With greater degrees of freedom, optimal non-uniform beams provide more conformal target dose distributions than optimal uniform beams. Therefore, optimal non-uniform beams have better dose distributions and smaller theoretical errors than optimal uniform beams. Conceptually, we can increase the degrees of freedom even more by by allowing non-standard off-tangential beam orientations to enlarge the solution space. By applying similar arguments, an optimal oriented non-uniform treatment plan at least as good as the tangentially oriented optimal non-uniform treatment plan must necessarily exist. Optimally oriented beams allow better conformality of the target dose distribution compared to tangentially oriented beams and, therefore, smaller theoretical errors. Quantifying the impact of non-uniform beams on breast cancer radiotherapy, with respect to normal tissue complication probabilities and normalized target coverage, as well as determining and quantifying the influence of optimal beam orientations on breast cancer radiotherapy are both subjects of study.

1.3.1 Tangential Uniform Beams

The typical treatment plan for primary radiotherapy employs two tangentially oriented uniform beams. Generally, the field borders are determined clinically at the time of simulation and the central slice is used to optimize the target dose homogeneity. The
treatment plan assumes the breast is shaped like a hemicylinder rather than a hemisphere and, therefore, introduces some dosimetric errors due to missing tissue effects. Regions of high dose are found in the breast, tangential to the beam, particularly the infra-mammary and areolar regions. Wedges are often used as missing tissue compensators to improve dose homogeneity along the axis of the dose gradient but, because they only wedge along a single axis, they cannot completely compensate the breast in both directions. The standard wedged tangential uniform 2-beam treatment technique has several disadvantages.

The dose calculation used in the standard technique has its limitations. Using the central slice to calculate the dose is not representative of the entire breast. A full three-dimensional dose calculation requires volumetric data from a CT scan. However, imaging itself introduces a sampling error since the planning position and the treatment position are not necessarily identical. Furthermore, organ movement, such as breathing, as well as other setup uncertainties, complicates an accurate calculation of dose.

Uniform beam techniques are not as good as non-uniform beam techniques. The increased degrees of freedom within the non-uniform beam allow finer modulation of segment intensity, optimizing the compromise between underdosing the target and overdosing the organs at risk. In principle, non-uniform beam techniques are always at least as good as uniform beam techniques since it can be viewed as a superset of the latter. Awkward volumes of interest, such as when the internal mammary chain is included, are particularly difficult to irradiate with uniform beams due to the potentially large volume of heart within the irradiated field. Therefore, these cases are expected to benefit the most with non-uniform beam techniques.

Treatment evaluation often ignores relevant complications. Fortunately, early stage breast cancer patients receiving primary RT do remarkably well. As a result, there is less impetus to seek technical improvements. In the past, late cardiac mortality was not explicitly considered. In part, this was due to the lack of volumetric data required to calculate the cardiac dose and uncertainty in the complication risk. More recently, cardiovascular complications are becoming recognized as a significant cause of mortality [27,41-44]. Accurate estimation of cardiac risk is difficult due to several confounders such as long latency period, low incidence and lack of reliable dosimetric, volumetric and outcome data. Nonetheless, given the seriousness of this complication, they should not be ignored when determining treatment merit in patient subsets with large MHDs.

Tangentially oriented non-uniform beams are sub-optimal for some patients. About a quarter of presenting left-sided breast cancer patients have a MHD greater than 2.0 cm. In these cases, the standard tangential beam orientation is associated with the overlapping breast and heart volumes. Due to the penetrating nature of the photons, one cannot simultaneously cover the breast and spare the heart with the same segment. Al-
though tangential uniform beams are nearly optimally directed, they are sub-optimal if applied to non-uniform beams. A major topic of study is devoted to determining the optimal non-uniform 2-beam orientation is left-sided breast cancer patients with large MHDs.

These observations provide the rationale for the topics of study. Each individual study represents a small improvement in the treatment technique. The ultimate aim of the thesis is the devise a class solution treatment technique to reduce late cardiac complications for left-sided breast cancer patients. Incorporating all the improvements together into a final class solution is the subject of last study of the thesis.

### 1.4 AIMS

The aims of the thesis are to improve radiotherapy treatment in breast cancer and can be summarized as follows:

1. improving breast radiotherapy by:
   a. reducing practical errors in:
      i. dosimetric accuracy, specifically examining the dosimetric influence of variant effects, such as contour changes and tissue inhomogeneities, on target dose-volume histograms.
   b. reducing theoretical errors in:
      i. treatment technique, specifically comparing non-uniform against uniform and mixed modality beam techniques irradiating the left breast and upper ipsilateral internal mammary lymph node chain.
      ii. treatment complication, specifically comparing the reduction in cardiac and pulmonary complications rates between uniform and non-uniform beam techniques.
      iii. beam orientation, specifically evaluating the difference between uniform and non-uniform beam techniques on the optimal 2-beam orientations.

2. devising a class solution using simplified intensity modulated radiotherapy using predefined segment, specifically describing a class solution that is easy to implement clinically with conformal dose distributions to spare heart.

### 1.5 REFERENCES


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